Amgen Comments: Follow-on Biologics: Impact of Recent Legislative and Regulatory Naming Proposals on Competition

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Appendix: Frequently Cited Materials

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PURE RED-CELL APLASIA AND ANTIERYTHROPOIETIN ANTIBODIES IN PATIENTS TREATED WITH RECOMBINANT ERYTHROPOIETIN

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ABSTRACT

Background Within a period of three years, we identified 13 patients in whom pure red-cell aplasia developed during treatment with recombinant human erythropoietin (epoetin). We investigated whether there was an immunologic basis for the anemia in these patients.

Methods Serum samples from the 13 patients with pure red-cell aplasia were tested for neutralizing antibodies that could inhibit erythroid-colony formation by normal bone marrow cells in vitro. The presence of antierythropoietin antibodies was identified by means of binding assays with the use of radiolabeled intact, deglycosylated, or denatured epoetin.

Results Serum from all 13 patients blocked the formation of erythroid colonies by normal bone marrow cells. The inhibition was reversed by epoetin. Antibodies from 12 of the 13 patients bound only conformational epitopes in the protein moiety of epoetin; serum from the remaining patient bound to both conformational and linear epitopes in erythropoietin. In all the patients, the antibody titer slowly decreased after the discontinuation of treatment with epoetin.

Conclusions Neutralizing antierythropoietin antibodies and pure red-cell aplasia can develop in patients with the anemia of chronic renal failure during treatment with epoetin. (N Engl J Med 2002;346:469-75.)

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THE production of erythrocytes requires the hormone erythropoietin,[1] which in adults is produced mainly by the kidney. A lack of erythropoietin is the reason for the development of anemia in chronic renal failure.[2] The hormone is not absent in chronic renal failure, however, because the liver and partially functioning kidneys produce enough erythropoietin to maintain a low level of erythropoiesis, as evidenced by the presence of erythroblasts in the bone marrow and reticulocytes in the blood.

The gene for human erythropoietin was cloned in 1985,[3,4] and recombinant human erythropoietin (epoetin) was approved for marketing in France in 1988 for the treatment of anemia in patients undergoing dialysis for chronic renal failure. Endogenous erythropoietin is a heavily glycosylated protein, and glycosylation is essential for its biologic activity. Endogenous erythropoietin and epoetin have different patterns of glycosylation, which involve primarily the sialic acid composition of oligosaccharide groups.[5] Epoetin alfa (Johnson & Johnson, Manati, Puerto Rico) and epoetin beta (Roche, Mannheim, Germany) are produced by recombinant methods in Chinese-hamster–ovary cells. They have slight differences in glycosylation; epoetin alfa has more sialic acid residues than epoetin beta.[6]

Since the introduction of epoetin into clinical practice, only three cases in which antierythropoietin antibodies developed after the administration of epoetin have been reported.[7-9] We studied 13 patients with chronic renal failure in whom severe transfusion-dependent anemia developed after an initial hematologic response to epoetin. In all 13 patients, the ane-

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mia was due to pure red-cell aplasia in association with neutralizing antierythropoietin antibodies.

METHODS

Bone Marrow Cultures

Otherwise normal patients undergoing hip-replacement surgery gave written informed consent for the collection of bone marrow cells. Erythroid and granulocytic cultures were established as previously described[10] with use of either normal pooled serum from 10 healthy volunteers (the control group) or each patient's serum at a final concentration of 20 percent. Erythroid and granulocytic colonies were assessed on days 7 and 14, respectively.

Binding of ^{125}I-Labeled Epoetin

Highly purified epoetin was labeled with iodine-125 as previously described, with specific activities ranging from 2.5×10^7 to 5×10^7 counts per minute (cpm) per microgram.[11] Approximately 100,000 cpm of ^{125}I-labeled epoetin in 200 μl of Tween bovine serum albumin in TRIS-buffered saline (consisting of 10 mM TRIS-hydrochloric acid, pH 7.4; 150 mM sodium chloride; 0.02 percent sodium azide; 0.1 percent bovine serum albumin; and 0.1 percent Tween 20) was incubated overnight at 4°C with different concentrations of patient serum or 20 μl of control serum. Protein G Sepharose (50 μl) (Pharmacia, Uppsala, Sweden) was added, and the tubes were incubated for another hour with continuous stirring. Then, 2 ml TRIS-buffered saline–Tween bovine serum albumin was added, and the tubes were centrifuged for 15 minutes at $1500\times g$. The resulting pellets were washed twice, and the radioactivity was counted. This sensitive method can detect antibodies able to bind 200 mU of erythropoietin per milliliter of serum.[10]

Deglycosylation Studies

Deglycosylation of epoetin was performed as previously described.[12] ^{125}I-labeled epoetin was diluted with 200 μl of 50 mM sodium phosphate buffer (pH 5.0) containing 0.1 percent nonaethyleneglycol octylphenyl ether (NP40) and 0.02 percent sodium azide and sequentially deglycosylated by incubation for 1 hour at 37°C with *Arthrobacter ureafaciens* neuraminidase and for 18 hours with a mixture of *O*-glycosidase, endoglycosidase F, and *N*-glycosidase F (all from Roche, Mannheim, Germany). The efficiency of deglycosylation was monitored with the use of polyacrylamide-gel electrophoresis, and the extent of deglycosylation of unlabeled erythropoietin was confirmed by mass spectrometry.

Denaturation of Epoetin

Deglycosylated, ^{125}I-labeled epoetin was denatured by boiling in 0.1 percent sodium dodecyl sulfate and 50 mM dithiothreitol in phosphate-buffered saline. The solution was boiled for five minutes before 250 mM iodoacetamide was added, and the solution was then incubated for one hour at 20°C in the dark. NP40 was added to achieve a final concentration of 1 percent, and the solution was diluted 1:1000 with TRIS-buffered saline before use. In control experiments, epoetin was added after dilution of the incubation medium containing sodium dodecyl sulfate, dithiothreitol, NP40, and iodoacetamide; these experiments showed that the final concentrations of these compounds did not affect the binding of antibody to epoetin.

RESULTS

Patients

The 13 patients we studied were identified during standard treatment of anemia due to chronic renal failure from May 1998 to November 2000. The clinical features of the 13 patients were similar (Table 1). Twelve patients were receiving treatment in France and one was being treated in the United Kingdom. Eleven patients were undergoing hemodialysis, one was undergoing peritoneal dialysis, and one was not undergoing dialysis. All patients had been treated with epoetin by the subcutaneous route, and severe anemia that was resistant to epoetin had developed in all after 3 to 67 months of treatment. Twelve patients received epoetin alfa in the last few months before their disease became refractory to treatment (Table 1); one patient (Patient 3) was treated exclusively with epoetin beta, and her anemia also became refractory to treatment. The diagnosis of pure red-cell aplasia was based on the absence of erythroid cells in the bone marrow in 12 patients and the absence of circulating reticulocytes in 1 patient (Patient 11).

Thoracic and abdominal computed tomographic scans showed no evidence of thymoma, lymphoma, or solid tumor. The results of serologic tests for parvovirus B19, human immunodeficiency virus, Epstein–Barr virus, hepatitis viruses, and cytomegalovirus were negative. In serum samples collected at the time of the diagnosis of pure red-cell aplasia, serum erythropoietin (measured by an enzyme-linked immunosorbent assay with a commercial kit [R and D Systems Europe, Abington, United Kingdom]) was undetectable in 10 patients and within the normal range in 3 patients. This finding was surprising, because serum erythropoietin levels are usually very high in patients with pure red-cell aplasia.[13] Because antierythropoietin antibodies in serum can interfere with erythropoietin measurements by forming complexes with erythropoietin molecules, serum samples from these patients were tested for the presence of antierythropoietin antibodies.

Therapy with epoetin was discontinued when the presence of antierythropoietin antibodies was confirmed. As of September 2001, 6 of the 13 patients (Patients 2, 3, 6, 7, 8, and 9) had recovered some erythropoietic function after receiving immunosuppressive therapy or a renal allograft (Table 2). Two other patients (Patients 1 and 4), after a follow-up of more than two years, remain transfusion-dependent despite immunosuppressive treatment. Another patient (Patient 5) did not receive immunosuppressive treatment and remains transfusion-dependent 34 months after the onset of anemia. The follow-up period for the four remaining patients (Patients 10, 11, 12, and 13) was too short for conclusions to be drawn regarding their clinical course.

Bone Marrow Cultures

We evaluated the ability of serum from epoetin-treated patients to inhibit the proliferation of erythroid progenitor cells by using cultured bone marrow cells from healthy donors. All 13 samples inhibited

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TABLE 1. CHARACTERISTICS OF THE 13 PATIENTS.

PATIENT NO.	AGE	RENAL DISEASE	DATE HEMODIALYSIS BEGUN	DATE SC EPOETIN THERAPY BEGUN*	INTERVAL FROM START OF THERAPY TO REFRACTORY ANEMIA	DATE OF DIAGNOSIS OF RED-CELL APLASIA BY BONE MARROW EXAMINATION
	yr				mo	
1†	71	Glomerulonephropathy	12/93	12/93, epoetin beta 4/97, epoetin alfa	53	2/99
2	22	Renal agenesis	6/98	7/98, epoetin alfa	3	2/99
3	40	IgA nephropathy	2/98	3/98, epoetin beta	7	2/99
4	64	Nephroangiosclerosis	11/98	2/99, epoetin alfa	4	8/99
5	68	Extramembranous glomerulonephritis	10/90	2/93, epoetin alfa‡	67	1/99
6§	29	IgA nephropathy	Not given	1/99, epoetin alfa 5/99, epoetin beta	5	7/99
7	44	Membranoproliferative nephropathy	3/98	11/98, epoetin alfa	10	11/99
8	44	Vascular nephropathy	3/99	6/99, epoetin alfa	3	10/99
9	72	Chronic pyelonephritis	1/99	10/98, epoetin alfa	12	10/99
10	71	Undetermined	6/00	11/99, epoetin alfa	4	3/00
11	85	Nephroangiosclerosis	3/99	3/00, epoetin alfa	7	10/00¶
12	55	Vascular nephropathy	3/98‖	6/00, epoetin alfa	5	2/01
13†	53	Undetermined	12/97	12/97, epoetin beta 12/98, epoetin alfa	32	11/00

*SC denotes subcutaneous.

†Patients 1 and 13 first received epoetin beta, which was replaced by epoetin alfa at the indicated times.

‡Patient 5 received intravenous epoetin from February 1993 until June 1998, when subcutaneous therapy was begun.

§Patient 6 first received epoetin alfa, which was replaced by epoetin beta.

¶Bone marrow examination was not performed in Patient 11, who presented with a profound anemia without reticulocytes.

‖Patient 12 underwent peritoneal dialysis.

the growth of erythroid progenitor cells but did not modify the formation of granulocytic colonies (Table 3). Tests performed on 12 of 13 serum samples showed that the addition of epoetin to the culture reversed the inhibitory effects of patients' serum on erythroid-colony formation (Fig. 1 and Table 3). Using serum from Patient 1, we found that inhibition of erythroid-colony formation was due to IgG. Removal of the IgG fraction of this serum with the use of immobilized G protein abolished its inhibitory effect, whereas IgG purified from the patient's serum inhibited erythroid-colony formation (Fig. 1). In contrast, IgG purified from control serum did not inhibit erythroid-colony formation. These results strongly suggested that the patients' serum contained neutralizing antierythropoietin antibodies. We therefore determined whether antierythropoietin antibodies were present in serum samples collected at the time of the diagnosis of pure red-cell aplasia.

Binding of ^{125}I-Labeled Epoetin

To test for the presence of antierythropoietin antibodies, we incubated increasing concentrations of serum (1 to 20 μl of serum per 200 μl of incubation medium) with ^{125}I-labeled epoetin and separated immune complexes using protein G Sepharose. The results for Patient 1 are shown in Figure 2. Using the amount of serum required to bind 50 percent of the radioactivity in the presence of immobilized G protein, we estimated that 1 ml of this patient's serum was able to bind approximately 40 U of epoetin (Table 3). This value is in good agreement with the neutralization capacity estimated from results obtained with normal progenitor cells (Fig. 1). Serum from all 13 patients was found to bind epoetin (Table 3). In contrast, normal serum did not bind ^{125}I-labeled epoetin. As controls, serum samples from patients treated with epoetin who did not have pure red-cell aplasia were tested and found to be negative.

Characterization of Antierythropoietin Antibodies

Scatchard analysis[14] of the binding of antibodies in serum from Patient 1 to epoetin yielded an apparently straight line (Fig. 3), suggesting the presence of homogeneous binding sites, although the presence of some heterogeneity in the binding antibod-

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TABLE 2. TREATMENT AND OUTCOME OF PURE RED-CELL APLASIA.*

PATIENT NO.	DATE OF ONSET OF ANEMIA	FOLLOW-UP (MO)	TREATMENT	OUTCOME
1	5/98	38	Immune globulin	Decrease in antibody titers; no decrease in transfusion requirements
2	10/98	33	Immune globulin, plasmapheresis, and corticosteroids	Disappearance of antibodies; no transfusion given since September 1999; hemoglobin level stable (10 g/dl)
3	10/98	33	Immune globulin and corticosteroids, followed by kidney transplantation in November 2000	No decrease in transfusion requirements until kidney transplantation; hemoglobin level then stable (11 g/dl) without transfusions
4	6/99	24	Corticosteroids	Progressive decrease in antibody titers; no decrease in transfusion requirements
5	9/98	34	No treatment	Progressive decrease in antibody titers; no decrease in transfusion requirements
6	6/99	24	Corticosteroids and cyclosporine	Disappearance of antibodies; no transfusion given since October 1999; hemoglobin level stable (13 g/dl)
7	9/99	22	Corticosteroids	Progressive decrease in antibody titers; no transfusion since June 2000; hemoglobin level stable (12 g/dl)
8	9/99	22	Corticosteroids	Progressive decrease in antibody titers; no transfusion since February 2000; hemoglobin level stable (8.5 g/dl)
9	10/99	21	Cyclophosphamide and corticosteroids	Progressive decrease in antibody titers; no transfusion since December 2000; hemoglobin level stable (11 g/dl)
10	3/00	16	Corticosteroids	No decrease in transfusion requirements
11	10/00	8	Corticosteroids	Slight decrease in antibody titers; no decrease in transfusion requirements
12	11/00	7	Immune globulin and corticosteroids	No decrease in transfusion requirements
13	8/00	10	No treatment	No decrease in transfusion requirements

*Corticosteroids were usually given at a dose of 1 mg per kilogram of body weight per day and gradually reduced when a decrease in antierythropoietin antibodies was seen. Immune globulin (1 g per kilogram per day) was injected intravenously on two consecutive days. Cyclosporine was given at a dose of 100 mg twice a day. Cyclophosphamide was given as an intravenous bolus every four weeks for a total of three times.

ies is possible, since they are not monoclonal. The apparent dissociation affinity constant was 110 pM, and the maximal binding capacity was 0.6 μg (60 U) of erythropoietin per milliliter (Fig. 3). This result was in good agreement with our rough estimates obtained from Figure 2. The same experiments were conducted with serum from all 13 patients, and antibodies with similar characteristics were found (Table 3). Two classes of binding sites were detected in the serum of the one patient (Patient 3) who had received epoetin beta exclusively.

Because erythropoietin molecules are heavily glycosylated and the glycosylation of recombinant molecules differs slightly from that of the endogenous molecule,[5] we tested the ability of antibodies to recognize the carbohydrate and the protein moieties of the molecule. Intact and deglycosylated ^{125}I-labeled epoetin was incubated with patients' serum, and radioactivity bound to IgG was counted and analyzed by polyacrylamide-gel electrophoresis. Antibodies from all patients bound both glycosylated and deglycosylated ^{125}I-labeled epoetin with the same efficiency, showing that the antibodies were directed against the protein moiety of the erythropoietin molecule rather than the carbohydrate moiety (data not shown).

Serum from 12 of the 13 patients did not bind denatured ^{125}I-labeled epoetin, suggesting that the antibodies recognized conformational epitopes only. Serum from the patient treated only with epoetin beta (Patient 3) reproducibly bound denatured and deglycosylated ^{125}I-labeled epoetin. To evaluate this serum sample we used Scatchard analysis and either deglycosylated or deglycosylated denatured ^{125}I-labeled epoetin. Two binding sites with dissociation affinity

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TABLE 3. CHARACTERISTICS OF ANTIERYTHROPOIETIN ANTIBODIES.

PATIENT NO.	INHIBITION OF ERYTHROID-COLONY FORMATION*	REVERSAL OF INHIBITION†	BINDING CAPACITY‡	APPARENT DISSOCIATION AFFINITY CONSTANT§
			U/ml	pM
1	+	+	42	110
2	+	+	29	92
3	+	±	67	105, 410¶
4	+	±	86	350
5	+	+	36	100
6	±	ND	4	200
7	+	+	6	110
8	+	+	14	390
9	+	+	38	370
10	±	±	3	180
11	±	+	4	90
12	+	+	11	120
13	+	±	4	115

*Inhibition of erythroid-colony formation was tested with use of normal bone marrow and 1 U of epoetin per milliliter. Plus signs indicate complete inhibition, with no colonies formed, and plus–minus signs partial inhibition, with fewer than 50 percent of colonies in cultures containing control serum formed in the presence of serum from the patients.

†Reversal of inhibition was assessed by adding 100 U of epoetin per milliliter to the culture. Plus signs indicate complete reversal, with the number of hemoglobinized colonies equal to that in control cultures, and plus–minus signs partial reversal, with some erythroid colonies formed, but not as many as in control cultures. ND denotes not done.

‡Binding capacity is expressed as the amount of radiolabeled epoetin bound per milliliter of the patient's serum after adjustment for the level of background activity. Binding was undetectable in control serum (binding capacity less than 200 mU per milliliter).

§The apparent dissociation affinity constant was determined with use of Scatchard analysis.

¶Patient 3 had two populations of antibodies with different binding affinities.

constants of 80 and 360 pM were found with deglycosylated ^{125}I-labeled epoetin. With deglycosylated denatured epoetin, a single class of binding sites with a dissociation affinity constant of 70 pM was observed, suggesting that this patient produced antibodies against both a linear and a conformational epitope of erythropoietin (data not shown).

DISCUSSION

We investigated the development of pure red-cell aplasia in 13 patients who were receiving epoetin as treatment for the anemia of chronic renal failure. All patients had received a diagnosis of pure red-cell aplasia within the preceding three years. After an initial response to epoetin, they became severely anemic and dependent on transfusions. In all patients, neutralizing antibodies against the protein moiety of epoetin were detected.

We have reported the presence of neutralizing antierythropoietin antibodies in a patient with pure red-cell aplasia who had never received epoetin.[10] We are not aware of similar cases and believe that neutralizing antibodies against erythropoietin are very rare. In the cases described here, the most plausible explanation is that the antierythropoietin antibodies were induced by epoetin therapy. This view is supported by the results of tests on serum samples from 4 of the 13 patients that were obtained from 1 to 15 months before the onset of pure red-cell aplasia. These samples did not contain detectable antierythropoietin activity.

We are aware of only three previous reports of antierythropoietin antibodies in patients receiving epoetin.[7-9] The identification within a three-year period of 13 patients in whom neutralizing antibodies against erythropoietin and pure red-cell aplasia developed during treatment with epoetin strongly suggests that the recombinant hormone had a role in causing the disorder. We do not, however, have information on how the hormone might trigger the formation of antierythropoietin antibodies. Of the 13 patients in our study, 11 were receiving epoetin alfa at the time of onset of anemia. Another patient had been receiving epoetin alfa and was switched to epoetin beta one month before the diagnosis of anemia. One patient received epoetin beta exclusively.

After epoetin therapy was stopped, there was a slow decline in antibody titers in all patients. Immunosuppressive treatment appeared to hasten the disappearance of the antibodies and might have allowed erythropoiesis to recover to the levels present before the initiation of epoetin treatment.

Scatchard analysis showed a linear pattern of erythropoietin binding by the antierythropoietin antibodies in each patient's serum. This result could have been due to the presence of a homogeneous population of antibodies, the recognition of a single epitope in erythropoietin by antierythropoietin antibodies, or both. The affinity of the antibodies for erythropoietin was slightly increased when they were tested with the use of deglycosylated epoetin, possibly reflecting some masking of epitopes by the bulky carbohydrate chains. Except for one patient who had been treated exclusively with epoetin beta, all patients had antibodies that recognized only conformational epitopes in the erythropoietin molecule — that is, no binding was noted after the denaturation of epoetin. Serum from the patient who had received only epoetin beta contained high-affinity antibodies that bound both native and denatured epoetin, a result suggesting that these antibodies were directed against both linear and conformational epitopes.

The antibodies in these 13 patients were able to neutralize very high concentrations of epoetin, and

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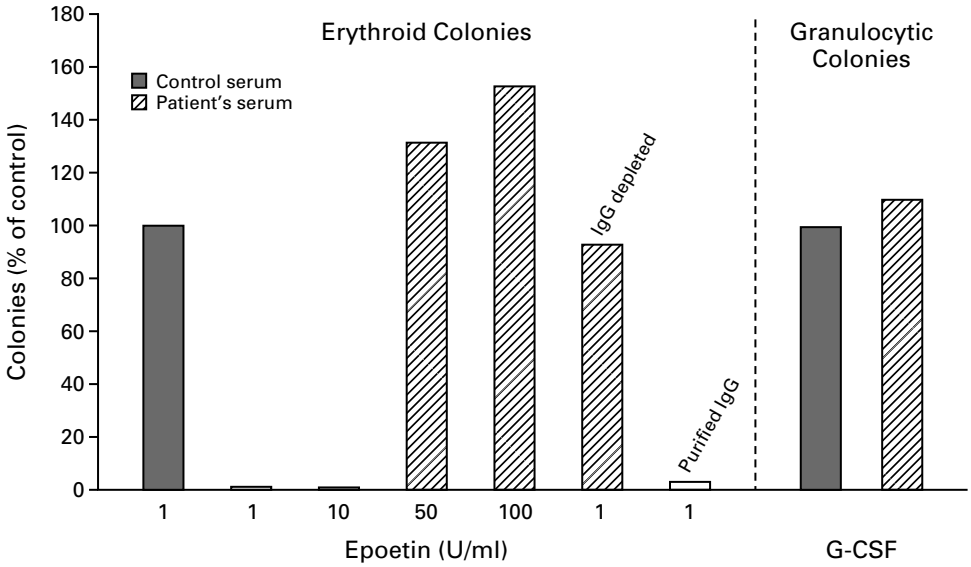

Figure 1. Inhibition of Erythroid-Colony Formation by Serum from Patient 1.

Erythroid cells in normal bone marrow were stimulated with 1 U of epoetin per milliliter in the presence of 20 percent pooled control serum; with 1, 10, 50, or 100 U of epoetin per milliliter in the presence of 20 percent serum from Patient 1; or with 1 U of epoetin per milliliter in the presence of 20 percent serum from Patient 1 in which IgG had been depleted with protein G Sepharose or in the presence of 100 μg of purified IgG per milliliter from Patient 1. Erythroid colonies were scored after seven days of culture. The results are expressed as percentages of colonies formed in the presence of control serum and 1 U of epoetin per milliliter. Granulocytic colonies were grown for 14 days in 0.8 percent methylcellulose in Iscove's medium (Terry Fox Laboratories, Vancouver, B.C., Canada), containing 1 percent deionized bovine serum albumin and 200 ng of recombinant granulocyte colony–stimulating factor (G-CSF) (Amgen, Thousand Oaks, Calif.) per milliliter.

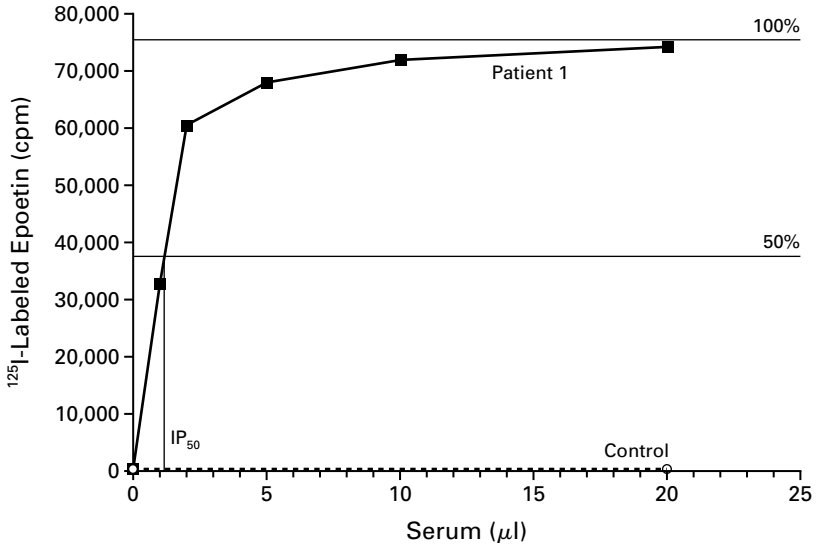

Figure 2. Binding of ^{125}I-Labeled Epoetin by Serum from Patient 1.

Binding capacity was calculated as the amount of serum from Patient 1 required to bind 50 percent of the radiolabeled epoetin after adjustment for the background level (IP_{50}). Pooled serum from 10 healthy volunteers was used as a control.

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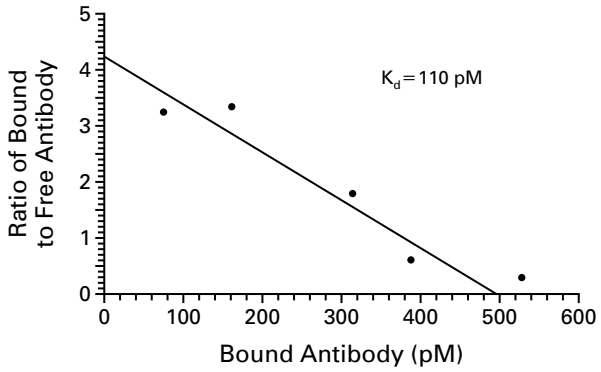

Figure 3. Scatchard Analysis of Binding of ^{125}I-Labeled Epoetin to Patient's Antibodies.

Three microliters of serum from Patient 1 was incubated with various concentrations of ^{125}I-labeled epoetin in a total volume of 200 μl of TRIS-buffered saline–Tween bovine serum albumin, and the degree of binding of antibody by the radiolabeled epoetin was determined after adjustment for the degree of nonspecific binding. Nonspecific binding of ^{125}I-labeled epoetin was determined with the use of 3 μl of control serum instead of the patient's serum. The results were analyzed according to the method of Scatchard.[14] K_d denotes the dissociation affinity constant.

their affinity for erythropoietin is roughly similar to that of the erythropoietin receptor.[15] The efficient neutralization of erythropoietin by these antibodies most likely accounts for their ability to inhibit erythropoiesis in vitro and in vivo.

We recommend that patients receiving epoetin be tested for the presence of neutralizing antierythropoietin antibodies as soon as possible after the onset of unexplained anemia. If such antibodies are found, epoetin should be discontinued immediately. We do not recommend challenging these patients with another erythropoietic protein, since the antibodies that we found cross-reacted with all commercially available recombinant erythropoietic products (epoetin alfa, epoetin beta, and darbepoetin alfa) (Swanson S, Amgen: personal communication).

Although we did not detect such neutralizing antibodies in patients treated with epoetin for reasons other than the anemia of chronic renal failure, we cannot exclude the possibility of their development in such patients or in athletes who illegally use epoetin to enhance their performance ("blood doping"). The severity and duration of the anemia in our patients, necessitating red-cell transfusions, argue against the use of epoetin for unlicensed indications.

Note added in proof: During the preparation of our article, we identified nine more patients treated with epoetin alfa who presented with pure red-cell aplasia and similar neutralizing antierythropoietin antibodies.

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APPENDIX

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EXPERT OPINION

1. Introduction
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3. Expert opinion

Pharmacovigilance and biosimilars: considerations, needs and challenges

Nicole Casadevall, I Ralph Edwards, Thomas Felix, Peter R Graze, Jason B Litten[†], Bruce E Strober & David G Warnock
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Introduction: Biosimilars are biologic medicines that are highly similar to approved biologics, notwithstanding minor differences in clinically inactive components. Since 2007, biosimilars have been approved for use in patients in the European Union (EU) and other regions. European experience provides several lessons as the United States (US) healthcare system prepares for biosimilar approvals. These lessons emphasize the need for adequate efficacy and safety studies, post-marketing surveys and a robust pharmacovigilance system that can accurately track and trace biologics, including biosimilars and their reference products, from the patient to the manufacturer.
Areas covered: We review the EU experience with biosimilar pharmacovigilance and discuss the implications for biosimilar pharmacovigilance in the USA. Furthermore, we review several aspects of biosimilar pharmacovigilance, including cohort event monitoring, traceability, biosimilar interchangeability, pharmacovigilance system development, nomenclature and counterfeit tracking.
Expert opinion: The availability of biosimilars as lower-cost biologics must carefully consider issues of safety, efficacy and traceability. Stringent pharmacovigilance procedures are required to detect potential differences in safety signals between biosimilars and their reference products. Pharmacovigilance of biologics should include processes that are easily used by prescribing practitioners to ensure that data are consistent and new safety signals are properly reported and assigned to the correct product.

Keywords: biosimilar, follow-on biologic, pharmacovigilance, reference product, safety, similar biologic medicinal products, similar biotherapeutic, traceability

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1. Introduction

Medicinal products resulting from biotechnology were first approved in the 1980s. Since that time, these medicines, termed 'biologics', have been used to treat dozens of conditions in millions of patients worldwide. During the past decade, legislation in several countries has been enacted to allow the approval of a new group of derivative biologics called biosimilars (**Table 1**). In the USA, a biosimilar is a biologic product that is highly similar to the reference product notwithstanding minor differences in clinically inactive components; for the approved conditions of use, no clinically meaningful differences exist between the biological product and the reference product in terms of safety, purity and potency [1]. These new laws are generally intended to improve patient access to less costly, but similarly safe and effective, biologics and foster a competitive environment for biologic drug development and commercialization. In the USA, the Patient Protection and Affordable Care Act provided an abbreviated approval pathway for biosimilars and conferred authority to the US Food and Drug Administration (FDA) to

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Article highlights.

- A biosimilar may not be exactly the same as the original biologic product because of differences in manufacturing.
- Stringent pharmacovigilance is required to detect differences in safety signals between the biosimilar and reference product.
- Healthcare professionals, manufacturers and regulatory agencies should not only be able to accurately identify the biosimilar used, but also distinguish between biosimilar products once they are approved.
- A unique INN/USAN will facilitate effective tracking and tracing for biosimilars.
- Tracking AEs attributed to biosimilars with the same INN/USAN may be difficult; if the specific product associated with an AE is not accurately identified, the AE may potentially be attributed to the drug class when it is molecule-specific.

This box summarizes key points contained in the article.

approve biosimilars. This pathway bases the approval of a biosimilar on the determination of its similarity to an approved biologic, not on the determination of efficacy and safety de novo. Therefore, biosimilars are expected to be approved for patient use based on fewer patient data than were required for the initial approval of the reference product [2,3].

Implementation of this abbreviated approval pathway for biosimilars adds to the need for collection and analysis of safety data after approval through effective post-approval safety surveillance systems that accurately track and trace all biologics from the patient to the manufacturer. This ongoing surveillance, known as pharmacovigilance, refers to all scientific and data-gathering activities related to detecting, assessing, understanding, preventing and communicating any potential or identified safety problems associated with a product, including a biosimilar [4]. Ultimately, the goal of pharmacovigilance is to identify and evaluate safety signals associated with drug products in a timely manner so that safety risks can be managed appropriately. In this article, we review the European Union (EU) experience with biosimilar pharmacovigilance since 2006 – when the first biosimilars were approved in that region – and discuss the implications of this experience for biosimilar pharmacovigilance in the USA. Examples based on experience with erythropoietins are provided because they illustrate important aspects of biosimilar pharmacovigilance that are relevant for a broad range of biosimilars under development, from biosimilar insulin products to tumor necrosis factor-alpha inhibitors. We will also discuss key topics with potential implications for biosimilar pharmacovigilance, such as cohort event monitoring and traceability for non-interchangeable and interchangeable biosimilars produced by different manufacturers in the USA, development of pharmacovigilance systems, biosimilar nomenclature and counterfeit tracking.

2. Manuscript body

2.1 Current legislation and regulations

Biologics comprise a highly complex and diverse category of drugs that are manufactured using living cells. In contrast to small-molecule drugs, biologics may have more complex structure and, as proteins, may be hundreds of times larger. Furthermore, most small-molecule drugs are manufactured using well-defined chemical processes, which can be implemented to produce identical drugs that are marketed as generics, whereas biologics manufacturers use unique cell lines and proprietary processes that are not available in the public domain. As such, a biosimilar manufacturer must develop new cell lines and, often new processes to produce a biosimilar of an approved biologic. These differences in manufacturing processes result in an end product that is expected to be similar, but is not identical, to the reference product.

It is currently not possible to predict how these subtle product differences may affect the efficacy or safety profile of a particular biosimilar. Perhaps the best clinical example of how changes in biologic manufacturing can impact the efficacy or safety of a biologic is from 2002 to 2003, when European patients with chronic renal failure who received recombinant human erythropoietin developed antibody-mediated pure red cell aplasia (PRCA), characterized by severe anemia that was refractory to exogenous erythropoietin and dependent on transfusion [5,6]. Most of the cases of PRCA in Europe were traced to a specific preparation of erythropoietin (Eprex® [epoetin alfa], Janssen-Cilag GmbH, Neuss, Germany). This episode and other examples of PRCA observed in subsequent years appear to have resulted from several possible factors, including those stemming from differences in manufacturing, formulation and primary container (e.g., tungsten-induced aggregation, albumin vs. polysorbate 80 in the formulation and immunogenicity associated with organic leachates from uncoated rubber syringe stoppers), as well as inappropriate transport, storage and handling [7,8]. The development of PRCA following recombinant human erythropoietin use in Europe and other areas highlights the need for robust pharmacovigilance practices for biosimilars, in particular, traceability.

Recognizing that biosimilar medicines cannot be considered to be generic medicines, the EU pioneered the biosimilar regulatory pathways with the EU Directive 2001/83/EC (as amended) that established the legal basis for biosimilars in the EU in 2004 [9]. This legislation stated that the type and quantity of non-clinical and clinical data required for approval of a biosimilar will be determined on a case-by-case basis following relevant scientific guidelines [9]. The Committee for Medicinal Products for Human Use of the European Medicines Agency (EMA) subsequently issued a series of guidelines, beginning in 2005, which outline the basic principles of the EU regulatory approach for biosimilars [10-13]. Among these were guidelines for different classes of biologics (e.g., therapeutic proteins and monoclonal antibodies) with

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Table 1. Glossary.

The patient protection and affordable care act	US law enacted March 2010 that established comprehensive health insurance reforms and included the biologic price competition and innovation act of 2009
Biologic price competition and innovation act of 2009	US law enacted March 2010 that authorizes the FDA to oversee an abbreviated approval pathway for biosimilars
Biosimilar	A biologic that is highly similar to and has no clinically meaningful differences from the reference product, notwithstanding minor differences in clinically inactive components
Interchangeability	FDA designation of a biosimilar based on additional evidence demonstrating that the biosimilar can be expected to produce the same clinical result as the reference product in any given patient, and if administered more than once to an individual, the risks in terms of safety or diminished efficacy of switching between the biosimilar and the reference product are not greater than using the reference product alone
Pharmacovigilance	Procedures that monitor the safety of medicines to detect, assess, understand and prevent adverse events or other safety-related issues
Reference product	The innovator product that the biosimilar product is intended to copy
Substitution	Refers to a pharmacist's decision to switch from a branded or innovator medicine to a generic or biosimilar medicine without the prescribing physician's approval

FDA: US Food and Drug Administration.

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suggested approaches for their analytic characterization, as well as non-clinical and clinical approaches to establish biosimilarity [11,13]. In the USA, the Biologics Price Competition and Innovation (BPCI) Act of 2009, part of the Patient Protection and Affordable Care Act, authorized the FDA to oversee an abbreviated approval pathway for biosimilars [1]. In February 2012, the FDA issued three draft guidance documents that provide recommendations on the scientific and regulatory considerations for potential biosimilar applicants [14-16].

Both the EMA's biosimilar guidelines and the FDA's biosimilar draft guidelines reinforce that there are differences between small-molecule generics and biosimilars due to the complexity of biologic drugs. EMA's guidelines state that 'similar biologic medicinal products are not generic medicinal products, since it could be expected that there may be subtle differences between similar biological medicinal products from different manufacturers or compared with reference products' [10]. The EMA guidelines also indicate that the approach to evaluating chemically derived generic products is not appropriate for biosimilars: 'The standard generic approach (demonstration of bioequivalence with a reference medicinal product by appropriate bioavailability studies) is normally applied to chemically derived [small molecule] medicinal products. Due to the complexity of biological/biotechnology-derived products the [small molecule] generic approach is scientifically not appropriate for these products' [10]. Because it is not possible to predict whether, or how, differences between a biosimilar and its reference product will affect patients, both the EMA and FDA currently suggest head-to-head clinical trials to demonstrate clinical equivalence of the biosimilar to its reference product [11,14].

Distinct from the EU approach to biosimilars, the BPCI Act of 2009 includes a provision that allows biosimilar applicants to pursue a designation of interchangeability for a biosimilar. This higher level of fidelity to the reference product requires the applicant to demonstrate that (1) the biosimilar 'can be expected to produce the same clinical result as the reference product in any given patient' and (2) if 'administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biologic product and the reference product is not greater than the risk of using the reference product without such alternation or switch' [1]. US statute defines 'interchangeable' to mean the biological product may be substituted for the reference product without the intervention of the prescribing healthcare provider [1]. This potential substitution at the pharmacy level has important implications for pharmacovigilance, including assessment of efficacy and safety, and ensuring traceability. The possibility of interchangeable biosimilars further emphasizes the need to accurately identify which product was used, because interchange may result in switching between the innovator and the biosimilar(s) multiple times. Such switching may introduce challenges for tracking which product a patient has received, thereby making attribution of adverse events (AEs) difficult. This is particularly important if the immunogenicity profile of the product evolves over time.

In an effort to rigorously monitor patient safety in the context of such complexity, it may be necessary to use targeted

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monitoring, cohort event monitoring or formal pharmacoepidemiological investigation – active surveillance methods designed to capture the AEs associated with a particular drug through patient follow-up of an unselected cohort of consecutive patients begun at, or near, the time of approval. AEs in the cohort can be captured by any of several means, such as insurance prescription data or longitudinal patient records. In this approach, AEs are retrieved from patient records over an appropriate period, assuming that adequate safety data are available, for broad comparison with the reference product. Though such surveillance methods are relatively inexpensive and broad in coverage, they are limited in that they only allow for qualitative event signals and do not indicate the frequency of an AE in the treated population. Thus, rigorous evaluation by other methods is recommended.

2.2 Pharmacovigilance

Systematic and ongoing safety monitoring is necessary to detect and evaluate post-approval safety signals for any approved drug. These signals may include the impact of intrinsic differences in immunogenicity among products [8] and the detection of rare events that may be uniquely associated with a particular product. The FDA guidance on good pharmacovigilance states that post-marketing safety data collection and risk assessment based on observational data are critical for evaluating and characterizing a product's risk profile and for making informed decisions about risk minimization [4]. To achieve this goal, pharmacovigilance systems should be practical to encourage AE reporting by healthcare professionals, provide drug manufacturers with a data framework to effectively monitor and report events for their approved drugs and ensure traceability of AEs to a particular manufacturer's product.

With the introduction of biosimilars, the importance and complexity of attributing AEs to the appropriate drug product are magnified. The EMA has required biosimilar applicants to propose and register rigorous pharmacovigilance systems and, when necessary, a risk-management system [11,17]. According to EMA guidance on pharmacovigilance, elements of a proposed biosimilar pharmacovigilance system should include qualified staff responsible for pharmacovigilance; identification of the organization and locations of the principal pharmacovigilance activities and databases; documented procedures for data collection, processing and mandatory reporting (e.g., individual case safety reports and periodic safety update reports); and databases compatible with electronic reporting [17]. EudraVigilance, a central EMA computer database created in 2001, is a major component of pharmacovigilance in the EU [18]. EudraVigilance is a data-processing network and management system for evaluating AE reports received from drug regulatory agencies and pharmaceutical companies across the EU. Additionally, the EMA initiated the European Risk Management Strategy in 2002 [19]. This program is aimed at strengthening safety monitoring of medical products by promoting early detection, assessment, minimization and communication of risks of medicines throughout their life cycle.

The introduction of biosimilars has been largely successful, but has also presented important challenges to the healthcare system regarding tracking and tracing of AEs in relation to a specific product. From 2006 to 2010, 7 distinct biosimilar products were authorized for marketing in the EU under 14 different trade names [20]. These products included two erythropoiesis-stimulating agents (ESAs), three granulocyte colony-stimulating factor products and two human growth hormone products. Identifying a biologic only by a shared non-proprietary name may hamper correct attribution of an AE to the administered biosimilar or reference product. For example, AEs associated with a biosimilar identified only by non-proprietary name may be incorrectly attributed to the reference product based solely on the familiarity of the reporting physician with the trade name of the reference product.

In 2006, the EMA emphasized that data from preauthorization clinical studies may not be sufficient to identify all of the potential differences between the biosimilar and the reference product [11]. The guidelines state that 'clinical safety of similar biological medicinal products must be monitored closely on an ongoing basis during the post-approval phase including continued benefit-risk assessment'. In this regard, the impact of the more extensive experience with the reference product relative to the biosimilar may be a confounding influence. Additionally, biosimilar applicants are required to submit a risk-management program/pharmacovigilance plan that considers known risks, as well as potential risks, associated with the biosimilar. Furthermore, any safety monitoring required for either the reference product or the individual products within the product class should be taken into consideration in the risk-management plan [11]. In line with the EMA's recommendation, three French societies (Société de Néphrologie, Société Francophone de Dialyse and Société de Néphrologie Pédiatrique) issued a position statement in 2007 on the use of erythropoietic biosimilars, noting that because EMA guidelines do not directly address all of the issues surrounding biosimilars, national and local involvement may be necessary [21].

Following the reauthorization of the recombinant human erythropoietin Eprex®, the Prospective Immunogenicity Surveillance (PRIMS) registry was initiated to assess the incidence of PRCA in patients with chronic kidney disease receiving subcutaneous ESAs [22]. The incidence of antibody-mediated PRCA identified in PRIMS was low, with only three cases observed among the 15,333 patients enrolled, and no differences in antibody-mediated PRCA were observed between the ESAs evaluated. However, the necessity of accurate tracking and tracing of AEs to a specific product is further underscored by additional cases of PRCA occurring after patients with kidney disease were treated with recombinant human erythropoietin products. In the first example, which occurred in Thailand in 2008 in the absence of rigorous quality standards for biosimilars, neutralizing anti-erythropoietin antibodies were detected in 23 of 30 patients with chronic kidney disease who had received one of a number of immunogenic epoetins and subsequently developed PRCA [23,24]. This

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observation prompted the development of a prospective surveillance registry to monitor immunogenicity of ESAs in Thailand. The multicenter prospective cohort will be periodically reviewed to estimate the incidence of anti-erythropoietin-associated PRCA and to shed light on managing biosimilar ESAs. In the second example, a randomized controlled trial evaluating the safety and immunogenicity of subcutaneous HX575, a recombinant human erythropoietin-alfa biosimilar, was suspended in 2009 following the development of neutralizing antibodies in 2 of 163 patients in the HX575 treatment arm [25]. This incidence of neutralizing antibodies was higher than expected based on the background incidence of anti-erythropoietin–associated PRCA (e.g., 0.2 – 6 cases per 100,000 patient-years) [26]. The manufacturer's inquiry into the possible causes of this increased immunogenicity identified high levels of tungsten – believed to have leached from the pins used in syringe manufacturing – in some of the prefilled syringes. Elevated tungsten levels in these syringes are believed to have contributed to denaturation and aggregation of HX575 [27].

Though biosimilars have not yet been introduced to the US healthcare system, pharmacovigilance requirements for biosimilars, as with all drugs, will include voluntary, spontaneous reporting of AEs and medication errors by healthcare professionals to the FDA or manufacturer and mandatory reporting by manufacturers of those reports received to the FDA [28]. These reports are entered into the FDA's Adverse Event Reporting System for analysis, and potential safety signals associated with a drug are reported through MedWatch [29]. If the FDA determines (through analysis of the potential signals) that a drug is associated with a new or altered significant safety risk, the product's prescribing information may be updated and a Risk Evaluation and Mitigation Strategy, including a medication guide, post-approval pharmacoepidemiologic studies, or randomized clinical trials, may be required. However, concerning observational evaluations, it is important to consider the statistical power of comparisons to be made at a time when the predominant product on the market is the reference product, and/or the comparison of multiple simultaneously released biosimilars between each other and the reference product. For rare AEs (e.g., PRCA), the confidence interval may be too wide to differentiate between products based on AE rates until sufficient use of a biosimilar is achieved. Alternatively, the difference in rates would have to be large to permit prompt attribution of an event to a newly released product.

Current EU and US pharmacovigilance systems rely heavily on voluntary, spontaneous reporting for decision-making purposes. It is recognized, however, that only a minority of AEs are reported with the existing systems. Furthermore, the quality of reports may vary, and they do not always identify the product potentially associated with the AE. Consequently, products are often identified by either proprietary or non-proprietary names (actual or suspected) and infrequently by available product identification and/or lot/batch numbers. Furthermore, institutional voluntary event reporting has been associated with inconsistent compliance and wide variation in reporting efficiency among hospitals [30-32]. Therefore, given the challenges of accurate post-approval assessment of the safety profiles of biosimilars, novel approaches aimed to generate more complete and/or meaningful reporting of safety data are needed. One such approach involves carefully designed patient registries to evaluate safety signals from spontaneous case reports or other sources [4,33]. Such registries may be especially useful for collecting treatment information from multiple sources [4]. Cohort event monitoring, prescription event monitoring and use of the 'black triangle' designation (▼) are potential methods for obtaining additional safety information for product comparisons. In the UK, a black triangle is a symbol assigned to the product label of a new drug, a new drug combination or an established drug with a new route of delivery or target indication that indicates a need for heightened surveillance for AEs associated with the product. Implementing cohort event monitoring for biosimilars could facilitate comparisons that provide quantitative information. In contrast, the 'black triangle' does not provide denominator data. Moreover, a 'black triangle' designation for a biosimilar but not for a reference product may heighten caution surrounding the biosimilar and, therefore, bias reporting practices. As such, any pharmacovigilance measure must be able to accurately trace reported AEs to a particular biologic, whether or not it is a biosimilar. According to Directive 2010/84/EU and Regulation (EU) No 1235/2010, which were adopted in July 2012 to strengthen pharmacovigilance, the summaries of product characteristics and package leaflets for new biological medicinal products and biosimilars in the EU should include the black symbol and an appropriate standardized explanatory sentence [34,35].

Another approach to obtain additional safety data leverages the widespread implementation of electronic medical records in the USA. The FDA Sentinel System, which is currently in development, is a nationally integrated electronic data network for safety surveillance that will include electronic medical records and administrative healthcare data from 100 million patients [36,37]. However, these measures will only improve our ability to trace outcomes if systems are in place that can accurately differentiate all biologics within a class and if medical records have sufficient relevant information. Additional advances in collecting and modeling safety events are expected to improve pharmacovigilance [38,39]. One example of such advances is the 'rapid-learning healthcare model' that is in early development. This model, when implemented, will coordinate real-time clinical data from the patient care and research settings in a unified database system monitored by a single source [39]. The successful development of the model will depend on national and local collaboration to ensure the accurate and meaningful capture of relevant patient data.

2.3 Biosimilar naming

Though advances in pharmacovigilance are expected to improve the quality and quantity of information available, these improvements will depend, in large part, on the ability

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of a reporter (usually a healthcare provider or patient) to correctly identify and report the drug product associated with a particular AE. This concern magnifies the importance of a rational approach to drug nomenclature. The World Health Organization (WHO) confers a non-proprietary name (scientific or generic name) to prescription drugs, whereas national health authorities also assign a proprietary name (brand or trade name). The United States Adopted Names Council (USANC) collaborates with the WHO International Nonproprietary Name (INN) Expert Committee to select non-proprietary names for all new drugs, using rational classifications based on pharmacologic and chemical relationships [40]. Before approval, the FDA reviews proposed proprietary names to ensure that they are unlikely to cause product confusion errors, which affect prescribing [40]. Currently, proprietary names are assigned by the manufacturer and subject to regulatory approval; however, language differences and other factors may result in variations in the proprietary name approved for a product among geographical regions.

Because small-molecule generic drugs are identical to their reference products, they are given the same non-proprietary name and, thus, are not subject to the USANC naming process [40]. In contrast, the naming of biosimilars is complicated by the fact that, although similar in many respects to the reference product, biosimilars are not identical to the reference product, raising the issue of whether they should have the same non-proprietary name as the reference product. Though an ideal approach to biosimilar nomenclature remains elusive, experts suggest using a common root and a unique suffix (e.g., XXX [Greek letter] or XXX [manufacturer]) to demonstrate the similarity, yet uniqueness, of reference biologics and all subsequent biosimilars [41]. Beyond the scientific rationale of this approach, this naming is expected to facilitate accurate tracking and tracing of all biologics. Using a common element to denote that a product is a biosimilar would also support search strategies and detection of safety signals from spontaneous reports. It appears that the EMA continues to grapple with this issue. For example, five recombinant human erythropoietin products have received marketing authorization in the EU as biosimilars of Eprex®/Erypo® (epoetin alfa, Janssen-Cilag GmbH, Neuss, Germany) [42,43]. Three of the products (Abseamed®, Binocrit®, and Epoetin alfa Hexal® [Rentschler Biotechnologie GmbH, Laupheim, Germany]), which were found to have differences in glycosylation relative to the reference product, were assigned the same INN: epoetin alfa [43]. The two other biosimilars, Retacrit® (Hospira, Warwickshire, UK) and Silapo® (STADA Arzneimittel AG, Bad Vilbel, Germany), displayed differences in relative amounts of O-glycan chain variants compared with the reference product and were designated the INN epoetin zeta. A practice of designating biosimilar erythropoietic products with differing Greek letter identifiers has been adopted by the Australian Therapeutic Goods Administration. In addition to these biosimilar recombinant erythropoietin products, the Greek letter naming convention has been used for the innovator recombinant human erythropoietin theta Eporatio® (Ratiopharm UK, Hampshire, UK) [44]. A potential complexity of differentiating non-proprietary names by a suffix is that data fields for reporting of AEs may have character limits; thus, if the non-proprietary name exceeds the length of the data field, a differentiating suffix may not be recorded. Furthermore, it should be considered whether a differentiating prefix has advantages over a differentiating suffix. Educating potential reporters of AEs (e.g., prescribers, pharmacists and patients) on the importance of providing a full product name will also be critical for robust pharmacovigilance.

The Uppsala Monitoring Centre is working to include identifiable biosimilars in the WHO Drug Dictionary, which is linked to the WHO global adverse drug reactions database (VigiBase). Currently, brand names provided on reports are searchable in VigiBase, but the provision of brand names is not obligatory. A larger project is under development by the WHO and International Medical Products Anti-Counterfeiting Taskforce that will allow accurate product identification in the field for the detection of spurious, substandard, falsely-labeled, falsified and counterfeit (SSFFC) medicines [45]. This project, which is widely endorsed in the EU and USA, could potentially be used to identify biologics suspected of causing adverse drug reactions and/or failure of effectiveness. Lastly, reporting adverse drug reactions with phone applications, which is being used in some African countries, could also facilitate accurate product identification. However, telephone applications could be potentially difficult to use as a result of the association between multiple letters and a particular numeral on a telephone dial or touchpad, regions without letters assigned to numbers and the use of non-Latin alphabets. Accordingly, development of a worldwide naming system based on naming, rather than on numerical designations (e.g., National Drug Code [NDC] in the USA), could be a challenge.

Though a strict naming convention for biosimilars has not yet been implemented in the EU, the EMA recognizes that, to support pharmacovigilance, the specific medicinal product given to the patient should be clearly identified [10]. In 2010, the European Parliament issued a directive to its member states to ensure that 'measures are taken to identify clearly any biological medicinal product prescribed, dispensed, or sold in their territory which is the subject of a suspected adverse reaction report, with due regard to the name of the medicinal product' [34]. In an effort to embrace this EMA directive, several EU member states require or encourage physicians to prescribe biologic medicinal products, including biosimilars, by brand name [46]. As in the EU, pharmacovigilance in the USA relies heavily on distinct product names [41]. Although the FDA has not yet defined an approach to nomenclature of biosimilars, recent statements by FDA officials show that rational naming to ensure accurate tracking and tracing is a key priority [47].

2.4 Conclusion

In the USA, the BPCI Act of 2009 has created an abbreviated pathway for the review and approval of biosimilars [14]. In

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anticipation of the first biosimilar approval, robust pharmacovigilance strategies must be implemented to record, and thus ensure the safety of these medicines [4,14]. An ideal post-approval safety surveillance program includes precise AE tracking and tracing capabilities to detect and evaluate safety signals and promote efficient and coordinated responses (e.g., recalls and alerts). Accurate traceability of safety reports to specific medicinal products requires rational nomenclature for each biosimilar, including a unique non-proprietary name, Healthcare Common Procedure Coding System/NDC and lot number.

Biopharmaceutical research and development has led to the production of an ever-expanding number of biologic agents. To protect patients on an international scale, it is critical to establish a useful nomenclature that accurately distinguishes all unique products. There is also a need to upgrade the current international pharmacovigilance system so that it is capable of real-time data collection and of maintaining the flexibility needed to identify and assess unexpected or unpredictable AEs, which may differ between a biosimilar and reference product (e.g., immunogenicity). The success of an international pharmacovigilance program will depend on an adequate and reportable records system and on consistent and continual cooperation from patients and healthcare professionals.

3. Expert opinion

The introduction of biosimilars to the US healthcare system is imminent and will expand the delivery of safe and effective medicines to patients, especially to those who have limited access to healthcare. However, the availability of a lower-cost biologic should not trump issues of safety, efficacy or traceability. Furthermore, after approval, the biosimilar must be readily identified as a distinct drug with a distinct INN/USAN. Notably, pharmacovigilance systems used in the evaluation of safety and efficacy of any biosimilar should involve processes that are easily used by the prescribing practitioner. Overly complex pharmacovigilance systems (e.g., systems that require multiple and redundant identifiers) could generate inconsistent or unintelligible data that may inappropriately assign a new signal to the reference product, biosimilar or drug class. Such misattributions could undermine the accuracy and reliability of a pharmacovigilance system and expose patients to unnecessary risks.

Because all efforts in national and global pharmacovigilance require sufficient identification of the agent suspected for an AE, it is imperative for healthcare practitioners to be precise in their product identification during reporting. Biosimilars pose a major challenge in this respect because a broad identification of the active substance (e.g., through a non-proprietary name) does not provide a sufficient molecular description to differentiate possible safety issues resulting from differences between the biosimilar and reference product in manufacturing and product handling. Either mandatory and easily distinguishable brand names or distinguishable non-proprietary names should be used to ensure adequate specificity for an accurate pharmacovigilance system. The burden for accurately identifying the agent suspected for an AE, as well as for recording and reporting the event, is on healthcare professionals. Thus, there is a need for education on biosimilar pharmacovigilance. Additional research and development is warranted to simplify reporting of accurate, detailed information on products using information technology methods, such as smart phone applications and real-time electronic data collection.

Acknowledgment

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Declaration of interest

The first author has received research support from Amgen Inc., Roche, and Johnson & Johnson; served as an advisor to Novartis and Shire; and participated in lectures and/or boards sponsored by Amgen Inc., Johnson & Johnson, Shire, Novartis, and Roche. The second author has served in an advisory role for Amgen Inc. The fourth author has participated in clinical research studies sponsored by Amgen Inc. The third and fifth authors are employees of and own stock in Amgen Inc. The sixth author has served on advisory boards for Abbott, Amgen Inc., Janssen, Pfizer, and Celgene; served as a consultant to Abbott, Amgen Inc., Janssen, Novartis, Pfizer, Celgene, Maruho, and Lilly; and received honoraria for speakers bureau participation from Abbott. The senior author has received grants from Genzyme and Amgen Inc.; participated in clinical research studies sponsored by Amicus; served as a consultant to Amgen Inc., Genzyme, Reata, Allocure, Parion, and Takeda; and has stock options in Reata, Parion, Relypsa, and Allocure.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125294Orig1s000

PROPRIETARY NAME REVIEW(S)

Memorandum

Date August 2, 2012

From Biological Product Naming Working Group

Subject BLA 125294 – [xxx]-filgrastim

To File

FDA has determined that a unique nonproprietary name will be required for Teva Pharmaceuticals' (Teva) proposed product for which it is seeking approval in BLA 125294 ([xxx]-filgrastim), a biological product submitted in a 351(a) biologics license application (BLA), to distinguish the product from Neupogen (filgrastim), a previously licensed biological product submitted in a different 351(a) BLA by Amgen, Inc. (Amgen) that contains a related drug substance. Specifically, Teva's proposed xxx-filgrastim is indicated for the reduction in the duration of severe neutropenia in patients with non myeloid malignancies receiving myelosuppressive anti cancer drugs associated with a clinically significant incidence of febrile neutropenia. Amgen's Neupogen (filgrastim) was first licensed on February 20, 1991. Neupogen has been indicated:

- to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever
- for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of adults with AML
- to reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by marrow transplantation
- for the mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis
- for chronic administration to reduce the incidence and duration of sequelae of neutropenia (eg, fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia

FDA has concluded that a nonproprietary name for Teva's product that is distinct from Amgen's product will help to minimize medication errors by (1) preventing a patient from receiving a product different than what was intended to be prescribed and (2) reducing confusion among healthcare providers who may consider use of the same nonproprietary name to mean that the biological products are

Reference ID: 3169145

indistinguishable from a clinical standpoint. FDA also has concluded that unique nonproprietary names will facilitate postmarketing safety monitoring by providing a clear means of determining which "filgrastim" product is dispensed to patients. Due to the fact that health care providers may use nonproprietary names instead of proprietary names when prescribing and ordering products, and pharmacovigilance systems often do not require inclusion of proprietary names, the use of distinct proprietary names is insufficient to address these concerns.

Amgen's Neupogen and Teva's proposed xxx-filgrastim are the subject of separate BLAs submitted by different manufacturers, Amgen and Teva respectively. For this reason, FDA has concluded that a unique nonproprietary name is warranted for the subsequently licensed product.

FDA's decision to require a unique nonproprietary name in the form of [prefix]–filgrastim for Teva's product, for which licensure is sought under section 351(a) of the PHS Act, is separate from any decision FDA may make in the future regarding the naming convention for biosimilar and interchangeable products under section 351(k) of the PHS Act. FDA is still considering the appropriate naming scheme for such products, and FDA does not anticipate that any decision on nomenclature for biosimilar and interchangeable products will conflict with FDA's determination regarding the nonproprietary name for this product.

FDA notes that a prefix previously has been used to distinguish one biological product from another biological product that contains a related drug substance, although the prefix was directly appended to the stem (without a hyphen) given the nature of the differences between those products. For example, the nonproprietary names for botulinum toxin products were changed to add prefixes (e.g., onabotulinumtoxinA, abobotulinumtoxinA) to emphasize the non-interchangeable potency units of each botulinum toxin product in an effort to prevent medication errors and serious adverse events. In addition, there is precedent for using a hyphen in biological product nonproprietary names, e.g., interferon alfa-2b.

Amgen and Teva products are the subject of different marketing applications held by different manufacturers. Identifying Teva's xxx-filgrastim with a unique nonproprietary name will reinforce these differences, help to prevent medication errors involving the two products, and facilitate pharmacovigilance. For these reasons, the Teva product will be identified as Neutroval ([xxx]-filgrastim).

In the September 29, 2010 Complete Response letter, FDA described the need to differentiate Teva's product from Amgen's filgrastim product and explained that FDA is requiring the use of a prefix with the "filgrastim" stem. FDA requested that Teva propose a 3-4 letter prefix to be added to the non-proprietary stem, "filgrastim." Teva proposed the following prefixes in their February 29, 2012 submission:

- (b) (4)
- tbo-filgrastim
- (b) (4)
- 1 (b) (4)

Reference ID: 3169145

FDA evaluated those names with a hyphen inserted between the proposed prefixes and the filgrastim stem, using the criteria outlined in the September 29, 1010 communication to Teva, and determined that "tbo-" or (b) (4) are acceptable prefixes proposed by Teva. Specifically, FDA made the following determinations:

- (b) (4)
- The second prefix "tbo-" does not appear to raise concerns related to conveying specific meaning, being promotional or looking or sounding similar to a currently marketed product. FDA notes that "tbo" stands for the medical abbreviation, "toluidine blue O.[2]" However, it is not thought that this abbreviation would cause confusion in this context or conflict with the proper name, "tbo-filgrastim" and therefore FDA has no objection to its possible selection. The proposed prefix "tbo-" is acceptable based on the criteria outlined in the July 17, 2012 communication to sanofi.
- (b) (4)
- (b) (4)

Of the four prefixes proposed by Teva, FDA has no objection to:

- tbo-filgrastim
- (b) (4)
-

[1] Oxford Dictionaries Online. http://oxforddictionaries.com/definition/american_english/bio-?region=us&q=bio- Accessed 08/02/2012.
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In a communication dated April 5, 2012, the Division of Hematology Products was informed of a change in sponsorship of BLA 125294 from Teva Pharmaceuticals USA to SICOR Biotech UAB. Teva Global Branded Pharmaceutical Products R&D will serve as the US agent. Therefore, all future communications will be directed to SICOR Biotech UAB and the US agent.

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/s/

LEAH A CHRISTL
08/02/2012
Memo entered into DARRTS on behalf of the Biological Product Naming Working Group

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Proprietary Name Review

Date:	July 16, 2012
Reviewer:	Sarah K. Vee, PharmD, Safety Evaluator Division of Medication Prevention and Analysis
Team Leader	Yelena Maslov, PharmD, Acting Team Leader Division of Medication Prevention and Analysis
Deputy Director	Kellie Taylor, PharmD, MPH Division of Medication Prevention and Analysis
Division Director	Carol A. Holquist, RPh Division of Medication Prevention and Analysis
Drug Name(s) and Strength(s):	Neutroval (XM-02) Injection 300 mcg/0.5 mL, 480 mcg/0.8 mL prefilled syringes
Application Type/Number:	BLA 125294
Applicant/Sponsor:	Teva
OSE RCM #:	2012-951

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed proprietary name, Neutroval, from a safety and promotional perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A, respectively.

1.1 REGULATORY HISTORY

Neutroval was reviewed under IND 103,188 (OSE Review # 2009-1414) and BLA 125,294 (OSE Review # 2010-1) and was found conditionally acceptable. The application received a Complete Response on September 29, 2010. On April 17, 2012, the Applicant resubmitted Neutroval for review and stated that the product characteristics have not changed from the original BLA submission.

The proper name for this product is pending at this time. Although this is a 351(a) stand alone biologic application, this product has the same product characteristics as Neupogen. The discussion regarding the proper name nomenclature is still ongoing, and thus the active ingredient will be referenced as XM-02 throughout this review.

1.2 PRODUCT INFORMATION

The following product information is provided in the July 10, 2009 proprietary name submission.

- Active Ingredient: XM-02
- Indication of Use: Reduction in the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.
- Route of Administration: subcutaneous injection (b) (4)
- Dosage Form: solution for injection
- Strength: 300 mcg/0.5 mL, 480 mcg/0.8 mL
- Dose and Frequency: 5 mcg/kg/day 1st dose should be administered no earlier than 24 hours following myelosuppressive chemotherapy (b) (4) Daily dosing should continue (b) (4) until neutrophil count has recovered to the normal range.
- How Supplied: 300 mcg/0.5 mL, 480 mcg/0.8 mL single use prefilled syringe
    - Packs of 1, 5, and 10 without a safety needle guard
    - Packs of 1, 5, and 10 with a safety needle guard in trays
    - Packs of 1, 5, and 10 with a safety needle guard in blisters
- Storage: Refrigerated at 36° to 46°F (2° to 8°C), may be allowed to reach room temperature for a maximum of (b) (4)

- Container and Closure Systems: Primary: Type I glass syringe barrel, (b) (4) rubber stopper, steel needle. Secondary: cardboard cartons (1, 5, or 10 syringes)

2. RESULTS

The following sections provide the information obtained and considered in the evaluation of the proposed proprietary name.

2.1 PROMOTIONAL ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined the proposed name is acceptable from a promotional perspective. DMEPA and the Division of Hematology Products concurred with the findings of OPDP's promotional assessment of the proposed name.

2.2 SAFETY ASSESSMENT

The following aspects of the name were considered in the overall safety evaluation.

2.2.1 United States Adopted Names (USAN) Search

The May 7, 2012 search of the United States Adopted Name (USAN) stems did not identify that a USAN stem is present in the proposed proprietary name.

2.2.2 Components of the Proposed Proprietary Name

The Applicant indicated in their submission that the proposed name, Neutroval, is crafted from the concept of strong neutrophils, utilizing the prefix of the Latin word validus, meaning strong or powerful. This proprietary name is comprised of a single word that does not contain any components (i.e. a modifier, route of administration, dosage form, etc.) that are misleading or can contribute to medication error.

2.2.3 Medication Error Data Selection of Cases

DMEPA searched Adverse Event Reporting System (AERS) database for medication errors involving confusion with proprietary names Neupogen and Neulasta, which would be relevant for this review, because this name pair shares the same beginning letter string, 'neu', as well as similar product characteristics.

The May 4, 2012 search of the AERS database used the following search terms: filgrastim, neupogen, neupo%, filgras%, Medication Errors (HLT), and Product Quality Issues (HLT) with no specific time frame.

Each report was reviewed for relevancy and duplication. Duplicate reports were merged into a single case. The NCC MERP Taxonomy of Medication Errors was used to code the case outcome and error root causes when provided by the reporter.

After individual review, 79 reports were not included in the final analysis for the following reasons:

Dose omission	1	Wrong time	2
Duplicate therapy	1	Wrong technique	4
Accidental Exposure	1	Deteriorated drug	5
Intentional overdose	1	Wrong route	7
Underdose	1	Overdose	19
Wrong patient	2	No medication error	32
Near miss (NeoProfen vs. Neupogen)	1	Wrong drug (Neupogen vs. Nutropin)	1
Wrong drug (GM-CSF vs. G-CSF)	1		

Following exclusions, the search yielded six relevant cases of wrong drug errors.

- 3 Cases: Neulasta administered instead of Neupogen

One case reported that the patient was routinely receiving Neupogen but an accidental dose of Neulasta was administered following a chemotherapy cycle. The patient experienced white blood cell count increase. The patient recovered but no further information was provided.

The second case reported that Neulasta 6 mcg was given instead of Neupogen. As a result, the patient's subsequent chemotherapy cycle may have been delayed.

The third case from Italy, involved a pediatric patient where a nurse confused the vial of pegfilgrastim with filgrastim and gave the contents of the entire vial (6 mg) of pegfilgrastim. The patient did not experience any adverse events.

- 2 Cases: Neupogen administered instead of Neulasta

One foreign case from Germany reported that a patient was on Neulasta therapy but filgrastim (Neupogen) was accidentally prescribed and administered. No outcomes were reported for this case.

Another foreign case from Germany reported that a patient received Neupogen instead of Neulasta. The pharmacist reported that the patient did not receive the scheduled dose of Neulasta after the mistaken dose of Neupogen. According to the reporter, Neupogen worked well for the patient and the patient did not experience any adverse event.

None of the five cases reported possible root causes of the confusion. However, given the fact that all patients, with the exception of the pediatric case, were on chemotherapy and both products are indicated for the same patient population, with the same route of administration and product presentation as prefilled syringes, product selection confusion is likely due to the name confusion.

- 1 Case: Neupogen administered instead of Neumega

  One case involved a patient receiving a dose of Neupogen instead of Neumega. The reporter commented that "these names are too similar" and that the "nurse should have double checked." This case demonstrates that even though Neumega is a powder for injection and Neupogen is a solution, the name similarity (i.e. same beginning letter string, 'neu'), similar dose (5 mcg/kg/day vs. 50 mcg/kg/day), and same route of administration (subcutaneous) outweighed this difference in product characteristics. .

The report of Neupogen and Neumega confusion demonstrates that minor orthographic differences cannot overcome name similarity in the presence of shared product characteristics.

2.2.4 FDA Name Simulation Studies

Twenty-nine practitioners participated in DMEPA's prescription studies. The interpretations did not overlap with or appear or sound similar to any currently marketed products. Of the 29 participants, 19 identified the name as Neutroval. See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

2.2.5 Comments from Other Review Disciplines

In response to the OSE, April 27, 2012 e-mail, the Division of Hematology Products (DHP) did not forward any comments or concerns relating to the proposed name at the initial phase of the proprietary name review.

2.2.6 Failure Mode and Effects Analysis of Similar Names

Appendix B lists possible orthographic and phonetic misinterpretations of the letters appearing in the proposed proprietary name, Neutroval. Table 1 lists the names with orthographic, phonetic, or spelling similarity to the proposed proprietary name, Neutroval identified by the primary reviewer, the Expert Panel Discussion (EPD), and other review disciplines. Since Neutroval was evaluated twice previously, this review focused on names that start with the prefix "neu" and its variations, since we identified medication errors involving name confusion between Neupogen and Neulasta name pair and Neupogen and Neumega name pair.

Table 1: Collective List of Potentially Similar Names (DMEPA, EPD, Other Disciplines, FDA Name Simulation Studies, and External Name Study if applicable)

Look Similar		Look Similar		Look Similar	
Name	***Source***	***Name***	***Source***	***Name***	***Source***
Hectorol	EPD	(b) (4)	EPD	Nexterone	EPD
Neulasta	EPD/Previous review	Neurolite	EPD	Nuedexta	(b) (4)
Neumega	EPD/Previous review	Neutrexin	EPD	Nulecit	EPD
Neupogen	External/Previous review	(b) (4)**	EPD	Nutrament	EPD
Neuramate	EPD	Neutroval***	EPD	Uroxatral	EPD
(b) (4)	(b) (4)				
Sound Similar		**Sound Similar**		**Look and Sound Similar**	
Mebaral	EPD			NeutraSal	EPD

Our analysis of the 18 names contained in Table 1 considered the information obtained in the previous sections along with their product characteristics. We determined 13 of the 18 total number of names will not pose a risk for confusion as described in Appendix D and E. However, the proposed name could be confused with Neupogen, Neulasta, Neumega, NeutraSal, and (b) (4) The rationale for the risk of confusion between Neutroval and Neupogen, Neutroval and Neulasta, Neutroval and Neumega, and Neutroval and NeutraSal is described below and in section 3.1. The rationale for risk of confusion between pending application name, (b) (4) and Neutroval is described below. Since (b) (4) is not approved, DMEPA cannot provide specifics on the proposed similarity of this name pair to the Applicant, Teva.

The proposed proprietary name, Neutroval, is orthographically similar to and shares product characteristics with an investigational product (IND (b) (4), (b) (4)

(b) (4)

*** This document contains proprietary information that should not be released to the public

The orthographic similarity stems from the fact that the name pair has the same beginning letter string 'Neu' and length (9 letters).

Neutroval 400 mg

(b) (4)

Moreover, the products share product characteristics including (b) (4)

As seen by the medication error cases describing the name confusion between Neupogen and Neulasta, orthographic differences beyond the letter string 'neu' does not eliminate the potential for name confusion when product characteristics overlap. Therefore, if the two products were marketed, medication errors could occur.

2.2.7 Communication of DMEPA's Final Decision to Other Disciplines

DMEPA communicated our findings to the Division of Hematology Products via e-mail on June 7, 2012. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from the Division of Hematology Products on June 7, 2012, they stated no additional concerns with the proposed proprietary name, Neutroval.

3 CONCLUSIONS

The proposed proprietary name is acceptable from a promotional perspective but not acceptable from a safety perspective. The proposed name is vulnerable to name confusion with Neupogen, Neulasta, Neumega, NeutraSal, and (b) (4) Therefore, the decision to deny the name will be communicated to the Applicant/Sponsor via letter (See ***section 3.1).***

If you have further questions or need clarifications, please contact Sue Kang, OSE project manager, at 301-796-4216.

3.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Neutroval, and have concluded that this name is unacceptable due to the following reasons.

A. ORTHOGRAPHIC SIMILARITIES WITH NEUPOGEN, NEULASTA, AND NEUMEGA

1. Neutroval and Neupogen

The proposed proprietary name is orthographically similar to Neupogen (filgrastim injection). Neutroval and Neupogen are similar in length (9 vs. 8 letters) and share the

beginning letter string, 'neu'. Moreover, the name pair has identical product characteristics such as indication (to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever), dosage form (solution for injection), route of administration (subcutaneous (b) (4) strengths (300 mcg/0.5 mL, 480 mcg/0.8 mL), dose (5 mcg/kg/day), frequency of administration (once daily), and product presentation (single use prefilled syringe). However, the two products are not interchangeable.

neutroval
neupogen

Although the ending letter strings differ, there is significant overlap with product characteristics. We are concerned with name confusion based on prior errors with name pairs that share the same beginning letter string but end differently (Neutroval vs. Neulasta, Neupogen, or Neumega). These name pairs also shared product characteristics such as dosage form, route of administration, indication, patient population, and product presentation. Thus, confusion between this name pair may result in mediation errors if both are marketed.

2. Neutroval and Neulasta

The proposed proprietary name is orthographically similar to Neulasta (pegfilgrastim injection). Neutroval and Neulasta are similar in shape (3 up strokes), length (9 vs. 8 letters), and share the beginning letter string, 'neu'. Moreover, the name pair shares product characteristics including dosage form (solution for injection), route of administration (subcutaneous), indication (decrease in incidence of febrile neutropenia), patient population (patients receiving myelosuppressive anti-cancer drugs), and product presentation (single use prefilled syringes).

neutroval
neulasta

The minor orthographic differences in the endings of the names may not sufficiently distinguish the name pair given the orthographic similarities stated previously. Thus, confusion between this name pair may result in mediation errors if both are marketed as demonstrated by post marketing medication error.

3. Neutroval and Neumega

The proposed proprietary name is orthographically similar to Neumega (oprelvekin for injection). Neutroval and Neumega are similar in length (9 vs. 7 letters) and share the beginning letter string, 'neu'. The two products have similar product characteristics including route of administration (subcutaneous), patient population (cancer patients),

similarity in dose (5 mcg/kg vs. 50 mcg/kg), and frequency of administration (once daily).

neutroval

neumega

The minor orthographic differences in the endings of the names may not sufficiently distinguish the name pair given the orthographic similarities stated previously. Thus, confusion between this name pair may result in mediation errors if both are marketed as demonstrated by post marketing medication error data.

B. ORTHOGRAPHIC AND PHONETIC SIMILARITIES OF NEUTROVAL WITH NEUTRASAL

The proposed proprietary name, Neutroval, is orthographically and phonetically similar to the marketed product, Neutrasal.

Neutrasal (powder for supersaturated calcium phosphate rinse) is a 510(k) product marketed as a device. Indications for use are[1]:

- NeutraSal® is also indicated as an adjunct to standard oral care in relieving the discomfort associated with oral mucositis that may be caused by radiation or high dose chemotherapy. Relief of dryness of the oral mucosa in these conditions is associated with the amelioration of pain.
- NeutraSal® may be used for relief of dryness of the oral mucosa when hyposalivation results from the following: surgery, radiotherapy near the salivary glands, chemotherapy, infection or dysfunction of the salivary glands; emotional factors such as fear or anxiety; obstruction of the salivary glands; Sjogren's Syndrome .
- NeutraSal® is also indicated for the dryness of the mouth (hyposalivation, xerostomia).
- NeutraSal® is indicated for dryness of the oral mucosa due to drugs such as antihistamines, atropine, and other anticholinergic agents that suppress salivary secretion.

The orthographic and phonetic similarities stem from the fact that the name pair has the same length (9 letters) and are nearly identical with only differences in the two letters as indicated here (Neutr***ov***al vs. Neutr***as***al). Thus the names appear and sound similar when scripted and spoken.

[1] http://neutrasal.com/

neutroval
neutrasal

The two products also have similar product characteristics such as overlapping patient population (cancer patients) and prescribers.

We carefully considered whether differences in product characteristics such as dosage form, strength, and route and frequency of administration for your product compared to NeutraSal would minimize the potential for error between Neutroval and NeutraSal. We concluded that these aspects will not eliminate the potential for name confusion and medication errors.

Although Neutrasal has some differences in product characteristics, because the name pair has such strong orthographic and phonetic similarities, differences in product characteristics are not enough to overcome the similarities. We identified post marketing confusion between products with different product characteristics when strong orthographic and phonetic similarities exist. For example, ISMP recently published a report where Arixtra (fondaparinux) was confused with Arista (a device used in surgical procedures as an adjunctive hemostatic device to assist when control of capillary, venous, and arteriolar bleeding).[1] The report demonstrates that differing product characteristics cannot overcome overwhelming orthographic and/or phonetic similarities, particularly for products used in the same setting of care.

Thus, confusion between this name pair may result in medication errors if both products are marketed.

C. ORTHOGRAPHIC SIMILARITIES WITH A PENDING PROPRIETARY NAME

The proposed proprietary name, Neutroval, is also vulnerable to name confusion that could lead to medication errors with a pending proposed proprietary name due to orthographic similarity and shared product characteristics.

We acknowledge that the conclusions of this review differ from the March 22, 2010 letter finding your name conditionally acceptable. This difference is accounted for by the recently identified medication error reports among Neupogen and Neulasta as well as Neupogen and Neumega. Because your name is constructed similar to these name pairs and share similar product characteristics, we have determined that these reports indicate your name is prone to confusion with Neupogen, Neulasta, and Neumega. Additionally, two new names (i.e. NeutraSal and pending proprietary name) were identified during this cycle that were not available for review during the previous review cycle. Therefore we conclude that the proposed proprietary name, Neutroval, is not acceptable from a safety perspective.

[1] http://www.ismp.org/newsletters/acutecare/issues/20120517.pdf

4. REFERENCES

1. ***Micromedex Integrated Index (http://csi.micromedex.com)***

   Micromedex contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

2. ***Phonetic and Orthographic Computer Analysis (POCA)***

   POCA is a database which was created for the Division of Medication Error Prevention and Analysis, FDA. As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion.

3. ***Drug Facts and Comparisons, online version, St. Louis, MO (http://factsandcomparisons.com)***

   Drug Facts and Comparisons is a compendium organized by therapeutic course; it contains monographs on prescription and OTC drugs, with charts comparing similar products. This database also lists the orphan drugs.

4. ***FDA Document Archiving, Reporting & Regulatory Tracking System [DARRTS]***

   DARRTS is a government database used to organize Applicant and Sponsor submissions as well as to store and organize assignments, reviews, and communications from the review divisions.

5. ***Division of Medication Errors Prevention and Analysis proprietary name consultation requests***

   This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

6. ***Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)***

   Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and "Chemical Type 6" approvals.

7. ***U.S. Patent and Trademark Office (http://www.uspto.gov)***

   USPTO provides information regarding patent and trademarks.

8. ***Clinical Pharmacology Online (www.clinicalpharmacology-ip.com)***

   Clinical Pharmacology contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. It also provides a keyword search engine.

9. ***Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at (www.thomson-thomson.com)***

   The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and trade names that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

10. ***Natural Medicines Comprehensive Databases (www.naturaldatabase.com)***

    Natural Medicines contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

11. ***Access Medicine (www.accessmedicine.com)***

    Access Medicine® from McGraw-Hill contains full-text information from approximately 60 titles; it includes tables and references. Among the titles are: Harrison's Principles of Internal Medicine, Basic & Clinical Pharmacology, and Goodman and Gilman's The Pharmacologic Basis of Therapeutics.

12. ***USAN Stems (http://www.ama-assn.org/ama/pub/about-ama/our-people/coalitions-consortiums/united-states-adopted-names-council/naming-guidelines/approved-stems.shtml)***

    USAN Stems List contains all the recognized USAN stems.

13. ***Red Book (www.thomsonhc.com/home/dispatch)***

    Red Book contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

14. ***Lexi-Comp (www.lexi.com)***

    Lexi-Comp is a web-based searchable version of the Drug Information Handbook.

15. ***Medical Abbreviations (www.medilexicon.com)***

    Medical Abbreviations dictionary contains commonly used medical abbreviations and their definitions.

16. ***CVS/Pharmacy (www.CVS.com)***

    This database contains commonly used over the counter products not usually identified in other databases.

17. ***Walgreens (www.walgreens.com)***

    This database contains commonly used over the counter products not usually identified in other databases.

18. ***Rx List (www.rxlist.com)***

    RxList is an online medical resource dedicated to offering detailed and current pharmaceutical information on brand and generic drugs.

19. Dogpile (www.dogpile.com)

Dogpile is a Metasearch engine that searches multiple search engines including Google, Yahoo! and Bing, and returns the most relevant results to the search.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment considers the promotional and safety aspects of a proposed proprietary name. The promotional review of the proposed name is conducted by OPDP. OPDP evaluates proposed proprietary names to determine if they are overly fanciful, so as to misleadingly imply unique effectiveness or composition, as well as to assess whether they contribute to overstatement of product efficacy, minimization of risk, broadening of product indications, or making of unsubstantiated superiority claims. OPDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.

The safety assessment is conducted by DMEPA. DMEPA staff search a standard set of databases and information sources to identify names that are similar in pronunciation, spelling, and orthographically similar when scripted to the proposed proprietary name. Additionally, we consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.). DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

Following the preliminary screening of the proposed proprietary name, DMEPA gathers to discuss their professional opinions on the safety of the proposed proprietary name. This meeting is commonly referred to the Center for Drug Evaluation and Research (CDER) Expert Panel discussion. DMEPA also considers other aspects of the name that may be misleading from a safety perspective. DMEPA staff conducts a prescription simulation studies using FDA health care professionals. When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name and misleading nature of the proposed proprietary name with a focus on the avoidance of medication errors.

DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting where the product is likely to be used based on the characteristics of the proposed product. DMEPA considers the product characteristics associated with the proposed product throughout the risk assessment because the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

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[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www nccmerp.org/aboutMedErrors html. Last accessed 10/11/2007.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed proprietary name include, but are not limited to; established name of the proposed product, proposed indication of use, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. DMEPA considers how these product characteristics may or may not be present in communicating a product name throughout the medication use system. Because drug name confusion can occur at any point in the medication use process, DMEPA considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.[1]

The DMEPA considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA compares the proposed proprietary name with the proprietary and established name of existing and proposed drug products and names currently under review at the FDA. DMEPA compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names because verbal communication of medication names is common in clinical settings. DMEPA examines the phonetic similarity using patterns of speech. If provided, DMEPA will consider the Sponsor's intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Sponsor has little control over how the name will be spoken in clinical practice. The orthographic appearance of the proposed name is evaluated using a number of different handwriting samples. DMEPA applies expertise gained from root-cause analysis of postmarketing medication errors to identify sources of ambiguity within the name that could be introduced when scripting (e.g.,"T" may look like "F," lower case 'a' looks like a lower case 'u,' etc). Additionally, other orthographic attributes that determine the overall appearance of the drug name when scripted (see Table 1 below for details).

[1] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

Table 1. Criteria Used to Identify Drug Names that Look- or Sound-Similar to a Proposed Proprietary Name.

Type of Similarity	**Considerations when Searching the Databases**		
	Potential Causes of Drug Name Similarity	*Attributes Examined to Identify Similar Drug Names*	*Potential Effects*
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	• Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication • Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name/Similar shape Upstrokes Down strokes Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	• Names may look similar when scripted, and lead to drug name confusion in written communication
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	• Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Lastly, DMEPA considers the potential for the proposed proprietary name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. Consequently, DMEPA considers and evaluates these broader safety implications of the name throughout this assessment and the medication error staff provides additional comments related to the

safety of the proposed proprietary name or product based on professional experience with medication errors.

1. Database and Information Sources

DMEPA searches the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to the proposed proprietary name. A standard description of the databases used in the searches is provided in the reference section of this review. To complement the process, the DMEPA uses a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, DMEPA reviews the USAN stem list to determine if any USAN stems are present within the proprietary name. The individual findings of multiple safety evaluators are pooled and presented to the CDER Expert Panel. DMEPA also evaluates if there are characteristics included in the composition that may render the name unacceptable from a safety perspective (abbreviation, dosing interval, etc.).

2. Expert Panel Discussion

DMEPA gathers gather CDER professional opinions on the safety of the proposed product and discussed the proposed proprietary name (Expert Panel Discussion). The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Office of Prescription Drug Promotion (OPDP). We also consider input from other review disciplines (OND, ONDQA/OBP). The Expert Panel also discusses potential concerns regarding drug marketing and promotion related to the proposed names.

The primary Safety Evaluator presents the pooled results of the database and information searches to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend additional names, additional searches by the primary Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

3. FDA Prescription Simulation Studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically

scanned and one prescription is delivered to a random sample of participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants record their interpretations of the orders which are recorded electronically.

4. Comments from Other Review Disciplines

DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA's final decision on the proposed name.

Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

5. Safety Evaluator Risk Assessment of the Proposed Proprietary Name

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, considers all aspects of the name that may be misleading or confusing, conducts a Failure Mode and Effects Analysis, and provides an overall decision on acceptability dependent on their risk assessment of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.[1] When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed proprietary name to be confused with another drug name because of name confusion and, thereby, cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to orthographically or phonetically similar drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the primary Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is has not been marketed, the primary Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product

[1] Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

characteristics listed in Section 1.2 of this review. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, Expert Panel Discussion, and prescription studies, external studies, and identifies potential failure modes by asking:

> ***"Is the proposed proprietary name convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting? And are there any components of the name that may function as a source of error beyond sound/look-alike?"***

An affirmative answer indicates a failure mode and represents a potential for the proposed proprietary name to be confused with another proprietary or established drug name because of look- or sound-alike similarity or because of some other component of the name. If the answer to the question is no, the Safety Evaluator is not convinced that the names posses similarity that would cause confusion at any point in the medication use system, thus the name is eliminated from further review.

In the second stage of the Risk Assessment, the primary Safety Evaluator evaluates all potential failure modes to determine the likely *effect* of the drug name confusion, by asking:

> ***"Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?"***

The answer to this question is a central component of the Safety Evaluator's overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would not ultimately be a source of medication errors in the usual practice setting, the primary Safety Evaluator eliminates the name from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend the use of an alternate proprietary name.

Moreover, DMEPA will object to the use of proposed proprietary name when the primary Safety Evaluator identifies one or more of the following conditions in the Overall Risk Assessment:

a. OPDP finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with OPDP's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].

b. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].

c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.

d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.

e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product but involve a naming characteristic that when incorporated into a proprietary name, may be confusing, misleading, cause or contribute to medication errors.

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA generally recommends that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name. In that instance, DMEPA may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEPA will provide a contingency objection based on the date of approval. Whichever product, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

The threshold set for objection to the proposed proprietary name may seem low to the Applicant/Sponsor. However, the safety concerns set forth in criteria a through e above are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), the Joint Commission, and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names, confusing, or misleading names and called for regulatory authorities to address the issue prior to approval. Additionally, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and preventable source of medication error that, in many instances, the Agency and/or Sponsor can identify and rectify prior to approval to avoid patient harm.

Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors involving drug name confusion. Sponsors have undertaken higher-leverage strategies, such as drug name changes, in the

past but at great financial cost to the Sponsor and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Sponsors' have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioners' vocabulary, and as a result, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval.

Appendix B: Letters with Possible Orthographic or Phonetic Misinterpretation

Letters in Name, Neutroval	Scripted May Appear as	Spoken May Be Interpreted as
N	h, k, m, u, r, s, v, x	
e	a, i, l, o, u, p	Any vowel
u	c, n, v, w, y, any vowel	Any vowel
t	r, f, x, A	
r	e, n, s, v	
o	a, c, e, u	Any vowel
v	r, u	
a	el, ci, cl, d, o, u	Any vowel
l	b, e, i, s, A, P	

Appendix C: Prescription Simulation Samples and Results

Figure 1. Neutroval Study (Conducted on April 27, 2012)

Handwritten Requisition Medication Order	Verbal Prescription
Medication Order: Neutroval 300mcg (b) (4) once daily	Neutroval 480 mcg (b) (4)
Outpatient Prescription: Neutroval 480mcg	

FDA Prescription Simulation Responses (Aggregate 1 Rx Studies Report)

84 People Received Study

29 People Responded

Study Name: Neutroval

Total	12	8	9	
INTERPRETATION	**INPATIENT**	**VOICE**	**OUTPATIENT**	**TOTAL**
KEUTROVAL	0	0	1	1
NEUTRAVAL	0	3	0	3
NEUTROVAL	11	2	6	19
NUTRAVAL	0	3	0	3
REUTROVAL	0	0	1	1
VEUTROVAL	1	0	0	1
XEUTROVAL	0	0	1	1

Appendix D: Proprietary names not likely to be confused or not used in usual practice settings for the reasons described.

Proprietary Name	Active Ingredient	Similarity to Neutroval	Failure preventions
Mebaral	mephobarbital	Phonetic	The pair has sufficient phonetic differences.
Neuramate	meprobamate	Orthographic	The pair has sufficient orthographic differences.
			(b) (4)
Neutrexin	trimerexate	Orthographic	NDA 20326 withdrawn on 3/13/2009 FR effective
Neutroval***	xxx-filgrastim	Both	The subject of this review
Nulecit	sodium ferric gluconate	Orthographic	The pair has sufficient orthographic differences.

*** This document contains proprietary information that should not be released to the public

Appendix E: Risk of medication errors due to product confusion minimized by dissimilarity of the names and/ or use in clinical practice for the reasons described.

Proposed name: Neutroval (XM02/xxx-filgrastim) **Strength and Dosage Form: 300 mcg/0.5 mL, 480 mcg/0.8 mL solution in prefilled syringes for sub-q (b) (4) injection** **Usual Dose:** **5 mcg/kg/day**	**Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion** **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
Hectorol (doxercalciferol) - 0.5 mcg, 1 mcg, 2.5 mcg oral capsules - 4 mcg/2 mL solution for injection - Dialysis: 10 mcg by mouth 3 times weekly @dialysis to max of 20 mcg 3 times weekly; - Pre-dialysis: 1 mcg by mouth once daily to max of 3.5 mcg once daily - IV: 4 mcg 3 times weekly (max of 18 mcg/week)	**Orthographic Similarities** - 'Ne' and 'He' may appear similar when scripted **Overlapping Product Characteristics** - Dosage Form (solution for injection) - Units of measure (mcg) (b) (4)	**Orthographic Differences** - 'u' and 'c' does not appear similar when scripted - 'troval' and 'torol' appear different when scripted due to the distance between the 2 up strokes (wider for 'troval' than 'torol' **Differing Product Characteristics** - Strength (300 mcg/0.5 mL, 480 mcg/0.8 mL vs. 0.5 mcg, 1 mcg, 2.5 mcg, 4 mcg/2 mL with no overlap) - Dose (5 mcg/kg * 60 kg = 300 mcg vs. 1 mcg to 10 mcg with no overlap)

Proposed name: Neutroval (XM02/xxx-filgrastim) **Strength and Dosage Form: 300 mcg/0.5 mL, 480 mcg/0.8 mL solution in prefilled syringes for sub-q (b)(4) injection** **Usual Dose:** **5 mcg/kg/day**	**Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion** **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
Neulasta (pegfilgrastim) - 6 mg/0.6 mL solution in prefilled syringes for injection - 6 mg sub-q injection once per chemotherapy cycle	**Orthographic Similarities** - 'Neut' and 'Neul' may appear similar when scripted **Overlapping Product Characteristics** - Dosage Form (solution in prefilled syringes) - Route of Administration (sub-q)	**Orthographic Differences** - 'roval' appear longer and different than 'asta' when scripted due to the position of the up strokes (9th vs. 7th) **Differing Product Characteristics** - Strength (300 mcg/0.5 mL, 480 mcg/0.8 mL vs. 6 mg/0.6 mL with no overlap) - Dose (5 mcg/kg * 60 kg = 300 mcg vs. 6 mg with no overlap)

Proposed name: Neutroval (XM02/xxx-filgrastim) Strength and Dosage Form: 300 mcg/0.5 mL, 480 mcg/0.8 mL solution in prefilled syringes for sub-q (b) (4) injection Usual Dose: 5 mcg/kg/day	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion Causes (could be multiple)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
(b) (4)		

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Proposed name: Neutroval (XM02/xxx-filgrastim) **Strength and Dosage Form: 300 mcg/0.5 mL, 480 mcg/0.8 mL solution in prefilled syringes for sub-q (b)(4) injection** **Usual Dose:** **5 mcg/kg/day**	**Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion** **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
Neumega (oprelvekin) - 5 mg/vial powder for injection - 50 mcg/kg sub-q injection once daily - CrCl less than 30 mL/min: 25 mcg/kg	**Orthographic Similarities** - Both contain the letter string 'Neu' in the beginning **Overlapping Product Characteristics** - Route of Administration (sub-q) - Dose (5 mcg/kg vs. 50 mcg/kg) - Frequency (once daily)	**Orthographic Differences** - 'troval' appears longer and different than 'mega' when scripted due to: 2 up strokes vs. 1 down stroke and 2 more letters in 'troval'
Neupogen (filgrastim) - 300 mcg/1 mL, 480 mcg/1.6 mL solution in vial, 300 mcg/ 0.5 mL, 480 mcg/0.8 mL solution in prefilled syringe for injection - 5 mcg/kg/day	**Orthographic Similarities** - Both contain the letter string 'Neu' in the beginning **Overlapping Product Characteristics** - All aspects of product characteristics are identical	**Orthographic Differences** - 'troval' appears longer and different than 'pogen' due to: 2 up strokes vs. 2 down strokes

Proposed name: Neutroval (XM02/xxx-filgrastim) **Strength and Dosage Form: 300 mcg/0.5 mL, 480 mcg/0.8 mL solution in prefilled syringes for sub-q (b) (4) injection** **Usual Dose:** **5 mcg/kg/day**	**Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion** **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
Neurolite (technetium TC-99M Bicisate) Kit - 70 kg patient: 370 MBq to 1110 MBq (10 mCi to 30 mCi)	**Orthographic Similarities** - Both contain the letter string 'Neu' in the beginning - Both have 9 letters **Overlapping Product Characteristics** (b) (4)	**Orthographic Differences** - 'troval' and 'ralite' appear different when scripted due to the positions of the up strokes (4th & 9th vs. 6th & 8th) **Differing Product Characteristics** - Strength (300 mcg/0.5 mL, 480 mcg/0.8 mL vs. per batch single strength with no overlap) - Setting of Use (Clinic vs. Radiology Suite) - Units of Measure (mg or mL vs. MBq or mCi where dose must be checked by radioactive callibration system immediately before administering)
NeutraSal (calcium chloride, sodium phosphate) - 510(k) - powder for oral rinse - Dissolve or disperse 1 packet in 30 mL (1 ounce) of tap water. Swish the solution in the mouth thoroughly for 1 min with ½ of the solution and spit out. Repeat with the remaining ½ of the solution. Use 2 to 10 times daily as needed	**Orthographic Similarities** - 'Neutroval' and 'Neutrasal' appear similar when scripted - Both have 9 letters **Phonetic Similarities** - 'Neutro' and 'Neutra' sound the same when spoken - Both names end with 'al'	**Differing Product Characteristics** - Strength (300 mcg/0.5 mL, 480 mcg/0.8 mL vs. single strength with no overlap) - Dose (5mcg/kg/day vs. 1 packet) - Route of Administration (Sub-q (b) (4) vs. oral rinse)

Proposed name: Neutroval (XM02/xxx-filgrastim) Strength and Dosage Form: 300 mcg/0.5 mL, 480 mcg/0.8 mL solution in prefilled syringes for sub-q (b) (4) injection Usual Dose: 5 mcg/kg/day	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion Causes (could be multiple)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
(b) (4)		

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Proposed name: Neutroval (XM02/xxx-filgrastim) **Strength and Dosage Form: 300 mcg/0.5 mL, 480 mcg/0.8 mL solution in prefilled syringes for sub-q (b) (4) injection** **Usual Dose:** **5 mcg/kg/day**	**Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion** **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
Nexterone (amiodarone) - 150 mg/3 mL, 450 mg/9 mL, 900 mg/18 mL solution in vials, 150 mg/3 mL solution in prefilled syringe for injection - Initial: 150 mg over the 1st 10 minutes (15 mg/min) then 360 mg over the next 6 hours (1mg/min) then 540 mg over the remaining 18 hours (0.5 mg/min) intravenous infusion	**Orthographic Similarities** - 'Neut' and 'Next' may appear similar when scripted - Both have 9 letters **Overlapping Product Characteristics** - Dosage Form (solution for injection, prefilled syringe) (b) (4)	**Orthographic Differences** - 'roval' and 'erone' appear different when scripted due to the up stroke 'l' **Differing Product Characteristics** - Strength (300 mcg/0.5 mL, 480 mcg/0.8 mL vs. 150 mg/3 mL, 450 mg/9 mL, 900 mg/18 mL, 150 mg/3 mL with no overlap) - Dose (5 mcg/kg/day vs. 150 mg to 540 mg)
Nuedexta (dextromethorphan, quinidine) - 20mg/10 mg oral capsules - 1 capsules once daily for 7 days then 1 capsule every 12 hours	**Orthographic Similarities** - 'Neut' and 'Nued' may appear similar when scripted **Overlapping Product Characteristics** - Frequency (once daily)	**Orthographic Differences** - 'roval' appear different and longer than 'exta' when scripted due to the different position of the up stroke (9th vs. 7th) **Differing Product Characteristics** - Strength (300 mcg/0.5 mL, 480 mcg/0.8 mL vs. 20 mg/10 mg with no overlap) - Dose (5 mcg/kg/day vs. 1 capsule)

Proposed name: Neutroval (XM02/xxx-filgrastim) **Strength and Dosage Form: 300 mcg/0.5 mL, 480 mcg/0.8 mL solution in prefilled syringes for sub-q (b)(4) injection** **Usual Dose:** **5 mcg/kg/day**	**Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion** **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
Nutrament (nutritional supplement) - Use as directed	**Orthographic Similarities** - Both start with 'N' - 'tro' and 'tra' may appear similar when scripted - Both have 9 letters	**Orthographic Differences** - 'eu' and 'u' appear different when scripted - 'val' and 'ment' appear different when scripted **Differing Product Characteristics** - Strength (300 mcg/0.5 mL, 480 mcg/0.8 mL vs. single strength with no overlap) - Dose (5 mcg/kg/day vs. 1 can) - Route of Administration (sub-q, (b)(4) vs. oral)
Uroxatral (alfuzosin) - 10 mg oral tablets - 1 tablet once daily	**Orthographic Similarities** - 'Neu' and 'Uro' may appear similar when scripted - 'val' and 'ral' may appear similar when scripted **Overlapping Product Characteristics** - Frequency (once daily)	**Orthographic Differences** - 'tro' and 'xat' appear different when scripted due to the different position of the up stroke 't' **Differing Product Characteristics** - Strength (300 mcg/0.5 mL, 480 mcg/0.8 mL vs. single strength (10 mg) with no overlap) - Dose (5 mcg/kg/day vs. 1 tablet) - Route of Administration (sub-q, (b)(4) vs. oral)

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/s/

SARAH K VEE
07/16/2012

YELENA L MASLOV
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CAROL A HOLQUIST on behalf of KELLIE A TAYLOR
07/16/2012

CAROL A HOLQUIST
07/16/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	March 19, 2010
To:	Patricia Keegan, MD, Director Division of Biologic Oncology Products
Through:	Kristina C. Arnwine, PharmD, Team Leader 3/19/2010 Denise P. Toyer, PharmD, Deputy Director 3/19/2010. Carol A. Holquist, RPh, Director 3/19/2010 Division of Medication Error Prevention and Analysis (DMEPA)
From:	Loretta Holmes, BSN, PharmD, Safety Evaluator 3/19/2010 Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Proprietary Name Review
Drug Name:	Neutroval [redacted] (b) (4) Injection 300 mcg/0.5 mL and 480 mcg/0.8 mL
Application Type/Number:	BLA 125294
Applicant:	Teva Pharmaceuticals USA
OSE RCM #:	2010-1

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EXECUTIVE SUMMARY

Neutroval is the proposed proprietary name for (b) (4) Injection. This proposed name was evaluated from a safety and promotional perspective based on the product characteristics provided by the Applicant. Our evaluation did not identify concerns that would render the name unacceptable based on the product characteristics and safety profile known at the time of this review. Thus, DMEPA finds the proposed proprietary name, Neutroval, conditionally acceptable for this product. The proposed proprietary name must be re-reviewed 90 days before approval of the BLA.

Additionally, if any of the proposed product characteristics as stated in this review are altered, DMEPA rescinds this finding and the name must be resubmitted for review. The conclusions upon re-review are subject to change.

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a December 23, 2009 request from Teva Pharmaceuticals USA for an assessment of the proposed proprietary name, Neutroval, regarding potential name confusion with other proprietary or established drug names in the usual practice settings.

Additionally, the container labels, carton and insert labeling are being evaluated for their potential contribution to medication errors under separate cover (OSE Review 2009-2469).

1.2 REGULATORY HISTORY

DMEPA previously reviewed the proposed proprietary name, Neutroval, under IND 103188 (OSE Review 2009-1414, dated November 10, 2009). We found the name conditionally acceptable at that time.

1.3 PRODUCT INFORMATION

Neutroval is the proposed proprietary name for (b) (4) Injection. Neutroval is a granulocyte colony-stimulating factor (G-CSF) indicated for the reduction in the duration of severe neutropenia and the incidence of febrile neutropenia in patients treated with established myelosuppressive chemotherapy for cancer. The recommended dosage is 5 mg/kg/day subcutaneously (b) (4) no earlier than 24 hours following myelosuppressive chemotherapy (b) (4) .

Neutroval will be supplied in prefilled syringes (with and without a safety needle guard) containing 300 mcg/0.5 mL or 480 mcg/0.8 mL in 1, 5, and 10-count packages.

2 METHODS AND MATERIALS

Appendix A describes the general methods and materials used by the Division of Medication Error Prevention and Analysis (DMEPA) when conducting a proprietary name risk assessment for all proprietary names. Section 2.1 identifies specific information associated with the methodology for the proposed proprietary name, Neutroval. We did not repeat the inpatient, outpatient and verbal prescription studies since they were conducted on August 31, 2009.

2.1 SEARCH CRITERIA

For this review, particular consideration was given to drug names beginning with the letter 'N' when searching to identify potentially similar drug names, as 75% of the confused drug names reported by the USP-ISMP Medication Error Reporting Program involve pairs beginning with the same letter.[1,2]

To identify drug names that may look similar to Neutroval, the DMEPA staff also considers the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (nine letters), upstrokes (two, lower case letters 't' and 'l'), downstrokes (none), cross strokes (one, lower case letter 't'), and dotted letters (none). Additionally, several letters in Neutroval may be vulnerable to ambiguity when scripted (see Appendix B). As a result, the DMEPA staff also considers these alternate appearances when identifying drug names that may look similar to Neutroval.

When searching to identify potential names that may sound similar to Neutroval, the DMEPA staff search for names with similar number of syllables (three), stresses (NEU-tro-val, neu-TRO-val or neu-tro-VAL), and placement of vowel and consonant sounds. Additionally, the DMEPA staff considers that pronunciation of parts of the name can vary (see Appendix B). The Applicant provided their intended pronunciation of the proprietary name (nue' troe val) in the proposed name submission and, therefore, it was taken into consideration. Moreover, names are often mispronounced and/or spoken with regional accents and dialects, so other potential pronunciations of the name are considered.

3 RESULTS

3.1 DATABASE AND INFORMATION SOURCES

The searches yielded a total of 29 names as having some similarity to the name Neutroval. Nineteen of these names (Neulasta, Neutrexin, Neutracare, Neutralin, Natrova, Introvale, Nutropin, Nutracort, Nizoral, MetroGel, Nicotrol, Neupogen, Nitronal, Naquival, Neutontin, Nortrel, Neutralox, Neoral, and Nutrivit) were identified and evaluated in our previous review and will not be discussed further since the Neutroval product characteristics have not changed since our previous review.

Of the ten remaining names, seven were thought to look like Neutroval (Natrecor, Nausetrol, Neuradiab, Nitro-Dur, Nitro-Bid, Retrovir, Neutrospec). One name, Notrel, was thought to look and sound similar to Neutroval and two names (Nutr-E-Sol and Neutrosol) were thought to look and sound similar to Neutroval.

Additionally, DMEPA staff did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name as of January 31, 2010.

3.2 CDER EXPERT PANEL DISCUSSION

The Expert Panel reviewed the pool of names identified by DMEPA staff (see Section 3.1 above) and noted no additional names thought to have orthographic or phonetic similarity to Neutroval.

DDMAC had no concerns regarding the proposed name from a promotional perspective, however, they commented that "Neutroval may sound like the existing trade names Neulasta and/or Neupogen".

---

[1] Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at http://www.ismp.org/Tools/confuseddrugnames.pdf

[2] Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005)

3.3 SAFETY EVALUATOR RISK ASSESSMENT

Independent searches by the primary Safety Evaluator resulted in identification of four additional names which were thought to look and/or sound similar to Neutroval and represent a potential source of drug name confusion. The names identified to have look-alike similarities are Nutrivir and (b) (4) The names, Neuroval (foreign) and Neuroval (domestic), were identified to have look-alike and sound-alike similarities.

When compiling the list of potentially similar drug names, we were unable to identify the drug name, Notrel, in any common drug references. We determined the name was misspelled during the transcription process and should have been Nortrel. Since Nortrel was evaluated in our previous review, it will not be discussed further.

Therefore, 13 new names were considered for their potential similarity to Neutroval.

4 DISCUSSION

4.1 PROMOTIONAL REVIEW

DDMAC did not find the name Neutroval promotional. The Division of Biologic Oncology Products and the Division of Medication Error Prevention and Analysis concurred with this assessment.

4.2 SAFETY REVIEW

The review team (e.g., clinical, chemistry, etc.) did not express any concerns with the proposed name.

Since the time the name was reviewed in the IND phase, 13 new names were identified as potential sources of confusion. DMEPA did not identify other aspects of the name that could function as a source of error. Five of the twelve names were not evaluated further for the following reasons: two names are foreign products, one name is a discontinued product, one name is an orphan drug product that has not been approved for marketing, and one name had only limited information available and could not be found in DMEPA's commonly used references (see Appendices C through F).

Failure mode and effects analysis (FMEA) was then applied to determine if the proposed name could potentially be confused with the remaining eight names and lead to medication errors. This analysis determined that the name similarity between Neutroval was unlikely to result in medication errors with any of the eight products for the reasons presented in Appendices G and H.

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Neutroval, is not promotional nor is it vulnerable to name confusion that could lead to medication errors. Thus, the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Neutroval, for this product at this time.

However, if any of the proposed product characteristics as stated in this review are altered prior to approval of the product, DMEPA rescinds this Risk Assessment finding and the name must be resubmitted for review. In the event that our Risk Assessment finding is rescinded, the evaluation of the name on resubmission is independent of the previous Risk Assessment, and as such, the conclusions on re-review of the name are subject to change. If the approval of this application is delayed beyond 90 days from the signature date of this review, the proposed name must be re-evaluated. If you have further questions or need clarifications, please contact Sarah Simon, OSE Project Manager, at 301-796-5205.

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5.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Neutroval, and have concluded that it is acceptable. Neutroval will be re-reviewed 90 days prior to the approval of the BLA. If we find the name unacceptable following the re-review, we will notify you.

6 REFERENCES

1. Micromedex Integrated Index (http://csi.micromedex.com)

Contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

2. Phonetic and Orthographic Computer Analysis (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion. This is a database which was created for the Division of Medication Error Prevention and Analysis, FDA.

3. Drug Facts and Comparisons, online version, St. Louis, MO (http://factsandcomparisons.com)

Drug Facts and Comparisons is a compendium organized by therapeutic course; contains monographs on prescription and OTC drugs, with charts comparing similar products.

4. FDA Document Archiving, Reporting & Regulatory Tracking System [DARRTS]

DARRTS is a government database used to organize Applicant and Sponsor submissions as well as to store and organize assignments, reviews, and communications from the review divisions.

5. Division of Medication Errors Prevention and Analysis proprietary name consultation requests

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

6. Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and "Chemical Type 6" approvals.

7. Electronic online version of the FDA Orange Book (http://www.fda.gov/cder/ob/default.htm)

Provides a compilation of approved drug products with therapeutic equivalence evaluations.

8. U.S. Patent and Trademark Office (http://www.uspto.gov)

Provides information regarding patent and trademarks.

9. Clinical Pharmacology Online (www.clinicalpharmacology-ip.com)

Contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. Provides a keyword search engine.

10. Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at (www.thomson-thomson.com)

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and trade names that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

11. Natural Medicines Comprehensive Databases (www.naturaldatabase.com)

Contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

12. Stat!Ref (www.statref.com)

Contains full-text information from approximately 30 texts. Includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolph's Pediatrics, Basic Clinical Pharmacology and Dictionary of Medical Acronyms Abbreviations.

13. USAN Stems (http://www.ama-assn.org/ama/pub/category/4782.html)

List contains all the recognized USAN stems.

14. Red Book Pharmacy's Fundamental Reference

Contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

15. Lexi-Comp (www.lexi.com)

A web-based searchable version of the Drug Information Handbook.

16. Medical Abbreviations Book

Contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name and the proprietary and established names of drug products existing in the marketplace and those pending IND, NDA, BLA, and ANDA products currently under review by the Center. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [3]

For the proposed proprietary name, DMEPA staff search a standard set of databases and information sources to identify names with orthographic and phonetic similarity and hold a Center for Drug Evaluation and Research (CDER) Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name. DMEPA staff also conducts internal CDER prescription analysis studies. When provided, DMEPA considers external prescription analysis study results and incorporate into the overall risk assessment.

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name, and focuses on the avoidance of medication errors.

FMEA is a systematic tool for evaluating a process and identifying where and how it might fail. [4] DMEPA uses FMEA to analyze whether the drug names identified with orthographic or phonetic similarity to the

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[3] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors.html. Last accessed 10/11/2007.

[4] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

proposed proprietary name could cause confusion that subsequently leads to medication errors in the clinical setting. DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting where the product is likely to be used based on the characteristics of the proposed product.

In addition, the product characteristics provide the context for the verbal and written communication of the drug names and can interact with the orthographic and phonetic attributes of the names to increase the risk of confusion when there is overlap or, in some instances, decrease the risk of confusion by helping to differentiate the products through dissimilarity. Accordingly, the DMEPA staff considers the product characteristics associated with the proposed drug throughout the risk assessment because the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed proprietary name include, but are not limited to; established name of the proposed product, proposed indication of use, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur at any point in the medication use process, DMEPA staff considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.[5] DMEPA provides the product characteristics considered for this review in section one.

The Division of Medication Error Prevention and Analysis considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA also compares the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly in spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. DMEPA staff also examines the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly and even dissimilarly spelled drug name pairs to appear very similar to one another. The similar appearance of drug names when scripted has led to medication errors. The DMEPA staff applies expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (e.g.,"T" may look like "F," lower case 'a' looks like a lower case 'u,' etc). Additionally, other orthographic attributes that determine the overall appearance of the drug name when scripted (see Table 1 below for details). In addition, the DMEPA staff compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names because verbal communication of medication names is common in clinical settings. If provided, DMEPA will consider the Applicant's intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Applicant has little control over how the name will be spoken in clinical practice.

[5] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

Table 1. Criteria used to identify drug names that look- or sound-similar to a proposed proprietary name.

Type of similarity	Considerations when searching the databases		
	Potential causes of drug name similarity	*Attributes examined to identify similar drug names*	*Potential Effects*
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	• Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication • Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name Upstrokes Down strokes Cross-stokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	• Names may look similar when scripted, and lead to drug name confusion in written communication
nd-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	• Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Lastly, the DMEPA staff also considers the potential for the proposed proprietary name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. Consequently, DMEPA considers and evaluates these broader safety implications of the name throughout this assessment and the medication error staff provides additional comments related to the safety of the proposed proprietary name or product based on professional experience with medication errors.

1. Database and Information Sources

DMEPA staff conducts searches of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to the proposed proprietary name using the criteria outlined in Section 2.1. Section 6 provides a standard description of the databases used in the searches. To complement the process, the DMEPA staff use a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, the DMEPA staff review the USAN stem list to determine if any USAN stems are present within the

proprietary name. The individual findings of multiple safety evaluators are pooled and presented to the CDER Expert Panel.

2. CDER Expert Panel Discussion

DMEPA conducts an Expert Panel Discussion to gather CDER professional opinions on the safety of the proposed product and the proposed proprietary name. The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The Expert Panel also discusses potential concerns regarding drug marketing and promotion related to the proposed names.

The primary Safety Evaluator presents the pooled results of the DMEPA staff to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the primary Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

3. Safety Evaluator Risk Assessment of the Proposed Proprietary Name

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, conducts a Failure Mode and Effects Analysis, and provides an overall risk assessment of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.[6] When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed proprietary name to be confused with another drug name because of name confusion and, thereby, cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to orthographically or phonetically similar drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the primary Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is has not been marketed, the primary Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Section one. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, Expert Panel Discussion, and prescription studies, external studies, and identifies potential failure modes by asking:

> ***"Is the proposed proprietary name convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?"***

An affirmative answer indicates a failure mode and represents a potential for the proposed proprietary name to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names posses similarity that would cause confusion at any point in the medication use system, thus the name is eliminated from further review.

In the second stage of the Risk Assessment, the primary Safety Evaluator evaluates all potential failure modes to determine the likely *effect* of the drug name confusion, by asking:

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[6] Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

"Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?"

The answer to this question is a central component of the Safety Evaluator's overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would not ultimately be a source of medication errors in the usual practice setting, the primary Safety Evaluator eliminates the name from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend the use of an alternate proprietary name.

DMEPA will object to the use of proposed proprietary name when the primary Safety Evaluator identifies one or more of the following conditions in the Risk Assessment:

a. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with DDMAC's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].

b. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].

c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), <u>and</u> demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.

d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.

e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product.

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA is likely to recommend that the Applicant select an alternative proprietary name and submit the alternate name to the Agency for DMEPA to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name. In that instance, DMEPA may be able to provide the Applicant with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEPA will provide a contingency objection based on the date of approval. Whichever product, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

The threshold set for objection to the proposed proprietary name may seem low to the Applicant. However, the safety concerns set forth in criteria a through e are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), Joint Commission on Accreditation of Hospitals (JCOAH), and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names and called for regulatory authorities to address the issue prior to approval. Additionally, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a

predictable and a preventable source of medication error that, in many instances, the Agency and/or Applicant can identify and rectify prior to approval to avoid patient harm.

Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors involving drug name confusion. Applicants have undertaken higher-leverage strategies, such as drug name changes, in the past but at great financial cost to the Applicant and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Applicants' have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioners' vocabulary, and as a result, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval. (See Section 4 for limitations of the process).

Appendix B: Letters with possible orthographic or phonetic misinterpretation

Letters in Name **"Neutroval"**	**When scripted may appear as:**	**When spoken may be interpreted as:**
Capital 'N'	'V', 'M', lower case 'h'	M
Lower case 'e'	'a', 'i', 'l', or 'o'	
Lower case 'u'	'a', 'm', 'n', 'o', 'v', or 'w'	you
Lower case 't'	x', 'l' (if uncrossed)	
Lower case 'r'	'n', 's', 't', or 'v'	
Lower case 'o'	'a', 'e', or 'u'	'oh'
Lower case 'v'	upper case 'L', 'n', 'r', or 'u'	
Lower case 'a'	'e', 'ci', 'ce', 'o', or 'u'	Combination letters 'au' or 'aw'
Lower case 'l'	'e' or 'i'	
Combination letters '-eu-'	'cu' or 'w'	'u' or combination letters 'ew', 'oo'
Combination letters '-tr-'		Combination letters 'ch'
Combination letters 'Neu-'		Combination letters 'Nu', 'New', or 'Pneu'

Appendix C: Proprietary or Established Name used only in a Foreign Country

Proprietary Name	**Similarity to Neutroval**	**Country**	**Description/Comments**
Neuroval••• (Dipyrone and Diazepam)	Look and Sound	Indonesia	No additional product information available.
Neutrosol (Electrolyte infusion)	Look and Sound	Venezuela	No additional product information available.

••• There were two different products identified with this name, one foreign and one domestic.

Appendix D: Drug name not found in commonly referenced databases (See Section 6, References 1 through 16)

Name	Similarity to Neutroval	Comments
Neuroval[•••] (Phenobarbital)	Look and Sound	This name could not be found in Red Book, the NDC Directory, Facts and Comparisons, Drugs@FDA, the Orange Book, or Clinical Pharmacology Online. This name was found at the webmd.com and healthsquare.com websites via a Google search. These websites are not among our commonly referenced databases. The active ingredient is phenobarbital, however, the only information available about the product at these websites was general information concerning oral phenobarbital. There was no product specific information available. DMEPA was unable to determine the manufacturer of this product or its availability.

Appendix E: Drug product that is discontinued and no generic equivalent is available

Proprietary Name	Similarity to Neutroval	Status and Date
(b) (4)	Look	(b) (4)

[•••] There were two different products identified with this name, one foreign and one domestic.

[***] **This document contains proprietary and confidential information that should not be released to the public.[***]**

Appendix F: Orphan drug that is not approved for marketing

Proprietary Name	Similarity to Neutroval	Status and Date
Neurodiab (Anti-tenasin 81c6 Monoclonal Antibody Labeled with I 131)	Look	This is an orphan drug that has not been approved for marketing

Appendix G: Products with no numerical overlap in strength, dose and/or route of administration

Product name with potential for confusion	Similarity to Neutroval	Strength	Signa
Neutroval	**N/A**	**300 mcg/0.5 ml and 480 mcg/0.8 mL**	**5 mcg/kg/day administered as a daily subcutaneous injection** (b) (4) (b) (4)
Nitro-Bid (Nitroglycerin Ointment)	Look	2%	½ inch to 2 inches to skin twice daily
NutriVir Nutritional Supplement Over-the-Counter (OTC) product	Look	Each serving contains: (whey protein concentrate, fructose, dextrose, malto dextrin, vanilla and vanillin, "Enzyme Blend (amyloglucosidase, amylase, arotease, acid protease, cellulase, lipase), Vitamin A 5,000 IU, Vitamin C 1000 mg, Vitamin D 200 IU, Vitamin E 400 IU, Thiamin 1.5 mg, Riboflavin 1.7 mg, Niacin 10 mg, Vitamin B-6 25 mg, Folate 800 mcg, Vitamin B-12 1000 mg, Biotin 300 mcg, Pantothenic Acid 50 mg, Calcium 160 mg, Phosphorus 120 mg, Iodine 35.5 mcg, Magnesium 240 mg, Zinc 5.25 mg, Selenium 200 mcg, Manganese 2 mg, Chromium 200 mcg, Molybdenum 11.25 mcg, Sodium 180 mg, Potassium 160 mg, Medium Chain Triglycderides 6 g, N-Acetyl Cysteine 2 g, L-Cartinitine Magnesium Citrate 1g, Taurine 500 mg, Alpha-Lipoic Acid 100 mg, Choline 100 mg, Inositol 100 mg, Inosine 50 mg, Pyridoxine Alpha-Ketoglutarate 25 mg, Lutein 6 mg, Lycopene 3 mg, Boron 1.5 mg, and Vanadium 50 mcg.	5 tablespoonsful in 8 oz. of cold beverage once daily

Product name with potential for confusion	Similarity to Neutroval	Strength	Signa
Neutroval	**N/A**	**300 mcg/0.5 ml and 480 mcg/0.8 mL**	**5 mcg/kg/day administered as a daily subcutaneous injection** (b) (4) (b) (4)
NeutroSpec [Technetium (99m Tc) Fanolesomab] Injection *Marketing and sales of this product were suspended in 2005 due to reports of serious adverse events. There are no generics available.*	Look	0.25 mg	Adults: 75 mcg to 125 mcg labeled with 10 mCi to 20 mCi intravenously once Children (5 years of age and older): 0.21 mCi/kg to a maximum of 20 mCi.

Appendix H: Products with overlap in strength, dose or achievable dose with multiple differentiating product characteristics

Product name with potential for confusion	**Similarity to Neutroval**	**Strength**	**Signa**	**Differentiating Product Characteristics (Neutroval vs. Product)**
Neutroval	**N/A**	**300 mcg/0.5 ml and 480 mcg/0.8 mL**	**5 mcg/kg/day subcutaneously (b) (4) (b) (4) (b) (4) to begin no earlier than 24 hours following chemotherapy and to continue until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range.**	**N/A**
Retrovir (Zidovudine) Capsules Tablets Syrup Injection	Look	Capsules: 100 mg Tablets: 300 mg Syrup: 50 mg/5 mL Injection: 10 mg/mL	Adults: 600 mg per day in divided doses orally or intravenously	The beginning portion of Neutroval appears longer in length ("Neu" vs. "Re") which helps to differentiate the names. Additionally, the ending letter "l" in Neutroval has an upstroke characteristic which also helps to differentiate the names. *Frequency of administration*: Once daily vs. two or three times per day
Nutr-E-Sol (Vitamin E) Oral Liquid OTC product	Look	400 IU/15 mL	15 mL (1 tablespoonful) once daily	The beginning portion of Neutroval appears longer in length because it contains three letters whereas Nutresol contains two ("Neu" vs. "Nu"). *Dosage form*: Injection vs. oral liquid *Route of administration*: Subcutaneous (b) (4) vs. oral *Status*: Prescription vs. OTC

Product name with potential for confusion	**Similarity to Neutroval**	**Strength**	**Signa**	**Differentiating Product Characteristics** **(Neutroval vs. Product)**
Neutroval	**N/A**	**300 mcg/0.5 ml and 480 mcg/0.8 mL**	**5 mcg/kg/day subcutaneously** (b) (4) (b) (4) (b) (4) **to begin no earlier than 24 hours following chemotherapy and to continue until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range.**	**N/A**
Nausetrol Solution OTC Product	Look	Dextrose 1.87 g, Fructose 1.87g, and Phosphoric Acid 21.5 g per 5 mL	5 mL, 10 mL, 15 mL or 30 mL every 15 minutes until nausea is gone; take no more than 5 doses in one hour or a maximum of 5 doses	Both names contain the letters "tro". However, these three letters are in the middle portion of Neu**tro**val and in the ending portion of Nause**trol** which helps to differentiate the names. Additionally, the letters "tro" are followed by three letters ("val") in Neutroval and one letter ("l") in Nausetrol which further differentiates the names. *Dosage form*: Injection vs. oral solution *Route of administration*: Subcutaneous (b) (4) vs. oral *Frequency of administration*: Once daily vs. every 15 minutes *Status*: Prescription vs. OTC
Nitro-Dur (Nitroglycerin Transdermal Patch)	Look	0.1 mg/hr, 0.2 mg/hr, 0.3 mg/hr, 0.4 mg/hr, 0.6 mg/hr, and 0.8 mg/hr patches	0.2 mg/hr to 0.8 mg/hr patch applied to skin once daily, on for 10 to 12 hours then off for 12 to 14 hours	Both names contain the letters "tro". However, the letters ("eu" vs. "i") in the beginning of the names look different. The ending letters ("val" vs. "dur") look different as well due to the upstroke characteristic of the letter "d". *Dosage form*: Injection vs. transdermal patch *Route of administration*: Subcutaneous (b) (4) vs. topical

Product name with potential for confusion	Similarity to Neutroval	Strength	Signa	Differentiating Product Characteristics (Neutroval vs. Product)
Neutroval	**N/A**	**300 mcg/0.5 ml and 480 mcg/0.8 mL**	**5 mcg/kg/day subcutaneously** (b) (4) (b) (4) (b) (4) **to begin no earlier than 24 hours following chemotherapy and to continue until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range.**	**N/A**
Natrecor (Nesiritide) for Injection	Look	1.5 mg vial	2 mcg/kg intravenous bolus then 0.01 mcg/kg/min intravenous infusion	The beginning portion of Neutroval appears longer in length because it contains three letters whereas Natrecor contains two ("Neu" vs. "Na"). Additionally, the ending letters of the names look different ("val" vs. "cor"). *Dose:* 5 mcg/kg vs. 2 mcg/kg and 0.01 mcg/kg/min *Frequency of administration*: (b) (4) (b) (4) vs. a continuous infusion.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125418Orig1s000

PROPRIETARY NAME REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date July 27, 2012

From Biological Product Naming Working Group

Subject Memorandum Addendum -- BLA 125418 – Zaltrap ([xxx]-aflibercept) manufactured by sa
aventis, U.S., LLC

To File

As detailed in a memorandum dated July 15, 2012, FDA determined that a unique nonproprietary name will be required for sanofi-aventis' (sanofi) Zaltrap ([xxx]-aflibercept), a biological product submitted in a 351(a) biologics license application (BLA) to distinguish the product from Eylea (aflibercept), a previously licensed biological product submitted in a different 351(a) BLA by Regeneron Pharmaceuticals Inc. (Regeneron) that contains similar drug substance. In sum, Regeneron's and sanofi's products are the subject of different marketing applications held by different manufacturers; have different indications, different formulations, and different routes of administration; and are manufactured at different sites. Identifying sanofi's Zaltrap with a unique nonproprietary name will reinforce these differences and help to prevent medication errors involving the two products. For these reasons, FDA determined that the sanofi product will be identified as Zaltrap ([xxx]-aflibercept).

FDA communicated this decision to sanofi on July 17, 2012. By email of July 20, 2012 (attached to this addendum), sanofi proposed three nonproprietary names (b) (4), but objected to the use of an underscore (b) (4)

(b) (4)

Reference ID: 3165699

FDA has considered sanofi's position on use of the underscore, and has concluded that separating the prefix from the aflibercept stem with a punctuation mark is the appropriate mechanism by which to effectuate the goals underlying the decision to require a distinct nonproprietary name for sanofi's product. As described in the July 15, 2012 memorandum, FDA has determined that the nonproprietary name of a biological product for which licensure is sought under section 351(a) of the Public Health Service Act (PHS Act) that shares a similar drug substance to a previously licensed product should indicate both distinction from, and relation to, that other product in order to minimize medication errors and facilitate postmarketing safety monitoring. Removal of the mark changes both the visual and auditory impact of the prefix in a way that diminishes the desired effect of the use of the prefix and the clear preservation of the stem.

In addition, appending a prefix directly to the related product's stem for the purposes of distinguishing products in different 351(a) BLAs submitted by different manufacturers risks significant confusion and potentially could be misleading in light of the United States Adopted Names (USAN) Council's nomenclature practices related to prefix use. Specifically, the USAN Council's practice for naming biological substances uses prefixes directly appended to a stem (b) (4) For example, darbepoetin, (b) (4) has a prefix "darb" appended directly to the epoetin stem. No such determination has been made here.

However, FDA acknowledges that an underscore is not a mark normally used in handwriting, and that use of an underscore may result in the mark not being easily seen in handwriting and/or computer systems. FDA thus has determined that a prefix should be followed by a hyphen preceding aflibercept rather than an underscore. A hyphen is a common mark used in writing and is a more easily recognized mark.

(b) (4) (b) (4) In addition, there is precedent for using a hyphen in biological product nonproprietary names, e.g., interferon alfa-2b, as well as in the proprietary and nonproprietary nomenclature of drug products. FDA is not aware of any incompatibility that has resulted from use of the hyphen for interferon products, or more generally, of any inherent incompatibility of using hyphens with prescribing systems.

(b) (4)

FDA's decision to require a unique nonproprietary name in the form of [prefix]–aflibercept for Zaltrap, for which licensure is sought under section 351(a) of the PHS Act, is separate from any decision FDA may make in the future regarding the naming convention for biosimilar and interchangeable products under section 351(k) of the PHS Act. FDA is still considering the appropriate naming scheme for such products, and FDA does not anticipate that any decision on nomenclature for biosimilar and interchangeable products will conflict with FDA's determination regarding the nonproprietary name for this product

FDA reviewed the three proper names that sanofi proposed in decreasing order of preference:

(b) (4)

(iii) zivaflibercept

FDA evaluated those names with a hyphen inserted between the proposed prefixes and the aflibercept stem, using the criteria outlined in the July 17, 2012 communication to sanofi, and determined that "ziv-" is the only acceptable prefix provided by sanofi. Specifically, FDA made the following determinations:

(b) (4)

[1] Medical Abbreviations; 14th Edition; Neil M Davis.

[2] Davis, NM. Medical Abbreviations: 26,000 Conveniences at the Expense of Communication and Safety. 12th ed., at 269.

Reference ID: 3165699

(b) (4)

- The (b) (4) prefix, “ziv-” does not appear to raise concerns related to conveying specific meaning, being promotional or looking or sounding similar to a currently marketed product. The proposed prefix “ziv-” is acceptable based on the criteria outlined in the July 17, 2012 communication to sanofi.

[3] Webster's New World College Dictionary, 4th ed. 1999, at 1043; Stedman's Medical Dictionary, 26th ed. 1995, at 1292.

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/s/

LEAH A CHRISTL
07/27/2012
Memo entered into DARRTS on behalf of the Biological Product Naming Working Group

Memorandum

Date July 17, 2012

From Biological Product Naming Working Group

Subject BLA 125418 – Zaltrap ([xxx]_aflibercept) manufactured by sanofi-aventis, U.S., LLC

To File

FDA has determined that a unique nonproprietary name will be required for sanofi-aventis' (sanofi) Zaltrap ([xxx]_aflibercept), a biological product submitted in a 351(a) biologics license application (BLA) to distinguish the product from Eylea (aflibercept), a previously licensed biological product submitted in a different 351(a) BLA by Regeneron Pharmaceuticals Inc. (Regeneron) that contains similar drug substance. Specifically, Zaltrap ([xxx]_aflibercept), is a solution for infusion for use in combination with irinotecan-fluoropyrimidine-based chemotherapy for treatment of patients with metastatic colorectal cancer (mCRC) who were previously treated with an oxaliplatin-containing regimen. Regeneron's Eylea (aflibercept) was licensed for macular degeneration on November 18, 2011.

FDA has concluded that a nonproprietary name for sanofi's product that is distinct from Regeneron's product will minimize medication errors by (1) preventing a patient from receiving a product different than what was intended to be prescribed and (2) reducing confusion among healthcare providers who may consider use of the same nonproprietary name to mean that the biological products are indistinguishable from a clinical standpoint. FDA also has concluded that unique nonproprietary names will facilitate postmarketing safety monitoring by providing a clear means of determining which "afilbercept" product is dispensed to patients. Due to the fact that health care providers may use nonproprietary names instead of proprietary names when prescribing and ordering products, and pharmacovigilance systems often do not require inclusion of proprietary names, the use of distinct proprietary names is insufficient to address these concerns.

Eylea and Zaltrap are the subject of separate BLAs submitted by different manufacturers, Regeneron and sanofi respectively, although we are aware that they have a business relationship. For this reason, FDA has concluded that a unique nonproprietary name is warranted for the subsequently licensed product. In addition, the following factors also support the decision to designate a unique non-proprietary name for Zaltrap.

- Eylea and Zaltrap have different formulations. Eylea is formulated at 2 mg/mL, while Zaltrap is formulated at 25 mg/mL. Zaltrap differs from Eylea in (b) (4) vial size.

Reference ID: 3160382

- [redacted] (b) (4) As the products are manufactured at different sites under different BLAs held by different manufacturers, there is concern that, among other things, the two products may drift over time.

- Eylea and Zaltrap have different routes of administration. Eylea is administered by intravitreal injection while Zaltrap is administered by intravenous infusion in combination with chemotherapy.

- Eylea and Zaltrap have different indications. Eylea is indicated for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD), while Zaltrap is indicated in patients with metastatic colorectal cancer.

To differentiate Regeneron's aflibercept product from sanofi's product, FDA is requesting that sanofi propose a 3-4 letter prefix to be added to the non-proprietary stem, "aflibercept."

This decision for the aflibercept products is similar to the decision to revise the nonproprietary names for the botulinum toxin products. The nonproprietary names for botulinum toxin products were changed to emphasize the non-interchangeable potency units of each botulinum toxin product in an effort to prevent medication errors and serious adverse events. The potency units are specific to each botulinum toxin product, and the doses or units of biological activity cannot be compared or converted from one product to any other botulinum toxin product. The new nonproprietary names (which incorporated a 3-4 letter distinguishing prefix to the "botulinumtoxinA" or "botulinumtoxinB" stem) reinforced these differences and the lack of interchangeability among botulinum toxin products.

Regeneron and sanofi products are the subject of different marketing applications held by different manufacturers; have different indications, different formulations, and different routes of administration; and are manufactured at different sites. Identifying sanofi's Zaltrap with a unique nonproprietary name will reinforce these differences and help to prevent medication errors involving the two products. For these reasons, the sanofi product will be identified as Zaltrap ([xxx]_aflibercept).

Reference ID: 3160382

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/s/

SUE P LIM
07/17/2012
Memo entered into DARRTS on behalf of the Biological Product Naming Working Group

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Proprietary Name Review--Final

Date:	June 18, 2012
Reviewer:	James Schlick, RPh, MBA Division of Medication Error Prevention and Analysis
Team Leader	Todd Bridges, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Zaltrap (Aflibercept) Injection, 100 mg/4 mL and 200 mg/8 mL
Application Type/Number:	BLA 125418
Applicant:	Sanofi-Aventis
OSE RCM #:	2012-410

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1 INTRODUCTION

This re-assessment of the proposed proprietary name, Zaltrap, is written in response to the anticipated approval of this BLA within 90 days from the date of this review. DMEPA found the proposed name, Zaltrap, acceptable in OSE Review 2011-4363 dated February 13, 2012.

2 METHODS AND DISCUSSION

For re-assessments of proposed proprietary names, DMEPA searches a standard set of databases and information sources (see section 4) to identify names with orthographic and phonetic similarity to the proposed name that have been approved since the previous OSE proprietary name review. For this review we used the same search criteria described in OSE Review 2011-4363. We note that none of the proposed product characteristics were altered. However, we evaluated the previously identified names of concern considering any lessons learned from recent post-marketing experience, which may have altered our previous conclusion regarding the acceptability of the proposed proprietary name. The searches of the databases yielded 2 new names (Zebeta and (b) (4) ***) thought to look or sound similar to Zaltrap and represent a potential source of drug name confusion. Failure mode and effects analysis was applied to determine if the proposed proprietary name could potentially be confused with Zaltrap and lead to medication errors. This analysis determined that the name similarity between Zaltrap and the identified names was unlikely to result in medication error for the reasons presented in Appendix A.

Additionally, DMEPA searched the USAN stem list to determine if the name contains any USAN stems as of the last USAN updates. The Safety Evaluator did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name, as of June 13, 2012. The Office of Prescription Drug Promotion OPDP re-reviewed the proposed name on May 3, 2012 and had no concerns regarding the proposed name from a promotional perspective.

3 CONCLUSIONS

The re-evaluation of the proposed proprietary name, Zaltrap, did not identify any vulnerability that would result in medication errors with any additional name(s) noted in this review. Thus, DMEPA has no objection to the proprietary name, Zaltrap, for this product at this time.

DMEPA considers this a final review; however, if approval of the BLA is delayed beyond 90 days from the date of this review, the Division of Oncology Products 2 (DOP2) should notify DMEPA because the proprietary name must be re-reviewed prior to the new approval date.

If you have further questions or need clarifications, please contact Sue Kang, OSE project manager, at 301-796-4216.

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4 REFERENCES

1. **OSE Review # 2011-4363** ***Proposed Proprietary Name Review for Zaltrap, February 13, 2012.***

2. ***Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)***

   Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and "Chemical Type 6" approvals.

3. ***USAN Stems (http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/naming-guidelines/approved-stems.page?)***

   USAN Stems List contains all the recognized USAN stems.

4. ***Division of Medication Error Prevention and Analysis Proprietary Name Consultation Request***

   Compiled list of proposed proprietary names submitted to the Division of Medication Error Prevention and Analysis for review. The list is generated on a weekly basis from the Access database/tracking system.

APPENDIX A: FMEA TABLE

Zaltrap (Aflibercept) Injection 100 mg/4 mL and 200 mg/8 mL 25 mg/mL 4 mg/kg via Intravenous Infusion Once Every Two Weeks	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion: Causes (could be multiple)	Prevention of Failure Mode
		(b) (4)

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Zaltrap (Aflibercept) Injection 100 mg/4 mL and 200 mg/8 mL 25 mg/mL 4 mg/kg via Intravenous Infusion Once Every Two Weeks	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion: Causes (could be multiple)	Prevention of Failure Mode
Zebeta (Bisoprolol) Tablet 5 mg and 10 mg <u>Usual Dose</u> 5 mg or 10 mg orally twice daily	<u>Orthographic</u> The letter string 'Zeb' can look similar to the letter string 'Zal' when scripted. Both names have the cross stroke letter 't' after an upstroke letter.	<u>Orthographic</u> The name Zebeta does not have a downstroke letter at the end of the name. The name Zebeta has the letter 'e' between the upstroke letter 'b' and cross stroke letter 't' where the name Zaltrap has the cross stroke letter 't' immediately after the upstroke letter 'l'. <u>Strength</u> Multiple strengths vs. single strength and no overlap or numerical similarity in strength. Thus, Zebeta's strength will be specified vs. Zaltrap's strength may be omitted. <u>Dose</u> No overlap or numerical similarity in dose <u>Frequency of Administration</u> Twice daily vs. Once every two weeks

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/s/

JAMES H SCHLICK
06/18/2012

TODD D BRIDGES
06/18/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Proprietary Name Review

Date:	February 13, 2012
Reviewer(s):	James Schlick, RPh, MBA Division of Medication Error Prevention and Analysis
Team Leader	Todd Bridges, RPh Division of Medication Error Prevention and Analysis
Division Director	Carol Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name(s) and Strength(s):	Zaltrap (Aflibercept) Injection, 100 mg/4 mL and 200 mg/8 mL
Application Type/Number:	BLA 125418
Applicant:	Sanofi-Aventis
OSE RCM #:	2011-4363

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1 INTRODUCTION

This review evaluates the proposed proprietary name, Zaltrap, from a safety and promotional perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A respectively.

1.1 REGULATORY HISTORY

The proposed proprietary name, Zaltrap, was found acceptable by DMEPA in OSE Review 2010-1837, dated November 30, 2010 under IND 009948. Sanofi Aventis submitted a proprietary name request on February 2, 2012 which is the topic of this review.

1.2 PRODUCT INFORMATION

The following product information is provided in the February 2, 2012 proprietary name submission.

- Established Name: Aflibercept Injection
- Indication of Use: For the treatment of metastatic colorectal cancer in combination with the chemotherapy regimen Fluorouracil, Irinotecan, and Leucovorin (FOLFIRI).
- Route of administration: Intravenous infusion
- Dosage form: Solution for injection
- Strength: 25 mg/mL
- Dose: 4 mg/kg via intravenous infusion over one hour every two weeks
- How Supplied: [redacted] (b) (4) vials
- Storage: Refrigerated at 2 to 8°C (36 to 46°F)
- Container and Closure systems: Supplied in either 5 mL or 10 mL [redacted] (b) (4) glass vial, sealed with flanged stopper with flip-off cap [redacted] (b) (4) containing 100 mg or 200 mg of aflibercept. The 100 mg vial comes in 1 vial or 3 vial cartons and the 200 mg vial comes in 1 vial cartons.

2 RESULTS

The following sections provide the information obtained and considered in the evaluation of the proposed proprietary name.

2.1 PROMOTIONAL ASSESSMENT

OPDP determined the proposed name is acceptable from a promotional perspective. DMEPA and the Division of Oncology Products 2 concurred with the findings of OPDP's promotional assessment of the proposed name.

2.2 SAFETY ASSESSMENT

The following aspects of the name were considered in the overall evaluation.

2.2.1 United States Adopted Names (USAN) SEARCH

On February 10, 2012 the United States Adopted Name (USAN) stem search, identified that a USAN stem is not present in the proposed proprietary name.

2.2.2 Components of the Proposed Proprietary Name

This proprietary name is comprised of a single word that does not contain any components such as a modifier, route of administration, or dosage form that is misleading or can contribute to medication error. The Applicant notes in their submission that the derivation of the proprietary name has no intended reference to a proposed indication or usage setting.

2.2.3 FDA Name Simulation Studies

Thirty-five practitioners participated in DMEPA's prescription studies. One prescription study name, (b) (4) is a direct match to a currently trademarked name with the US Patent and Trademark Office (USPTO) that was identified by the FDA (see Table 1). Our evaluation of this name can be found in Appendix E. Thirty-one out of thirty-five participants interpreted the written or verbal prescription correctly. The most common misinterpretation was the letter "S" and "X" for the letter "Z" in the voice study. See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

2.24 Comments from Other Review Disciplines

In response to the OSE, December 13, 2011 e-mail, the Division of Oncology Products 2 (DOP2) did not forward any comments or concerns relating to the proposed name at the initial phase of the proprietary name review.

2.2.5 Failure Mode and Effects Analysis of Similar Names

Appendix B lists possible orthographic and phonetic misinterpretations of the letters appearing in the proposed proprietary name Zaltrap. Table 1 lists the names with orthographic, phonetic, or spelling similarity to the proposed proprietary name, Zaltrap, identified by the primary reviewer, the Expert Panel Discussion (EPD), and other review disciplines. Table 1 also includes the names identified from the FDA Prescription Simulation.

Table 1: Collective List of Potentially Similar Names (DMEPA, EPD, Other Disciplines, FDA Name Simulation Studies, and External Name Study if applicable)

Look Similar				Look and Sound Similar	
Name	***Source***	***Name***	***Source***	***Name***	***Source***
(b) (4)***	FDA	Zanaflex	FDA	Zelboraf	FDA
Altatapp	FDA	Zantac	FDA	Zentrip	FDA
Betatrex	FDA	Zantryl	FDA	Zaltrap***	FDA
Liotrix	FDA	Zelapar	FDA	(b) (4)***	FDA
Lotapp	FDA	Zeldox	FDA		
Lotrel	FDA	Zoladex	FDA		
Multaq	FDA	Zolinza	FDA		
Salitop	FDA	Zoloft	FDA		
Silapap	FDA	Zolpidem	FDA		
Siltrax	FDA	Zolyse	FDA		
Teldrin	FDA	Zometa	FDA		
Tetracap	FDA	Zomig	FDA		
Val Tran	FDA	Zyvox	FDA		
Valstar	FDA				
Valtrex	FDA				
Valtropin	FDA				
Valtrum	FDA				
Xalkori	FDA				
Zactran	FDA				
(b) (4)***	FDA				
Zaleplon	FDA				
Zalestra	FDA				
(b) (4)***	FDA				

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Our analysis of the 40 names contained in Table 1 considered the information obtained in the previous sections along with their product characteristics. We determined all 40 names will not pose a risk for confusion as described in Appendix D through F.

2.2.6 Communication of DMEPA's Final Decision to Other Disciplines

DMEPA communicated our findings to the Division of Oncology Products 2 via e-mail on January 9, 2012. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from the Division of Oncology Products 2 on February 13, 2012 they stated no additional concerns with the proposed proprietary name, Zaltrap.

3 CONCLUSIONS

The proposed proprietary name is acceptable from both a promotional and safety perspective. The proposed proprietary name, Zaltrap, must be re-reviewed 90 days before approval of the BLA.

If you have further questions or need clarifications, please contact Sue Kang, OSE project manager, at 301-796-4216.

3.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Zaltrap, and have concluded that this name is acceptable. However, if any of the proposed product characteristics as stated in your February 2, 2012 submission are altered, DMEPA rescinds this finding and the name must be resubmitted for review. Additionally, this proprietary name must be re-evaluated 90 days prior to the approval of the application. The conclusions upon re-review are subject to change.

4 REFERENCES

1. ***Micromedex Integrated Index (http://csi.micromedex.com)***

   Micromedex contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

2. ***Phonetic and Orthographic Computer Analysis (POCA)***

   POCA is a database which was created for the Division of Medication Error Prevention and Analysis, FDA. As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion.

3. ***Drug Facts and Comparisons, online version, St. Louis, MO (http://factsandcomparisons.com)***

   Drug Facts and Comparisons is a compendium organized by therapeutic course; it contains monographs on prescription and OTC drugs, with charts comparing similar products. This database also lists the orphan drugs.

4. ***FDA Document Archiving, Reporting & Regulatory Tracking System [DARRTS]***

   DARRTS is a government database used to organize Applicant and Sponsor submissions as well as to store and organize assignments, reviews, and communications from the review divisions.

5. ***Division of Medication Errors Prevention and Analysis proprietary name consultation requests***

   This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

6. ***Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)***

   Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and "Chemical Type 6" approvals.

7. ***U.S. Patent and Trademark Office (http://www.uspto.gov)***

   USPTO provides information regarding patent and trademarks.

8. ***Clinical Pharmacology Online (www.clinicalpharmacology-ip.com)***

   Clinical Pharmacology contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common,

combination, nutraceutical and nutritional products. It also provides a keyword search engine.

9. ***Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at (www.thomson-thomson.com)***

   The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and trade names that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

10. ***Natural Medicines Comprehensive Databases (www.naturaldatabase.com)***

    Natural Medicines contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

11. ***Access Medicine (www.accessmedicine.com)***

    Access Medicine® from McGraw-Hill contains full-text information from approximately 60 titles; it includes tables and references. Among the titles are: Harrison's Principles of Internal Medicine, Basic & Clinical Pharmacology, and Goodman and Gilman's The Pharmacologic Basis of Therapeutics.

12. ***USAN Stems (http://www.ama-assn.org/ama/pub/about-ama/our-people/coalitions-consortiums/united-states-adopted-names-council/naming-guidelines/approved-stems.shtml)***

    USAN Stems List contains all the recognized USAN stems.

13. ***Red Book Pharmacy's Fundamental Reference***

    Red Book contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

14. ***Lexi-Comp (www.lexi.com)***

    Lexi-Comp is a web-based searchable version of the Drug Information Handbook.

15. ***Medical Abbreviations Book***

    Medical Abbreviations Book contains commonly used medical abbreviations and their definitions.

16. ***CVS/Pharmacy (www.CVS.com)***

    This database contains commonly used over the counter products not usually identified in other databases.

17. ***Walgreens (www.walgreens.com)***

    This database contains commonly used over the counter products not usually identified in other databases.

18. Rx List (www.rxlist.com)

RxList is an online medical resource dedicated to offering detailed and current pharmaceutical information on brand and generic drugs.

19. Dogpile (www.dogpile.com)

Dogpile is a Metasearch engine that searches multiple search engines including Google, Yahoo! and Bing, and returns the most relevant results to the search.

20. OSE Reviews

Toliver, Kristina. OSE Review 2010-1837: Proprietary Name Review for Zaltrap, November 30, 2010.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment considers the promotional and safety aspects of a proposed proprietary name. The promotional review of the proposed name is conducted by OPDP. OPDP evaluates proposed proprietary names to determine if they are overly fanciful, so as to misleadingly imply unique effectiveness or composition, as well as to assess whether they contribute to overstatement of product efficacy, minimization of risk, broadening of product indications, or making of unsubstantiated superiority claims. OPDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.

The safety assessment is conducted by DMEPA. DMEPA staff search a standard set of databases and information sources to identify names that are similar in pronunciation, spelling, and orthographically similar when scripted to the proposed proprietary name. Additionally, we consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.). DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

Following the preliminary screening of the proposed proprietary name, DMEPA gathers to discuss their professional opinions on the safety of the proposed proprietary name. This meeting is commonly referred to the Center for Drug Evaluation and Research (CDER) Expert Panel discussion. DMEPA also considers other aspects of the name that may be misleading from a safety perspective. DMEPA staff conducts a prescription simulation studies using FDA health care professionals. When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name and misleading nature of the proposed proprietary name with a focus on the avoidance of medication errors.

DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting where the product is likely to be used based on the characteristics of the proposed product. DMEPA considers the product characteristics associated with the proposed product throughout the risk assessment because the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

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[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www nccmerp.org/aboutMedErrors html. Last accessed 10/11/2007.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed proprietary name include, but are not limited to; established name of the proposed product, proposed indication of use, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. DMEPA considers how these product characteristics may or may not be present in communicating a product name throughout the medication use system. Because drug name confusion can occur at any point in the medication use process, DMEPA considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.[2]

The DMEPA considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA compares the proposed proprietary name with the proprietary and established name of existing and proposed drug products and names currently under review at the FDA. DMEPA compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names because verbal communication of medication names is common in clinical settings. DMEPA examines the phonetic similarity using patterns of speech. If provided, DMEPA will consider the Sponsor's intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Sponsor has little control over how the name will be spoken in clinical practice. The orthographic appearance of the proposed name is evaluated using a number of different handwriting samples. DMEPA applies expertise gained from root-cause analysis of post marketing medication errors to identify sources of ambiguity within the name that could be introduced when scripting (e.g.,"T" may look like "F," lower case 'a' looks like a lower case 'u,' etc). Additionally, other orthographic attributes that determine the overall appearance of the drug name when scripted (see Table 1 below for details).

[2] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

Table 1. Criteria Used to Identify Drug Names that Look- or Sound-Similar to a Proposed Proprietary Name.

Type of Similarity	**Considerations when Searching the Databases**		
	Potential Causes of Drug Name Similarity	*Attributes Examined to Identify Similar Drug Names*	*Potential Effects*
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	• Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication • Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name/Similar shape Upstrokes Down strokes Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	• Names may look similar when scripted, and lead to drug name confusion in written communication
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	• Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Lastly, DMEPA considers the potential for the proposed proprietary name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. Consequently, DMEPA considers and evaluates these broader safety implications of the name throughout this assessment and the medication error staff provides additional comments related to the

safety of the proposed proprietary name or product based on professional experience with medication errors.

1. Database and Information Sources

DMEPA searches the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to the proposed proprietary name. A standard description of the databases used in the searches is provided in the reference section of this review. To complement the process, the DMEPA uses a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, DMEPA reviews the USAN stem list to determine if any USAN stems are present within the proprietary name. The individual findings of multiple safety evaluators are pooled and presented to the CDER Expert Panel. DMEPA also evaluates if there are characteristics included in the composition that may render the name unacceptable from a safety perspective (abbreviation, dosing interval, etc.).

2. Expert Panel Discussion

DMEPA gathers gather CDER professional opinions on the safety of the proposed product and discussed the proposed proprietary name (Expert Panel Discussion). The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Division of Drug Marketing, Advertising, and Communications (OPDP). We also consider input from other review disciplines (OND, ONDQA/OBP). The Expert Panel also discusses potential concerns regarding drug marketing and promotion related to the proposed names.

The primary Safety Evaluator presents the pooled results of the database and information searches to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend additional names, additional searches by the primary Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

3. FDA Prescription Simulation Studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically

scanned and one prescription is delivered to a random sample of participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants record their interpretations of the orders which are recorded electronically.

4. Comments from Other Review Disciplines

DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA's final decision on the proposed name.

Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

5. Safety Evaluator Risk Assessment of the Proposed Proprietary Name

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, considers all aspects of the name that may be misleading or confusing, conducts a Failure Mode and Effects Analysis, and provides an overall decision on acceptability dependent on their risk assessment of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.[3] When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed proprietary name to be confused with another drug name because of name confusion and, thereby, cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to orthographically or phonetically similar drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the primary Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is has not been marketed, the primary Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product

[3] Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

characteristics listed in Section 1.2 of this review. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, Expert Panel Discussion, and prescription studies, external studies, and identifies potential failure modes by asking:

> ***"Is the proposed proprietary name convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting? And Are there any components of the name that may function as a source of error beyond sound/look-alike"***

An affirmative answer indicates a failure mode and represents a potential for the proposed proprietary name to be confused with another proprietary or established drug name because of look- or sound-alike similarity or because of some other component of the name. If the answer to the question is no, the Safety Evaluator is not convinced that the names posses similarity that would cause confusion at any point in the medication use system, thus the name is eliminated from further review.

In the second stage of the Risk Assessment, the primary Safety Evaluator evaluates all potential failure modes to determine the likely *effect* of the drug name confusion, by asking:

> ***"Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?"***

The answer to this question is a central component of the Safety Evaluator's overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would not ultimately be a source of medication errors in the usual practice setting, the primary Safety Evaluator eliminates the name from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend the use of an alternate proprietary name.

Moreover, DMEPA will object to the use of proposed proprietary name when the primary Safety Evaluator identifies one or more of the following conditions in the Overall Risk Assessment:

a. OPDP finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with OPDP's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].

b. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].

c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.

d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.

e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product but involve a naming characteristic that when incorporated into a proprietary name, may be confusing, misleading, cause or contribute to medication errors.

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA generally recommends that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name. In that instance, DMEPA may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEPA will provide a contingency objection based on the date of approval. Whichever product, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

The threshold set for objection to the proposed proprietary name may seem low to the Applicant/Sponsor. However, the safety concerns set forth in criteria a through e above are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), the Joint Commission, and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names, confusing, or misleading names and called for regulatory authorities to address the issue prior to approval. Additionally, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and preventable source of medication error that, in many instances, the Agency and/or Sponsor can identify and rectify prior to approval to avoid patient harm.

Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors involving drug name confusion. Sponsors have undertaken higher-leverage strategies, such as drug name changes, in the

past but at great financial cost to the Sponsor and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Sponsors' have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioners' vocabulary, and as a result, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval.

Appendix B: Letters with Possible Orthographic or Phonetic Misinterpretation

Letters in Name, NAME	Scripted May Appear as	Spoken May Be Interpreted as
Capital 'Z'	B, X, L, M, T, S, V	C, S, X
lowercase 'z'	g, n, r, m, s, v	c, s, x
Lowercase 'a'	el, ci, cl, d, o, u	Any vowel
Lowercase 'l'	b, e, i, t, d	none
Lowercase 't'	f, l, x	d
Lowercase 'r'	s, n, e, v	none
Lowercase 'a'	el, ci, cl, d, o, u	Any vowel
Lowercase 'p'	yn, ys, g, j, q	b

Appendix C: Prescription Simulation Samples and Results

Figure 1. Zaltrap Study (Conducted on December 12, 2011)

Handwritten Requisition Medication Order	Verbal Prescription
Medication Order: Zaltrap 300mg intravenously over 1 hour x1	Zaltrap 8 mL vial #2 Bring to Infusion Center

Outpatient Prescription:	
Zaltrap 8mL vial #2 to outpatient infusion center	

FDA Prescription Simulation Responses

INPATIENT MEDICATION ORDER	VOICE PRESCRIPTION	OUTPATIENT PERSCRIPTION
ZALTRAP (14)	SALTRAP (1)	ZALTRAP (10)
ZALTRAYS (1)	XALTRAP (1)	
	ZALTRAP (7)	
	ZELTRAP (1)	

Appendix D: Proprietary names determined in OSE Review 2010-1837 not likely to lead to a medication error.

Proprietary Name	Active Ingredient	Similarity to Zaltrap
Valtrex	Valacyclovir	Look and Sound
Valtropin	Somatropin	Look
	Zaleplon	Look
Zantac	Ranitidine	Look
Zentrip	Meclizine	Look and Sound
Zolinza	Vorinostat	Look
Zoloft	Sertraline	Look

Appendix E: Proprietary names not likely to be confused or not used in usual practice settings for the reasons described.

Proprietary Name	Active Ingredient	Similarity to Zaltrap	Failure preventions
			(b) (4)
Betatrex	Betamethasone Valerate	Look	Lack of convincing orthographic similarity
Liotrix	Active ingredient for Euthroid	Look	Lack of convincing orthographic similarity
Lotapp	Brompheniramine/ phenylpropanolamine	Look	As of November 2000, the United States Food and Drug Administration (FDA) has recommended the removal of phenylpropanolamine from all drug products due to a public health advisory concerning the risk of hemorrhagic stroke associated with its use. The only source this name is located in is Red Book. The electronic version marks its status as "Inactive"
Lotrel	Amlodipine/ Benazepril	Look	Lack of convincing orthographic similarity
Silapap	Acetaminophen	Look	Lack of convincing orthographic similarity
Siltrax	Epinephrine	Look	Coated cotton cord soaked in epinephrine and used in dental extraction procedures. Based on the different practice settings, it is unlikely that confusion will occur with the proposed name.
Zactran	Gamithromycin	Look	Antibiotic approved for use in animals
			(b) (4)
Zanaflex	Tizanidine	Look	Lack of convincing orthographic similarity
Zantryl	Phentermine	Look	Lack of convincing orthographic similarity
Zometa	Zoledronic acid	Look	Lack of convincing orthographic similarity
Zomig	Zolmitriptan	Look	Lack of convincing orthographic similarity
Zyvox	Linezolid	Look	Lack of convincing orthographic similarity
			(b) (4)

*** This document contains proprietary and confidential information that should not be released to the public.

Proprietary Name	Active Ingredient	Similarity to Zaltrap	Failure preventions
			(b) (4)
Val-Tran	Valerian extract, Vitamin B6, Magnesium Gluconate, Magnesium Oxide	Look	Herbal supplement that is used as a sleep aid. This product will unlikely be written on prescription orders.
Zalestra	Green Tea Extract	Look	Herbal supplement with multiple uses. This product will unlikely be written on prescription orders.
Zaltrap***	Aflibercept	Look and Sound	Trademarked by Regeneron Pharmaceuticals. Regeneron is a partner in developing this drug product with Sanofi-Aventis, who is the Applicant for this NDA

*** This document contains proprietary and confidential information that should not be released to the public.

Appendix F: Risk of medication errors due to product confusion minimized by dissimilarity of the names and/ or use in clinical practice for the reasons described.

Zaltrap **(Aflibercept) Injection**	**100 mg/4 mL and 200 mg/8 mL** **25 mg/mL**	**4 mg/kg via Intravenous Infusion Once Every Two Weeks**
Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion	**Causes**	**Prevention of Failure Mode**
Multaq (Dronedarone) Tablet 400mg Usual Dose 400 mg orally twice daily with morning and evening meals	Orthographic Both names begin with similar letter strings 'Mul' and 'Zal' Both names have similar letter strings at the end of each name 'aq' and 'ap' Dose 400 mg vs. 160 mg to 600 mg based on weight	Frequency of Administration Twice daily vs. Once every two weeks Storage Room Temperature vs. Refrigerator
Salitop (Salicylic acid) 6% Cream and 6% Lotion Usual Dose Apply to affected area at night; place under occlusion and wash off in the morning.	Orthographic Both names contain the letter string 'al' in the same location. Also, the letter strings 'top' and 'trap' look similar when scripted.	Orthographic The first letter 'S' in Salitop is unlikely to be confused with the first letter 'Z' in Zaltrap when scripted. Frequency of Administration Once daily at night vs. Once every two weeks Dose Apply cream as directed vs. 160 mg to 600 mg based on weight Storage Room Temperature vs. Refrigerator

Zaltrap (Aflibercept) Injection	100 mg/4 mL and 200 mg/8 mL 25 mg/mL	4 mg/kg via Intravenous Infusion Once Every Two Weeks
Altatapp (Brompheniramine/Pseudoephedrine) Elixir 2 mg/5 mL – 12.5 mg/5 mL Usual Dose 6-11 years old: 10 mL every 6 hours 12 years and older: 20 mL every 6 hours	Orthographic Both names have the letter string 'alt' in similar locations Both names have a 't' and 'p' in similar locations	Orthographic The first letter 'A' in Altatapp is unlikely to be confused with the first letter 'Z' in Zaltrap when scripted. Frequency of Administration Every 6 hours vs. Once every two weeks Dose 10 to 20 mL or 4 mg/25 mg to 8 mg/50 mg vs. 160 mg to 600 mg based on weight Storage Room Temperature vs. Refrigerator
Teldrin (Chlorpheniramine) Tablet 4 mg Usual Dose Children 6-11 years old: 2 mg orally every 4-6 hours Children 12 years and older and Adults: 4 mg orally every 4-6 hours	Orthographic Both names begin with similar letter strings 'Teld' and 'Zalt'	Orthographic The last letter 'n' in Teldrin does not have a down stroke where the last letter 'p' in Zaltrap has a down stroke. The second to last letter 'i' in Teldrin has a raised dot when scripted while the second to last letter 'a' in Zaltrap does not. The fourth letter 'd' in Teldrin does not have a cross stroke when compared to the fourth letter 't' in Zaltrap Frequency of Administration Every 4 to 6 hours vs. Once every two weeks Dose 2 to 4 mg vs. 160 mg to 600 mg based on weight Storage Room Temperature vs. Refrigerator

Zaltrap (Aflibercept) Injection	100 mg/4 mL and 200 mg/8 mL 25 mg/mL	4 mg/kg via Intravenous Infusion Once Every Two Weeks
Tetracap (Tetracycline hydrochloride) Capsule 250 mg Usual Dose Children 8 years or older: 250 mg three times daily to 500 mg four times daily Adults: 500 mg twice daily to 500 mg four times daily	Orthographic Both names begin with similar letter strings 'Tet' and 'Zal' Both names have the same letter strings at the end of each name 'ap' Dose 250 to 500 mg vs. 160 mg to 600 mg based on weight	Orthographic The third and fourth letters 'tr' in Tetracap have only one up stroke while the third and fourth letter 'lt' in Zaltrap have two up stroke letters. Frequency of Administration Twice a day to four times per day vs. Once every two weeks Storage Room Temperature vs. Refrigerator
Valstar (Valrubicin) Intravesical Instillation Vial 200 mg/5 mL Usual Dose 800 mg intravesically weekly for 6 weeks	Orthographic Both names begin with similar letter strings 'Val' and 'Zal' Storage Both are stored in the refrigerator Setting Both products are used in oncology	Orthographic The last letter 'r' in Valstar does not have a down stroke where the last letter 'p' in Zaltrap has a down stroke. Valstar has the letter 's' between the letters 'l' and 't', Zaltrap does not have a letter between 'l' and 't'. The last letter 'p' in Zaltrap has a down stroke when scripted. The last letter 'r' in Valstar does not have a down stroke when scripted. Frequency of Administration Once weekly vs. every two weeks Dose Fixed 800 mg dose vs. 160 mg to 600 mg based on weight

Zaltrap (Aflibercept) Injection	100 mg/4 mL and 200 mg/8 mL 25 mg/mL	4 mg/kg via Intravenous Infusion Once Every Two Weeks
Valtrum (Camphor 3%/Menthol 3%) Ointment Usual Dose Apply to affected area every 6 hours	Orthographic Both names begin with similar letter strings 'Valtr' and 'Zaltr'	Orthographic The last letter 'p' in Zaltrap has a down stroke when scripted. The last letter 'm' in Valtrum does not have a down stroke when scripted. Frequency of Administration Every 6 hours vs. Once every two weeks Dose Apply to affected area as directed vs. 160 mg to 600 mg based on weight Storage Room Temperature vs. Refrigerator
Xalkori (Crizotinib) Capsule 200 mg and 250 mg Usual Dose 250 mg twice daily	Orthographic Both names begin with similar letter strings 'Xal' and 'Zal' Setting Both products are used in oncology Dose 250 mg twice daily vs. 160 mg to 600 mg based on weight	Orthographic The last letter 'p' in Zaltrap has a down stroke when scripted. Frequency of Administration Twice daily vs. Once every two weeks Storage Room Temperature vs. Refrigerator

Zaltrap (Aflibercept) Injection	100 mg/4 mL and 200 mg/8 mL 25 mg/mL	4 mg/kg via Intravenous Infusion Once Every Two Weeks
Zelapar (Selegiline) Oral Disintegrating tablet (ODT) 1.25 mg Usual Dose 1.25 mg to 2.5 mg daily	Orthographic Both names begin with similar letter strings 'Zel' and 'Zal'	Orthographic The fourth letter 't' in Zaltrap has an up stroke. The fourth letter 'a' in Zelapar does not have an up stroke. The last letter 'p' in Zaltrap has a down stroke when scripted. The last letter 'r' in Zelapar does not have a down stroke when scripted. Frequency of Administration Once daily vs. Once every two weeks Storage Room Temperature vs. Refrigerator Dose 1.25 mg to 2.5 mg vs. 160 mg to 600 mg based on weight
Zelboraf (Vemurafenib) Tablet 240 mg Usual Dose 960 mg twice daily 720 mg twice daily 480 mg twice daily	Orthographic Both names begin with similar letter strings 'Zel' and 'Zal' Phonetic The letter string 'zel' and 'zal' sound similar when spoken Setting Both products are used in oncology Dose 480 mg and 720 mg vs. 160 mg to 600 mg based on weight	Frequency of Administration Twice daily vs. Once every two weeks Storage Room Temperature vs. Refrigerator Phonetic Zelboraf has three syllables when spoken while Zaltrap has two syllables when spoken. The letter string 'boraf' in Zelboraf does not sound similar to 'trap' in Zaltrap when spoken.

Zaltrap (Aflibercept) Injection	100 mg/4 mL and 200 mg/8 mL 25 mg/mL	4 mg/kg via Intravenous Infusion Once Every Two Weeks
Zeldox (Ziprasidone) - Canadian Brand Name Capsule: 20 mg, 40 mg, 60 mg, 80 mg Injection: 20 mg powder for injection Usual Dose Oral: 20 mg to 80 mg daily Injection: 10 mg to 20 mg every 2 to 4 hours. Max 40 mg per day	Both names begin with similar letter strings 'Zel' and 'Zal'	Frequency of Administration Once daily or Every 2 to 4 hours vs. Once every two weeks Dose 20 mg to 80 mg vs. 160 mg to 600 mg based on weight Storage Room Temperature vs. Refrigerator Orthographic The last letter 'p' in Zaltrap has a down stroke. The last letter 'x' in Zeldox does not have a down stroke.
Zoladex (Goserelin) Injection for Implant 3.6 mg monthly implant, 10.8 mg 3 month implant Usual Dose 3.6 mg every month or 10.8 mg every 3 months	Orthographic Both names begin with similar letter strings 'Zol' and 'Zal' Setting Both products are used in oncology	Frequency of Administration Every month or Every 3 months vs. Once every two weeks Dose 3.6 mg or 10.8 mg vs. 160 mg to 600 mg based on weight Storage Room Temperature vs. Refrigerator Orthographic The last letter 'p' in Zaltrap has a down stroke. The last letter 'x' in Zoladex does not have a down stroke.

Zaltrap (Aflibercept) Injection	100 mg/4 mL and 200 mg/8 mL 25 mg/mL	4 mg/kg via Intravenous Infusion Once Every Two Weeks
Zolpidem (Ambien) Tablet (Sublingual, Biphasic) and Spray Tablet: 5 mg, 6.25 mg, 10 mg, 12.5 mg Oral Mucosal Spray: 5 mg per actuation Usual Dose 5 mg to 12.5 mg or 1 to 2 sprays daily at bedtime	Orthographic Both names begin with similar letter strings 'Zol' and 'Zal'	Frequency of Administration Once daily at bedtime vs. Once every two weeks Dose 5 mg to 12.5 mg or 1 to 2 sprays vs. 160 mg to 600 mg based on weight Storage Room Temperature vs. Refrigerator Orthographic The fourth letter 'p' in Zolpidem has a down stroke. The fourth letter 't' in Zaltrap has an upstroke. The last letter 'p' in Zaltrap has a down stroke where the last letter 'm' in Zolpidem does not.
Zolyse (Chymotrypsin) Ophthalmic Solution for Injection 750 Units per vial; 150 units/mL after reconstitution Usual Dose 0.25 mL to 2 mL or 37.5 mg to 300 mg once via irrigation to the eye during eye surgery	Orthographic Both names begin with similar letter strings 'Zol' and 'Zal'	Orthographic The fourth letter 't' in Zaltrap has an upstroke. The fourth letter 'y' in Zolyse has a down stroke. The last letter 'p' in Zaltrap has a down stroke when scripted. The last letter 'e' in Zolyse does not have a down stroke when scripted. Frequency of Administration Once during eye surgery vs. Once every two weeks Storage Room Temperature vs. Refrigerator

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/s/

JAMES H SCHLICK
02/14/2012

TODD D BRIDGES
02/14/2012

CAROL A HOLQUIST
02/14/2012

DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 6 November 2001

on the Community code relating to medicinal products for human use

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Having regard to the proposal from the Commission;

Having regard to the opinion of the Economic and Social Committee [1],

Acting in accordance with the procedure laid down in Article 251 of the Treaty [2],

Whereas:

(1) — Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products [3], Council Directive 75/318/EEC of 20 May 1975 on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products [4], Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products [5], Council Directive 89/342/EEC of 3 May 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC and laying down additional provisions for immunological medicinal products consisting of vaccines, toxins or serums and allergens [6], Council Directive 89/343/EEC of 3 May 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC and laying down additional provisions for radiopharmaceuticals [7], Council Directive 89/381/EEC of 14 June 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products and laying down special provisions for proprietary medicinal products derived from human blood or human plasma [8], Council Directive 92/25/EEC of 31 March 1992 on the wholesale distribution of medicinal products for human use [9], Council Directive 92/26/EEC of 31 March 1992 concerning the classification for the supply of medicinal products for human use [10], Council Directive 92/27/EEC of 31 March 1992 on the labelling of medicinal products for human use and on package leaflets [11], Council Directive 92/28/EEC of 31 March 1992 on the advertising of medicinal products for human use [12], Council Directive 92/73/EEC of 22 September 1992 widening the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products and laying down additional provisions on homeopathic medicinal products [13] have been frequently and substantially amended. In the interests of clarity and rationality, the said Directives should therefore be codified by assembling them in a single text.

(2) — The essential aim of any rules governing the production, distribution and use of medicinal products must be to safeguard public health.

(3) — However, this objective must be attained by means which will not hinder the development of the pharmaceutical industry or trade in medicinal products within the Community.

(4) — Trade in medicinal products within the Community is hindered by disparities between certain national provisions, in particular between provisions relating to medicinal products (excluding substances or combinations of substances which are foods, animal feeding-stuffs or toilet preparations), and such disparities directly affect the functioning of the internal market.

(5) — Such hindrances must accordingly be removed; whereas this entails approximation of the relevant provisions.

(6) — In order to reduce the disparities which remain, rules should be laid down on the control of medicinal products and the duties incumbent upon the Member States' competent authorities should be specified with a view to ensuring compliance with legal requirements.

(1) OJ C 368, 20.12.1999, p. 3.
(2) Opinion of the European Parliament of 3 July 2001 (not yet published in the Official Journal) and Council Decision of 27 September 2001.
(3) OJ 22, 9.2.1965, p. 369/65. Directive as last amended by Directive 93/39/EEC (OJ L 214, 24.8.1993, p. 22).
(4) OJ L 147, 9.6.1975, p. 1. Directive as last amended by Commission Directive 1999/83/EC (OJ L 243, 15.9.1999, p. 9).
(5) OJ L 147, 9.6.1975, p. 13. Directive as last amended by Commission Directive 2000/38/EC (OJ L 139, 10.6.2000, p. 28).
(6) OJ L 142, 25.5.1989, p. 14.
(7) OJ L 142, 25.5.1989, p. 16.
(8) OJ L 181, 28.6.1989, p. 44.
(9) OJ L 113, 30.4.1992, p. 1.
(10) OJ L 113, 30.4.1992, p. 5.
(11) OJ L 113, 30.4.1992, p. 8.
(12) OJ L 113, 30.4.1992, p. 13.
(13) OJ L 297, 13.10.1992, p. 8.

(7) The concepts of harmfulness and therapeutic efficacy can only be examined in relation to each other and have only a relative significance depending on the progress of scientific knowledge and the use for which the medicinal product is intended. The particulars and documents which must accompany an application for marketing authorization for a medicinal product demonstrate that potential risks are outweighed by the therapeutic efficacy of the product.

(8) Standards and protocols for the performance of tests and trials on medicinal products are an effective means of control of these products and hence of protecting public health and can facilitate the movement of these products by laying down uniform rules applicable to tests and trials, the compilation of dossiers and the examination of applications.

(9) Experience has shown that it is advisable to stipulate more precisely the cases in which the results of toxicological and pharmacological tests or clinical trials do not have to be provided with a view to obtaining authorization for a medicinal product which is essentially similar to an authorized product, while ensuring that innovative firms are not placed at a disadvantage.

(10) However, there are reasons of public policy for not conducting repetitive tests on humans or animals without over-riding cause.

(11) The adoption of the same standards and protocols by all the Member States will enable the competent authorities to arrive at their decisions on the basis of uniform tests and by reference to uniform criteria and will therefore help to avoid differences in evaluation.

(12) With the exception of those medicinal products which are subject to the centralized Community authorization procedure established by Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products [1] a marketing authorization for a medicinal product granted by a competent authority in one Member State ought to be recognized by the competent authorities of the other Member States unless there are serious grounds for supposing that the authorization of the medicinal product concerned may present a risk to public health. In the event of a disagreement between Member States about the quality, the safety or the efficacy of a medicinal product, a scientific evaluation of the matter should be undertaken according to a Community standard, leading to a single decision on the area of disagreement binding on the Member States concerned. Whereas this decision should be adopted by a rapid procedure ensuring close cooperation between the Commission and the Member States.

(13) For this purpose, a Committee for Proprietary Medicinal Products should be set up attached to the European Agency for the Evaluation of Medicinal Products established in the abovementioned Regulation (EEC) No 2309/93.

(14) This Directive represents an important step towards achievement of the objective of the free movement of medicinal products. Further measures may abolish any remaining barriers to the free movement of proprietary medicinal products will be necessary in the light of experience gained, particularly in the abovementioned Committee for Proprietary Medicinal Products.

(15) In order better to protect public health and avoid any unnecessary duplication of effort during the examination of application for a marketing authorization for medicinal products, Member States should systematically prepare assessment reports in respect of each medicinal product which is authorized by them, and exchange the reports upon request. Furthermore, a Member State should be able to suspend the examination of an application for authorization to place a medicinal product on the market which is currently under active consideration in another Member State with a view to recognizing the decision reached by the latter Member State.

(16) Following the establishment of the internal market, specific controls to guarantee the quality of medicinal products imported from third countries can be waived only if appropriate arrangements have been made by the Community to ensure that the necessary controls are carried out in the exporting country.

(17) It is necessary to adopt specific provisions for immunological medicinal products, homeopathic medicinal products, radiopharmaceuticals, and medicinal products based on human blood or human plasma.

(18) Any rules governing radiopharmaceuticals must take into account the provisions of Council Directive 84/466/Euratom of 3 September 1984 laying down basic measures for the radiation protection of persons undergoing medical examination or treatment [2]. Account should also be taken of Council Directive 80/836/Euratom of 15 July 1980 amending the Directives laying down the basic safety standards for the health protection of the general public and workers

[1] OJ L 214, 24.8.1993, p. 1. Regulation as amended by Commission Regulation (EC) No 649/98 (OJ L 88, 24.3.1998, p. 7).

[2] OJ L 265, 5.10.1984, p. 1. Directive repealed with effect from 13 May 2000 by Directive 97/43/Euratom (OJ L 180, 9.7.1997, p. 22).

against—the—dangers—of—ionizing—radiation ([1]),—the—objective of which is to prevent the exposure of workers—or patients to excessive or unnecessarily high—levels of—ionizing—radiation,—and—in—particular—of—Article—5c—thereof,—which—requires—prior—authorization—for—the—addition of radioactive substances to medicinal products—as—well—as—for—the—importation—of—such—medicinal—products.—

(19) — The—Community—entirely—supports—the—efforts—of—the—Council of Europe to promote voluntary unpaid—blood—and— plasma— donation— to— attain— self-sufficiency—throughout—the—Community—in—the—supply—of—blood—products, and to ensure respect for ethical principles in—trade in therapeutic substances of human origin.—

(20) — The rules designed to guarantee the quality, safety—and—efficacy—of—medicinal—products—derived—from—human—blood—or—human—plasma—must—be—applied—in—the—same—manner to both public and private establishments,—and—to blood and plasma imported from third countries.—

(21) — Having—regard—to the particular—characteristics—of—these—homeopathic medicinal products, such as the very low—level of active principles they contain and the difficulty—of applying to them the conventional statistical methods—relating—to—clinical—trials,—it—is—desirable—to—provide—a—special,—simplified—registration—procedure—for—those—homeopathic—medicinal—products—which—are—placed—on—the—market—without—therapeutic—indications—in—a—pharmaceutical form and dosage which do not present a—risk for the patient.—

(22) — The anthroposophic medicinal products described in an—official pharmacopoeia and prepared by a homeopathic—method—are—to—be—treated,—as—regards—registration—and—marketing— authorization,— in— the— same— way— as—homeopathic medicinal products.—

(23) — It—is—desirable—in—the—first—instance—to—provide—users—of—these homeopathic medicinal products with a very clear—indication—of—their—homeopathic—character—and—with—sufficient guarantees of their quality and safety.—

(24) — The—rules—relating—to—the—manufacture,—control—and—inspection of homeopathic medicinal products must be—harmonized—to—permit—the—circulation—throughout—the—Community of medicinal products which are safe and of—good quality.—

(25) — The usual rules governing the—authorization—to market—medicinal—products—should—be—applied—to—homeopathic—medicinal—products—placed—on—the—market—with—therapeutic indications or in a form which may present—risks—which—must—be—balanced—against—the—desired—therapeutic—effect.—In—particular,—those—Member—States—which have a homeopathic tradition should be able to—apply particular rules for the evaluation of the results of—tests—and—trials—intended—to—establish—the—safety—and—efficacy of these medicinal products provided—that they—notify them to the Commission.—

(26) — In—order—to—facilitate—the—movement—of—medicinal—products and to prevent the controls carried out in one—Member—State—from—being—repeated—in—another,—minimum—requirements—should—be—laid—down—for—manufacture—and—imports—coming—from—third—countries—and for the grant of the authorization relating thereto.—

(27) — It—should—be—ensured—that,—in—the—Member—States,—the—supervision and control of the manufacture of medicinal—products—is—carried—out—by—a—person—who—fulfils—minimum conditions of qualification.—

(28) — Before—an—authorization—to—market—an—immunological—medicinal—product—or—derived—from—human—blood—or—human plasma can be granted, the manufacturer must—demonstrate— his— ability— to— attain— batch-to-batch—consistency.—Before—an—authorization—to—market—a—medicinal product derived from human blood or human—plasma—can—be—granted,—the—manufacturer—must—also—demonstrate the absence of specific viral contamination,—to the extent that the state of technology permits.—

(29) — The—conditions—governing—the—supply—of—medicinal—products to the public should be harmonized.—

(30) — In—this—connection—persons—moving—around—within—the—Community—have—the—right—to—carry—a—reasonable—quantity—of—medicinal—products—lawfully—obtained—for—their personal use. It must also be possible for a person—established in one Member State to receive from another—Member—State—a—reasonable—quantity—of—medicinal—products intended for his personal use.—

(31) — In addition, by virtue of—Regulation (EC)—No—2309/93,—certain—medicinal—products—are—the—subject—of—a—Community—marketing—authorization.—In—this—context,—the—classification—for—the—supply—of—medicinal—products—covered by a Community marketing authorization needs—to—be—established.—It—is—therefore—important—to—set—the—criteria on the basis of which Community decisions will—be taken.—

(32) — It—is—therefore—appropriate,—as—an—initial—step,—to—harmonize—the—basic—principles—applicable—to—the—classification for the supply of medicinal products in the—Community—or—in—the—Member—State—concerned,—while—taking—as—a—starting—point—the—principles—already—established on this subject by the Council of Europe as—well as the work of harmonization completed within the—framework—of—the—United—Nations,—concerning—narcotic—and psychotropic substances.—

([1]) —OJ—L—246,—17.9.1980,—p.—1.—Directive—as—amended—by—Directive—84/467/Euratom (OJ L 265, 5.10.1984, p. 4), repealed with effect—from—13—May—2000—by—Directive—96/29/Euratom—(OJ—L—314,—4.12.1996, p. 20).—

(33) — The provisions dealing with the classification of medicinal products for the purpose of supply do not infringe the national social security arrangements for reimbursement or payment for medicinal products on prescription.—

(34) — Many operations involving the wholesale distribution of medicinal products for human use may cover several Member States simultaneously.—

(35) — It is necessary to exercise control over the entire chain of distribution of medicinal products, from their manufacture or import into the Community through to supply to the public, so as to guarantee that such products are stored, transported and handled in suitable conditions. The requirements which must be adopted for this purpose will considerably facilitate the withdrawal of defective products from the market and allow more effective efforts against counterfeit products.—

(36) — Any person involved in the wholesale distribution of medicinal products should be in possession of a special authorization. Pharmacists and persons authorized to supply medicinal products to the public, and who confine themselves to this activity, should be exempt from obtaining this authorization. It is however necessary, in order to control the complete chain of distribution of medicinal products, that pharmacists and persons authorized to supply medicinal products to the public keep records showing transactions in products received.—

(37) — Authorization must be subject to certain essential conditions and it is the responsibility of the Member State concerned to ensure that such conditions are met; whereas each Member State must recognize authorizations granted by other Member States.—

(38) — Certain Member States impose on wholesalers who supply medicinal products to pharmacists and on persons authorized to supply medicinal products to the public certain public service obligations. Those Member States must be able to continue to impose those obligations on wholesalers established within their territory. They must also be able to impose them on wholesalers in other Member States on condition that they do not impose any obligation more stringent than those which they impose on their own wholesalers and provided that such obligations may be regarded as warranted on grounds of public health protection and are proportionate in relation to the objective of such protection.—

(39) — Rules should be laid down as to how the labelling and package leaflets are to be presented.—

(40) — The provisions governing the information supplied to users should provide a high degree of consumer protection, in order that medicinal products may be used correctly on the basis of full and comprehensible information.—

(41) — The marketing of medicinal products whose labelling and package leaflets comply with this Directive should not be prohibited or impeded on grounds connected with the labelling or package leaflet.—

(42) — This Directive is without prejudice to the application of measures adopted pursuant to Council Directive 84/450/EEC of 10 September 1984 relating to the approximation of the laws, regulations and administrative provisions of the Member States concerning misleading advertising [1].—

(43) — All Member States have adopted further specific measures concerning the advertising of medicinal products. There are disparities between these measures. These disparities are likely to have an impact on the functioning of the internal market, since advertising disseminated in one Member State is likely to have effects in other Member States.—

(44) — Council Directive 89/552/EEC of 3 October 1989 on the coordination of certain provisions laid down by law, regulation or administrative action in Member States concerning the pursuit of television broadcasting activities [2] prohibits the television advertising of medicinal products which are available only on medical prescription in the Member State within whose jurisdiction the television broadcaster is located. This principle should be made of general application by extending it to other media.—

(45) — Advertising to the general public, even of non-prescription medicinal products, could affect public health, were it to be excessive and ill-considered. Advertising of medicinal products to the general public, where it is permitted, ought therefore to satisfy certain essential criteria which ought to be defined.—

(46) — Furthermore, distribution of samples free of charge to the general public for promotional ends must be prohibited.—

(47) — The advertising of medicinal products to persons qualified to prescribe or supply them contributes to the information available to such persons. Nevertheless, this advertising should be subject to strict conditions and effective monitoring, referring in particular to the work carried out within the framework of the Council of Europe.—

(48) — Advertising of medicinal products should be subject to effective, adequate monitoring. Reference in this regard should be made to the monitoring mechanisms set up by Directive 84/450/EEC.—

(49) — Medical sales representatives have an important role in the promotion of medicinal products. Therefore, certain obligations should be imposed upon them, in particular the obligation to supply the person visited with a summary of product characteristics.—

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[1] OJ L 250, 19.9.1984, p. 17. Directive as amended by Directive 97/55/EC (OJ L 290, 23.10.1997, p. 18).—

[2] OJ L 298, 17.10.1989, p. 23. Directive as amended by Directive 97/36/EC (OJ L 202, 30.7.1997, p. 60).—

(50) — Persons qualified to prescribe medicinal products must be able to carry out these functions objectively without being influenced by direct or indirect financial inducements.—

(51) — It should be possible within certain restrictive conditions to provide samples of medicinal products free of charge to persons qualified to prescribe or supply them so that they can familiarize themselves with new products and acquire experience in dealing with them.—

(52) — Persons qualified to prescribe or supply medicinal products must have access to a neutral, objective source of information about products available on the market. Whereas it is nevertheless for the Member States to take all measures necessary to this end, in the light of their own particular situation.—

(53) — Each undertaking which manufactures or imports medicinal products should set up a mechanism to ensure that all information supplied about a medicinal product conforms with the approved conditions of use.—

(54) — In order to ensure the continued safety of medicinal products in use, it is necessary to ensure that pharmacovigilance systems in the Community are continually adapted to take account of scientific and technical progress.—

(55) — It is necessary to take account of changes arising as a result of international harmonisation of definitions, terminology and technological developments in the field of pharmacovigilance.—

(56) — The increasing use of electronic networks for communication of information on adverse reactions to medicinal products marketed in the Community is intended to allow competent authorities to share the information at the same time.—

(57) — It is the interest of the Community to ensure that the pharmacovigilance systems for centrally authorised medicinal products and those authorised by other procedures are consistent.—

(58) — Holders of marketing authorisations should be proactively responsible for on-going pharmacovigilance of the medicinal products they place on the market.—

(59) — The measures necessary for the implementation of this Directive should be adopted in accordance with Council Decision 1999/468/EC of 28 June 1999 laying down the procedures for the exercise of implementing powers conferred on the Commission ([1]).—

([1]) OJ L 184, 17.7.1999, p. 23.—

(60) — The Commission should be empowered to adopt any necessary changes to Annex I in order to take into account scientific and technical progress.—

(61) — This Directive should be without prejudice to the obligations of the Member States concerning the time-limits for transposition of the Directives set out in Annex II, Part B.—

HAVE ADOPTED THIS DIRECTIVE:—

TITLE I—

DEFINITIONS

Article 1

For the purposes of this Directive, the following terms shall bear the following meanings:—

1.— *Proprietary medicinal product:*

Any ready-prepared medicinal product placed on the market under a special name and in a special pack.—

2.— *Medicinal product:*

Any substance or combination of substances presented for treating or preventing disease in human beings.—

Any substance or combination of substances which may be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings is likewise considered a medicinal product.—

3.— *Substance:*

Any matter irrespective of origin which may be:—

human, e.g.—

human blood and human blood products;—

animal, e.g.—

micro-organisms, whole animals, parts of organs, animal secretions, toxins, extracts, blood products;—

vegetable, e.g.—

micro-organisms, plants, parts of plants, vegetable secretions, extracts;—

chemical, e.g.—

elements, naturally occurring chemical materials and chemical products obtained by chemical change or synthesis.—

4.— *Immunological medicinal product:*

Any medicinal product consisting of vaccines, toxins, serums or allergen products:

(a) vaccines, toxins and serums shall cover in particular:

(i) agents used to produce active immunity, such as cholera vaccine, BCG, polio vaccines, smallpox vaccine;

(ii) agents used to diagnose the state of immunity, including in particular tuberculin and tuberculin PPD, toxins for the Schick and Dick Tests, brucellin;

(iii) agents used to produce passive immunity, such as diphtheria antitoxin, anti-smallpox globulin, antilymphocytic globulin;

(b) 'allergen product' shall mean any medicinal product which is intended to identify or induce a specific acquired alteration in the immunological response to an allergizing agent.

5.— *Homeopathic medicinal product:*

Any medicinal product prepared from products, substances or compositions called homeopathic stocks in accordance with a homeopathic manufacturing procedure described by the European Pharmacopoeia or, in absence thereof, by the pharmacopoeias currently used officially in the Member States.

A homeopathic medicinal product may also contain a number of principles.

6.— *Radiopharmaceutical:*

Any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose.

7.— *Radionuclide generator:*

Any system incorporating a fixed parent radionuclide from which is produced a daughter radionuclide which is to be obtained by elution or by any other method and used in a radiopharmaceutical.

8.— *Radionuclide kit:*

Any preparation to be reconsitituted or combined with radionuclides in the final radiopharmaceutical, usually prior to its administration.

9.— *Radionuclide precursor:*

Any other radionuclide produced for the radio-labelling of another substance prior to administration.

10.— *Medicinal products derived from human blood or human plasma:*

Medicinal products based on blood constitutents which are prepared industrially by public or private establishments, such medicinal products including, in particular, albumin, coagulating factors and immunoglobulins of human origin.

11.— *Adverse reaction:*

A response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function.

12.— *Serious adverse reaction:*

An adverse reaction which results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

13.— *Unexpected adverse reaction:*

An adverse reaction, the nature, severity or outcome of which is not consistent with the summary of product characteristics.

14.— *Periodic safety update reports:*

The periodical reports containing the records referred to in Article 104.

15.— *Post-authorisation safety study:*

A pharmacoepidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorisation, conducted with the aim of identifying or quantifying a safety hazard relating to an authorised medicinal product.

16.— *Abuse of medicinal products:*

Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effets.

17.—*Wholesale distribution of medicinal products:*

All activities consisting of procuring, holding, supplying or exporting medicinal products, apart from supplying medicinal products to the public. Such activities are carried out with manufacturers or their depositories, importers, other wholesale distributors or with pharmacists and persons authorized or entitled to supply medicinal products to the public in the Member State concerned.—

18.—*Public service obligation:*

The obligation placed on wholesalers to guarantee permanently an adequate range of medicinal products to meet the requirements of a specific geographical area and to deliver the supplies requested within a very short time over the whole of the area in question.—

19.—*Medicinal Prescription:*

Any medicinal prescription issued by a professional person qualified to do so.—

20.—*Name of the medicinal product:*

The name given to a medicinal product, which may be either an invented name or a common or scientific name, together with a trade mark or the name of the manufacturer; the invented name shall not be liable to confusion with the common name.—

21.—*Common name:*

The international non-proprietary name recommended by the World Health Organization, or, if one does not exist, the usual common name.—

22.—*Strength of the medicinal product:*

The content of the active substances expressed quantitatively per dosage unit, per unit of volume or weight according to the dosage form.—

23.—*Immediate packaging:*

The container or other form of packaging immediately in contact with the medicinal product.—

24.—*Outer packaging:*

The packaging into which is placed the immediate packaging.—

25.—*Labelling:*

Information on the immediate or outer packaging.—

26.—*Package leaflet:*

A leaflet containing information for the user which accompanies the medicinal product.—

27.—*Agency:*

The European Agency for the Evaluation of Medicinal Products established by Regulation (EEC) No 2309/93.—

28.—*Risk to public health:*

All risks with regard to the quality, safety and efficacy of the medicinal product.—

TITLE II—

SCOPE

Article 2

The provisions of this Directive shall apply to industrially produced medicinal products for human use intended to be placed on the market in Member States.—

Article 3

This Directive shall not apply to:—

1.—Any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient (commonly known as the magistral formula).—

2.—Any medicinal product which is prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and is intended to be supplied directly to the patients served by the pharmacy in question (commonly known as the official formula).—

3.—Medicinal products intended for research and development trials.—

4.—Intermediate products intended for further processing by an authorized manufacturer.—

5.—Any radionuclides in the form of sealed sources.—

6.—Whole blood, plasma or blood cells of human origin.—

Article 4

1.— Nothing in this Directive shall in any way derogate from the Community rules for the radiation protection of persons undergoing medical examination or treatment, or from the Community rules laying down the basic safety standards for the health protection of the general public and workers against the dangers of ionizing radiation.—

2. This Directive shall be without prejudice to Council Decision 86/346/EEC of 25 June 1986 accepting on behalf of the Community the European Agreement on the Exchange of Therapeutic Substances of Human Origin ([1]).

3. The provisions of this Directive shall not affect the powers of the Member States' authorities either as regards the setting of prices for medicinal products or their inclusion in the scope of national health insurance schemes, on the basis of health, economic and social conditions.

4. This Directive shall not affect the application of national legislation prohibiting or restricting the sale, supply or use of medicinal products as contraceptives or abortifacients. The Member States shall communicate the national legislation concerned to the Commission.

Article 5

A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorized health care professional and for use by his individual patients on his direct personal responsibility.

TITLE III

PLACING ON THE MARKET

CHAPTER 1

Marketing authorization

Article 6

1. No medicinal product may be placed on the market of a Member State unless a marketing authorization has been issued by the competent authorities of that Member State in accordance with this Directive or an authorization has been granted in accordance with Regulation (EEC) No 2309/93.

2. The authorisation referred to in paragraph 1 shall also be required for radionuclide generators, radionuclide kits, radionuclide precursor radiopharmaceuticals and industrially prepared radiopharmaceuticals.

Article 7

A marketing authorization shall not be required for a radiopharmaceutical prepared at the time of use by a person or by an establishment authorized, according to national legislation, to use such medicinal products in an approved health care establishment exclusively from authorized radionuclide generators, radionuclide kits or radionuclide precursors in accordance with the manufacturer's instructions.

Article 8

1. In order to obtain an authorization to place a medicinal product on the market regardless of the procedure established by Regulation (EEC) No 2309/93, an application shall be made to the competent authority of the Member State concerned.

2. A marketing authorization may only be granted to an applicant established in the Community.

3. The application shall be accompanied by the following particulars and documents, submitted in accordance with Annex I:

(a) Name or corporate name and permanent address of the applicant and, where applicable, of the manufacturer.

(b) Name of the medicinal product.

(c) Qualitative and quantitative particulars of all the constituents of the medicinal product in usual terminology, but excluding empirical chemical formulae, with mention of the international non-proprietary name recommended by the World Health Organization where such name exists.

(d) Description of the manufacturing method.

(e) Therapeutic indications, contra-indications and adverse reactions.

(f) Posology, pharmaceutical form, method and route of administration and expected shelf life.

(g) If applicable, reasons for any precautionary and safety measures to be taken for the storage of the medicinal product, its administration to patients and for the disposal of waste products, together with an indication of any potential risks presented by the medicinal product for the environment.

(h) Description of the control methods employed by the manufacturer (qualitative and quantitative analysis of the constituents and of the finished product, special tests, e.g. sterility tests, tests for the presence of pyrogenic substances, the presence of heavy metals, stability tests, biological and toxicity tests, controls carried out at an intermediate stage of the manufacturing process).

(i) Results of:

physico-chemical, biological or microbiological tests,

toxicological and pharmacological tests,

clinical trials.

([1]) OJ L 207, 30.7.1986, p. 1.

(j)—A summary, in accordance with Article 11, of the product—characteristics, one or more specimens or mock-ups of the—outer—packaging—and—the—immediate—packaging—of—the—medicinal product, together with a package leaflet.—

(k)—A document showing that the manufacturer is authorised—in his own country to produce medicinal products.—

(l)—Copies—of any authorisation obtained in another Member—State or in a third country to place the medicinal product—on the market, together with a list of those Member States—in—which—an—application—for—authorisation—submitted—in—accordance—with—this—Directive—is—under—examination.—Copies—of—the—summary—of—the—product—characteristics—proposed by—the applicant—in accordance with—Article 11—or approved by—the competent authorities of the Member—State in accordance with Article 21. Copies of the package—leaflet proposed in accordance with Article 59 or approved—by—the—competent—authorities—of—the—Member—State—in—accordance—with—Article—61.—Details—of—any—decision—to—refuse—authorization,—whether—in—the—Community—or—in—a—third country, and the reasons for such a decision.—

This information shall be updated on a regular basis.—

Article 9

In addition to the requirements set out in Articles 8 and 10(1),—an—application—for—authorization—to—market—a—radionuclide—generator—shall—also—contain—the—following—information—and—particulars:—

a general description of the system together with a detailed—description—of—the components—of the—system—which—may—affect the composition or quality of the daughter nucleid—preparation,—

qualitative and quantitative particulars of the eluate or the—sublimate.—

Article 10

1.— In derogation of Article 8(3)(i), and without prejudice to—the law relating to the protection of industrial and commercial—property:—

(a)—The—applicant—shall not be required to provide the results—of toxicological and pharmacological tests or the results of—clinical trials if he can demonstrate:—

(i)—either—that the medicinal product is essentially similar—to a medicinal product authorized in the Member State—concerned—by—the—application—and—that—the—holder—of—the marketing authorization for the original medicinal—product— has— consented— to— the— toxicological,—pharmacological and/or clinical references contained in—the file—on—the original medicinal product being—used—for—the—purpose—of—examining—the—application—in—question;—

(ii)—or that the constituent or constituents of the medicinal—product—have—a—well—established—medicinal—use,—with—recognized efficacy and an acceptable level of safety, by—means of a detailed scientific bibliography;—

(iii) or that the medicinal product is essentially similar to a—medicinal—product—which—has—been—authorized—within—the—Community,—in—accordance—with—Community—provisions in force, for not less than six years and is—marketed—in—the—Member—State—for—which—the—application—is made. This period shall be—extended to—10—years—in—the—case—of—high-technology—medicinal—products—having—been—authorised—according—to—the—procedure—laid—down—in—Article—2(5)—of—Council—Directive 87/22/EEC ([1]). Furthermore,—a Member State—may—also—extend—this—period—to—10—years—by—a—single—Decision covering all the medicinal products marketed—on its territory where it considers this necessary in the—interest of public health. Member States are at liberty—not—to—apply—the—six-year—period—beyond—the—date—of—expiry—of—a—patent—protecting—the—original—medicinal—product.—

However, where the medicinal product is intended for—a—different—therapeutic—use—from—that—of—the—other—medicinal products marketed or is to be administered—by different routes or in different doses, the results of—appropriate—toxicological—and—pharmacological—tests—and/or of appropriate clinical trials must be provided.—

(b)—In the case of new medicinal products containing—known—constituents—not—hitherto—used—in—combination—for—therapeutic—purposes,—the—results—of—toxicological—and—pharmacological tests and of clinical trials relating to that—combination—must—be—provided,—but—it—shall—not—be—necessary to provide references relating to each individual—constituent.—

2. — Annex I shall apply by analogy where, pursuant to point—(ii)—of—paragraph—1,—(a),—bibliographic—references—to—published—data are submitted.—

Article 11

The summary of the product characteristics shall contain the—following information:—

1. — Name of the medicinal product.—

2. — Qualitative and quantitative composition in terms of the—active—substances—and—constituents—of—the—excipient,—knowledge— of— which— is— essential— for— proper—administration—of—the—medicinal—product.—The—usual—common name or chemical description shall be used.—

([1])—OJ—L—15,—17.1.1987,—p.—38.—Directive—repealed—by—Directive—93/41/EEC (OJ L 214, 24.8.1993, p. 40).—

3. — Pharmaceutical form.—

4. — Pharmacological properties and, in so far as this information is useful for therapeutic purposes, pharmacokinetic particulars.—

5. — Clinical particulars:—

5.1.—therapeutic indications,—

5.2.—contra-indications,—

5.3.—adverse reactions (frequency and seriousness),—

5.4.—special precautions for use and, in the case of immunological medicinal products, any special precautions to be taken by persons handling such products and administering them to patients, together with any precautions to be taken by the patient,—

5.5.—use during pregnancy and lactation,—

5.6.—interaction with other medicaments and other forms of interaction,—

5.7.—posology and method of administration for adults and, where necessary, for children,—

5.8.—overdose (symptoms, emergency procedures, antidotes),—

5.9.—special warnings,—

5.10. effects on ability to drive and to use machines.—

6. — Pharmaceutical particulars:—

6.1.—major incompatibilities,—

6.2.—shelf life, when necessary after reconstitution of the medicinal product or when the immediate packaging is opened for the first time,—

6.3.—special precautions for storage,—

6.4.—nature and contents of the immediate packaging,—

6.5.—special precautions for disposal of unused medicinal products or waste materials derived from such medicinal products, if appropriate.—

7. — Name or corporate name and permanent address of the marketing authorization holder.—

8. — For radiopharmaceuticals, full details of internal radiation dosimetry.—

9. — For radiopharmaceuticals, additional detailed instructions for extemporaneous preparation and quality control of such preparation and, where appropriate, maximum storage time during which any intermediate preparation such as an eluate or the ready-to-use pharmaceutical will conform with its specifications.—

Article 12

1.— Member States shall take all appropriate measures to ensure that the documents and particulars listed in Article 8(3)(h) and (i), and Article 10(1)(a)(ii) are drawn up by experts with the necessary technical or professional qualifications before they are submitted to the competent authorities. These documents and particulars shall be signed by the experts.—

2.— The duties of the experts according to their respective qualifications shall be:—

(a) to perform tasks falling within their respective disciplines (analysis, pharmacology and similar experimental sciences, clinical trials) and to describe objectively the results obtained (qualitatively and quantitatively);—

(b) to describe their observations in accordance with Annex I, and to state, in particular:—

in the case of the analyst, whether the medicinal product is consistent with the declared composition, giving any substantiation of the control methods employed by the manufacturer;—

in the case of the pharmacologist or the specialist with similar experimental competence, the toxicity of the medicinal product and the pharmacological properties observed;—

in the case of the clinician, whether he has been able to ascertain effects on persons treated with the medicinal product which correspond to the particulars given by the applicant in accordance with Articles 8 and 10, whether the patient tolerates the medicinal product well, the posology the clinician advises and any contra-indications and adverse reactions;—

(c) where applicable, to state the grounds for using the bibliography mentioned in point (a)(ii) of Article 10(1).—

3.— Detailed reports by the experts shall form part of the particulars accompanying the application which the applicant submits to the competent authorities.—

CHAPTER 2

Specific provisions applicable to homeopathic medicinal products

Article 13

1.— Member States shall ensure that homeopathic medicinal products manufactured and placed on the market within the

Community are registered or authorized in accordance with Articles 14, 15 and 16, except where the products are covered by a registration or authorization which was granted under national law on or before 31 December 1993 (and whether or not that registration or authorization has been renewed after that date). Each Member State shall take due account of registrations and authorizations previously granted by another Member State.

2. A Member State may refrain from establishing a special, simplified registration procedure for the homeopathic medicinal products referred to in Article 14. A Member State shall inform the Commission accordingly. The Member State concerned shall allow the use in its territory of homeopathic medicinal products registered by other Member States in accordance with Articles 14 and 15.

Article 14

1. Only homeopathic medicinal products which satisfy all of the following conditions may be subject to a special, simplified registration procedure:

they are administered orally or externally,

no specific therapeutic indication appears on the labelling of the medicinal product or in any information relating thereto,

there is a sufficient degree of dilution to guarantee the safety of the medicinal product; in particular, the medicinal product may not contain either more than one part per 10 000 of the mother tincture or more than 1/100th of the smallest dose used in allopathy with regard to active substances whose presence in an allopathic medicinal product results in the obligation to submit a doctor's prescription.

At the time of registration, Member States shall determine the classification for the dispensing of the medicinal product.

2. The criteria and rules of procedure provided for in Article 4(4), Article 17(1) and Articles 22 to 26, 112, 116 and 125 shall apply by analogy to the special, simplified registration procedure for homeopathic medicinal products, with the exception of the proof of therapeutic efficacy.

3. The proof of therapeutic efficacy shall not be required for homeopathic medicinal products registered in accordance with paragraph 1 of this Article, or, where appropriate, admitted in accordance with Article 13(2).

Article 15

An application for special, simplified registration may cover a series of medicinal products derived from the same homeopathic stock or stocks. The following documents shall be included with the application in order to demonstrate, in particular, the pharmaceutical quality and the batch-to-batch homogeneity of the products concerned:

scientific name or other name given in a pharmacopoeia of the homeopathic stock or stocks, together with a statement of the various routes of administration, pharmaceutical forms and degree of dilution to be registered,

dossier describing how the homeopathic stock or stocks is/are obtained and controlled, and justifying its/their homeopathic nature, on the basis of an adequate bibliography,

manufacturing and control file for each pharmaceutical form and a description of the method of dilution and potentization,

manufacturing authorization for the medicinal product concerned,

copies of any registrations or authorizations obtained for the same medicinal product in other Member States,

one or more specimens or mock-ups of the outer packaging and the immediate packaging of the medicinal products to be registered,

data concerning the stability of the medicinal product.

Article 16

1. Homeopathic medicinal products other than those referred to in Article 14(1) shall be authorized and labelled in accordance with Articles 8, 10 and 11.

2. A Member State may introduce or retain in its territory specific rules for the toxicological and pharmacological tests and clinical trials of homeopathic medicinal products other than those referred to in Article 14(1) in accordance with the principles and characteristics of homeopathy as practised in that Member State.

In this case, the Member State concerned shall notify the Commission of the specific rules in force.

3. Title IX shall apply to homeopathic medicinal products, with the exception of those referred to in Article 14(1).

CHAPTER 3

Procedures relevant to the marketing authorization

Article 17

1. Member States shall take all appropriate measures to ensure that the procedure for granting an authorization to place a medicinal product on the market is completed within 210 days of the submission of a valid application.

2.— Where a Member State notes that an application for authorization is already under active examination in another Member State in respect of that medicinal product, the Member State concerned may decide to suspend the detailed examination of the application in order to await the assessment report prepared by the other Member State in accordance with Article 21(4).—

The Member State concerned shall inform the other Member State and the applicant of its decision to suspend detailed examination of the application in question. As soon as it has completed the examination of the application and reached a decision, the other Member State shall forward a copy of its assessment report to the Member State concerned.—

Article 18

Where a Member State is informed in accordance with Article 8(3)(l) that another Member State has authorized a medicinal product which is the subject of an application for authorization in the Member State concerned, that Member State shall forthwith request the authorities of the Member State which has granted the authorization to forward to it the assessment report referred to in Article 21(4).—

Within 90 days of the receipt of the assessment report, the Member State concerned shall either recognize the decision of the first Member State and the summary of the product characteristics as approved by it or, if it considers that there are grounds for supposing that the authorization of the medicinal product concerned may present a risk to public health, it shall apply the procedures set out in Articles 29 to 34.—

Article 19

In order to examine the application submitted in accordance with Articles 8 and 10(1), the competent authority of the Member State:—

1.— must verify whether the particulars submitted in support of the application comply with the said Articles 8 and 10(1) and examine whether the conditions for issuing an authorization to place medicinal products on the market (marketing authorization) are complied with.—

2.— may submit the medicinal product, its starting materials and, if need be, its intermediate products or other constituent materials, for testing by a State laboratory or by a laboratory designated for that purpose in order to ensure that the control methods employed by the manufacturer and described in the particulars accompanying the application in accordance with Article 8(3)(h) are satisfactory.—

3.— may, where appropriate, require the applicant to supplement the particulars accompanying the application in respect of the items listed in the Articles 8(3) and 10(1).— Where the competent authority avails itself of this option, the time limits laid down in Article 17 shall be suspended until such time as the supplementary information required has been provided. Likewise, these time limits shall be suspended for the time allowed the applicant, where appropriate, for giving oral or written explanation.—

Article 20

Member States shall take all appropriate measures to ensure that:—

(a) the competent authorities verify that manufacturers and importers of medicinal products coming from third countries are able to carry out manufacture in compliance with the particulars supplied pursuant to Article 8(3)(d), and/or to carry out controls according to the methods described in the particulars accompanying the application in accordance with Article 8(3)(h);—

(b) the competent authorities may allow manufacturers and importers of medicinal products coming from third countries, in exceptional and justifiable cases, to have certain stages of manufacture and/or certain of the controls referred to in (a) carried out by third parties; in such cases, the verifications by the competent authorities shall also be made in the establishment designated.—

Article 21

1.— When the marketing authorization is issued, the holder shall be informed, by the competent authorities of the Member State concerned, of the summary of the product characteristics as approved by it.—

2.— The competent authorities shall take all necessary measures to ensure that the information given in the summary is in conformity with that accepted when the marketing authorization is issued or subsequently.—

3.— The competent authorities shall forward to the Agency a copy of the authorization together with the summary of the product characteristics.—

4.— The competent authorities shall draw up an assessment report and comments on the dossier as regards the results of the analytical and pharmacotoxicological tests and the clinical trials of the medicinal product concerned. The assessment report shall be updated whenever new information becomes available which is of importance for the evaluation of the quality, safety or efficacy of the medicinal product concerned.—

Article 22

In exceptional circumstances, and following consultation with the applicant, an authorization may be granted subject to certain specific obligations, including:—

the carrying out of further studies following the granting of authorization,—

the notification of adverse reactions to the medicinal product.—

These exceptional decisions may be adopted only for objective and verifiable reasons and shall be based on one of the causes referred to in Part 4 (G) of Annex I.—

Article 23

After an authorization has been issued, the authorization holder must, in respect of the methods of manufacture and control provided for in Article 8(3)(d) and (h), take account of scientific and technical progress and introduce any changes that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods.

These changes shall be subject to the approval of the competent authority of the Member State concerned.

Article 24

Authorization shall be valid for five years and shall be renewable for five-year periods, on application by the holder at least three months before the expiry date and after consideration by the competent authority of a dossier containing in particular details of the data on pharmacovigilance and other information relevant to the monitoring of the medicinal product.

Article 25

Authorization shall not affect the civil and criminal liability of the manufacturer and, where applicable, of the marketing authorization holder.

Article 26

The marketing authorisation shall be refused if, after verification of the particulars and documents listed in Articles 8 and 10(1), it proves that:

(a) the medicinal product is harmful in the normal conditions of use, or

(b) that its therapeutic efficacy is lacking or is insufficiently substantiated by the applicant, or

(c) that its qualitative and quantitative composition is not as declared.

Authorisation shall likewise be refused if the particulars and documents submitted in support of the application do not comply with Articles 8 and 10(1).

CHAPTER 4

Mutual recognition of authorizations

Article 27

1. In order to facilitate the adoption of common decisions by Member States on the authorization of medicinal products on the basis of the scientific criteria of quality, safety and efficacy, and to achieve thereby the free movement of medicinal products within the Community, a Committee for Proprietary Medicinal Products, hereinafter referred to as 'the Committee', is hereby set up. The Committee shall be part of the Agency.

2. In addition to the other responsibilities conferred upon it by Community law, the Committee shall examine any question relating to the granting, variation, suspension or withdrawal of marketing authorization which is submitted to it in accordance with this Directive.

3. The Committee shall draw up its own Rules of Prodecure.

Article 28

1. Before submitting the application for recognition of a marketing authorization, the holder of the authorization shall inform the Member State which granted the authorization on which the application is based (hereinafter 'reference Member State'), that an application is to be made in accordance with this Directive and shall notify it of any additions to the original dossier; that Member State may require the applicant to provide it with all the particulars and documents necessary to enable it to check that the dossiers filed are identical.

In addition the holder of the authorization shall request the reference Member State to prepare an assessment report in respect of the medicinal product concerned, or, if necessary, to update any existing assessment report. That Member State shall prepare the assessment report, or update it, within 90 days of the receipt of the request.

At the same time as the application is submitted in accordance with paragraph 2, the reference Member State shall forward the assessment report to the Member State or Member States concerned by the application.

2. In order to obtain the recognition according to the procedures laid down in this Chapter in one or more of the Member States of a marketing authorization issued by a Member State, the holder of the authorization shall submit an application to the competent authorities of the Member State or Member States concerned, together with the information and particulars referred to in Articles 8, 10(1) and 11. He shall testify that the dossier is identical to that accepted by the reference Member State, or shall identify any additions or amendments it may contain. In the latter case, he shall certify that the summary of the product characteristics proposed by him in accordance with Article 11 is identical to that accepted by the reference Member State in accordance with Article 21. Moreover, he shall certify that all the dossiers filed as part of the procedure are identical.

3. The holder of the marketing authorization shall communicate the application to the Agency, inform it of the Member States concerned and of the dates of submission of the application and send it a copy of the authorization granted by the reference Member State. He shall also send the Agency copies of any such authorization which may have been granted by the other Member States in respect of the medicinal product concerned, and shall indicate whether any application for authorization is currently under consideration in any Member State.

4.— Save in the exceptional case provided for in Article 29(1), each Member State shall recognize the marketing authorization granted by the reference Member State within 90 days of receipt of the application and the assessment report. It shall inform the reference Member State which granted the initial authorization, the other Member States concerned by the application, the Agency, and the marketing authorization holder.—

Article 29

1.— Where a Member State considers that there are grounds for supposing that the marketing authorization of the medicinal product concerned may present a risk to public health, it shall forthwith inform the applicant, the reference Member State which granted the initial authorization, any other Member States concerned by the application and the Agency. The Member State shall state its reasons in detail and shall indicate what action may be necessary to correct any defect in the application.—

2.— All the Member States concerned shall use their best endeavours to reach agreement on the action to be taken in respect of the application. They shall provide the applicant with the opportunity to make his point of view known orally or in writing. However, if the Member States have not reached agreement within the time limit referred to in Article 28(4) they shall forthwith refer the matter to the Agency with regard to the Committee's reference for the application of the procedure laid down in Article 32.—

3.— Within the time limit referred to in Article 28(4), the Member States concerned shall provide the Committee with a detailed statement of the matters on which they have been unable to reach agreement and the reasons for their disagreement. The applicant shall be provided with a copy of this information.—

4.— As soon as he is informed that the matter has been referred to the Committee, the applicant shall forthwith forward to the Committee a copy of the information and particulars referred to in Article 28(2).—

Article 30

If several applications submitted in accordance with Articles 8, 10(1) and Article 11 have been made for marketing authorization for a particular medicinal product, and Member States have adopted divergent decisions concerning the authorization of the medicinal product or its suspension or withdrawal, a Member State, or the Commission, or the marketing authorization holder may refer the matter to the Committee for application of the procedure laid down in Article 32.—

The Member State concerned, the marketing authorization holder or the Commission shall clearly identify the question which is referred to the Committee for consideration and, where appropriate, shall inform the holder.—

The Member State and the marketing authorization holder shall forward to the Committee all available information relating to the matter in question.—

Article 31

The Member States or the Commission or the applicant or holder of the marketing authorization may, in specific cases where the interests of the Community are involved, refer the matter to the Committee for the application of the procedure laid down in Article 32 before reaching a decision on a request for a marketing authorization or on the suspension or withdrawal of an authorization, or on any other variation to the terms of a marketing authorization which appears necessary, in particular to take account of the information collected in accordance with Title IX.—

The Member State concerned or the Commission shall clearly identify the question which is referred to the Committee for consideration and shall inform the marketing authorization holder.—

The Member States and the marketing authorization holder shall forward to the Committee all available information relating to the matter in question.—

Article 32

1.— When reference is made to the procedure described in this Article, the Committee shall consider the matter concerned and issue a reasoned opinion within 90 days of the date on which the matter was referred to it.—

However, in cases submitted to the Committee in accordance with Articles 30 and 31, this period may be extended by 90 days.—

In case of urgency, on a proposal from its Chairman, the Committee may agree to a shorter deadline.—

2.— In order to consider the matter, the Committee may appoint one of its members to act as rapporteur. The Committee may also appoint individual experts to advise it on specific questions. When appointing experts, the Committee shall define their tasks and specify the time-limit for the completion of these tasks.—

3.— In the cases referred to in Articles 29 and 30, before issuing its opinion, the Committee shall provide the marketing authorization holder with an opportunity to present written or oral explanations.—

In the case referred to in Article 31, the marketing authorization holder may be asked to explain himself orally or in writing.—

If it considers it appropriate, the Committee may invite any other person to provide information relating to the matter before it.—

The Committee may suspend the time limit referred to in paragraph 1 in order to allow the marketing authorization holder to prepare explanations.—

4.— The Agency shall forthwith inform the marketing authorization holder where the opinion of the Committee is that:—

the application does not satisfy the criteria for authorization, or—

the summary of the product characteristics proposed by the applicant in accordance with Article 11 should be amended, or—

the authorization should be granted subject to conditions, with regard to conditions considered essential for the safe and effective use of the medicinal product including pharmacovigilance, or—

a marketing authorization should be suspended, varied or withdrawn.—

Within 15 days of the receipt of the opinion, the marketing authorization holder may notify the Agency in writing of his intention to appeal. In that case, he shall forward the detailed grounds for appeal to the Agency within 60 days of receipt of the opinion. Within 60 days of receipt of the grounds for appeal, the Committee shall consider whether its opinion should be revised, and the conclusions reached on the appeal shall be annexed to the assessment report referred to in paragraph 5.—

5.— Within 30 days of its adoption, the Agency shall forward the final opinion of the Committee to the Member States, the Commission and the marketing authorization holder together with a report describing the assessment of the medicinal product and stating the reasons for its conclusions.—

In the event of an opinion in favour of granting or maintaining an authorization to place the medicinal product concerned on the market, the following documents shall be annexed to the opinion.—

(a) a draft summary of the product characteristics, as referred to in Article 11;—

(b) any conditions affecting the authorization within the meaning of paragraph 4.—

Article 33

Within 30 days of the receipt of the opinion, the Commission shall prepare a draft of the decision to be taken in respect of the application, taking into account Community law.—

In the event of a draft decision which envisages the granting of marketing authorization, the documents referred to in Article 32(5)(a) and (b) shall be annexed.—

Where, exceptionally, the draft decision is not in accordance with the opinion of the Agency, the Commission shall also annex a detailed explanation of the reasons for the differences.—

The draft decision shall be forwarded to the Member States and the applicant.—

Article 34

1.— A final decision on the application shall be adopted in accordance with the procedure referred to in Article 121(2).—

2.— The rules of procedure of the Standing Committee established by Article 121(1) shall be adjusted to take account of the tasks incumbent upon it in accordance with this Chapter.—

These adjustments shall involve the following:—

except in cases referred to in the third paragraph of Article 33, the opinion of the Standing Committee shall be obtained in writing,—

each Member State is allowed at least 28 days to forward written observations on the draft decision to the Commission,—

each Member State is able to require in writing that the draft decision be discussed by the Standing Committee, giving its reasons in detail.—

Where, in the opinion of the Commission, the written observations of a Member State raise important new questions of a scientific or technical nature which have not been addressed in the opinion of the Agency, the Chairman shall suspend the procedure and refer the application back to the Agency for further consideration.—

The provisions necessary for the implementation of this paragraph shall be adopted by the Commission in accordance with the procedure referred to in Article 121(2).—

3.— A decision as referred to in paragraph 1 shall be addressed to the Member States concerned by the matter and reported to the marketing authorization holder. The Member States shall either grant or withdraw marketing authorization, or vary the terms of a marketing authorization as necessary to comply with the decision within 30 days of its notification. They shall inform the Commission and the Agency thereof.—

Article 35

1.— Any application by the marketing authorization holder to vary a marketing authorization which has been granted in accordance with the provisions of this Chapter shall be submitted to all the Member States which have previously authorized the medicinal product concerned.—

The Commission shall, in consultation with the Agency, adopt appropriate arrangements for the examination of variations to the terms of a marketing authorization.—

These arrangements shall include a notification system or administration procedures concerning minor variations and define precisely the concept of 'a minor variation'.—

These arrangements shall be adopted by the Commission in the form of an implementing Regulation in accordance with the procedure referred to in Article 121(2).—

2.— In case of arbitration submitted to the Commission, the procedure laid down in Articles 32, 33 and 34 shall apply by analogy to variations made to marketing authorizations.—

Article 36

1.— Where a Member State considers that the variation of a marketing authorization which has been granted in accordance with the provisions of this Chapter or its suspension or withdrawal is necessary for the protection of public health, the Member State concerned shall forthwith refer the matter to the Agency for the application of the procedures laid down in Articles 32, 33 and 34.—

2.— Without prejudice to the provisions of Article 31, in exceptional cases, where urgent action is essential to protect public health, until a definitive decision is adopted a Member State may suspend the marketing and the use of the medicinal product concerned on its territory. It shall inform the Commission and the other Member States no later than the following working day of the reasons for its action.—

Article 37

Articles 35 and 36 shall apply by analogy to medicinal products authorized by Member States following an opinion of the Committee given in accordance with Article 4 of Directive 87/22/EEC before 1 January 1995.—

Article 38

1.— The Agency shall publish an annual report on the operation of the procedures laid down in this Chapter and shall forward that report to the European Parliament and the Council for information.—

2.— By 1 January 2001, the Commission shall publish a detailed review of the operation of the procedures laid down in this Chapter and shall propose any amendments which may be necessary to improve these procedures.—

The Council shall decide, under the conditions provided for in the Treaty, on the Commission proposal within one year of its submission.—

Article 39

The provisions referred to in Articles 27 to 34 shall not apply to the homeopathic medicinal products referred to in Article 16(2).—

TITLE IV—

MANUFACTURE AND IMPORTATION

Article 40

1.— Member States shall take all appropriate measures to ensure that the manufacture of the medicinal products within their territory is subject to the holding of an authorization. This manufacturing authorization shall be required nothwithstanding that the medicinal products manufactured are intended for export.—

2.— The authorization referred to in paragraph 1 shall be required for both total and partial manufacture, and for the various processes of dividing up, packaging or presentation.—

However, such authorization shall not be required for preparation, dividing up, changes in packaging or presentation where these processes are carried out, solely for retail supply, by pharmacists in dispensing pharmacies or by persons legally authorized in the Member States to carry out such processes.—

3.— Authorization referred to in paragraph 1 shall also be required for imports coming from third countries into a Member State; this Title and Article 118 shall have corresponding application to such imports as they have to manufacture.—

Article 41

In order to obtain the manufacturing authorization, the applicant shall meet at least the following requirements:—

(a) specify the medicinal products and pharmaceutical forms which are to be manufactured or imported and also the place where they are to be manufactured and/or controlled;—

(b) have at his disposal, for the manufacture or import of the above, suitable and sufficient premises, technical equipment and control facilities complying with the legal requirements which the Member State concerned lays down as regards both manufacture and control and the storage of medicinal products, in accordance with Article 20;—

(c) have at his disposal the services of at least one qualified person within the meaning of Article 48.—

The applicant shall provide particulars in support of the above in his application.—

Article 42

1.— The competent authority of the Member State shall issue the manufacturing authorization only after having made sure of the accuracy of the particulars supplied pursuant to Article 41, by means of an inquiry carried out by its agents.—

2.— In order to ensure that the requirements referred to in Article 41 are complied with, authorization may be made conditional on the carrying out of certain obligations imposed either when authorization is granted or at a later date.—

3.— The authorization shall apply only to the premises specified in the application and to the medicinal products and pharmaceutical forms specified in that same application.—

Article 43

The Member States shall take all appropriate measures to ensure that the time taken for the procedure for granting the manufacturing authorization does not exceed 90 days from the day on which the competent authority receives the application.—

Article 44

If the holder of the manufacturing authorization requests a change in any of the particulars referred to in points (a) and (b) of the first paragraph of Article 41, the time taken for the procedure relating to this request shall not exceed 30 days. In exceptional cases this period of time may be extended to 90 days.—

Article 45

The competent authority of the Member State may require from the applicant further information concerning the particulars supplied pursuant to Article 41 and concerning the qualified person referred to in Article 48; where the competent authority concerned exercises this right, application of the time-limits referred to in Article 43 and 44 shall be suspended until the additional data required have been supplied.—

Article 46

The holder of a manufacturing authorization shall at least be obliged:—

(a) to have at his disposal the services of staff who comply with the legal requirements existing in the Member State concerned both as regards manufacture and controls;—

(b) to dispose of the authorized medicinal products only in accordance with the legislation of the Member States concerned;—

(c) to give prior notice to the competent authority of any changes he may wish to make to any of the particulars supplied pursuant to Article 41; the competent authority shall, in any event, be immediately informed if the qualified person referred to in Article 48 is replaced unexpectedly;—

(d) to allow the agents of the competent authority of the Member State concerned access to his premises at any time;—

(e) to enable the qualified person referred to in Article 48 to carry out his duties, for example by placing at his disposal all the necessary facilities;—

(f) to comply with the principles and guidelines of good manufacturing practice for medicinal products as laid down by Community law.—

Article 47

The principles and guidelines of good manufacturing practices for medicinal products referred to in Article 46(f) shall be adopted in the form of a directive, in accordance with the procedure referred to in Article 121(2).—

Detailed guidelines in line with those principles will be published by the Commission and revised necessary to take account of technical and scientific progress.—

Article 48

1.— Member States shall take all appropriate measures to ensure that the holder of the manufacturing authorization has permanently and continuously at his disposal the services of at least one qualified person, in accordance with the conditions laid down in Article 49, responsible in particular for carrying out the duties specified in Article 51.—

2.— If he personally fulfils the conditions laid down in Article 49, the holder of the authorization may himself assume the responsibility referred to in paragraph 1.—

Article 49

1.— Member States shall ensure that the qualified person referred to in Article 48 fulfils the minimum conditions of qualification set out in paragraphs 2 and 3.—

2.— A qualified person shall be in possession of a diploma, certificate or other evidence of formal qualifications awarded on completion of a university course of study, or a course recognized as equivalent by the Member State concerned, extending over a period of at least four years of theoretical and practical study in one of the following scientific disciplines: pharmacy, medicine, veterinary medicine, chemistry, pharmaceutical chemistry and technology, biology.—

However, the minimum duration of the university course may be three and a half years where the course is followed by a period of theoretical and practical training of a minimum duration of one year and including a training period of at least six months in a pharmacy open to the public, corroborated by an examination at university level.—

Where two university courses or two courses recognized by the State as equivalent co-exist in a Member State and where one of these extends over four years and the other over three years, the three-year course leading to a diploma, certificate or other evidence of formal qualifications awarded on completion of a university course or its recognized equivalent shall be considered to fulfil the condition of duration referred to in the second subparagraph in so far as the diplomas, certificates or other evidence of formal qualifications awarded on completion of both courses are recognized as equivalent by the State in question.—

The course shall include theoretical and practical study bearing upon at least the following basic subjects:—

Applied physics—

General and inorganic chemistry—

Organic chemistry—

Analytical chemistry—

Pharmaceutical chemistry, including analysis of medicinal products—

General and applied biochemistry (medical)—

Physiology—

Microbiology—

Pharmacology—

Pharmaceutical technology—

Toxicology—

Pharmacognosy (study of the composition and effects of the natural active substances of plant and animal origin).—

Studies in these subjects should be so balanced as to enable the person concerned to fulfil the obligations specified in Article 51.—

In so far as certain diplomas, certificates or other evidence of formal qualifications mentioned in the first subparagraph do not fulfil the criteria laid down in this paragraph, the competent authority of the Member State shall ensure that the person concerned provides evidence of adequate knowledge of the subjects involved.—

3.— The qualified person shall have acquired practical experience over at least two years, in one or more undertakings which are authorized to manufacture medicinal products, in the activities of qualitative analysis of medicinal products, of quantitative analysis of active substances and of the testing and checking necessary to ensure the quality of medicinal products.—

The duration of practical experience may be reduced by one year where a university course lasts for at least five years and by a year and a half where the course lasts for at least six years.—

Article 50

1.— A person engaging in the activities of the person referred to in Article 48 from the time of the application of Directive 75/319/EEC, in a Member State without complying with the provisions of Article 49 shall be eligible to continue to engage in those activities in the State concerned.—

2.— The holder of a diploma, certificate or other evidence of formal qualifications awarded on completion of a university course or a course recognized as equivalent by the Member State concerned in a scientific discipline allowing him to engage in the activities of the person referred to in Article 48 in accordance with the laws of that State may if he began his course prior to 21 May 1975 be considered as qualified to carry out in that State the duties of the person referred to in Article 48 provided that he has previously engaged in the following activities for at least two years before 21 May 1985 following notification of this directive in one or more undertakings authorized to manufacture: production supervision and/or qualitative and quantitative analysis of active substances, and the necessary testing and checking under the direct authority of the person referred to in Article 48 to ensure the quality of the medicinal products.—

If the person concerned has acquired the practical experience referred to in the first subparagraph before 21 May 1965, a further one year's practical experience in accordance with the conditions referred to in the first subparagraph will be required to be completed immediately before he engages in such activities.—

Article 51

1.— Member States shall take all appropriate measures to ensure that the qualified person referred to in Article 48, without prejudice to his relationship with the holder of the manufacturing authorization, is responsible, in the context of the procedures referred to in Article 52, for securing:—

(a) in the case of medicinal products manufactured within the Member States concerned, that each batch of medicinal products has been manufactured and checked in compliance with the laws in force in that Member State and in accordance with the requirements of the marketing authorization;—

(b) in the case of medicinal products coming from third countries, that each production batch has undergone in the importing Member State a full qualitative analysis, a quantitative analysis of at least all the active constituents and all the other tests or checks necessary to ensure the quality of medicinal products in accordance with the requirements of the marketing authorization.—

The batches of medicinal products which have undergone such controls in a Member State shall be exempt from the controls if they are marketed in another Member State, accompanied by the control reports signed by the qualified person.—

2.— In the case of medicinal products imported from a third country, where appropriate arrangements have been made by the Community with the exporting country to ensure that the manufacturer of the medicinal product applies standards of good manufacturing practice at least equivalent to those laid down by the Community, and to ensure that the controls referred to under point (b) of the first subparagraph of paragraph 1 have been carried out in the exporting country, the qualified person may be relieved of responsibility for carrying out those controls.—

3.— In all cases and particularly where the medicinal products are released for sale, the qualified person must certify in a register or equivalent document provided for that purpose, that each production batch satisfies the provisions of this Article; the said register or equivalent document must be kept

up to date as operations are carried out and must remain at the disposal of the agents of the competent authority for the period specified in the provisions of the Member State concerned and in any event for at least five years.

Article 52

Member States shall ensure that the duties of qualified persons referred to in Article 48 are fulfilled, either by means of appropriate administrative measures or by making such persons subject to a professional code of conduct.

Member States may provide for the temporary suspension of such a person upon the commencement of administrative or disciplinary procedures against him for failure to fulfil his obligations.

Article 53

The provisions of this Title shall also apply to homeopathic medicinal products.

TITLE V

LABELLING AND PACKAGE LEAFLET

Article 54

The following particulars shall appear on the outer packaging of medicinal products or, where there is no outer packaging, on the immediate packaging:

(a) the name of the medicinal product followed by the common name where the product contains only one active substance and if its name is an invented name; where a medicinal product is available in several pharmaceutical forms and/or several strengths, the pharmaceutical form and/or the strength (baby, child or adult as appropriate) must be included in the name of the medicinal product;

(b) a statement of the active substances expressed qualitatively and quantitatively per dosage unit or according to the form of administration for a given volume or weight, using their common names;

(c) the pharmaceutical form and the contents by weight, by volume or by number of doses of the product;

(d) a list of those excipients known to have a recognized action or effect and included in the guidelines published pursuant to Article 65. However, if the product is injectable, or a topical or eye preparation, all excipients must be stated;

(e) the method and, if necessary, the route of administration;

(f) a special warning that the medicinal product must be stored out of reach of children;

(g) a special warning, if this is necessary for the medicinal product;

(h) the expiry date in clear terms (month/year);

(i) special storage precautions, if any;

(j) special precautions for disposal of unused medicinal products or waste materials from medicinal products, if appropriate;

(k) the name and address of the holder of the authorization for placing the medicinal product on the market;

(l) the number of the authorization for placing the medicinal product on the market;

(m) the manufacturer's batch number;

(n) in the case of self-medication, instructions on the use of the medicinal products.

Article 55

1. The particulars laid down in Articles 54 and 62 shall appear on immediate packagings other than those referred to in paragraphs 2 and 3.

2. The following particulars at least shall appear on immediate packagings which take the form of blister packs and are placed in an outer packaging that complies with the requirements laid down in Articles 54 and 62.

the name of the medicinal product as laid down in Article 54(a),

the name of the holder of the authorization for placing the product on the market,

the expiry date,

the batch number.

3. The following particulars at least shall appear on small immediate packaging units on which the particulars laid down in Articles 54 and 62 cannot be displayed:

the name of the medicinal product and, if necessary, the strength and the route of administration,

the method of administration,

the expiry date,

the batch number,

the contents by weight, by volume or by unit.

Article 56

The particulars referred to in Articles 54, 55 and 62 shall be easily legible, clearly comprehensible and indelible.

Article 57

Notwithstanding Article 60, Member States may require the use of certain forms of labelling of the medicinal product making it possible to ascertain:

the price of the medicinal product,

the reimbursement conditions of social security organizations,

the legal status for supply to the patient, in accordance with Title VI,

identification and authenticity.

Article 58

The inclusion in the packaging of all medicinal products of a package leaflet shall be obligatory unless all the information required by Articles 59 and 62 is directly conveyed on the outer packaging or on the immediate packaging.

Article 59

1. The package leaflet shall be drawn up in accordance with the summary of the product characteristics; it shall include, in the following order:

(a) for the identification of the medicinal product:

the name of the medicinal product, followed by the common name if the product contains only one active substance and if its name is an invented name; where a medicinal product is available in several pharmaceutical forms and/or several strengths, the pharmaceutical form and/or the strength (for example, baby, child, adult) must be included in the name of the medicinal product,

a full statement of the active substances and excipients expressed qualitatively and a statement of the active substances expressed quantitatively, using their common names, in the case of each presentation of the medicinal product,

the pharmaceutical form and the contents by weight, by volume or by number of doses of the product, in the case of each presentation of the product,

the pharmaco-therapeutic group, or type of activity in terms easily comprehensible for the patient,

the name and address of the holder of the authorization for placing the medicinal product on the market and of the manufacturer;

(b) the therapeutic indications;

(c) list of information which is necessary before taking the medicinal product:

contra-indications,

appropriate precautions for use,

forms of interaction with other medicinal products and other forms of interaction

(e.g. alcohol, tobacco, foodstuffs) which may affect the action of the medicinal product,

special warnings;

this list must:

take into account the particular condition of certain categories of users (e.g. children, pregnant or breastfeeding women, the elderly, persons with specific pathological conditions),

mention, if appropriate, potential effects on the ability to drive vehicles or to operate machinery,

detail those excipients, knowledge of which is important for the safe and effective use of the medicinal product and included in the guidelines published pursuant to Article 65;

(d) the necessary and usual instructions for proper use, in particular:

the dosage,

the method and, if necessary, route of administration,

the frequency of administration, specifying if necessary, the appropriate time at which the medicinal product may or must be administered,

and, as appropriate, depending on the nature of the product:

the duration of treatment, where it should be limited,

the action to be taken in the case of an overdose (e.g., symptoms, emergency procedures),

the course of action to take when one or more doses have not been taken,

indication, if necessary, of the risk of withdrawal effects;

(e) a description of the undesirable effects which can occur under normal use of the medicinal product and, if necessary, the action to be taken in such a case; the patient should be expressly invited to communicate any

undesirable effect which is not mentioned in the leaflet to his doctor or to his pharmacist;—

(f)—a reference to the expiry date indicated on the label, with:—

a warning against using the product after this date,—

where appropriate, special storage precautions,—

if necessary, a warning against certain visible signs of deterioration;—

(g)—the date on which the package leaflet was last revised.—

2.— Notwithstanding paragraph 1(b), the authority competent may decide that certain therapeutic indications shall not be mentioned in the package leaflet, where the dissemination of such information might have serious disadvantages for the patient.—

Article 60

Member States may not prohibit or impede the placing on the market of medicinal products within their territory on grounds connected with labelling or the package leaflet where these comply with the requirements of this Title.—

Article 61

1.— One or more specimens or mock-ups of the outer packaging and the immediate packaging of a medicinal product, together with the draft package leaflet, shall be submitted to the authorities competent for authorizing marketing when the marketing authorization is requested.—

2.— The competent authority shall refuse the marketing authorization if the labelling or the package leaflet do not comply with the provisions of this Title or if they are not in accordance with the particulars listed in the summary of product characteristics.—

3.— All proposed changes to an aspect of the labelling or the package leaflet covered by this Title and not connected with the summary of product characteristics shall be submitted to the authorities competent for authorizing marketing. If the competent authorities have not opposed a proposed change within 90 days following the introduction of the request, the applicant may put the change into effect.—

4.— The fact that the competent authority do not refuse a marketing authorization pursuant to paragraph 2 or a change to the labelling or the package leaflet pursuant to paragraph 3 does not alter the general legal liability of the manufacturer or as appropriate the marketing authorization holder.—

Article 62

The outer packaging and the package leaflet may include symbols or pictograms designed to clarify certain information mentioned in Articles 54 and 59(1) and other information compatible with the summary of the product characteristics which is useful for health education, to the exclusion of any element of a promotional nature.—

Article 63

1.— The particulars for labelling listed in Articles 54, 59 and 62 shall appear in the official language or languages of the Member State where the product is placed on the market.—

The first subparagraph shall not prevent these particulars from being indicated in several languages, provided that the same particulars appear in all the languages used.—

2.— The package leaflet must be written in clear and understandable terms for the users and be clearly legible in the official language or languages of the Member State where the medicinal product is placed on the market.—

The first subparagraph shall not prevent the package leaflet being printed in several languages, provided that the same information is given in all the languages used.—

3.— The competent authorities may exempt labels and package leaflets for specific medicinal products from the obligation that certain particulars shall appear and that the leaflet must be in the official language or languages of the Member State where the product is placed on the market, when the product is not intended to be delivered to the patient for self-administration.—

Article 64

Where the provisions of this Title are not complied with, and a notice served on the person concerned has remained without effect, the competent authorities of the Member States may suspend the marketing authorization, until the labelling and the package leaflet of the medicinal product in question have been made to comply with the requirements of this Title.—

Article 65

As necessary, the Commission shall publish guidelines concerning in particular:—

the formulation of certain special warnings for certain categories of medicinal products,—

the particular information needs relating to self-medication,—

the legibility of particulars on the labelling and package leaflet,—

methods—for—the—identification—and—authentication—of—medicinal products,—

the list of excipients which must feature on the labelling of—medicinal products and the way these excipients must be—indicated.—

These guidelines shall be adopted in the form of a Directive, in—accordance with the procedure referred to in Article 121(2).—

Article 66

1.— The outer carton and the container of medicinal products—containing—radionuclides—shall—be—labelled—in—accordance—with—the regulations—for the safe—transport—of radioactive—materials—laid—down—by—the—International—Atomic—Energy—Agency.—Moreover,—the—labelling—shall—comply—with—the—provisions—set—out in paragraphs 2 and 3.—

2.— The—label—on—the—shielding—shall—include—the—particulars—mentioned—in—Article—54.—In—addition,—the—labelling—on—the—shielding shall explain in full, the codings used on the vial and—shall indicate, where necessary, for a given time and date, the—amount of radioactivity per dose or per vial and the number of—capsules,—or,—for—liquids,—the—number—of—millilitres—in—the—container.—

3.— The vial shall be labelled with the following information:—

the name or code of the medicinal product, including the—name or chemical symbol of the radionuclide,—

the batch identification and expiry date,—

the international symbol for radioactivity,—

the name of the manufacturer,—

the amount of radioactivity as specified in paragraph 2.—

Article 67

The—competent—authority—shall—ensure—that—a—detailed—instruction—leaflet—is—enclosed—with—the—packaging—of—radiopharmaceuticals, radionuclide generators, radionuclide kits—or—radionuclide—precursors.—The—text—of—this—leaflet—shall—be—established in accordance with the provisions of Article 59. In—addition, the leaflet shall include any precautions to be taken—by—the—user—and—the—patient—during—the—preparation—and—administration— of— the— medicinal— product— and— special—precautions for the disposal of the packaging and its unused—contents.—

Article 68

Without— prejudice— to— the— provisions— of— Article— 69,—homeopathic— medicinal— products— shall— be— labelled— in—accordance—with—the—provisions—of—this—title—and—shall—be—identified—by—a—reference—on—their—labels,—in—clear—and—legible—form, to their homeopathic nature.—

Article 69

1.— In—addition—to—the—clear—mention—of—the—words—'homeopathic—medicinal—product',—the—labelling—and,—where—appropriate,—the—package—insert—for—the—medicinal—products—referred—to—in—Article—14(1)—shall—bear—the—following,—and—no—other, information:—

the scientific name of the stock or stocks followed by the—degree—of—dilution,—making—use—of—the—symbols—of—the—pharmacopoeia used in accordance with Article 1(5),—

name—and—address—of—the—registration—holder—and,—where —appropriate, of the manufacturer, —

method of administration and, if necessary, route, —

expiry date, in clear terms (month, year), —

pharmaceutical form, —

contents of the sales presentation, —

special storage precautions, if any, —

a special warning if necessary for the medicinal product, —

manufacturer's batch number, —

registration number, —

'homeopathic— medicinal— product— without— approved—therapeutic indications',—

a—warning—advising—the—user—to—consult—a—doctor—if—the—symptoms persist during the use of the medicinal product.—

2.— Notwithstanding—paragraph—1,—Member—States—may—require the use of certain types of labelling in order to show:—

the price of the medicinal product, —

the conditions for refunds by social security bodies. —

TITLE VI—

CLASSIFICATION OF MEDICINAL PRODUCTS

Article 70

1.— When—a—marketing—authorization—is—granted,—the—competent—authorities—shall—specify—the—classification—of—the—medicinal product into:—

a medicinal product subject to medical prescription,—

a medicinal product not subject to medical prescription.—

To this end, the criteria laid down in Article 71(1) shall apply.—

2.— The competent authorities may fix sub-categories for medicinal products which are available on medical prescription only.—In that case,—they shall refer to the following classification:—

(a) medicinal products on renewable or non-renewable medical prescription;—

(b) medicinal products subject to special medical prescription;—

(c) medicinal products on restricted medical prescription, reserved for use in certain specialized areas.—

Article 71

1.— Medicinal products shall be subject to medical prescription where they:—

are likely to present a danger either directly or indirectly, even when used correctly, if utilized without medical supervision, or—

are frequently and to a very wide extent used incorrectly, and as a result are likely to present a direct or indirect danger to human health, or—

contain substances or preparations thereof, the activity and/or adverse reactions of which require further investigation, or—

are normally prescribed by a doctor to be administered parenterally.—

2.— Where Member States provide for the sub-category of medicinal products subject to special medical prescription, they shall take account of the following factors:—

the medicinal product contains, in a non-exempt quantity, a substance classified as a narcotic or a psychotropic substance within the meaning of the international conventions in force, such as the United Nations Conventions of 1961 and 1971, or—

the medicinal product is likely, if incorrectly used, to present a substantial risk of medicinal abuse, to lead to addiction or be misused for illegal purposes, or—

the medicinal product contains a substance which, by reason of its novelty or properties, could be considered as belonging to the group envisaged in the second indent as a precautionary measure.—

3.— Where Member States provide for the sub-category of medicinal products subject to restricted prescription, they shall take account of the following factors:—

the medicinal product, because of its pharmaceutical characteristics or novelty or in the interests of public health, is reserved for treatments which can only be followed in a hospital environment,—

the medicinal product is used in the treatment of conditions which must be diagnosed in a hospital environment or in institutions with adequate diagnostic facilities, although administration and follow-up may be carried out elsewhere, or—

the medicinal product is intended for outpatients but its use may produce very serious adverse reactions requiring a prescription drawn up as required by a specialist and special supervision throughout the treatment.—

4.— A competent authority may waive application of paragraphs 1, 2 and 3 having regard to:—

(a) the maximum single dose, the maximum daily dose, the strength, the pharmaceutical form, certain types of packaging; and/or—

(b) other circumstances of use which it has specified.—

5.— If a competent authority does not designate medicinal products into sub-categories referred to in Article 70(2), it shall nevertheless take into account the criteria referred to in paragraphs 2 and 3 of this Article in determining whether any medicinal product shall be classified as a prescription-only medicine.—

Article 72

Medicinal products not subject to prescription shall be those which do not meet the criteria listed in Article 71.—

Article 73

The competent authorities shall draw up a list of the medicinal products subject, on their territory, to medical prescription, specifying, if necessary, the category of classification. They shall update this list annually.—

Article 74

On the occasion of the five-yearly renewal of the marketing authorization or when new facts are brought to their notice, the competent authorities shall examine and, as appropriate, amend the classification of a medicinal product, by applying the criteria listed in Article 71.—

Article 75

Each year, Member States shall communicate to the Commission and to the other Member States, the changes that have been made to the list referred to in Article 73.

TITLE VII

WHOLESALE DISTRIBUTION OF MEDICINAL PRODUCTS

Article 76

Without prejudice to Article 6, Member States shall take all appropriate action to ensure that only medicinal products in respect of which a marketing authorization has been granted in accordance with Community law are distributed on their territory.

Article 77

1. Member States shall take all appropriate measures to ensure that the wholesale distribution of medicinal products is subject to the possession of an authorization to engage in activity as a wholesaler in medicinal products, stating the place for which it is valid.

2. Where persons authorized or entitled to supply medicinal products to the public may also, under national law, engage in wholesale business, such persons shall be subject to the authorization provided for in paragraph 1.

3. Possession of a manufacturing authorization shall include authorization to distribute by wholesale the medicinal products covered by that authorization. Possession of an authorization to engage in activity as a wholesaler in medicinal products shall not give dispensation from the obligation to possess a manufacturing authorization and to comply with the conditions set out in that respect, even where the manufacturing or import business is secondary.

4. At the request of the Commission or any Member State, Member States shall supply all appropriate information concerning the individual authorizations which they have granted under paragraph 1.

5. Checks on the persons authorized to engage in the activity of wholesaler in medicinal products and the inspection of their premises, shall be carried out under the responsibility of the Member State which granted the authorization.

6. The Member State which granted the authorization referred to in paragraph 1 shall suspend or revoke that authorization if the conditions of authorization cease to be met. It shall forthwith inform the other Member States and the Commission thereof.

7. Should a Member State consider that, in respect of a person holding an authorization granted by another Member State under the terms of paragraph 1, the conditions of authorization are not, or are no longer met, it shall forthwith inform the Commission and the other Member State involved. The latter shall take the measures necessary and shall inform the Commission and the first Member State of the decisions taken and the reasons for those decisions.

Article 78

Member States shall ensure that the time taken for the procedure for examining the application for the distribution authorization does not exceed 90 days from the day on which the competent authority of the Member State concerned receives the application.

The competent authority may, if need be, require the applicant to supply all necessary information concerning the conditions of authorization. Where the authority exercises this option, the period laid down in the first paragraph shall be suspended until the requisite additional data have been supplied.

Article 79

In order to obtain the distribution authorization, applicants must fulfil the following minimum requirements:

(a) they must have suitable and adequate premises, installations and equipment, so as to ensure proper conservation and distribution of the medicinal products;

(b) they must have staff, and in particular, a qualified person designated as responsible, meeting the conditions provided for by the legislation of the Member State concerned;

(c) they must undertake to fulfil the obligations incumbent on them under the terms of Article 80.

Article 80

Holders of the distribution authorization must fulfil the following minimum requirements:

(a) they must make the premises, installations and equipment referred to in Article 79(a) accessible at all times to the persons responsible for inspecting them;

(b) they must obtain their supplies of medicinal products only from persons who are themselves in possession of the distribution authorization or who are exempt from obtaining such authorization under the terms of Article 77(3);

(c) they must supply medicinal products only to persons who are themselves in possession of the distribution authorization or who are authorized or entitled to supply medicinal products to the public in the Member State concerned;

(d) they must have an emergency plan which ensures effective implementation of any recall from the market ordered by the competent authorities or carried out in cooperation with the manufacturer or marketing authorization holder for the medicinal product concerned;—

(e) they must keep records either in the form of purchase/sales invoices, or on computer, or in any other form, giving for any transaction in medicinal products received or dispatched at least the following information:—

date,—

name of the medicinal product,—

quantity received or supplied,—

name and address of the supplier or consignee, as appropriate;—

(f) they must keep the records referred to under (e) available to the competent authorities, for inspection purposes, for a period of five years;—

(g) they must comply with the principles and guidelines of good distribution practice for medicinal products as laid down in Article 84.—

Article 81

With regard to the supply of medicinal products to pharmacists and persons authorized or entitled to supply medicinal products to the public, Member States shall not impose upon the holder of a distribution authorization which has been granted by another Member State, any obligation, in particular public service obligations, more stringent than those they impose on persons whom they have themselves authorized to engage in equivalent activities.—

The said obligations should, moreover, be justified, in keeping with the Treaty, on grounds of public health protection and be proportionate in relation to the objective of such protection.—

Article 82

For all supplies of medicinal products to a person authorized or entitled to supply medicinal products to the public in the Member State concerned, the authorized wholesaler must enclose a document that makes it possible to ascertain:—

the date,—

the name and pharmaceutical form of the medicinal product,—

the quantity supplied,—

the name and address of the supplier and consignor.—

Member States shall take all appropriate measures to ensure that persons authorized or entitled to supply medicinal products to the public are able to provide information that makes it possible to trace the distribution path of every medicinal product.—

Article 83

The provisions of this Title shall not prevent the application of more stringent requirements laid down by Member States in respect of the wholesale distribution of:—

narcotic or psychotropic substances within their territory,—

medicinal products derived from blood,—

immunological medicinal products,—

radiopharmaceuticals.—

Article 84

The Commission shall publish guidelines on good distribution practice. To this end, it shall consult the Committee for Proprietary Medicinal Products and the Pharmaceutical Committee established by Council Decision 75/320/EEC [1].—

Article 85

The provisions of this Title shall apply to homeopathic medicinal products, with the exception of those referred to in Article 14(1).—

TITLE VIII—

ADVERTISING

Article 86

1.— For the purposes of this Title, 'advertising of medicinal products' shall include any form of door-to-door information, canvassing activity or inducement designed to promote the prescription, supply, sale or consumption of medicinal products; it shall include in particular:—

the advertising of medicinal products to the general public,—

advertising of medicinal products to persons qualified to prescribe or supply them,—

visits by medical sales representatives to persons qualified to prescribe medicinal products,—

the supply of samples,—

[1] OJ L 187, 9.6.1975, p. 23.—

the provision of inducements to prescribe or supply medicinal products by the gift, offer or promise of any benefit or bonus, whether in money or in kind, except when their intrinsic value is minimal,—

sponsorship of promotional meetings attended by persons qualified to prescribe or supply medicinal products,—

sponsorship of scientific congresses attended by persons qualified to prescribe or supply medicinal products and in particular payment of their travelling and accommodation expenses in connection therewith.—

2.— The following are not covered by this Title:—

the labelling and the accompanying package leaflets, which are subject to the provisions of Title V,—

correspondence, possibly accompanied by material of a non-promotional nature, needed to answer a specific question about a particular medicinal product,—

factual, informative announcements and reference material relating, for example, to pack changes, adverse-reaction warnings as part of general drug precautions, trade catalogues and price lists, provided they include no product claims,—

statements relating to human health or diseases, provided there is no reference, even indirect, to medicinal products.—

Article 87

1.— Member States shall prohibit any advertising of a medicinal product in respect of which a marketing authorization has not been granted in accordance with Community law.—

2.— All parts of the advertising of a medicinal product must comply with the particulars listed in the summary of product characteristics.—

3.— The advertising of a medicinal product:—

shall encourage the rational use of the medicinal product, by presenting it objectively and without exaggerating its properties,—

shall not be misleading.—

Article 88

1.— Member States shall prohibit the advertising to the general public of medicinal products which:—

are available on medical prescription only, in accordance with Title VI,—

contain psychotropic or narcotic substances, such as the United Nations Conventions of 1961 and 1971,—

may not be advertised to the general public in accordance with the second subparagraph of paragraph 2.—

2.— Medicinal products may be advertised to the general public which, by virtue of their composition and purpose, are intended and designed for use without the intervention of a medical practitioner for diagnostic purposes or for the prescription or monitoring of treatment, with the advice of the pharmacist, if necessary.—

Member States shall prohibit the mentioning in advertising to the general public of therapeutic indications such as:—

tuberculosis,—

sexually transmitted diseases,—

other serious infectious diseases,—

cancer and other tumoral diseases,—

chronic insomnia,—

diabetes and other metabolic illnesses.—

3.— Member States shall be able to ban, on their territory, advertising to the general public of medicinal products the cost of which may be reimbursed.—

4.— The prohibition referred to in paragraph 1 shall not apply to vaccination campaigns carried out by the industry and approved by the competent authorities of the Member States.—

5.— The prohibition referred to in paragraph 1 shall apply without prejudice to Article 14 of Directive 89/552/EEC.—

6.— Member States shall prohibit the direct distribution of medicinal products to the public by the industry for promotional purposes; they may, however, authorize such distribution in special cases for other purposes.—

Article 89

1.— Without prejudice to Article 88, all advertising to the general public of a medicinal product shall:—

(a) be set out in such a way that it is clear that the message is an advertisement and that the product is clearly identified as a medicinal product;—

(b) include the following minimum information:—

the name of the medicinal product, as well as the common name if the medicinal product contains only one active substance,—

the information necessary for correct use of the medicinal product,—

an express, legible invitation to read carefully the instructions on the package leaflet or on the outer packaging, as the case may be.—

2.— Member States may decide that the advertising of a medicinal product to the general public may, notwithstanding paragraph 1, include only the name of the medicinal product if it is intended solely as a reminder.—

Article 90

The advertising of a medicinal product to the general public shall not contain any material which:—

(a) gives the impression that a medical consultation or surgical operation is unnecessary, in particular by offering a diagnosis or by suggesting treatment by mail;—

(b) suggests that the effects of taking the medicine are guaranteed, are unaccompanied by adverse reactions or are better than, or equivalent to, those of another treatment or medicinal product;—

(c) suggests that the health of the subject can be enhanced by taking the medicine;—

(d) suggests that the health of the subject could be affected by not taking the medicine; this prohibition shall not apply to the vaccination campaigns referred to in Article 88(4);—

(e) is directed exclusively or principally at children;—

(f) refers to a recommendation by scientists, health professionals or persons who are neither of the foregoing but who, because of their celebrity, could encourage the consumption of medicinal products;—

(g) suggests that the medicinal product is a foodstuff, cosmetic or other consumer product;—

(h) suggests that the safety or efficacy of the medicinal product is due to the fact that it is natural;—

(i) could, by a description or detailed representation of a case history, lead to erroneous self-diagnosis;—

(j) refers, in improper, alarming or misleading terms, to claims of recovery;—

(k) uses, in improper, alarming or misleading terms, pictorial representations of changes in the human body caused by disease or injury, or of the action of a medicinal product on the human body or parts thereof;—

(l) mentions that the medicinal product has been granted a marketing authorization.—

Article 91

1.— Any advertising of a medicinal product to persons qualified to prescribe or supply such products shall include:—

essential information compatible with the summary of product characteristics;—

the supply classification of the medicinal product.—

Member States may also require such advertising to include the selling price or indicative price of the various presentations and the conditions for reimbursement by social security bodies.—

2.— Member States may decide that the advertising of a medicinal product to persons qualified to prescribe or supply such products may, notwithstanding paragraph 1, include only the name of the medicinal product, if it is intended solely as a reminder.—

Article 92

1.— Any documentation relating to a medicinal product which is transmitted as part of the promotion of that product to persons qualified to prescribe or supply it shall include, as a minimum, the particulars listed in Article 91(1) and shall state the date on which it was drawn up or last revised.—

2.— All the information contained in the documentation referred to in paragraph 1 shall be accurate, up-to-date, verifiable and sufficiently complete to enable the recipient to form his or her own opinion of the therapeutic value of the medicinal product concerned.—

3.— Quotations as well as tables and other illustrative matter taken from medical journals or other scientific works for use in the documentation referred to in paragraph 1 shall be faithfully reproduced and the precise sources indicated.—

Article 93

1.— Medical sales representatives shall be given adequate training by the firm which employs them and shall have sufficient scientific knowledge to be able to provide information which is precise and as complete as possible about the medicinal products which they promote.—

2. During each visit, medical sales representatives shall give the persons visited, or have available for them, summaries of the product characteristics of each medicinal product they present together, if the legislation of the Member State so permits, with details of the price and conditions for reimbursement referred to in Article 91(1).

3. Medical sales representatives shall transmit to the scientific service referred to in Article 98(1) any information about the use of the medicinal products they advertise, with particular reference to any adverse reactions reported to them by the persons they visit.

Article 94

1. Where medicinal products are being promoted to persons qualified to prescribe or supply them, no gifts, pecuniary advantages or benefits in kind may be supplied, offered or promised to such persons unless they are inexpensive and relevant to the practice of medicine or pharmacy.

2. Hospitality at sales promotion shall always be reasonable in level and secondary to the main purpose of the meeting and must not be extended to other than health professionals.

3. Persons qualified to prescribe or supply medicinal products shall not solicit or accept any inducement prohibited under paragraph 1 or contrary to paragraph 2.

4. Existing measures or trade practices in Member States relating to prices, margins and discounts shall not be affected by paragraphs 1, 2 and 3.

Article 95

The provisions of Article 94(1) shall not prevent hospitality being offered, directly or indirectly, at events for purely professional and scientific purposes; such hospitality shall always be reasonable in level and remain subordinate to the main scientific objective of the meeting; it must not be extended to persons other than health professionals.

Article 96

1. Free samples shall be provided on an exceptional basis only to persons qualified to prescribe them and on the following conditions:

(a) the number of samples for each medicinal product each year on prescription shall be limited;

(b) any supply of samples shall be in response to a written request, signed and dated, from the prescribing agent;

(c) those supplying samples shall maintain an adequate system of control and accountability;

(d) each sample shall be identical with the smallest presentation on the market;

(e) each sample shall be marked 'free medical sample — not for sale' or shall show some other wording having the same meaning;

(f) each sample shall be accompanied by a copy of the summary of product characteristics;

(g) no samples of medicinal products containing psychotropic or narcotic substances within the meaning of international conventions, such as the United Nations Conventions of 1961 and 1971, may be supplied.

2. Member States may also place further restrictions on the distribution of samples of certain medicinal products.

Article 97

1. Member States shall ensure that there are adequate and effective methods to monitor the advertising of medicinal products. Such methods, which may be based on a system of prior vetting, shall in any event include legal provisions under which persons or organizations regarded under national law as having a legitimate interest in prohibiting any advertisement inconsistent with this Title, may take legal action against such advertisement, or bring such advertisement before an administrative authority competent either to decide on complaints or to initiate appropriate legal proceedings.

2. Under the legal provisions referred to in paragraph 1, Member States shall confer upon the courts or administrative authorities powers enabling them, in cases where they deem such measures to be necessary, taking into account all the interests involved, and in particular the public interest:

to order the cessation of, or to institute appropriate legal proceedings for an order for the cessation of, misleading advertising, or

if misleading advertising has not yet been published but publication is imminent, to order the prohibition of, or to institute appropriate legal proceedings for an order for the prohibition of, such publication,

even without proof of actual loss or damage or of intention or negligence on the part of the advertiser.

3. Member States shall make provision for the measures referred to in the second subparagraph to be taken under an accelerated procedure, either with interim effect or with definitive effect.

It shall be for each Member State to decide which of the two— options set out in the first subparagraph to select.—

4.— Member—States—may—confer—upon—the—courts—or— administrative authorities powers enabling them, with a view— to eliminating the continuing effects of misleading advertising— the cessation of which has been ordered by a final decision:—

to require publication of that decision in full or in part and— in such form as they deem adequate,—

to—require—in—addition—the—publication—of—a—corrective— statement.—

5.— Paragraphs 1 to 4 shall not exclude the voluntary control— of advertising of medicinal products by self-regulatory—bodies— and recourse to such bodies, if proceedings before such bodies— are—possible—in—addition—to—the—judicial—or—administrative— proceedings referred to in paragraph 1.—

Article 98

1.— The—marketing—authorization—holder—shall—establish,— within—his—undertaking,—a—scientific—service—in—charge—of— information about the medicinal products which he places on— the market.—

2.— The marketing authorization holder shall:—

keep—available for,—or communicate—to,—the authorities—or— bodies responsible for monitoring advertising of medicinal— products,—a—sample—of—all—advertisements—emanating—from— his—undertaking—together—with—a—statement—indicating—the— persons—to—whom—it—is—addressed,—the—method—of— dissemination and the date of first dissemination,—

ensure—that—advertising—of—medicinal—products—by—his— undertaking conforms to the requirements of this Title,—

verify—that—medical—sales—representatives—employed—by—his— undertaking—have—been—adequately—trained—and—fulfill—the— obligations imposed upon them by Article 93(2) and (3),—

supply the authorities or bodies responsible for monitoring— advertising of medicinal products with the information and— assistance they require to carry out their responsibilities,—

ensure that the decisions taken by the authorities or bodies— responsible—for—monitoring—advertising—of—medicinal— products are immediately and fully complied with.—

Article 99

Member States shall take the appropriate measures to ensure— that the provisions of this Title are applied and shall determine— in—particular—what—penalties—shall—be—imposed—should—the— provisions adopted in the execution of Title be infringed.—

Article 100

Advertising of the homeopathic medicinal products referred to— in—Article—13(2)—and—Article—14(1)—shall—be—subject—to—the— provisions of this Title with the exception of Article 87(1).—

However,—only the information specified in Article 69(1) may— be used in the advertising of such medicinal products.—

Moreover, each Member State may prohibit in its territory any— advertising of the homeopathic medicinal products referred to— in Article 13(2) and Article 14(1).—

TITLE IX—

PHARMACOVIGILANCE

Article 101

The—Member—States—shall—take—all—appropriate—measures—to— encourage—doctors—and—other—health—care—professionals—to— report—suspected—adverse—reactions—to—the—competent— authorities.—

The—Member—States—may—impose—specific—requirements—on— doctors and other health care professionals, in respect of the— reporting of suspected serious or unexpected adverse reactions,— in—particular—where—such—reporting—is—a—condition—of—the— marketing authorization.—

Article 102

In—order—to—ensure—the—adoption—of—appropriate—regulatory— decisions concerning the medicinal products authorized within— the Community, having regard to information obtained about— adverse—reactions—to—medicinal—products—under—normal— conditions—of—use,—the—Member—States—shall—establish—a— pharmacovigilance system. This system shall be used to collect— information—useful—in—the—surveillance—of—medicinal—products,— with particular reference to adverse reactions in human beings,— and to evaluate such information scientifically.—

Such information shall be collated with data on consumption— of medicinal products.—

This—system—shall—also—take—into—account—any—available— information on misuse and abuse of medicinal products which— may—have—an—impact—on—the—evaluation—of—their—benefits—and— risks.—

Article 103

The—marketing—authorization—holder—shall—have—permanently— and—continuously—at—his—disposal—an—appropriately—qualified— person responsible for pharmacovigilance.—

That qualified person shall be responsible for the following:

(a) the establishment and maintenance of a system which ensures that information about all suspected adverse reactions which are reported to the personnel of the company, and to medical representatives, is collected and collated in order to be accessible at least at one point within the Community;

(b) the preparation for the competent authorities of the reports referred to in Article 104, in such form as may be laid down by those authorities, in accordance with the guidance referred to in Article 106(1);

(c) ensuring that any request from the competent authorities for the provision of additional information necessary for the evaluation of the benefits and risks afforded by a medicinal product is answered fully and promptly, including the provision of information about the volume of sales or prescriptions of the medicinal product concerned;

(d) the provision to the competent authorities, of any other information relevant to the evaluation of the benefits and risks afforded by a medicinal product, including appropriate information on post-authorization safety studies.

Article 104

1. The marketing authorization holder shall be required to maintain detailed records of all suspected adverse reactions occurring either in the Community or in a third country.

2. The marketing authorization holder shall be required to record and to report all suspected serious adverse reactions which are brought to his attention by a health care professional immediately to the competent authority of the Member State in whose territory the incident occurred, and in no case later than 15 calendar days following the receipt of the information.

3. The marketing authorization holder shall be required to record and report all other suspected serious adverse reactions which meet the reporting criteria in accordance with the guidance referred to in Article 106(1) of which he can reasonably be expected to have knowledge immediately to the competent authority of the Member State in whose territory the incident occurred, and in no case later than 15 calendar days following the receipt of the information.

4. The marketing authorization holder shall ensure that all suspected serious and unexpected adverse reactions occurring in the territory of a third country and brought to his attention by a health care professional are reported immediately in accordance with the guidance referred to in Article 106(1), so that they are available to the Agency and to the competent authorities of the Member States where the medicinal product is authorised, and in no case later than 15 calendar days following the receipt of the information.

5. In the case of medicinal products which have been considered within the scope of Directive 87/22/EEC, or which have benefited from the procedures of mutual recognition foreseen in Articles 17 and 18 of this Directive, Article 28(4) of this Directive, and medicinal products for which there has been a referral to the procedures foreseen by Articles 32, 33 and 34 of this Directive, the marketing authorisation holder shall additionally ensure that all suspected serious adverse reactions occurring in the Community are reported in the format and at intervals to be agreed with the reference Member State, or a competent authority acting as the reference Member State, in such a way so as to be accessible to the reference Member State.

6. Unless other requirements have been laid down as a condition of the granting of authorisation, or subsequently as indicated in the guidance referred to in Article 106(1), records of all adverse reactions shall be submitted to the competent authorities in the form of a periodic safety update report, either immediately upon request or periodically as follows: six monthly for the first two years after authorisation, annually for the subsequent two years, and at the time of the first renewal. Thereafter the periodic safety update reports shall be submitted at five-yearly intervals together with the application for renewal of the authorisation. The periodic safety update reports shall include a scientific evaluation of the benefit and risks afforded by the medicinal products.

7. Following the granting of a marketing authorisation, the marketing authorisation holder may request the amendment of the periods referred to in this article according to the procedure laid down by Commission Regulation (EC) No 541/95 [1].

Article 105

1. The Agency, in collaboration with the Member States and the Commission shall set up a data-processing network to facilitate the exchange of pharmacovigilance information regarding medicinal products marketed in the Community intended to allow all competent authorities to share the information at the same time.

2. Making use of the network foreseen in paragraph 1, Member States shall ensure that reports of suspected serious adverse reactions that have taken place on their territory are immediately made available to the Agency and the other Member States, and in any case within 15 calendar days of their notification, at the latest.

3. The Member States shall ensure that reports of suspected serious adverse reactions that have taken place on their territory are immediately made available to the marketing authorisation holder, and in any case within 15 calendar days of their notification, at the latest.

[1] OJ L 55, 11.3.1995, p. 7. Regulation amended by Regulation (EC) No 1146/98 (OJ L 159, 3.6.1998, p. 31).

Article 106

1.— In order to facilitate the exchange of information about— pharmacovigilance within the Community, the Commission, in— consultation with the Agency, Member States and interested— parties, shall draw up guidance on the collection, verification— and— presentation— of— adverse— reaction— reports,— including— technical— requirements— for— electronic— exchange— of— pharmacovigilance— information— in— accordance— with— internationally agreed formats and shall publish a reference to— an internationally agreed medical terminology.—

This guidance shall be published in Volume 9 of The rules— governing medicinal products in the European Community and— shall take account of international harmonisation work carried— out in the field of pharmacovigilance.—

2.— For the interpretation of the definitions referred to in— Article 1 points 11 to 16 and the principles outlined in this— Title, the marketing authorisation holder and the competent— authorities shall refer to the guidance referred to in paragraph— 1.—

Article 107

1.— Where, as a result of the evaluation of pharmacovigilance— data, a Member State considers that a marketing authorisation— should be suspended, withdrawn or varied in accordance with— the guidance referred to in Article 106(1), it shall forthwith— inform— the— Agency,— the— other— Member— States— and— the— marketing authorisation holder.—

2.— In case of urgency, the Member State concerned may— suspend the marketing authorisation of a medicinal product,— provided the Agency, the Commission and the other Member— States are informed at the latest on the following working day.—

Article 108

Any— amendments— which— may— be— necessary— to— update— provisions of Articles 101 to 107 to take account of scientific— and technical progress shall be adopted in accordance with the— procedure referred to in Article 121(2).—

TITLE X—

SPECIAL PROVISIONS ON MEDICINAL PRODUCTS DERIVED FROM HUMAN BLOOD AND PLASMA

Article 109

1.— In respect of the use of human blood or human plasma— as— a— starting— material— for— the— manufacture— of— medicinal— products, Member States shall take the necessary measures to— prevent the transmission of infectious diseases. In so far as this— is covered by the amendments referred to in Article 121(1), as— well as the application of the monographs of the European— Pharmacopoeia regarding blood and plasma, these measures— shall comprise those recommended by the Council of Europe— and the World Health Organization, particularly with reference— to the selection and testing of blood and plasma donors.—

2.— Member States shall take the necessary measures to— ensure that human blood and human plasma donors and— donation centres are always clearly identifiable.—

3.— All the safety guarantees referred to in paragraphs 1 and— 2 must also be given by importers of human blood or human— plasma from third countries.—

Article 110

Member States shall take the necessary measures to promote— Community self-sufficiency in human blood or human plasma.— For this purpose, they shall encourage the voluntary unpaid— donation of blood and plasma and shall take the necessary— measures to develop the production and use of products— derived from human blood or human plasma coming from— voluntary unpaid donations. They shall notify the Commission— of such measures.—

TITLE XI—

SUPERVISION AND SANCTIONS

Article 111

1.— The competent authority of the Member State concerned— shall ensure, by means of repeated inspections, that the legal— requirements governing medicinal products are complied with.—

Such inspections shall be carried out by officials representing— the competent authority who shall be empowered to:—

(a) inspect manufacturing or commercial establishments and— any— laboratories— entrusted— by— the— holder— of— the— manufacturing authorization with the task of carrying out— checks pursuant to Article 20;—

(b) take samples;—

(c) examine any documents relating to the object of the— inspection, subject to the provisions in force in the— Member— States— on— 21— May— 1975— and— which— place— restrictions— on— these— powers— with— regard— to— the— descriptions of the method of preparation.—

2.— Member States shall take all appropriate steps to ensure— that the manufacturing processes used in the manufacture of— immunological— products— are— properly— validated— and— attain— batch-to-batch consistency.—

3.— After every inspection as referred to in paragraph 1, the— officials representing the competent authority shall report on— whether the manufacturer complies with the principles and—

guidelines of good manufacturing practice laid down in Article— 47. The content of such reports shall be communicated to the— manufacturer who has to undergo the inspection.—

Article 112

Member States shall take all appropriate measures to ensure— that the holder of the marketing authorization for a medicinal— product— and,— where— appropriate,— the— holder— of— the— manufacturing—authorization,—furnish—proof—of—the—controls— carried—out—on—the—medicinal—product—and/or—the—ingredients— and of the controls carried out at an intermediate stage of the— manufacturing—process,—in—accordance—with—the—methods—laid— down in Article 8(3)(h).—

Article 113

For the purpose of implementing Article 112, Member States— may—require—manufacturers—of—immunological—products—to— submit—to—a—competent—authority—copies—of—all—the—control— reports—signed—by—the—qualified—person—in—accordance—with— Article 51.—

Article 114

1.— Where it considers it necessary in the interests of public— health,—a—Member—State—may—require—the—holder—of—an— authorization for marketing:—

live vaccines,—

immunological—medicinal—products—used—in—the—primary— immunization of infants or of other groups at risk,—

immunological—medicinal—products—used—in—public—health— immunization programmes,—

new immunological medicinal products or immunological— medicinal—products—manufactured—using—new—or—altered— kinds of technology or new for a particular manufacturer,— during—a—transitional—period—normally—specified—in—the— marketing authorization,—

to—submit—samples—from—each—batch—of—the—bulk—and/or—the— medicinal product for examination—by a State laboratory or a— laboratory designated for that purpose before release on to the— market unless, in the case of a batch manufactured in another— Member State, the competent authority of that Member State— has previously examined the batch in question and declared it— to be in conformity with the approved specifications. Member— States—shall—ensure—that—any—such—examination—is—completed— within 60 days of the receipt of the samples.—

2.— Where,—in—the—interests—of—public—health,—the—laws—of—a— Member—State—so—provide,—the—competent—authorities—may— require—the—marketing—authorization—holder—for—medicinal— products—derived—from—human—blood—or—human—plasma—to— submit—samples—from—each—batch—of—the—bulk—and/or—the— medicinal—product—for—testing—by—a—State—laboratory—or—a— laboratory—designated—for—that—purpose—before—being—released— into—free—circulation,—unless—the—competent—authorities—of— another Member State have previously examined the batch in— question and declared it to be in conformity with the approved— specifications.—Member—States—shall—ensure—that—any—such— examination is completed within 60 days of the receipt of the— samples.—

Article 115

Member States shall take all necessary measures to ensure that— the—manufacturing—and—purifying—processes—used—in—the— preparation of medicinal products derived from human blood— or human plasma are properly validated, attain batch-to-batch— consistency—and—guarantee,—insofar as—the state—of technology— permits,—the—absence—of—specific—viral—contamination.—To—this— end manufacturers shall notify the competent authorities of the— method used to reduce or eliminate pathogenic viruses liable— to be transmitted by medicinal products derived from human— blood or human plasma. The competent authority may submit— samples of the bulk and/or the medicinal product for testing— by—a—State—laboratory—or—a—laboratory—designated—for—that— purpose,—either—during—the—examination—of—the—application— pursuant to Article 19, or after a marketing authorization has— been granted.—

Article 116

The competent authorities of the Member States shall suspend— or revoke an authorization to place a medicinal product on the— market where that product proves to be harmful in the normal— conditions of use, or where—its therapeutic efficacy—is lacking,— or where its qualitative and quantitative composition is not as— declared. Therapeutic efficacy is lacking when it is established— that therapeutic results cannot be obtained with the medicinal— product.—

An—authorization—shall—also—be—suspended—or—revoked—where— the—particulars—supporting—the—application—as—provided—for— in—Articles—8,—10(1)—and—11—are—incorrect—or—have—not—been— amended in accordance with Article 23, or where the controls— referred to in Article 112 have not been carried out.—

Article 117

1.— Notwithstanding—the—measures—provided—for—in—Article— 116,—Member—States—shall—take—all—appropriate—measures—to— ensure—that—the—supply—of—the—medicinal—product—shall—be— prohibited—and—the—medicinal—product—withdrawn—from—the— market if:—

(a)—the medicinal product proves to be harmful under normal— conditions of use, or—

(b)—it is lacking in therapeutic efficacy, or—

(c)—its—qualitative—and—quantitative—composition—is—not—as— declared, or—

(d) the controls on the medicinal product and/or on the ingredients and the controls at an intermediate stage of the manufacturing process have not been carried out or if some other requirement or obligation relating to the grant of the manufacturing authorization has not been fulfilled.—

2.— The competent authority may limit the prohibition to supply the product, or its withdrawal from the market, to those batches which are the subject of dispute.—

Article 118

1.— The competent authority shall suspend or revoke the marketing authorization for a category of preparations or all preparations where any one of the requirements laid down in Article 41 is no longer met.—

2.— In addition to the measures specified in Article 117, the competent authority may suspend manufacture or imports of medicinal products coming from third countries, or suspend or revoke the manufacturing authorization for a category of preparations or all preparations where Articles 42, 46, 51 and 112 are not complied with.—

Article 119

The provisions of this Title shall apply to homeopathic medicinal products, subject to the provisions of Article 14(3).—

TITLE XII—

STANDING COMMITTEE

Article 120

Any changes which are necessary in order to adapt Annex I to take account of scientific and technical progress shall be adopted in accordance with the procedure referred to in Article 121(2).—

Article 121

1.— The Commission shall be assisted by a Standing Committee on Medicinal Products for Human Use on the Adaptation to Technical Progress of the Directives on the Removal of Technical Barriers to Trade in the Medicinal Products Sector, (hereinafter referred to as the 'Standing Committee').—

2.— Where reference is made to this paragraph, Articles 5 and 7 of Decision 1999/468/EC shall apply, having regard to Article 8 thereof.—

The period provided for in Article 5(6) of Decision 1999/468/EC shall be set at three months.—

3.— The Standing Committee shall adopt its rules of procedure.—

TITLE XIII—

GENERAL PROVISIONS

Article 122

Member States shall take all appropriate measures to ensure that the competent authorities concerned communicate to each other such information as is appropriate to guarantee that the requirements for the manufacturing authorizations or marketing authorizations are fulfilled.—

Upon reasoned request, Member States shall forthwith communicate the reports referred to in Article 111(3) to the competent authorities of another Member State. If, after considering the reports, the Member State receiving the reports considers that it cannot accept the conclusions reached by the competent authorities of the Member State in which the report was established, it shall inform the competent authorities concerned of its reasons and may request further information. The Member States concerned shall use their best endeavours to reach agreement. If necessary, in the case of serious differences of opinion, the Commission shall be informed by one of the Member States concerned.—

Article 123

1.— Each Member State shall take all the appropriate measures to ensure that decisions authorizing marketing, refusing or revoking a marketing authorization, cancelling a decision refusing or revoking a marketing authorization, prohibiting supply, or withdrawing a product from the market, together with the reasons on which such decisions are based, are brought to the attention of the Agency forthwith.—

2.— The marketing authorization holder shall be obliged to notify the Member States concerned forthwith of any action taken by him to suspend the marketing of a medicinal product or to withdraw a medicinal product from the market, together with the reasons for such action if the latter concerns the efficacy of the medicinal product or the protection of public health. Member States shall ensure that this information is brought to the attention of the Agency.—

3.— Member States shall ensure that appropriate information about action taken pursuant to paragraphs 1 and 2 which may affect the protection of public health in third countries is forthwith brought to the attention of the World Health Organization, with a copy to the Agency.—

4.— The Commission shall publish annually a list of the medicinal products which are prohibited in the Community.—

Article 124

Member States shall communicate to each other all the information necessary to guarantee the quality and safety of homeopathic medicinal products manufactured and marketed within the Community, and in particular the information referred to in Articles 122 and 123.—

Article 125

Every decision referred to in this Directive which is taken by the competent authority of a Member State shall state in detail the reasons on which it is based.—

Such decision shall be notified to the party concerned, together with information as to the redress available to him under the laws in force and of the time-limit allowed for access to such redress.—

Marketing authorizations, and decisions to revoke such authorizations, shall be published by each Member State in the appropriate official publication.—

Article 126

An authorization to market a medicinal product shall not be refused, suspended or revoked except on the grounds set out in this Directive.—

No decision concerning suspension of manufacture or of importation of medicinal products coming from third countries, prohibition of supply or withdrawal from the market of a medicinal product may be taken except on the grounds set out in Articles 117 and 118.—

Article 127

1.— At the request of the manufacturer, the exporter or the authorities of an importing third country, Member States shall certify that a manufacturer of medicinal products is in possession of the manufacturing authorization. When issuing such certificates Member States shall comply with the following conditions:—

(a) they shall have regard to the prevailing administrative arrangements of the World Health Organization;—

(b) for medicinal products intended for export which are already authorized on their territory, they shall supply the summary of the product characteristics as approved in accordance with Article 21.—

2.— When the manufacturer is not in possession of a marketing authorization he shall provide the authorities responsible for establishing the certificate referred to in paragraph 1, with a declaration explaining why no marketing authorization is available.—

TITLE XIV—

FINAL PROVISIONS

Article 128

Directives 65/65/EEC, 75/318/EEC, 75/319/EEC, 89/342/EEC, 89/343/EEC, 89/381/EEC, 92/25/EEC, 92/26/EEC, 92/27/EEC, 92/28/EEC and 92/73/EEC, amended by the Directives referred to in Annex II, Part A, are repealed, without prejudice to the obligations of the Member States concerning the time-limits for implementation set out in Annex II, Part B.—

References to the repealed Directives shall be construed as references to this Directive and shall be read in accordance with the correlation table in Annex III.—

Article 129

This Directive shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Communities*.—

Article 130

This Directive is addressed to the Member States.—

Done at Brussels, 6 November 2001.—

For the European Parliament	*For the Council*
The President	*The President*
N. FONTAINE—	D. REYNDERS—

ANNEX I

ANALYTICAL, PHARMACOTOXICOLOGICAL AND CLINICAL STANDARDS AND PROTOCOLS IN RESPECT OF THE TESTING OF MEDICINAL PRODUCTS

INTRODUCTION—

The particulars and documents accompanying an application for marketing authorization pursuant to Articles 8 and— 10(1) shall be presented in four parts, in accordance with the requirements set out in this Annex and taking account of— the guidance published by the Commission in *The rules governing medicinal products in the European Community*,Volume II:— *Notice to applicants for marketing authorizations for medicinal products for human use in the Member States of the European Community*.—

In assembling the dossier for application for marketing authorization, applicants shall take into account the Community— guidelines relating to the quality, safety and efficacy of medicinal products published by the Commission in *The rules governing medicinal products in the European Community*, Volume III and its supplements: *Guidelines on the quality, safety and efficacy of medicinal products for human use*.—

All information which is relevant to the evaluation of the medicinal product concerned shall be included in the— application, whether favourable or unfavourable to the product. In particular, all relevant details shall be given of any— incomplete or abandoned pharmacotoxicological or clinical test or trial relating to the medicinal product. Moreover, in— order to monitor the benefit/risk assessment after marketing authorization has been granted, any change to the data in— the dossier, any new information not in the original application and all pharmacovigilance reports, shall be submitted— to the competent authorities.—

The general sections of this Annex give the requirements for all categories of medicinal products; they are— supplemented by sections containing additional special requirements for radiopharmaceuticals and for biological— medicinal products, such as immunological medicinal products derived from human blood or plasma. The additional— special requirements for biological medicinal products are also applicable to medicinal products obtained through— processes mentioned in Part A and the first indent of Part B of the Annex to Regulation (EEC) No 2309/93.—

Member States shall also ensure that all tests on animals are conducted in accordance with Council Directive— 86/609/EEC of 24 November 1986 on the approximation of laws, regulation and administrative provisions of the— Member States regarding the protection of animals for experimental and other scientific purposes ([1]).—

PART I—

SUMMARY OF THE DOSSIER

A.—**Administrative data**

The medicinal product which is the subject of the application shall be identified by name and name of the active— substance(s), together with the pharmaceutical form, the method of administration, the strength and the final— presentation, including packaging.—

The name and address of the applicant shall be given, together with the name and address of the manufacturers— and the sites involved in the different stages of the manufacture (including the manufacturer of the finished— product and the manufacturer(s) of the active substance(s)), and where relevant the name and address of the— importer.—

The applicant shall identify the number of volumes of documentation submitted in support of the application and— indicate what samples, if any, are also provided.—

Annexed to the administrative data shall be copies of the manufacturing authorization as defined in Article 40,— together with a list of countries in which authorization has been granted, copies of all the summaries of product— characteristics in accordance with Article 11 as approved by Member States and a list of countries in which an— application has been submitted.—

B.—**Summary of product characteristics**

The applicant shall propose a summary of the product characteristics, in accordance with Article 11.—

([1]) OJ L 358, 18.12.1986, p.1.—

In addition the applicant shall provide samples or mock-ups of the packaging, labels and package leaflets for the— medicinal product concerned.—

C.—**Expert reports**

In accordance with Article 12(2), expert reports must be provided on the chemical, pharmaceutical and biological— documentation, the pharmacotoxicological documentation and the clinical documentation respectively.—

The expert report shall consist of a critical evaluation of the quality of the medicinal product and the investigations— carried out on animals and human beings and bring out all the data relevant for evaluation. It shall be worded so— as to enable the reader to obtain a good understanding of the properties, quality, the proposed specifications and— control methods, the safety, the efficacy, the advantages and disadvantages of the medicinal product.—

All important data shall be summarized in an appendix to the expert report, whenever possible including report— formats in tabular or in graphic form. The expert report and the summaries shall contain precise cross references— to the information contained in the main documentation.—

Each expert report shall be prepared by a suitably qualified and experienced person. It shall be signed and dated by— the expert, and attached to the report shall be brief information about the educational background, training and— professional experience of the expert. The professional relationship of the expert to the applicant shall be declared.—

PART 2—

CHEMICAL, PHARMACEUTICAL AND BIOLOGICAL TESTING OF MEDICINAL PRODUCTS

All the test procedures shall correspond to the state of scientific progress at the time and shall be validated procedures;— results of the validation studies shall be provided.—

All the test procedure(s) shall be described in sufficiently precise detail so as to be reproducible in control tests, carried— out at the request of the competent authority; any special apparatus and equipment which may be used shall be— described in adequate detail, possibly accompanied by a diagram. The formulae of the laboratory reagents shall be— supplemented, if necessary, by the manufacturing method. In the case of test procedures included in the *European Pharmacopoeia* or the pharmacopoeia of a Member State, this description may be replaced by a detailed reference to the— pharmacopoeia in question.—

A.—**Qualitative and quantitative particulars of the constituents**

The particulars and documents which must accompany applications for marketing authorization, pursuant to point 3— of Article 8(3)(c) shall be submitted in accordance with the following requirements.—

1.— *Qualitative particulars*

1.1.—'Qualitative particulars' of all the constituents of the medicinal product shall mean the designation or description— of:—

the active substance(s),—

the constituent(s) of the excipients, whatever their nature or the quantity used, including colouring matter,— preservatives, adjuvants, stabilizers, thickeners, emulsifiers, flavouring and aromatic substances, etc.,—

the constituents, intended to be ingested or otherwise administered to the patient, of the outer covering of— the medicinal products— capsules, gelatine capsules, rectal capsules, etc.—

These particulars shall be supplemented by any relevant data concerning the container and, where appropriate, its— manner of closure, together with details of devices with which the medicinal product will be used or administered— and which will be delivered with the medicinal product.—

1.2.—In the context of a radiopharmaceutical kit, which is to be radiolabelled after supply by the manufacturer, the— active substance is considered to be that part of the formulation which is intended to carry or bind the— radionuclide. Details of the source of the radionuclide shall be stated. In addition, any compounds essential for the— radiolabelling shall be stated.—

In a generator, both mother and daughter radionuclides are to be considered as active substances.—

2. — The 'usual terminology', to be used in describing the constituents of medicinal products, shall mean, notwithstanding the application of the other provisions in Article 8(3)(c):

in respect of substances which appear in the *European Pharmacopoeia* or, failing this, in the national pharmacopoeia of one of the Member States, the main title at the head of the monograph in question, with reference to the pharmacopoeia concerned,

in respect of other substances, the international non-proprietary name recommended by the World Health Organization, which may be accompanied by another non-proprietary name, or, failing these, the exact scientific designation; substances not having an international non-proprietary name or an exact scientific designation shall be described by a statement of how and from what they were prepared, supplemented, where appropriate, by any other relevant details,

in respect of colouring matter, designation by the 'E' code assigned to them in Council Directive 78/25/EEC of 12 December 1977 on the approximation of the rules of the Member States concerning the colouring matters authorized for use in medicinal products [1].

3. — *Quantitative particulars*

3.1. In order to give 'quantitative particulars' of the active substances of the medicinal products, it is necessary, depending on the pharmaceutical form concerned, to specify the mass, or the number of units of biological activity, either per dosage-unit or per unit of mass or volume, of each active substance.

Units of biological activity shall be used for substances which cannot be defined chemically. Where an International Unit of biological activity has been defined by the World Health Organization, this shall be used. Where no International Unit has been defined, the units of biological activity shall be expressed in such a way as to provide unambiguous information on the activity of the substances.

Whenever possible, biological activity per units of mass shall be indicated.

This information shall be supplemented:

in respect of injectable preparations, by the mass or units of biological activity of each active substance in the unit container, taking into account the usable volume of the product, after reconstitution, where appropriate,

in respect of medicinal products to be administered by drops, by the mass or units of biological activity of each active substance contained in the number of drops corresponding to 1 ml or 1 g of the preparation,

in respect of syrups, emulsions, granular preparations and other pharmaceutical forms to be administered in measured quantities, by the mass or units of biological activity of each active substance per measured quantity.

3.2. Active substances present in the form of compounds or derivatives shall be designated quantitatively by their total mass, and if necessary or relevant, by the mass of the active entity or entities of the molecule.

3.3. For medicinal products containing an active substance which is the subject of an application for marketing authorization in any Member State for the first time, the quantitative statement of an active substance which is a salt or hydrate shall be systematically expressed in terms of the mass of the active entity or entities in the molecule. All subsequently authorized medicinal products in the Member States shall have their quantitative composition stated in the same way for the same active substance.

3.4. For allergen products, the quantitative particulars shall be expressed by units of biological activity, except for well defined allergen products for which the concentration may be expressed by mass/unit of volume.

3.5. The requirement to express the content of active substances in terms of the mass of active entities, as in point 3.3. above, may not apply to radiopharmaceuticals. For radionuclides, radioactivity shall be expressed in becquerels at a given date and, if necessary, time with reference to time zone. The type of radiation shall be indicated.

4. — *Development pharmaceutics*

4.1. An explanation should be provided with regard to the choice of composition, constituents and container and the intended function of the excipients in the finished product. This explanation shall be supported by scientific data on development pharmaceutics. The overage during manufacture, with justification thereof, should be stated.

[1] OJ L 11, 14.1.1978, p. 18. Directive as last amended by the 1985 Act of Accession.

4.2.—For radiopharmaceuticals, this should include a consideration of chemical/radiochemical purity and its relationship— to biodistribution.—

B. — **Description of manufacturing method**

1. — The description of the manufacturing method accompanying the application for marketing authorization pursuant— to Article 8(3)(d), shall be drafted in such a way as to give an adequate synopsis of the nature of the operations— employed.—

For this purpose it shall include at least:—

mention of the various stages of manufacture, so that an assessment can be made of whether the processes— employed in producing the pharmaceutical form might have produced an adverse change in the constituents,—

in the case of continuous manufacture, full details concerning precautions taken to ensure the homogeneity— of the finished product,—

the actual manufacturing formula, with the quantitative particulars of all the substances used, the quantities— of excipients, however, being given in approximate terms in so far as the pharmaceutical form makes this— necessary; mention shall be made of any substances that may disappear in the course of manufacture; any— overage shall be indicated and justified,—

a statement of the stages of manufacture at which sampling is carried out for in-process control tests, where— other data in the documents supporting the application show such tests to be necessary for the quality— control of the finished product,—

experimental studies validating the manufacturing process, where a non-standard method of manufacture is— used or where it is critical for the product,—

for sterile medicinal products, details of the sterilization processes and/or aseptic procedures used.—

2. — For radiopharmaceutical kits, the description of the manufacturing method shall also include details of the— manufacture of the kit and details of its recommended final processing to produce the radioactive medicinal— product.—

For radionuclides, the nuclear reactions involved shall be discussed.—

C. — **Controls of starting materials**

1. — For the purposes of this section, 'starting materials' shall mean all the constituents of the medicinal product and, if— necessary, of its container, as referred to in Section A, point 1, above.—

In the case of:—

an active substance not described in the *European Pharmacopoeia* or in the pharmacopoeia of a Member State,— or—

an active substance described in the *European Pharmacopoeia* or in the pharmacopoeia of a Member State— when prepared by a method liable to leave impurities not mentioned in the pharmacopoeial monograph and— for which the monograph is inappropriate to adequately control its quality,—

which is manufactured by a person different from the applicant, the latter may arrange for the detailed— description of the manufacturing method, quality control during manufacture and process validation to be— supplied directly to the competent authorities by the manufacturer of the active substance. In this case, the— manufacturer shall however provide the applicant with all the data which may be necessary for the latter to— take responsibility for the medicinal product. The manufacturer shall confirm in writing to the applicant that— he shall ensure batch to batch consistency and not modify the manufacturing process or specifications— without informing the applicant. Documents and particulars supporting the application for such a change— shall be supplied to the competent authorities.—

The particulars and documents accompanying the application for marketing authorization pursuant to Article— 8(3)(h) and (i) and 10(1), shall include the results of the tests, including batch analyses particularly for active— substances, relating to quality control of all the constituents used. These shall be submitted in accordance with the— following provisions.—

1.1.—Starting materials listed in pharmacopoeias—

The monographs of the *European Pharmacopoeia* shall be applicable to all substances appearing in it.—

In respect of other substances, each Member State may require observance of its own national pharmacopoeia— with regard to products manufactured in its territory.—

Constituents fulfilling the requirements of the *European Pharmacopoeia* or the pharmacopoeia of one of the Member States shall be deemed to comply sufficiently with Article 8(3)(h). In this case the description of the analytical methods may be replaced by a detailed reference to the pharmacopoeia in question.

However, where a starting material in the *European Pharmacopoeia* or in the pharmacopoeia of a Member State has been prepared by a method liable to leave impurities not controlled in the pharmacopoeia monograph, these impurities and their maximum tolerance limits must be declared and a suitable test procedure must be described.

Colouring matter shall, in all cases, satisfy the requirements of Directive 78/25/EEC.

The routine tests carried out on each batch of starting materials must be as stated in the application for marketing authorization. If tests other than those mentioned in the pharmacopoeia are used, proof must be supplied that the starting materials meet the quality requirements of that pharmacopoeia.

In cases where a specification contained in a monograph of the *European Pharmacopoeia* or in the national pharmacopoeia of a Member State might be insufficient to ensure the quality of the substance, the competent authorities may request more appropriate specifications from the marketing authorization holder.

The competent authorities shall inform the authorities responsible for the pharmacopoeia in question. The marketing authorization holder shall provide the authorities of that pharmacopoeia with the details of the alleged insufficiency and the additional specifications applied.

In cases where a starting material is described neither in the *European Pharmacopoeia* nor in the pharmacopoeia of a Member State, compliance with the monograph of a third country pharmacopoeia can be accepted; in such cases, the applicant shall submit a copy of the monograph accompanied where necessary by the validation of the test procedures contained in the monograph and by a translation where appropriate.

1.2. Starting materials not in a pharmacopoeia

Constituents which are not given in any pharmacopoeia shall be described in the form of a monograph under the following headings:

(a) the name of the substance, meeting the requirements of Section A, point 2, shall be supplemented by any trade or scientific synonyms;

(b) the definition of the substance, set down in a form similar to that used in the European Pharmacopoeia, shall be accompanied by any necessary explanatory evidence, especially concerning the molecular structure where appropriate; it must be accompanied by an appropriate description of the method of synthesis. Where substances can only be described by their manufacturing method, the description should be sufficiently detailed to characterize a substance which is constant both in its composition and in its effects;

(c) methods of identification may be described in the form of complete techniques as used for production of the substance, and in the form of tests which ought to be carried out as a routine matter;

(d) purity tests shall be described in relation to the sum total of predictable impurities, especially those which may have a harmful effect, and, if necessary, those which, having regard to the combination of substances to which the application refers, might adversely affect the stability of the medicinal product or distort analytical results;

(e) with regard to complex substances of plant or animal/human origin, a distinction must be made between the case where multiple pharmacological effects render chemical, physical or biological control of the principal constituents necessary, and the case of substances containing one or more groups of principles having similar activity, in respect of which an overall method of assay may be accepted;

(f) when materials of animal/human origin are used, measures to ensure freedom from potentially pathogenic agents shall be described;

(g) for radionuclides, the nature of the radionuclide, the identity of the isotope, likely impurities, the carrier, the use and the specific activity shall be given;

(h) any special precautions that may be necessary during storage of the starting material and, if necessary, the maximum period of storage before retesting shall be given.

1.3. Physico-chemical characteristics liable to effect bio-availability

The following items of information concerning active substances, whether or not listed in the pharmacopoeias, shall be provided as part of the general description of the active substances if the bio-availability of the medicinal product depends on them:

crystalline form and solubility coefficients,

particle size, where appropriate after pulverization,

state of solvation,

oil/water coefficient of partition ([1]).

The first three indents are not applicable to substances used solely in solution.

2. — For biological medicinal products, such as immunological medicinal products and medicinal products derived from human blood or plasma, the requirements of this paragraph shall apply.

For the purposes of this paragraph, starting materials shall mean any substance used in the manufacture of the medicinal product; this includes the constituents of the medicinal product, and, if necessary, of its container, as referred to in paragraph A, point 1 above, as well as source materials such as microorganisms, tissues of either plant or animal origin, cells or fluids (including blood) of human or animal origin, and biotechnological cell constructs. The origin and history of starting materials shall be described and documented.

The description of the starting material shall include the manufacturing strategy, purification/inactivation procedures with their validation and all in-process control procedures designed to ensure the quality, safety and batch to batch consistency of the finished product.

2.1. When cell banks are used, the cell characteristics shall be shown to have remained unchanged at the passage level used for the production and beyond.

2.2. Seed materials, cell banks, pools of serum or plasma and other materials of biological origin and, whenever possible, the source materials from which they are derived shall be tested for adventitious agents.

If the presence of potentially pathogenic adventitious agents is inevitable, the correspondant material shall be used only when further processing ensures their elimination and/or inactivation, and this shall be validated.

2.3. Whenever possible, vaccine production shall be based on a seed lot system and on established cell banks; for serums, defined pools of starting materials shall be used.

For bacterial and viral vaccines, the characteristics of the infectious agent shall be demonstrated on the seed. In addition, for live vaccines, the stability of the attenuation characteristics shall be demonstrated on the seed; if this proof is not sufficient, the attenuation characteristics shall also be demonstrated at the production stage.

2.4. For allergen products, the specifications and control methods for the source materials shall be described in as much detail as possible. The description shall include particulars concerning collection, pretreatment and storage.

2.5. For medicinal products derived from human blood or plasma, the origin and the criteria and procedures for collection, transportation and storage of the source material shall be described and documented.

Defined pools of source material shall be used.

3. — For radiopharmaceuticals, starting materials include irradiation target materials.

D.— **Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies**

The applicant must demonstrate that the medicinal product is manufactured in accordance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products and its updates, published by the Commission in Volume 3 of its publication *The rules governing medicinal products in the European Community*.

([1]) The competent authorities may also request the pK and pH values if they think this information is essential.

E.— **Control tests carried out at intermediate stages of the manufacturing process**

1. — The particulars and documents accompanying an application for marketing authorization, pursuant to Article 8(3)(h) and (i) and Article 10, paragraph 1 of this Directive, shall include particulars relating to the product control tests that may be carried out at an intermediate stage of the manufacturing process, with a view to ensuring the consistency of the technical characteristics and the production process.—

These tests are essential for checking the conformity of the medicinal product with the formula when, exceptionally, an applicant proposes an analytical method for testing the finished product which does not include the assay of all the active substances (or of all the excipient constituents subject to the same requirements as the active substances).—

The same applies where the quality control of the finished product depends on in-process control tests, particularly if the medicinal product is essentially defined by its method or preparation.—

2. — For biological medicinal products, such as immunological medicinal products and medicinal products derived from human blood or plasma, the procedures and the criteria of acceptability published as recommendations of the WHO (*Requirements for Biological Substances*) shall serve as guidelines for all controls of production stages which are not specified in the *European Pharmacopoeia*, or failing this, in the national pharmacopoeia of a Member State.—

For inactivated or detoxified vaccines, effective inactivation or detoxification shall be verified during each production run, unless this control is dependent upon a test for which the availability of susceptible animals is limited. In this case, the test shall be carried out until consistency of production and correlation with appropriate in process controls have been established and thereafter compensated by appropriate in-process controls.—

3. — For modified or adsorbed allergen products, the products shall be qualitatively and quantitatively characterized at an intermediate stage, as late as possible in the manufacturing process.—

F. — **Control tests on the finished product**

1. — For the control of the finished product, a batch of a medicinal product comprises all the units of a pharmaceutical form which are made from the same initial quantity of material and have undergone the same series of manufacturing and/or sterilization operations or, in the case of a continuous production process, all the units manufactured in a given period of time.—

The application for marketing authorization shall list those tests which are carried out routinely on each batch of finished product. The frequency of the tests which are not carried out routinely shall be stated. Release limits shall be indicated.—

The particulars and documents accompanying the application for marketing authorization pursuant to Article 8(3)(h) and (i) and Article 10(1) of this Directive, shall include particulars relating to control tests on the finished product at release. They shall be submitted in accordance with the following requirements.—

The provisions of the monographs for pharmaceutical forms, immunosera, vaccines and radiopharmaceutical preparations of the *European Pharmacopoeia* or failing that, of a Member State, shall be applicable to all products defined therein. For all controls of biological medicinal products such as immunological medicinal products and medicinal products derived from human blood or plasma which are not specified in the *European Pharmacopoeia* or failing this, in the pharmacopoeia of a Member State, the procedures and the criteria of acceptability published as recommendations in the WHO (*Requirements for Biological Substances*) shall serve as guidelines.—

If test procedures and limits other than those mentioned in the monographs of the *European Pharmacopoeia*, or — failing this, in the national pharmacopoeia of a Member State, are used, proof shall be supplied that the finished product would, if tested in accordance with those monographs, meet the quality requirements of that pharmacopoeia for the pharmaceutical form concerned.—

1.1.—General characteristics of the finished product—

Certain tests of the general characteristics of a product shall always be included among the tests on the finished product. These tests shall, wherever applicable, relate to the control of average masses and maximum deviations, to mechanical, physical or microbiological tests, organoleptic characteristics, physical characteristics such as density, pH, refractive index, etc. For each of these characteristics, standards and tolerance limits shall be specified by the applicant in each particular case.—

The conditions of the tests, where appropriate, the equipment/apparatus employed and the standards shall be described in precise details whenever they are not given in the *European Pharmacopoeia* or the pharmacopoeia of the Member States; the same shall apply in cases where the methods prescribed by such pharmacopoeias are not applicable.

Furthermore, solid pharmaceutical forms having to be administered orally shall be subjected to *in vitro* studies on the liberation and dissolution rate of the active substance or substances; these studies shall also be carried out where administration is by another means if the competent authorities of the Member State concerned consider this necessary.

1.2. Identification and assay of active substance(s)

Identification and assay of the active substance(s) shall be carried out either in an average representative sample from the production batch or in a number of dosage-units analysed individually.

Unless there is appropriate justification, the maximum acceptable deviation in the active substance content of the finished product shall not exceed ± 5 % at the time of manufacture.

On the basis of the stability tests, the manufacturer must propose and justify maximum acceptable tolerance limits in the active substance content of the finished product up to the end of the proposed shelf-life.

In certain exceptional cases of particularly complex mixtures, where assay of active substances which are very numerous or present in very low amounts would necessitate an intricate investigation difficult to carry out in respect of each production batch, the assay of one or more active substances in the finished product may be omitted, on the express condition that such assays are made at intermediate stages in the production process. This relaxation may not be extended to the characterization of the substances concerned. This simplified technique shall be supplemented by a method of quantitative evaluation, enabling the competent authority to have the conformity of the medicinal product with its specification verified after it has been placed on the market.

An *in vivo* or *in vitro* biological assay shall be obligatory when physico-chemical methods cannot provide adequate information on the quality of the product. Such an assay shall, whenever possible, include reference materials and statistical analysis allowing calculation of confidence limits. Where these tests cannot be carried out on the finished product, they may be performed at an intermediate stage, as late as possible in the manufacturing process.

Where the particulars given in section B show that a significant overage of an active substance is employed in the manufacture of the medicinal product, the description of the control tests on the finished product shall include, where appropriate, the chemical and, if necessary, the toxico-pharmacological investigation of the changes that this substance has undergone, and possibly the characterization and/or assay of the degradation products.

1.3. Identification and assay of excipient constituents

In so far as is necessary, the excipient(s) shall be subject at least to identification tests.

The test procedure proposed for identifying colouring matters must enable a verification to be made that such matters appear in the list annexed to Directive 78/25/EEC.

An upper and lower limit test shall be obligatory in respect of preserving agents and an upper limit test for any other excipient constituent liable to affect adversely organic functions; an upper and lower limit test shall be obligatory in respect of the excipient if it is liable to affect the bio-availability of an active substance, unless bio-availability is guaranteed by other appropriate tests.

1.4. Safety tests

1. — Apart from the pharmacotoxicological tests submitted with the application for marketing authorization, particulars of safety tests, such as sterility, bacterial endotoxin, pyrogenicity and local tolerance in animals shall be included in the analytical particulars wherever such tests must be undertaken as a matter of routine in order to verify the quality of the product.

2. — For all controls of biological medicinal products, such as immunological medicinal products and medicinal products derived from human blood or plasma, which are not specified in the *European Pharmacopoeia*, or failing this, in the national pharmacopoeia of a Member State, the procedures and the criteria of acceptability published as recommendations in the World Health Organization (*Requirements for Biological Substances*) shall serve as guidelines.

3. — For radiopharmaceuticals, radionuclidic purity, radiochemical purity and specific activity shall be described. For content of radioactivity, the deviation from that stated on the label should not exceed ± 10 %.

For generators, details on the testing for mother and daughter radionuclides are required. For generator-eluates, tests for mother radionuclides and for other components of the generator system shall be provided.

For kits, the specifications of the finished product shall include tests on performance of products after radiolabelling. Appropriate controls on radiochemical and radionuclidic purity of the radiolabelled compound shall be included. Any material essential for radiolabelling shall be identified and assayed.

G. — **Stability tests**

1. — The particulars and documents accompanying the application for marketing authorization pursuant to Article 8(3)(g) and (h) shall be submitted in accordance with the following requirements.

A description shall be given of the investigations by which the shelf life, the recommended storage conditions and the specifications at the end of the shelf-life proposed by the applicant have been determined.

Where a finished product is liable to give rise to degradation products, the applicant must declare these and indicate characterization methods and test procedures.

The conclusions shall contain the results of analyses, justifying the proposed shelf life under the recommended storage conditions and the specifications of the finished product at the end of the shelf-life under these recommended storage conditions.

The maximum acceptable level of degradation products at the end of shelf-life shall be indicated.

A study of the interaction between product and container shall be submitted wherever the risk of such interaction is regarded as possible, especially where injectable preparations or aerosols for internal use are concerned.

2. — Where for biological medicinal products, such as immunological medicinal products and medicinal products derived from human blood or plasma, stability tests cannot be carried out on the finished products, it is acceptable to carry out stability indicating tests at an intermediate stage of production as late as possible in the manufacturing process. In addition, there should be an evaluation of the stability of the finished product using other secondary tests.

3. — For radiopharmaceuticals, information on stability shall be given for radionuclide generators, radionuclide kits and radiolabelled products. The stability during use of radiopharmaceuticals in multi-dose vials shall be documented.

PART 3

TOXICOLOGICAL AND PHARMACOLOGICAL TESTS

I. — **Introduction**

1. — The particulars and documents accompanying the application for marketing authorization pursuant to Articles 8(3)(i) and 10(1) shall be given in accordance with the requirements below.

Member States shall ensure that the safety tests are carried out in conformity with the provisions relating to good laboratory practice laid down by Council Directives 87/18/EEC ([1]) and 88/320/EEC ([2]).

The toxicological and pharmacological tests must show:

(a) the potential toxicity of the product and any dangerous or undesirable toxic effects that may occur under the proposed conditions of use in human beings; these should be evaluated in relation to the pathological condition concerned;

([1]) OJ L 15, 17.1.1987, p. 29.
([2]) OJ L 145, 11.6.1988, p. 35. Directive as amended by Directive 90/18/EEC (OJ L 11, 13.1.1990, p. 37).

(b)—the—pharmacological—properties—of—the—product,—in—both—qualitative—and—quantitative—relationship—to—the—proposed—use—in—human—beings.—All—results—must—be—reliable—and—of—general—applicability.—Whenever—appropriate, mathematical and statistical procedures shall be used in designing the experimental methods and—in evaluating the results.—

Additionally, it is necessary for clinicians to be given information about the therapeutic potential of the product.—

2. — Where a medicinal product is intended for topical use, systemic absorption must be investigated, due account also—being taken of the possible use of the product on broken skin and absorption through—other relevant surfaces.—Only if it—is proved that systemic—absorption—under these conditions—is negligible may repeated—dose systemic—toxicity tests, foetal toxicity tests and studies of reproductive function be omitted.—

If, however, systemic absorption is demonstrated during therapeutic experimentation, toxicity tests shall be carried—out on animals, including where necessary, foetal toxicity tests.—

In all cases, tests of local tolerance after repeated application shall be carried out with particular care and include—histological—examinations;—the—possibility—of—sensitization—shall—be—investigated—and—any—carcinogenic—potential—investigated in the cases referred to in Section II E of this Part.—

3. — For biological medicinal products such as immunological medicinal products and medicinal products derived from—human blood or plasma, the requirements of this Part may have to be adapted for individual products; therefore—the testing programme carried out shall be justified by the applicant.—

In establishing the testing programme, the following shall be taken into consideration:—

all tests requiring repeated—administration of the product shall be designed to take account of the possible—induction of, and interference by, antibodies;—

examination of reproductive function, of embryo/foetal and perinatal toxicity, of mutagenic potential and of—carcinogenic—potential—shall—be—considered.—Where—components—other—than—the—active—substance(s)—are—incriminated, validation of their removal may replace the study.—

4. — For radiopharmaceuticals, it is appreciated that toxicity may be associated with a radiation dose. In diagnosis, this—is a consequence—of the use—of radiopharmaceuticals;—in therapy, it is the wanted property.—The evaluation of—safety—and—efficacy—of—radiopharmaceuticals—shall,—therefore,—address—requirements—for—medicinal—products—and—radiation—dosimetry—aspects.—Organ/tissue—exposure—to radiation shall—be—documented.—Absorbed—radiation—dose—estimates shall be calculated according to a specified, internationally recognized system by—a particular route of—administration.—

5. — The toxicology and pharmacokinetics of an excipient used for the first time in the pharmaceutical field shall be—investigated.—

6. — Where there is a possibility of significant degradation during storage of the medicinal product, the toxicology of—degradation products must be considered.—

II. — *PERFORMANCE OF TESTS*

A. — **Toxicity**

1. — *Single dose toxicity*

An—acute—test—is—a—qualitative—and—quantitative—study—of—the—toxic—reactions—which—may—result—from—a—single—administration of the active substance or substances contained in the medicinal product, in the proportions and—physico-chemical state in which they are present in the actual product.—

The acute toxicity test must be carried out in two or more mammalian species of known strain unless a single—species can be justified. At least two different routes of administration shall normally be used, one being identical—with—or—similar—to—that—proposed—for—use—in—human—beings—and—the—other—ensuring—systemic—exposure—to—the—substance.—

This study will cover the signs observed, including local reactions. The period during which the test animals are—observed shall be fixed by the investigator as being adequate to reveal tissue or organ damage or recovery, usually—for—a—period—of—14—days—but—not—less—than—7—days,—but—without—exposing—the—animals—to—prolonged—suffering.—

Animals dying during the observation period should be subject to autopsy as also should all animals surviving to— the end of the observation period. Histopathological examinations should be considered on any organ showing— macroscopic changes at autopsy. The maximum amount of information should be obtained from the animals— used in the study.—

The single dose toxicity tests should be conducted in such a way that signs of acute toxicity are revealed and the— mode of death assessed as far as reasonably possible. In suitable species, a quantitative evaluation of the— approximate lethal dose and information on the dose effect relationship should be obtained, but a high level of— precision is not required.—

These studies may give some indication of the likely effects of acute overdosage in man and may be useful for the— design of toxicity studies requiring repeated dosing on the suitable animal species.—

In the case of active substances in combination, the study must be carried out in such a way as to check whether— or not there is enhancement of toxicity or if novel toxic effects occur.—

2.— *Repeated dose toxicity (sub-acute or chronic toxicity)*

Repeated dose toxicity tests are intended to reveal any physiological and/or anatomo-pathological changes— induced by repeated administration of the active substance or combination of active substances under— examination, and to determine how these changes are related to dosage.—

Generally, it is desirable that two tests be performed: one short-term, lasting two to four weeks, the other— long-term. The duration of the latter shall depend on the conditions of clinical use. Its purpose shall be to— determine by experiment the non-toxic dose range of the product and normally it shall last three to six months.—

In respect of medicinal products to be administered once only to humans, a single test lasting two to four weeks— shall be performed.—

If however, having regard to the proposed duration of use in human beings, the investigator sees fit to carry out— experiments of greater or lesser duration than indicated above, he must give adequate reasons for doing so.—

Reasons should also be given for the dosages chosen.—

Repeated dose toxicity tests shall be carried out on two species of mammals one of which must be a non-rodent.— The choice of route(s) of administration employed shall depend on the intended therapeutic use and the— possibilities of systemic absorption. The method and frequency of dosage shall be clearly stated.—

The maximum dose should be chosen so as to bring harmful effects to light. The lower doses will then enable the— animal's tolerance of the product to be determined.—

Wherever possible, and always in experiments on small rodents, the design of the experiment and the control— procedures must be suited to the scale of the problem being tackled and enable fiducial limits to be determined.—

The evaluation of the toxic effects shall be based on observation of behaviour, growth, haematological and— biochemical tests, especially those relating to the excretory mechanism, and also on autopsy reports and— accompanying histological data. The choice and range of each group of tests will depend on the species of animal— used and the state of scientific knowledge at the time.—

In the case of new combinations of known substances that have been investigated in accordance with the— provisions of this Directive, the chronic long-term tests may, except where acute and sub-acute toxicity tests have— demonstrated potentiation or novel toxic effects, be suitably modified by the investigator who shall submit his— reasons for such modification.—

B.— **Examination of reproductive function**

If the results of other tests reveal anything suggesting harmful effects on progeny or impairment of male or— female reproductive function, this shall be investigated by appropriate tests.—

C.— **Embryo/foetal and perinatal toxicity**

This investigation comprises a demonstration of the toxic and especially the teratogenic effects observed in the— issue of conception when the medicinal product under investigation has been administered to the female during— pregnancy.—

Although up to the present these tests have had only a limited predictive value in regard to the application of the— results to human beings, they are thought to provide important information where the results show effects such— as resorptions and other anomalies.—

Omission of these tests, either because the medicinal product will not normally be used by women capable of— child-bearing or for other reasons, must be adequately justified.—

Embryo/foetal toxicity studies shall normally be conducted on two mammalian species, one of which should be— other than a rodent. Peri- and postnatal studies shall be conducted in at least one species. Where metabolism of a— medicinal product in a particular species is known to be similar to that in man, it is desirable to include this— species. Also, it is desirable that one of the species is the same as in the repeated dose toxicity studies.—

The details of the test (number of animals, amounts administered, timing of administration and criteria for— evaluation of results) shall depend on the state of scientific knowledge at the time when the application is lodged,— and the level of statistical significance that the results must attain.—

D.— **Mutagenic potential**

The purpose of the study of mutagenic potential is to reveal the changes which a substance may cause in the— genetic material of individuals or cells and which have the effect of making successors permanently and— hereditarily different from their predecessors. This study is obligatory for any new substance.—

The number and types of results and the criteria for their evaluation shall depend on the state of scientific— knowledge at the time when the application is lodged.—

E.— **Carcinogenic potential**

Tests to reveal carcinogenic effects shall normally be required:—

(a)— in respect of substances having a close chemical analogy with known carcinogenic or cocarcinogenic— compounds;—

(b)— in respect of substances which have given rise to suspicious changes during the long-term toxicological tests;—

(c)— in respect of substances which have given rise to suspicious results in the mutagenic-potential tests or in— other short-term carcinogenicity tests.—

Such tests may also be required in respect of substances to be included in medicinal products likely to be— administered regularly over a prolonged period of a patient's life.—

The state of scientific knowledge at the time when the application is lodged shall be taken into account when— determining the details of the tests.—

F.— **Pharmacodynamics**

This heading covers the variations caused by the medicinal product in the functions of the physiological systems,— whether these functions are normal or experimentally modified.—

This study shall follow two distinct lines of approach.—

Firstly, the actions on which the recommended application in therapeutic practice is based shall be adequately— described. The results shall be expressed in quantitative terms using, (e.g. dose-effect curves, time-effect curves— etc.), and wherever possible, compared with data relating to a substance whose activity is known. Where a higher— therapeutic potency is being claimed for a substance, the difference shall be demonstrated and shown to be— statistically significant.—

Secondly, the investigator shall provide a general pharmacological characterization of the substance, with special— reference to adverse reactions. In general, the main functions of the physiological systems should be investigated.— The depth of this investigation must be increased as the doses liable to produce adverse reactions approach those— producing the main effect for which the substance is being proposed.—

The experimental techniques, unless they are standard procedures, must be described in such detail as to allow them to be reproduced, and the investigator must establish their validity. The experimental results shall be set out clearly and, when relevant to the test, their statistical significance quoted.

Unless good reasons are given to the contrary, any quantitative modification of responses resulting from repeated administration of the substance shall be investigated.

Tests on combinations of active substances may be prompted either by pharmacological premisses or by indications of therapeutic effect.

In the first case, the pharmacodynamic study shall demonstrate those interactions which might make the combination of value in therapeutic use.

In the second case, where scientific justification for the combination is sought through therapeutic experimentation, the investigation shall determine whether the effects expected from the combination can be demonstrated in animals, and the importance of any collateral effects shall at least be investigated.

If a combination includes a novel active substance, the latter must previously have been studied in depth.

G.— **Pharmacokinetics**

Pharmacokinetics means the study of the fate of the active substance within the organism, and covers the study of the absorption, distribution, biotransformation and excretion of the substance.

The study of these different phases may be carried out both by means of physical, chemical or biological methods, and by observation of the actual pharmacodynamic activity of the substance itself.

Information on distribution and elimination (i.e. biotransformation and excretion) shall be necessary in all cases where such data are indispensable to determine the dosage for humans, and in respect of chemotherapeutic substances (antibiotics, etc.) and substances whose use depends on their non-pharmacodynamic effects (e.g. numerous diagnostic agents, etc.).

Pharmacokinetic investigation of pharmacologically active substances is necessary.

In the case of new combinations of known substances which have been investigated in accordance with the provisions of this Directive, pharmacokinetic studies may not be required, if the toxicity tests and therapeutic experimentation justify their omission.

H.— **Local tolerance**

The purpose of local tolerance studies is to ascertain whether medicinal products (both active substances and excipients) are tolerated at sites in the body which may come into contact with the medicinal product as a result of its administration in clinical use. The testing strategy shall be such that any mechanical effects of administration or purely physico-chemical actions of the product can be distinguished from toxicological or pharmacodynamic ones.

I.— **Well-established medicinal use**

For the purpose of demonstrating, pursuant to Article 10(1)(a)(ii), that the component(s) of a medicinal product have a well established use, with an acceptable level of safety, the following specific rules shall apply:

(a) Factors which have to be taken into account in order to establish a 'well established medicinal use' of components of medicinal products are the time over which a substance has been used, quantitative aspects of the use of the substance, the degree of scientific interest in the use of the substance (reflected in the published scientific literature) and the coherence of scientific assessments. Therefore different periods of time may be necessary for establishing 'well established use' of different substances. In any case, however, the period of time required for establishing a 'well established medicinal use' of a component of a medicinal product must not be less than one decade from the first systematic and documented use of that substance as a medicinal product in the Community.

(b)—The documentation submitted by the applicant should cover all aspects of the safety assessment and must— include or refer to a review of the relevant literature, taking into account pre- and postmarketing studies and— published scientific literature concerning experience in the form of epidemiological studies and in particular— of comparative epidemiological studies. All documentation, both favourable and unfavourable, should be— communicated.—

(c)—Particular attention must be paid to any missing information and justification must be given why— demonstration of an acceptable level of safety can be supported although some studies are lacking.—

(d)—The Expert report must explain the relevance of any data submitted which concern a product different from— the product intended for marketing. A judgment must be made whether the product studied can be— considered as similar to the product which will be granted a marketing authorisation in spite of the existing— differences.—

(e)—Post-marketing experience with other products containing the same components is of particular importance— and applicants should put a special emphasis on this issue.—

PART 4—

CLINICAL DOCUMENTATION

The particulars and documents accompanying applications for marketing authorizations pursuant to Articles 8(3)(i) and— 10(1) of this Directive shall be submitted in accordance with the provisions below.—

A clinical trial is any systematic study of medicinal products in human subjects whether in patients or non-patient— volunteers in order to discover or verify the effects of and/or identify any adverse reaction to investigational products,— and/or study their absorption, distribution, metabolism and excretion in order to ascertain the efficacy and safety of the— products.—

Evaluation of the application for marketing authorization shall be based on clinical trials including clinical— pharmacological trials designed to determine the efficacy and safety of the product under normal conditions of use,— having regard to the therapeutic indications for use in human beings. Therapeutic advantages must outweigh potential— risks.—

A.— **General requirements**

The clinical particulars to be provided pursuant to Articles 8(3)(i) and 10(1) must enable a sufficiently— well-founded and scientifically valid opinion to be formed as to whether the medicinal product satisfies the— criteria governing the granting of a marketing authorization. Consequently, an essential requirement is that the— results of all clinical trials should be communicated, both favourable and unfavourable.—

Clinical trials must always be preceded by adequate pharmacological and toxicological tests, carried out on— animals in accordance with the requirements of Part 3 of this Annex. The investigator must acquaint himself with— the conclusions drawn from the pharmacological and toxicological studies and hence the applicant must provide— him at least with the investigator's brochure, consisting of all the relevant information known prior to the onset— of a clinical trial including chemical, pharmaceutical and biological data, toxicological, pharmacokinetic and— pharmacodynamic data in animals and the results of earlier clinical trials, with adequate data to justify the nature,— scale and duration of the proposed trial; the complete pharmacological and toxicological reports shall be provided— on request. For materials of human or animal origin, all available means shall be employed to ensure safety from— transmission of infectious agents prior to the commencement of the trial.—

B.— **Conduct of trials**

1.— *Good clinical practice*

1.1.—All phases of clinical investigation, including bioavailability and bioequivalence studies, shall be designed,— implemented and reported in accordance with good clinical practice.—

1.2.—All clinical trials shall be carried out in accordance with the ethical principles laid down in the current revision of— the Declaration of Helsinki. In principle, the freely given informed consent of each trial subject shall be obtained— and documented.—

The trial protocol (including statistical design), the technical application and documentation shall be submitted by— the sponsor and/or investigator for an opinion to the relevant ethics committee. The trials shall not begin before— the opinion of this committee has been received in writing.—

1.3.—Pre-established, systematic written procedures for the organization, conduct, data collection, documentation and— verification of clinical trials shall be required.—

1.4.—In the case of radiopharmaceuticals, clinical trials shall be carried out under the responsibility of a medical doctor— authorized to use radionuclides for medical purposes.—

2. — *Archiving*

The marketing authorization holder shall make arrangements for archiving of documentation.—

(a)—The investigator shall arrange for the retention of the patient identification codes for at least 15 years after— the completion or discontinuation of the trial.—

(b)—Patient files and other source data shall be kept for the maximum period of time permitted by the hospital,— institution or private practice.—

(c)—The sponsor or other owner of the data shall retain all other documentation pertaining to the trial as long as— the product is authorized. These procedures shall include:—

the protocol including the rationale, objectives and statistical design and methodology of the trial, with— conditions under which it is performed and managed, and details of the investigational product, the— reference medicinal product and/or the placebo used,—

standard operating procedures,—

all written opinions on the protocol and procedures,—

the investigator's brochure,—

case report forms on each trial subject,—

final report,—

audit certificate(s), if available.—

(d)—The final report shall be retained by the sponsor or subsequent owner, for five years after the medicinal— product is no longer authorized.—

Any change of ownership of the data shall be documented.—

All data and documents shall be made available if requested by relevant authorities.—

C. — **Presentation of results**

1. — The particulars of each clinical trial must contain sufficient detail to allow an objective judgement to be made:—

the protocol, including the rationale, objectives and statistical design and methodology of the trial, with— conditions under which it is performed and managed, and details of the investigational medicinal product— used,—

audit certificate(s), if available,—

the list of investigator(s), and each investigator shall give his name, address, appointments, qualifications and— clinical duties, state where the trial was carried out and assemble the information in respect of each patient— individually, including case report forms on each trial subject,—

final report signed by the investigator and for multicentre trials, by all the investigators or the coordinating— (principal) investigator.—

2. — The particulars of clinical trials referred to above shall be forwarded to the competent authorities. However, in— agreement with the competent authorities, the applicant may omit part of this information. Complete— documentation shall be provided forthwith upon request.—

3. — The clinical observations shall be summarized for each trial indicating:—

(a)—the number and sex of patients treated;—

(b)—the selection and age-distribution of the groups of patients being investigated and the comparative tests;—

(c)—the number of patients withdrawn prematurely from the trials and the reasons for such withdrawal;—

(d)—where controlled trials were carried out under the above conditions, whether the control group: —

received no treatment, —

received a placebo, —

received another medicinal product of known effect, —

received treatment other than therapy using medicinal products; —

(e)—the frequency of observed adverse reactions;—

(f)—details concerning patients who may be at increased risk, e.g. elderly people, children, women during pregnancy or menstruation, or whose physiological or pathological condition requires special consideration;—

(g)—parameters or evaluation criteria of efficacy and the results in terms of these parameters;—

(h)—a statistical evaluation of the results when this is called for by the design of the trials and the variable factors involved.—

4. — The investigator shall, in his conclusions on the experimental evidence, express an opinion on the safety of the product under normal conditions of use, its tolerance, its efficacy and any useful information relating to indications and contra-indications, dosage and average duration of treatment as well as any special precautions to be taken during treatment and the clinical symptoms of overdosage. In reporting the results of a multi-centre study, the principal investigator shall, in his conclusions, express an opinion on the safety and efficacy of the investigational medicinal product on behalf of all centres.—

5. — In addition, the investigator shall always indicate his observations on:—

(a)—any signs of habituation, addiction or difficulty in weaning patients from the medicinal product;—

(b)—any interactions that have been observed with other medicinal products administered concomitantly;—

(c)—the criteria determining exclusion of certain patients from the trials;—

(d)—any deaths which occurred during the trial or within the follow-up period.—

6. — Particulars concerning a new combination of medicinal substances must be identical to those required for new medicinal products and must substantiate the safety and efficacy of the combination.—

7. — Total or partial omission of data must be explained. Should unexpected results occur during the course of the trials, further preclinical toxicological and pharmacological tests must be undertaken and reviewed.—

If the medicinal product is intended for long-term administration, particulars shall be given of any modification of the pharmacological action following repeated administration, as well as the establishment of long-term dosage.—

D. — **Clinical pharmacology**

1. — *Pharmacodynamics*

The pharmacodynamic action correlated to the efficacy shall be demonstrated including:—

the dose-response relationship and its time course,—

justification for the dosage and conditions of administration, —

the mode of action, if possible. —

The pharmacodynamic action not related to efficacy shall be described.—

The demonstration of pharmacodynamic effects in human beings shall not in itself be sufficient to justify conclusions regarding any particular potential therapeutic effect.—

2. — *Pharmacokinetics*

The following pharmacokinetic characteristics shall be described:—

absorption (rate and extent),—

distribution,—

metabolism,—

excretion.—

Clinically significant features including the implication of the kinetic data for the dosage regimen especially for patients at risk, and differences between man and animal species used in the preclinical studies, shall be described.—

3. — *Interactions*

If the medicinal product is normally to be administered concomitantly with other medicinal products, particulars shall be given of joint administration tests performed to demonstrate possible modification of the pharmacological action.—

If pharmacodynamic/pharmacokinetic interactions exist between the substance and other medical products or substances like alcohol, caffeine, tobacco or nicotine, likely to be taken simultaneously, or if such interactions are likely, they should be described and discussed; particularly from the point of view of clinical relevance and the relationship to the statement concerning interactions in the summary of product characteristics presented in accordance with Article 11 point 5.6.—

E. — **Bioavailability/bioequivalence**

The assessment of bioavailability must be undertaken in all cases where it is necessary, e.g. where the therapeutic dose is near the toxic dose or where the previous tests have revealed anomalies which may be related to pharmacodynamic properties, such as variable absorption.—

In addition, an assessment of bioavailability shall be undertaken where necessary to demonstrate bioequivalence for the medicinal products referred to in Article 10(1)(a).—

F. — **Clinical efficacy and safety**

1. — In general, clinical trials shall be done as 'controlled clinical trials' and if possible, randomized; any other design shall be justified. The treatment of the control groups will vary from case to case and also will depend on ethical considerations; thus it may, in some instances, be more pertinent to compare the efficacy of a new medicinal product with that of an established medicinal product of proven therapeutic value rather than with the effect of a placebo.—

As far as possible, and particularly in trials where the effect of the product cannot be objectively measured, steps shall be taken to avoid bias, including methods of randomization and blinding.—

2. — The protocol of the trial must include a thorough description of the statistical methods to be employed, the number and reasons for inclusion of patients (including calculations of the power of the trial), the level of significance to be used and a description of the statistical unit. Measures taken to avoid bias, particularly methods of randomization, shall be documented. Inclusion of a large number of subjects in a trial must not be regarded as an adequate substitute for a properly controlled trial.—

3. — Clinical statements concerning the efficacy or safety of a medicinal product under normal conditions of use which are not scientifically substantiated cannot be accepted as valid evidence.—

4. — The value of data on the efficacy and safety of a medicinal product under normal conditions of use will be very— greatly enhanced if such data come from several competent investigators working independently.—

5. — For vaccines and serums, the immunological status and age of the trial population and the local epidemiology are— of critical importance and shall be monitored during the trial and fully described.—

For live attenuated vaccines, clinical trials shall be so designed as to reveal potential transmission of the— immunizing agent from vaccinated to non-vaccinated subjects. If transmission is possible, the genotypic and— phenotypic stability of the immunizing agent shall be studied.—

For vaccines and allergen products, follow-up studies shall include appropriate immunological tests, and where— applicable, antibody assays.—

6. — The pertinence of the different trials to the assessment of safety and the validity of methods of evaluation shall be— discussed in the expert report.—

7. — All adverse events including abnormal laboratory values shall be presented individually and discussed, especially:—

in terms of overall adverse experience, and—

as a function of the nature, seriousness and causality of effects.—

8. — A critical assessment of relative safety, taking into account adverse reactions, shall be made in relation to:—

the disease to be treated,—

other therapeutic approaches,—

particular characteristics in sub-groups of patients,—

preclinical data on toxicology and pharmacology.—

9. — Recommendations shall be made for the conditions of use, with the intention of reducing the incidence of adverse— reactions.—

G. — **Documentation for applications in exceptional circumstances**

When, in respect of particular therapeutic indications, the applicant can show that he is unable to provide— comprehensive data on the efficacy and safety under normal conditions of use, because:—

the indications for which the product in question is intended are encountered so rarely that the applicant— cannot reasonably be expected to provide comprehensive evidence, or—

in the present state of scientific knowledge, comprehensive information cannot be provided, or—

it would be contrary to generally accepted principles of medical ethics to collect such information,—

marketing authorization may be granted on the following conditions:—

(a)— the applicant completes on identified programme of studies within a time period specified by the competent— authority, the results of which shall form the basis of a reassessment of the benefit/risk profile,—

(b)— the medicinal product in question may be supplied on medical prescription only and may in certain cases be— administered only under strict medical supervision, possibly in a hospital and for a radiopharmaceutical, by— an authorized person,—

(c)— the package leaflet and any medical information shall draw the attention of the medical practitioner to the— fact that the particulars available concerning the medicinal product in question are as yet inadequate in— certain specified respects.—

H. — **Post-marketing experience**

1. — If the medicinal product is already authorized in other countries, information shall be given in respect of adverse drug reactions of the medicinal product concerned and medicinal products containing the same active substance(s), in relation to the usage rates if possible. Information from worldwide studies relevant to the safety of the medicinal product shall be included.

   For this purpose, an adverse drug reaction is a reaction which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for the modification of physiological function.

2. — In the case of vaccines already authorized in other countries, information on the monitoring of vaccinated subjects to evaluate the prevalence of the disease in question as compared to nonvaccinated subjects shall be submitted, when available.

3. — For allergen products, response in periods of increased antigen exposure shall be identified.

I. — **Well-established medicinal use**

For the purpose of demonstrating, pursuant to Article 10(1)(a)(ii), that the component(s) of a medicinal product have a well established use, with recognised efficacy, the following specific rules shall apply:

(a) Factors which have to be taken into account in order to establish a 'well established medicinal use' of components of medicinal products are the time over which a substance has been used, quantitative aspects of the use of the substance, the degree of scientific interest in the use of the substance (reflected in the published scientific literature) and the coherence of scientific assessments. Therefore different periods of time may be necessary for establishing 'well established use' of different substances. In any case, however, the period of time required for establishing a 'well established medicinal use' of a component of a medicinal product must not be less than one decade from the first systematic and documented use of that substance as a medicinal product in the Community.

(b) The documentation submitted by the applicant should cover all aspects of the efficacy assessment and must include or refer to a review of the relevant literature, taking into account pre- and postmarketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies. All documentation, both favourable and unfavourable, should be communicated.

(c) Particular attention must be paid to any missing information and justification must be given why demonstration of efficacy can be supported although some studies are lacking.

(d) The Expert report must explain the relevance of any data submitted which concern a product different from the product intended for marketing. A judgment must be made whether the product studied can be considered as similar to the product which will be granted a marketing authorisation in spite of the existing differences.

(e) Post-marketing experience with other products containing the same components is of particular importance and applicants should put a special emphasis on this issue.

ANNEX II

PART A—

Repealed Directives, with their successive amendments (referred to by Article 128)

Council Directive 65/65/EEC (OJ 22, 9. 2. 1965, p. 369/65)—
- Council Directive 66/454/EEC (OJ 144, 5. 8. 1966, p. 2658/66)—
- Council Directive 75/319/EEC (OJ L 147, 9. 6. 1975, p. 13)—
- Council Directive 83/570/EEC (OJ L 332, 28. 11. 1983, p. 1)—
- Council Directive 87/21/EEC (OJ L 15, 17. 1. 1987, p. 36)—
- Council Directive 89/341/EEC (OJ L 142, 25. 5. 1989, p. 11)—
- Council Directive 92/27/EEC (OJ L 113, 30. 4. 1992, p. 8)—
- Council Directive 93/39/EEC (OJ L 214, 24. 8. 1993, p. 22)—

Council Directive 75/318/EEC (OJ L 147, 9. 6. 1975, p. 1)—
- Council Directive 83/570/EEC—
- Council Directive 87/19/EEC (OJ L 15, 17. 1. 1987, p. 31)—
- Council Directive 89/341/EEC—
- Commission Directive 91/507/EEC (OJ L 270, 26. 9. 1991, p. 32)—
- Council Directive 93/39/EEC—
- Commission Directive 1999/82/EC (OJ L 243, 15. 9. 1999, p. 7)—
- Commission Directive 1999/83/EC (OJ L 243, 15. 9. 1999, p. 9)—

Council Directive 75/319/EEC—
- Council Directive 78/420/EEC (OJ L 123, 11. 5. 1978, p. 26)—
- Council Directive 83/570/EEC—
- Council Directive 89/341/EEC—
- Council Directive 92/27/EEC—
- Council Directive 93/39/EEC—
- Commission Directive 2000/38/EC (OJ L 139, 10. 6. 2000, p. 28)—

Council Directive 89/342/EEC (OJ L 142, 25. 5. 1989, p. 14)—

Council Directive 89/343/EEC (OJ L 142, 25. 5. 1989, p. 16)—

Council Directive 89/381/EEC (OJ L 181, 28. 6. 1989, p. 44)—

Council Directive 92/25/EEC (OJ L 113, 30. 4. 1992, p. 1)—

Council Directive 92/26/EEC (OJ L 113, 30. 4. 1992, p. 5)—

Council Directive 92/27/EEC—

Council Directive 92/28/EEC (OJ L 113, 30. 4. 1992, p. 13)—

Council Directive 92/73/EEC (OJ L 297, 13. 10. 1992, p. 8)—

PART B—

Time-limits for transposition into national law (referred to by Article 128)

Directive—	Deadline for transposition—
Directive 65/65/EEC—	31 December 1966—
Directive 66/454/EEC—	
Directive 75/318/EEC—	21 November 1976—
Directive 75/319/EEC—	21 November 1976—
Directive 78/420/EEC—	
Directive 83/570/EEC—	31 October 1985—
Directive 87/19/EEC—	1 July 1987—
Directive 87/21/EEC—	1 July 1987—
	1 January 1992 ([1])—
Directive 89/341/EEC—	1 January 1992—
Directive 89/342/EEC—	1 January 1992—
Directive 89/343/EEC—	1 January 1992—
Directive 89/381/EEC—	1 January 1992—
Directive 91/507/EEC—	1 January 1992 ([2])—
	1 January 1995 ([3])—
Directive 92/25/EEC—	1 January 1993—
Directive 92/26/EEC—	1 January 1993—
Directive 92/27/EEC—	1 January 1993—
Directive 92/28/EEC—	1 January 1993—
Directive 92/73/EEC—	31 December 1993—
Directive 93/39/EEC—	1 January 1995 ([4])—
	1 January 1998 ([5])—
Directive 1999/82/EC—	1 January 2000—
Directive 1999/83/EC—	1 March 2000—
Directive 2000/38/EC—	5 December 2001—

([1])—Deadline for transposition applicable to Greece, Spain and Portugal.—
([2])—Except Section A, point 3.3 in Part II of the Annex.—
([3])—Deadline for transposition applicable to Section A, point 3.3 in Part II of the Annex.—
([4])—Except with regard to Article 1(6).—
([5])—Deadline for transposition applicable to Article 1(7).—

ANNEX III

CORRELATION TABLE—

This Dir.—	65/65/EEC—	75/318/EEC—	75/319/EEC—	89/342/EEC—	89/343/EEC—	89/381/EEC—	92/25/EEC—	92/26/EEC—	92/27/EEC—	92/28/EEC—	92/73/EEC—
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Art. 1(17) and— (18)—							Art. 1(2)—				
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Art. 1(28)—			Art. 10(1)—								
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Art. 115—						Art. 4(1)—					
Art. 116—	Art. 11—										
Art. 117—			Art. 28—								
Art. 118—			Art. 29—								
Art. 119—											Art. 4(1)—
Art. 120—		Art. 2a, 1st— paragraph—									
Art. 121—		Art. 2b—	Art. 37a—								
Art. 122—			Art. 30—								
Art. 123—			Art. 33—								
Art. 124—											Art. 5—
Art. 125—	Art. 12—		Art. 31—				Art. 4(2)—		Art. 11(2)—	Art. 12(3)—	
Art. 126, 1st— paragraph—	Art. 21—										
Art. 126, 2nd— paragraph—			Art. 32—								
Art. 127—			Art. 28a—								
Art. 128—											
Art. 129—											
Art. 130—											
Annex I—		Annex—									
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DIRECTIVES

DIRECTIVE 2010/84/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 15 December 2010

amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on the Functioning of the European Union, and in particular Article 114 and Article 168(4)(c) thereof,

Having regard to the proposal from the European Commission,

After transmission of the draft legislative act to the national parliaments,

Having regard to the opinion of the European Economic and Social Committee [1],

Having regard to the opinion of the Committee of the Regions [2],

Having regard to the opinion of the European Data Protection Supervisor [3],

Acting in accordance with the ordinary legislative procedure [4],

Whereas:

(1) Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use [5] lays down harmonised rules for the authorisation, supervision and pharmacovigilance of medicinal products for human use within the Union.

(2) Pharmacovigilance rules are necessary for the protection of public health in order to prevent, detect and assess adverse reactions to medicinal products placed on the Union market, as the full safety profile of medicinal products can only be known after they have been placed on the market.

(3) In the light of the experience acquired and following an assessment by the Commission of the Union system of pharmacovigilance, it has become clear that it is necessary to take measures in order to improve the operation of Union law on the pharmacovigilance of medicinal products.

(4) While the fundamental objective of the regulation of medicinal products is to safeguard public health, this aim should nevertheless be achieved by means that do not impede the free movement of safe medicinal products within the Union. It has emerged from the assessment of the Union system of pharmacovigilance that divergent actions by Member States in relation to safety issues pertaining to medicinal products are creating obstacles to the free movement of medicinal products. In order to prevent or eliminate those obstacles the existing pharmacovigilance provisions at Union level should be strengthened and rationalised.

(5) For the sake of clarity, the definition of the term 'adverse reaction' should be amended to ensure that it covers noxious and unintended effects resulting not only from the authorised use of a medicinal product at normal doses, but also from medication errors and uses outside the terms of the marketing authorisation, including the misuse and abuse of the medicinal product. The suspicion of an adverse drug reaction, meaning that there is at least a reasonable possibility of there being a causal relationship between a medicinal product and an adverse event, should be sufficient reason for reporting. Therefore, the term 'suspected adverse reaction' should be used when referring to reporting obligations. Without prejudice to the existing Union and national provisions and practices on medical confidentiality, Member States should ensure that reporting and processing of personal data related to suspected adverse reactions, including those associated with medication errors is carried out on a confidential basis. This should not affect Member States' obligations regarding the mutual exchange of

[1] OJ C 306, 16.12.2009, p. 28.
[2] OJ C 79, 27.3.2010, p. 50.
[3] OJ C 229, 23.9.2009, p. 19.
[4] Position of the European Parliament of 22 September 2010 [not yet published in the Official Journal] and Council Decision of 29 November 2010.
[5] OJ L 311, 28.11.2001, p. 67.

information on pharmacovigilance issues or their obligation to make available to the public important information on pharmacovigilance concerns. Furthermore, the principle of confidentiality should not affect the obligations of the persons concerned to provide information under criminal law.

(6) The pollution of waters and soils with pharmaceutical residues is an emerging environmental problem. Member States should consider measures to monitor and evaluate the risk of environmental effects of such medicinal products, including those which may have an impact on public health. The Commission should, based, inter alia, on data received from the European Medicines Agency, the European Environment Agency and Member States, produce a report on the scale of the problem, along with an assessment on whether amendments to Union legislation on medicinal products or other relevant Union legislation are required.

(7) The marketing authorisation holder should establish a pharmacovigilance system to ensure the monitoring and supervision of one or more of its authorised medicinal products, recorded in a pharmacovigilance system master file which should be permanently available for inspection. The competent authorities should undertake to supervise those pharmacovigilance systems. Applications for marketing authorisations should therefore be accompanied by a brief description of the corresponding pharmacovigilance system, which should include a reference to the location where the pharmacovigilance system master file for the medicinal product concerned is kept and available for inspection by the competent authorities.

(8) Marketing authorisation holders should plan pharmacovigilance measures for each individual medicinal product in the context of a risk management system. The measures should be proportionate to the identified risks, the potential risks, and the need for additional information on the medicinal product. It should also be ensured that any key measures included in a risk management system are made conditions of the marketing authorisation.

(9) It is necessary from a public health perspective to complement the data available at the time of authorisation with additional data about the safety and, in certain cases, the efficacy of authorised medicinal products. Competent authorities should therefore be empowered to impose on the marketing authorisation holder the obligation to conduct post-authorisation studies on safety and on efficacy. It should be possible to impose that obligation at the time of the granting of the marketing authorisation or later, and it should be a condition of the marketing authorisation. Such studies may be aimed at collecting data to enable the assessment of the safety or efficacy of medicinal products in everyday medical practice.

(10) It is essential that a strengthened system of pharmacovigilance not lead to the premature granting of marketing authorisations. However, some medicinal products are authorised subject to additional monitoring. This includes all medicinal products with a new active substance and biological medicinal products, including biosimilars, which are priorities for pharmacovigilance. Competent authorities may also require additional monitoring for specific medicinal products that are subject to the obligation to conduct a post-authorisation safety study or to conditions or restrictions with regard to the safe and effective use of the medicinal product. Medicinal products subject to additional monitoring should be identified as such by a black symbol and an appropriate standardised explanatory sentence in the summary of product characteristics and in the package leaflet. A publicly available list of medicinal products subject to additional monitoring should be kept up to date by the European Medicines Agency established by Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency [1] (hereinafter referred to as the 'Agency').

(11) The Commission should, in collaboration with the Agency and national competent authorities and following consultations with organisations representing patients, consumers, doctors and pharmacists, social health insurers, and other interested parties, present to the European Parliament and the Council an assessment report regarding the readability of the summaries of product characteristics and the package leaflets and their value to the healthcare professionals and the general public. Following an analysis of that data, the Commission should, if appropriate, make proposals to improve the layout and content of the summaries of product characteristics and of the package leaflets to ensure that they represent a valuable source of information for healthcare professionals and the general public respectively.

(12) Experience has shown that the responsibilities of marketing authorisation holders with regard to pharmacovigilance of authorised medicinal products should be clarified. The marketing authorisation holder should be responsible for continuously monitoring the safety of its medicinal products, for informing the authorities of any changes that might impact on the marketing authorisation, and for ensuring that the product information is kept up to date. As medicinal products could be used outside the terms of the marketing authorisation, the marketing authorisation holder's responsibilities should include providing all available information, including the results of clinical trials or other studies, as well as reporting any use of the medicinal product which is outside the terms of the marketing authorisation. It is also appropriate to ensure that all relevant information

[1] OJ L 136, 30.4.2004, p. 1.

collected on the safety of the medicinal product is taken into account when the marketing authorisation is being renewed.

(13) In order to ensure close cooperation between the Member States in the area of pharmacovigilance, the mandate of the coordination group set up by Article 27 of Directive 2001/83/EC should be enlarged to include the examination of questions related to the pharmacovigilance of all medicinal products authorised by the Member States. In order to fulfil its new tasks, the coordination group should be further strengthened through the adoption of clear rules as regards the expertise required, the procedures for reaching agreements or positions, transparency, independence and professional secrecy of its members, and the need for cooperation between Union and national bodies.

(14) With a view to ensuring the same level of scientific expertise in the area of pharmacovigilance decision-making at both Union and national levels, the coordination group should rely on the recommendations of the Pharmacovigilance Risk Assessment Committee when fulfilling its pharmacovigilance tasks.

(15) In order to avoid duplication of work, the coordination group should agree on a single position for pharmacovigilance assessments concerning medicinal products authorised in more than one Member State. Agreement within the coordination group should suffice for pharmacovigilance measures to be implemented throughout the Union. Where no agreement is reached within the coordination group, the Commission should be authorised to adopt a decision concerning the necessary regulatory action in respect of the marketing authorisation, addressed to the Member States.

(16) A single assessment should also be conducted in the case of pharmacovigilance issues which concern medicinal products authorised by the Member States and medicinal products authorised in accordance with Regulation (EC) No 726/2004. In such cases, the Commission should adopt harmonised measures for all medicinal products concerned on the basis of an assessment at Union level.

(17) Member States should operate a pharmacovigilance system to collect information that is useful for the monitoring of medicinal products, including information on suspected adverse reactions arising from use of a medicinal product within the terms of the marketing authorisation as well as from use outside the terms of the marketing authorisation, including overdose, misuse, abuse and medication errors, and suspected adverse reactions associated with occupational exposure. Member States should ensure the quality of the pharmacovigilance system through the follow-up of cases of suspected adverse reactions. For those tasks, Member States should establish a permanent pharmacovigilance system, supported by the appropriate expertise, so that the obligations under this Directive can be fully met.

(18) In order to further increase the coordination of resources between the Member States, Member State should be authorised to delegate certain pharmacovigilance tasks to another Member State.

(19) In order to simplify the reporting of suspected adverse reactions, the marketing authorisation holders and the Member States should report those reactions only to the Union pharmacovigilance database and data-processing network referred to in Article 57(1)(d) of Regulation (EC) No 726/2004 (the 'Eudravigilance database'). The Eudravigilance database should be equipped to immediately forward reports on suspected adverse reactions received from marketing authorisation holders to the Member States on whose territory the reaction occurred.

(20) In order to increase the level of transparency of the pharmacovigilance processes, the Member States should create and maintain medicines web-portals. To the same end, the marketing authorisation holders should provide the competent authorities with prior or simultaneous warnings about safety announcements and the competent authorities should also provide each other with advance notice of safety announcements.

(21) Union rules in relation to pharmacovigilance should continue to rely on the crucial role of healthcare professionals in monitoring the safety of medicinal products, and should take account of the fact that patients are also well placed to report suspected adverse reactions to medicinal products. It is therefore appropriate to facilitate the reporting of suspected adverse reactions to medicinal products by both healthcare professionals and patients, and to make methods for such reporting available to them.

(22) As a result of the submission of all suspected adverse reaction data directly to the Eudravigilance database, it is appropriate to amend the scope of periodic safety update reports so that they present an analysis of the risk-benefit balance of a medicinal product rather than a detailed listing of individual case reports already submitted to the Eudravigilance database.

(23) Obligations imposed in respect of periodic safety update reports should be proportionate to the risks posed by medicinal products. Periodic safety update reporting should therefore be linked to the risk management system for newly authorised medicinal products and routine reporting should not be required for generic medicinal products, for medicinal products containing an active substance for which well-established medicinal use has been demonstrated, for homeopathic medicinal products or for traditional-use registered herbal medicinal products. However, in the interests of public health, the competent authorities should require periodic safety update reports for such medicinal products when concerns arise relating to pharmacovigilance data or as a result of the lack of available safety data when the use of the active substance concerned is concentrated in medicinal products for which periodic safety update reporting is not routinely required.

(24) It is necessary to increase the shared use of resources between competent authorities for the assessment of periodic safety update reports. A single assessment of periodic safety update reports for medicinal products authorised in more than one Member State should be provided for. Moreover, procedures should be established to set single frequency and submission dates of periodic safety update reports for all medicinal products containing the same active substance or the same combination of active substances.

(25) Following a single assessment of periodic safety update reports, any resulting measures as regards the maintenance, variation, suspension or revocation of the marketing authorisations concerned should be adopted through a Union procedure leading to a harmonised result.

(26) The Member States should automatically submit certain safety issues related to medicinal products to the Agency thereby triggering a Union-wide assessment of the issue. Therefore it is appropriate to establish rules for an assessment procedure by the Pharmacovigilance Risk Assessment Committee, and for the subsequent follow-up as regards the marketing authorisations concerned with a view to the adoption of harmonised measures across the Union.

(27) In connection with the clarification and strengthening of the provisions relating to pharmacovigilance activities in Directive 2001/83/EC, it is also appropriate to further clarify the procedures for all Union-wide post-authorisation assessments of safety issues concerning medicinal products. To that end, the number of procedures for Union-wide assessment should be limited to two, one of which allows for a swift assessment and should be applied when urgent action is considered necessary. Regardless of whether the urgent procedure or the normal procedure is applied, and whether the medicinal product was authorised through the centralised or non-centralised procedure, the Pharmacovigilance Risk Assessment Committee should always give its recommendation when the reason for taking action is based on pharmacovigilance data. It is appropriate that the coordination group and the Committee for Medicinal Products for Human Use should rely on this recommendation when performing their assessment of the issue.

(28) It is necessary to introduce harmonised guiding principles for, and regulatory supervision of, post-authorisation safety studies that are requested by competent authorities and that are non-interventional, that are initiated, managed or financed by the marketing authorisation holder, and that involve the collection of data from patients or healthcare professionals and that therefore fall outside of the scope of Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use [1]. The supervision of such studies should be the responsibility of the Pharmacovigilance Risk Assessment Committee. Studies requested after the marketing authorisation of a medicinal product by only one competent authority to be conducted in only one Member State should be supervised by the national competent authority of the Member State in which the study is to be conducted. Provision should also be made for the subsequent follow-up, if appropriate, as regards the marketing authorisations concerned with a view to the adoption of harmonised measures across the Union.

(29) In order to enforce the provisions relating to pharmacovigilance, the Member States should ensure that effective, proportionate and dissuasive penalties are applied to marketing authorisation holders for non-compliance with pharmacovigilance obligations. If the conditions included in the marketing authorisation are not fulfilled within the given deadline, the national competent authorities should have the power to review the marketing authorisation.

[1] OJ L 121, 1.5.2001, p. 34.

(30) In order to protect public health, the pharmacovigilance activities of national competent authorities should be adequately funded. It should be ensured that adequate funding is possible for pharmacovigilance activities by empowering the national competent authorities to charge fees to marketing authorisation holders. However, the management of those collected funds should be under the permanent control of the national competent authorities in order to guarantee their independence in the performance of those pharmacovigilance activities.

(31) It should be possible for Member States to allow the relevant actors, under certain conditions, to deviate from certain provisions of Directive 2001/83/EC related to the requirements for labelling and packaging in order to address severe availability problems related to the potential lack of authorised medicinal products or of medicinal products placed on the market or shortages thereof.

(32) Since the objective of this Directive, namely to improve the safety of medicinal products placed on the market in the Union in a harmonised way across the Member States, cannot be sufficiently achieved by the Member States and can, by reason of the scale of the measures, be better achieved at Union level, the Union may adopt measures, in accordance with the principle of subsidiarity as set out in Article 5 of the Treaty on European Union (TEU). In accordance with the principle of proportionality, as set out in that Article, this Directive does not go beyond what is necessary in order to achieve this objective.

(33) This Directive shall apply without prejudice to Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data [1] and Regulation (EC) No 45/2001 of the European Parliament and of the Council of 18 December 2000 on the protection of individuals with regard to the processing of personal data by the Community institutions and bodies and on the free movement of such data [2]. In order to detect, assess, understand and prevent adverse reactions, and to identify and take actions to reduce the risks of, and increase the benefits from, medicinal products for the purpose of safeguarding public health, it should be possible to process personal data within the Eudravigilance system while respecting Union legislation relating to data protection. The purpose of safeguarding public health constitutes a substantial public interest and consequently the processing of personal data can be justified if identifiable health data are processed only when necessary and only when the parties involved assess this necessity at every stage of the pharmacovigilance process.

(34) The provisions on the monitoring of medicinal products in Directive 2001/83/EC constitute specific provisions within the meaning of Article 15(2) of Regulation (EC) No 765/2008 of the European Parliament and of the Council of 9 July 2008 setting out the requirements for accreditation and market surveillance relating to the marketing of products [3].

(35) The pharmacovigilance activities provided for in this Directive require that uniform conditions be established as concerns the contents and maintenance of the pharmacovigilance system master file, as well as the minimum requirements for the quality system for the performance of pharmacovigilance activities by the national competent authorities and marketing authorisation holders, the use of internationally agreed terminology, formats and standards for the performance of pharmacovigilance activities, and the minimum requirements for the monitoring of the data contained in the Eudravigilance database to determine whether there are new risks or whether risks have changed. The format and content of the electronic transmission of suspected adverse reactions by Member States and marketing authorisation holders, the format and content of electronic periodic safety update reports and risk management plans as well as the format of protocols, abstracts and final study reports for the post-authorisation safety studies should also be established. In accordance with Article 291 of the Treaty on the Functioning of the European Union (TFEU), rules and general principles concerning mechanisms for the control by Member States of the Commission's exercise of implementing powers are to be laid down in advance by a regulation adopted in accordance with the ordinary legislative procedure. Pending the adoption of that new regulation, Council Decision 1999/468/EC of 28 June 1999 laying down the procedures for the exercise of implementing powers conferred on the Commission [4] continues to apply, with the exception of the regulatory procedure with scrutiny, which is not applicable.

(36) The Commission should be empowered to adopt delegated acts in accordance with Article 290 TFEU in order to supplement the provisions in Articles 21a and 22a of Directive 2001/83/EC. The Commission should be empowered to adopt supplementary measures laying down the situations in which post-authorisation efficacy studies may be required. It is of particular importance that the Commission carry out appropriate consultations during its preparatory work, including at expert level.

(37) In accordance with point 34 of the Interinstitutional Agreement on better law-making [5], Member States are encouraged to draw up, for themselves and in the interests of the Union, their own tables illustrating, as far as possible, the correlation between this Directive and the transposition measures, and to make them public.

(38) Directive 2001/83/EC should be amended accordingly,

[1] OJ L 281, 23.11.1995, p. 31.
[2] OJ L 8, 12.1.2001, p. 1.
[3] OJ L 218, 13.8.2008, p. 30.
[4] OJ L 184, 17.7.1999, p. 23.
[5] OJ C 321, 31.12.2003, p. 1.

HAVE ADOPTED THIS DIRECTIVE:

Article 1

Amendments to Directive 2001/83/EC

Directive 2001/83/EC is hereby amended as follows:

1. Article 1 is amended as follows:

(a) point 11 is replaced by the following:

'11. Adverse reaction: A response to a medicinal product which is noxious and unintended.';

(b) point 14 is deleted;

(c) point 15 is replaced by the following:

'15. Post-authorisation safety study: Any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.';

(d) the following points are inserted:

'28b. Risk management system: a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to a medicinal product, including the assessment of the effectiveness of those activities and interventions.

28c. Risk management plan: a detailed description of the risk management system.

28d. Pharmacovigilance system: a system used by the marketing authorisation holder and by Member States to fulfil the tasks and responsibilities listed in Title IX and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance.

28e. Pharmacovigilance system master file: A detailed description of the pharmacovigilance system used by the marketing authorisation holder with respect to one or more authorised medicinal products.'.

2. Article 8(3) is amended as follows:

(a) point (ia) is replaced by the following:

'(ia) A summary of the applicant's pharmacovigilance system which shall include the following elements:

— proof that the applicant has at his disposal a qualified person responsible for pharmacovigilance,

— the Member States in which the qualified person resides and carries out his/her tasks,

— the contact details of the qualified person,

— a statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in Title IX,

— a reference to the location where the pharmacovigilance system master file for the medicinal product is kept.',

(b) the following point is inserted after point (ia):

'(iaa) The risk management plan describing the risk management system which the applicant will introduce for the medicinal product concerned, together with a summary thereof.';

(c) point (l) is replaced by the following:

'(l) Copies of the following:

— any authorisation, obtained in another Member State or in a third country, to place the medicinal product on the market, a summary of the safety data including the data contained in the periodic safety update reports, where available, and suspected adverse reactions reports, together with a list of those Member States in which an application for authorisation submitted in accordance with this Directive is under examination;

— the summary of the product characteristics proposed by the applicant in accordance with Article 11 or approved by the competent authorities of the Member State in accordance with Article 21 and the package leaflet proposed in accordance with Article 59 or approved by the competent authorities of the Member State in accordance with Article 61;

— details of any decision to refuse authorisation, whether in the Union or in a third country, and the reasons for such a decision.',

(d) point (n) is deleted;

(e) the following subparagraphs are added after the second subparagraph:

'The risk management system referred to in point (iaa) of the first subparagraph shall be proportionate to the identified risks and the potential risks of the medicinal product, and the need for post-authorisation safety data.

The information referred to in the first subparagraph shall be updated where and when appropriate.'.

3. In Article 11 the following subparagraphs are added:

'For medicinal products included on the list referred to in Article 23 of Regulation (EC) No 726/2004, the summary of product characteristics shall include the statement: "This medicinal product is subject to additional monitoring". This

statement shall be preceded by the black symbol referred to in Article 23 of Regulation (EC) No 726/2004 and followed by an appropriate standardised explanatory sentence.

For all medicinal products, a standard text shall be included expressly asking healthcare professionals to report any suspected adverse reaction in accordance with the national spontaneous reporting system referred to in Article 107a(1). Different ways of reporting, including electronic reporting, shall be available in compliance with the second subparagraph of Article 107a(1).'.

4. Article 16g(1) is replaced by the following:

'1. Article 3(1) and (2), Article 4(4), Article 6(1), Article 12, Article 17(1), Articles 19, 20, 23, 24, 25, 40 to 52, 70 to 85, 101 to 108b, Article 111(1) and (3), Articles 112, 116, 117, 118, 122, 123, 125, the second paragraph of Article 126, and Article 127 of this Directive as well as Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use (*) shall apply, by analogy, to traditional-use registration granted under this Chapter.

(*) OJ L 262, 14.10.2003, p. 22.'.

5. Article 17 is amended as follows:

(a) in the second subparagraph of paragraph 1, the words 'Articles 27' are replaced by the words 'Articles 28';

(b) in paragraph 2, the words 'Articles 27' are replaced by the words 'Articles 28';

6. In Article 18, the words 'Articles 27' are replaced by the words 'Articles 28'.

7. In Article 21, paragraphs 3 and 4 are replaced by the following:

'3. The national competent authorities shall, without delay, make publicly available the marketing authorisation together with the package leaflet, the summary of the product characteristics and any conditions established in accordance with Articles 21a, 22 and 22a, together with any deadlines for the fulfilment of those conditions for each medicinal product which they have authorised.

4. The national competent authorities shall draw up an assessment report and make comments on the file as regards the results of the pharmaceutical and pre-clinical tests, the clinical trials, the risk management system and the pharmacovigilance system of the medicinal product concerned. The assessment report shall be updated whenever new information becomes available which is important for the evaluation of the quality, safety or efficacy of the medicinal product concerned.

The national competent authorities shall make the assessment report publicly accessible without delay, together with the reasons for their opinion, after deletion of any information of a commercially confidential nature. The justification shall be provided separately for each indication applied for.

The public assessment report shall include a summary written in a manner that is understandable to the public. The summary shall contain, in particular, a section relating to the conditions of use of the medicinal product.'.

8. The following Article is inserted:

'Article 21a

In addition to the provisions laid down in Article 19, a marketing authorisation for a medicinal product may be granted subject to one or more of the following conditions:

(a) to take certain measures for ensuring the safe use of the medicinal product to be included in the risk management system;

(b) to conduct post-authorisation safety studies;

(c) to comply with obligations on the recording or reporting of suspected adverse reactions which are stricter than those referred to in Title IX;

(d) any other conditions or restrictions with regard to the safe and effective use of the medicinal product;

(e) the existence of an adequate pharmacovigilance system;

(f) to conduct post-authorisation efficacy studies where concerns relating to some aspects of the efficacy of the medicinal product are identified and can be resolved only after the medicinal product has been marketed. Such an obligation to conduct such studies shall be based on the delegated acts adopted pursuant to Article 22b while taking into account the scientific guidance referred to in Article 108a.

The marketing authorisation shall lay down deadlines for the fulfilment of these conditions where necessary.'.

9. Article 22 is replaced by the following:

'Article 22

In exceptional circumstances and following consultation with the applicant, the marketing authorisation may be granted subject to certain conditions, in particular relating to the safety of the medicinal product, notification to the national competent authorities of any incident relating to its use, and action to be taken.

The marketing authorisation may be granted only when the applicant can show that he is unable to provide comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use, for objective, verifiable reasons and must be based on one of the grounds set out in Annex I.

Continuation of the marketing authorisation shall be linked to the annual reassessment of these conditions.'.

10. The following Articles are inserted:

'Article 22a

1. After the granting of a marketing authorisation, the national competent authority may impose an obligation on the marketing authorisation holder:

(a) to conduct a post-authorisation safety study if there are concerns about the risks of an authorised medicinal product. If the same concerns apply to more than one medicinal product, the national competent authority shall, following consultation with the Pharmacovigilance Risk Assessment Committee, encourage the marketing authorisation holders concerned to conduct a joint post-authorisation safety study;

(b) to conduct a post-authorisation efficacy study when the understanding of the disease or the clinical methodology indicate that previous efficacy evaluations might have to be revised significantly. The obligation to conduct the post-authorisation efficacy study shall be based on the delegated acts adopted pursuant to Article 22b while taking into account the scientific guidance referred to in Article 108a.

The imposition of such an obligation shall be duly justified, notified in writing, and shall include the objectives and timeframe for submission and conduct of the study.

2. The national competent authority shall provide the marketing authorisation holder with an opportunity to present written observations in response to the imposition of the obligation within a time limit which it shall specify, if the marketing authorisation holder so requests within 30 days of receipt of the written notification of the obligation.

3. On the basis of the written observations submitted by the marketing authorisation holder, the national competent authority shall withdraw or confirm the obligation. Where the national competent authority confirms the obligation, the marketing authorisation shall be varied to include the obligation as a condition of the marketing authorisation and the risk management system shall be updated accordingly.

Article 22b

1. In order to determine the situations in which post-authorisation efficacy studies may be required under Articles 21a and 22a of this Directive, the Commission may adopt, by means of delegated acts in accordance with Article 121a, and subject to the conditions of Articles 121b and 121c, measures supplementing the provisions in Articles 21a and 22a.

2. When adopting such delegated acts, the Commission shall act in accordance with the provisions of this Directive.

Article 22c

1. The marketing authorisation holder shall incorporate any conditions referred to in Articles 21a, 22 or 22a in his risk management system.

2. The Member States shall inform the Agency of the marketing authorisations that they have granted subject to conditions pursuant to Articles 21a, 22 or 22a.'.

11. Article 23 is replaced by the following:

'Article 23

1. After a marketing authorisation has been granted, the marketing authorisation holder shall, in respect of the methods of manufacture and control provided for in Article 8(3)(d) and (h), take account of scientific and technical progress and introduce any changes that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods.

Those changes shall be subject to the approval of the competent authority of the Member State concerned.

2. The marketing authorisation holder shall forthwith provide the national competent authority with any new information which might entail the amendment of the particulars or documents referred to in Article 8(3), Articles 10, 10a, 10b and 11, or Article 32(5), or Annex I.

In particular, the marketing authorisation holder shall forthwith inform the national competent authority of any prohibition or restriction imposed by the competent authorities of any country in which the medicinal product is marketed and of any other new information which might influence the evaluation of the benefits and risks of the medicinal product concerned. The information shall include both positive and negative results of clinical trials or other studies in all indications and populations, whether or not included in the marketing authorisation, as well as data on the use of the medicinal product where such use is outside the terms of the marketing authorisation.

3. The marketing authorisation holder shall ensure that the product information is kept up to date with the current scientific knowledge, including the conclusions of the assessment and recommendations made public by means of the European medicines web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004.

4. In order to be able to continuously assess the risk-benefit balance, the national competent authority may at any time ask the marketing authorisation holder to forward data demonstrating that the risk-benefit balance remains favourable. The marketing authorisation holder shall answer fully and promptly any such request.

The national competent authority may at any time ask the marketing authorisation holder to submit a copy of the pharmacovigilance system master file. The marketing authorisation holder shall submit the copy at the latest 7 days after receipt of the request.'.

12. Article 24 is amended as follows:

(a) in paragraph 2, the second subparagraph is replaced by the following:

'To this end, the marketing authorisation holder shall provide the national competent authority with a consolidated version of the file in respect of quality, safety and efficacy, including the evaluation of data contained in suspected adverse reactions reports and periodic safety update reports submitted in accordance with Title IX, and information on all variations introduced since the marketing authorisation was granted, at least 9 months before the marketing authorisation ceases to be valid in accordance with paragraph 1.';

(b) paragraph 3 is replaced by the following:

'3. Once renewed, the marketing authorisation shall be valid for an unlimited period, unless the national competent authority decides, on justified grounds relating to pharmacovigilance, including exposure of an insufficient number of patients to the medicinal product concerned, to proceed with one additional five-year renewal in accordance with paragraph 2.'.

13. The title 'Chapter 4 Mutual recognition and decentralised procedure' is deleted.

14. Article 27 is amended as follows:

(a) paragraphs 1 and 2 are replaced by the following:

'1. A coordination group shall be set up for the following purposes:

(a) the examination of any question relating to a marketing authorisation of a medicinal product in two or more Member States in accordance with the procedures laid down in Chapter 4;

(b) the examination of questions related to the pharmacovigilance of medicinal products authorised by the Member States, in accordance with Articles 107c, 107e, 107g, 107k and 107q;

(c) the examination of questions relating to variations of marketing authorisations granted by the Member States, in accordance with Article 35(1).

The Agency shall provide the secretariat of this coordination group.

For the fulfilment of its pharmacovigilance tasks, including approving risk management systems and monitoring their effectiveness, the coordination group shall rely on the scientific assessment and the recommendations of the Pharmacovigilance Risk Assessment Committee provided for in Article 56(1)(aa) of Regulation (EC) No 726/2004.

2. The coordination group shall be composed of one representative per Member State appointed for a renewable period of 3 years. Member States may appoint an alternate for a renewable period of 3 years. Members of the coordination group may arrange to be accompanied by experts.

Members of the coordination group and experts shall, for the fulfilment of their tasks, rely on the scientific and regulatory resources available to national competent authorities. Each national competent authority shall monitor the level of expertise of the evaluations carried out and facilitate the activities of nominated coordination group members and experts.

Article 63 of Regulation (EC) No 726/2004 shall apply to the coordination group as regards transparency and the independence of its members.';

(b) the following paragraphs are added:

'4. The Executive Director of the Agency or his representative and representatives of the Commission shall be entitled to attend all meetings of the coordination group.

5. The members of the coordination group shall ensure that there is appropriate coordination between the tasks of that group and the work of national competent authorities, including the consultative bodies concerned with the marketing authorisation.

6. Save where otherwise provided for in this Directive, the Member States represented within the coordination group shall use their best endeavours to reach a position by consensus on the action to be taken. If such a consensus cannot be reached, the position of the majority of the Member States represented within the coordination group shall prevail.

7. Members of the coordination group shall be required, even after their duties have ceased, not to disclose information of the kind covered by the obligation of professional secrecy.'.

15. After Article 27 the following heading is inserted:

'*CHAPTER 4*

Mutual recognition and decentralised procedure'.

16. Article 31(1) is amended as follows:

(a) the first subparagraph is replaced by the following:

'The Member States, the Commission, the applicant or the marketing authorisation holder shall, in specific cases where the interests of the Union are involved, refer the matter to the Committee for application of the procedure laid down in Articles 32, 33 and 34 before any decision is reached on an application for a marketing authorisation or on the suspension or revocation of a marketing authorisation, or on any other variation of the marketing authorisation which appears necessary.';

(b) the following subparagraphs are inserted after the first subparagraph:

'Where the referral results from the evaluation of data relating to pharmacovigilance of an authorised medicinal product, the matter shall be referred to the Pharmacovigilance Risk Assessment Committee and Article 107j(2) may be applied. The Pharmacovigilance Risk Assessment Committee shall issue a recommendation according to the procedure laid down in Article 32. The final recommendation shall be forwarded to the Committee for Medicinal Products for Human Use or to the coordination group, as appropriate, and the procedure laid down in Article 107k shall apply.

However, where urgent action is considered necessary, the procedure laid down in Articles 107i to 107k shall apply.'.

17. Article 36 is deleted.

18. Article 59 is amended as follows:

(a) paragraph 1 is amended as follows:

(i) point (e) is replaced by:

'(e) a description of the adverse reactions which may occur under normal use of the medicinal product and, if necessary, the action to be taken in such a case.';

(ii) the following subparagraphs are added:

'For medicinal products included in the list referred to in Article 23 of Regulation (EC) No 726/2004, the following additional statement shall be included "This medicinal product is subject to additional monitoring". This statement shall be preceded by the black symbol referred to in Article 23 of Regulation (EC) No 726/2004 and followed by an appropriate standardised explanatory sentence.

For all medicinal products, a standardised text shall be included, expressly asking patients to communicate any suspected adverse reaction to his/her doctor, pharmacist, healthcare professional or directly to the national spontaneous reporting system referred to in Article 107a(1), and specifying the different ways of reporting available (electronic reporting, postal address and/or others) in compliance with the second subparagraph of Article 107a(1).';

(b) the following paragraph is added:

'4. By 1 January 2013, the Commission shall present to the European Parliament and the Council an assessment report on current shortcomings in the summary of product characteristics and the package leaflet and how they could be improved in order to better meet the needs of patients and healthcare professionals. The Commission shall, if appropriate, and on the basis of the report, and consultation with appropriate stakeholders, present proposals in order to improve the readability, layout and content of these documents. '

19. Article 63(3) is replaced by the following:

'3. When the medicinal product is not intended to be delivered directly to the patient, or where there are severe problems in respect of the availability of the medicinal product, the competent authorities may, subject to measures they consider necessary to safeguard human health, grant an exemption to the obligation that certain particulars should appear on the labelling and in the package leaflet. They may also grant a full or partial exemption to the obligation that the labelling and the package leaflet must be in the official language or languages of the Member State in which the medicinal product is placed on the market.'.

20. Title IX is replaced by the following:

'TITLE IX

PHARMACOVIGILANCE

CHAPTER 1

General provisions

Article 101

1. Member States shall operate a pharmacovigilance system for the fulfilment of their pharmacovigilance tasks and their participation in Union pharmacovigilance activities.

The pharmacovigilance system shall be used to collect information on the risks of medicinal products as regards patients' or public health. That information shall in particular refer to adverse reactions in human beings, arising from use of the medicinal product within the terms of the marketing authorisation as well as from use outside the terms of the marketing authorisation, and to adverse reactions associated with occupational exposure.

2. Member States shall, by means of the pharmacovigilance system referred to in paragraph 1, evaluate all information scientifically, consider options for risk minimisation and prevention and take regulatory action concerning the marketing authorisation as necessary. They shall perform a regular audit of their pharmacovigilance system and report the results to the Commission on 21 September 2013 at the latest and then every 2 years thereafter.

3. Each Member State shall designate a competent authority for the performance of pharmacovigilance tasks.

4. The Commission may request Member States to participate, under the coordination of the Agency, in international harmonisation and standardisation of technical measures in relation to pharmacovigilance.

Article 102

The Member States shall:

(a) take all appropriate measures to encourage patients, doctors, pharmacists and other healthcare professionals to report suspected adverse reactions to the national competent authority; for these tasks, organisations representing consumers, patients and healthcare professionals may be involved as appropriate;

(b) facilitate patient reporting through the provision of alternative reporting formats in addition to web-based formats;

(c) take all appropriate measures to obtain accurate and verifiable data for the scientific evaluation of suspected adverse reaction reports;

(d) ensure that the public is given important information on pharmacovigilance concerns relating to the use of a medicinal product in a timely manner through publication on the web-portal and through other means of publicly available information as necessary;

(e) ensure, through the methods for collecting information and where necessary through the follow-up of suspected adverse reaction reports, that all appropriate measures are taken to identify clearly any biological medicinal product prescribed, dispensed, or sold in their territory which is the subject of a suspected adverse reaction report, with due regard to the name of the medicinal product, in accordance with Article 1(20), and the batch number;

(f) take the necessary measures to ensure that a marketing authorisation holder who fails to discharge the obligations laid down in this Title is subject to effective, proportionate and dissuasive penalties.

For the purposes of point (a) and (e) of the first paragraph the Member States may impose specific obligations on doctors, pharmacists and other health-care professionals.

Article 103

A Member State may delegate any of the tasks entrusted to it under this Title to another Member State subject to a written agreement of the latter. Each Member State may represent no more than one other Member State.

The delegating Member State shall inform the Commission, the Agency and all other Member States of the delegation in writing. The delegating Member State and the Agency shall make that information public.

Article 104

1. The marketing authorisation holder shall operate a pharmacovigilance system for the fulfilment of his pharmacovigilance tasks equivalent to the relevant Member State's pharmacovigilance system provided for under Article 101(1).

2. The marketing authorisation holder shall by means of the pharmacovigilance system referred to in paragraph 1 evaluate all information scientifically, consider options for risk minimisation and prevention and take appropriate measures as necessary.

The marketing authorisation holder shall perform a regular audit of his pharmacovigilance system. He shall place a note concerning the main findings of the audit on the pharmacovigilance system master file and, based on the audit findings, ensure that an appropriate corrective action plan is prepared and implemented. Once the corrective actions have been fully implemented, the note may be removed.

3. As part of the pharmacovigilance system, the marketing authorisation holder shall:

(a) have permanently and continuously at his disposal an appropriately qualified person responsible for pharmacovigilance;

(b) maintain and make available on request a pharmacovigilance system master file;

(c) operate a risk management system for each medicinal product;

(d) monitor the outcome of risk minimisation measures which are contained in the risk management plan or which are laid down as conditions of the marketing authorisation pursuant to Articles 21a, 22 or 22a;

(e) update the risk management system and monitor pharmacovigilance data to determine whether there are new risks or whether risks have changed or whether there are changes to the benefit-risk balance of medicinal products.

The qualified person referred to in point (a) of the first subparagraph shall reside and operate in the Union and shall be responsible for the establishment and maintenance of the pharmacovigilance system. The marketing authorisation holder shall submit the name and contact details of the qualified person to the competent authority and the Agency.

4. Notwithstanding the provisions of paragraph 3, national competent authorities may request the nomination of a contact person for pharmacovigilance issues at national level reporting to the qualified person responsible for pharmacovigilance activities.

Article 104a

1. Without prejudice to paragraphs 2, 3 and 4 of this Article, holders of marketing authorisations granted before 21 July 2012 shall, by way of derogation from Article 104(3)(c), not be required to operate a risk management system for each medicinal product.

2. The national competent authority may impose an obligation on a marketing authorisation holder to operate a risk management system, as referred to in Article 104(3)(c), if there are concerns about the risks affecting the risk-benefit balance of an authorised medicinal product. In that context, the national competent authority shall also oblige the marketing authorisation holder to submit a detailed description of the risk-management system which he intends to introduce for the medicinal product concerned.

The imposition of such obligations shall be duly justified, notified in writing and shall include the timeframe for submission of the detailed description of the risk-management system.

3. The national competent authority shall provide the marketing authorisation holder with an opportunity to present written observations in response to the imposition of the obligation within a time limit which it shall specify, if the marketing authorisation holder so requests within 30 days of receipt of the written notification of the obligation.

4. On the basis of the written observations submitted by the marketing authorisation holder, the national competent authority shall withdraw or confirm the obligation. Where the national competent authority confirms the obligation, the marketing authorisation shall be varied accordingly to include the measures to be taken as part of the risk management system as conditions of the marketing authorisation referred to in point (a) of Article 21a.

Article 105

The management of funds intended for activities connected with pharmacovigilance, the operation of communication networks and market surveillance shall be under the permanent control of the national competent authorities in order to guarantee their independence in the performance of those pharmacovigilance activities.

The first paragraph shall not preclude the national competent authorities from charging fees to marketing authorisation holders for performing those activities by the national competent authorities on the condition that their independence in the performance of those pharmacovigilance activities is strictly guaranteed.

CHAPTER 2

Transparency and communications

Article 106

Each Member State shall set up and maintain a national medicines web-portal which shall be linked to the European medicines web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004. By means of the national medicines web-portals, the Member States shall make publicly available at least the following:

(a) public assessment reports, together with a summary thereof;

(b) summaries of product characteristics and package leaflets;

(c) summaries of risk management plans for medicinal products authorised in accordance with this Directive;

(d) the list of medicinal products referred to in Article 23 of Regulation (EC) No 726/2004;

(e) information on the different ways of reporting suspected adverse reactions to medicinal products to national competent authorities by healthcare professionals and patients, including the web-based structured forms referred to in Article 25 of Regulation (EC) No 726/2004.

Article 106a

1. As soon as the marketing authorisation holder intends to make a public announcement relating to information on pharmacovigilance concerns in relation to the use of a medicinal product, and in any event at the same time or before the public announcement is made, he shall be required to inform the national competent authorities, the Agency and the Commission.

The marketing authorisation holder shall ensure that information to the public is presented objectively and is not misleading.

2. Unless urgent public announcements are required for the protection of public health, the Member States, the Agency and the Commission shall inform each other not less than 24 hours prior to a public announcement relating to information on pharmacovigilance concerns.

3. For active substances contained in medicinal products authorised in more than one Member State, the Agency shall be responsible for the coordination between national competent authorities of safety announcements and shall provide timetables for the information being made public.

Under the coordination of the Agency, the Member States shall make all reasonable efforts to agree on a common message in relation to the safety of the medicinal product concerned and the timetables for their distribution. The Pharmacovigilance Risk Assessment Committee shall, at the request of the Agency, provide advice on those safety announcements.

4. When the Agency or national competent authorities make public information referred to in paragraphs 2 and 3, any information of a personal or commercially confidential nature shall be deleted unless its public disclosure is necessary for the protection of public health.

CHAPTER 3

Recording, reporting and assessment of pharmacovigilance data

Section 1

Recording and reporting of suspected adverse reactions

Article 107

1. Marketing authorisation holders shall record all suspected adverse reactions in the Union or in third countries which are brought to their attention, whether reported spontaneously by patients or healthcare professionals, or occurring in the context of a post-authorisation study.

Marketing authorisation holders shall ensure that those reports are accessible at a single point within the Union.

By way of derogation from the first subparagraph, suspected adverse reactions occurring in the context of a clinical trial shall be recorded and reported in accordance with Directive 2001/20/EC.

2. Marketing authorisation holders shall not refuse to consider reports of suspected adverse reactions received electronically or by any other appropriate means from patients and healthcare professionals.

3. Marketing authorisation holders shall submit electronically to the database and data-processing network referred to in Article 24 of Regulation (EC) No 726/2004 (hereinafter referred to as the "Eudravigilance database") information on all serious suspected adverse reactions that occur in the Union and in third countries within 15 days following the day on which the marketing authorisation holder concerned gained knowledge of the event.

Marketing authorisation holders shall submit electronically to the Eudravigilance database information on all non-serious suspected adverse reactions that occur in the Union, within 90 days following the day on which the marketing authorisation holder concerned gained knowledge of the event.

For medicinal products containing the active substances referred to in the list of publications monitored by the Agency pursuant to Article 27 of Regulation (EC) No 726/2004, marketing authorisation holders shall not be required to report to the Eudravigilance database the suspected adverse reactions recorded in the listed medical literature, but they shall monitor all other medical literature and report any suspected adverse reactions.

4. Marketing authorisation holders shall establish procedures in order to obtain accurate and verifiable data for the scientific evaluation of suspected adverse reaction reports. They shall also collect follow-up information on these reports and submit the updates to the Eudravigilance database.

5. Marketing authorisation holders shall collaborate with the Agency and the Member States in the detection of duplicates of suspected adverse reaction reports.

Article 107a

1. Each Member State shall record all suspected adverse reactions that occur in its territory which are brought to its attention from healthcare professionals and patients. Member States shall involve patients and healthcare professionals, as appropriate, in the follow-up of any reports they receive in order to comply with Article 102(c) and (e).

Member States shall ensure that reports of such reactions may be submitted by means of the national medicines web-portals or by other means.

2. For reports submitted by a marketing authorisation holder, Member States on whose territory the suspected adverse reaction occurred may involve the marketing authorisation holder in the follow-up of the reports.

3. Member States shall collaborate with the Agency and the marketing authorisation holders in the detection of duplicates of suspected adverse reaction reports.

4. Member States shall, within 15 days following the receipt of the reports of serious suspected adverse reactions referred to in paragraph 1, submit the reports electronically to the Eudravigilance database.

They shall, within 90 days from the receipt of reports referred to in paragraph 1, submit reports of non-serious suspected adverse reactions electronically to the Eudravigilance database.

Marketing authorisation holders shall access those reports through the Eudravigilance database.

5. Member States shall ensure that reports of suspected adverse reactions arising from an error associated with the use of a medicinal product that are brought to their attention are made available to the Eudravigilance database and to any authorities, bodies, organisations and/or institutions, responsible for patient safety within that Member State. They shall also ensure that the authorities responsible for medicinal products within that Member State are informed of any suspected adverse reactions brought to the attention of any other authority within that Member State. These reports shall be appropriately identified in the forms referred to in Article 25 of Regulation (EC) No 726/2004.

6. Unless there are justifiable grounds resulting from pharmacovigilance activities, individual Member States shall not impose any additional obligations on marketing authorisation holders for the reporting of suspected adverse reactions.

Section 2

Periodic safety update reports

Article 107b

1. Marketing authorisation holders shall submit to the Agency periodic safety update reports containing:

(a) summaries of data relevant to the benefits and risks of the medicinal product, including results of all studies with a consideration of their potential impact on the marketing authorisation;

(b) a scientific evaluation of the risk-benefit balance of the medicinal product;

(c) all data relating to the volume of sales of the medicinal product and any data in possession of the marketing authorisation holder relating to the volume of prescriptions, including an estimate of the population exposed to the medicinal product.

The evaluation referred to in point (b) shall be based on all available data, including data from clinical trials in unauthorised indications and populations.

The periodic safety update reports shall be submitted electronically.

2. The Agency shall make available the reports referred to in paragraph 1 to the national competent authorities, the members of the Pharmacovigilance Risk Assessment Committee, the Committee for Medicinal Products for Human Use and the coordination group by means of the repository referred to in Article 25a of Regulation (EC) No 726/2004.

3. By way of derogation from paragraph 1 of this Article, the holders of marketing authorisations for medicinal products referred to in Article 10(1), or Article 10a, and the holders of registrations for medicinal products referred to in Articles 14 or 16a, shall submit periodic safety update reports for such medicinal products in the following cases:

(a) where such obligation has been laid down as a condition in the marketing authorisation in accordance with Article 21a or Article 22; or

(b) when requested by a competent authority on the basis of concerns relating to pharmacovigilance data or due to the lack of periodic safety update reports relating to an active substance after the marketing authorisation has been granted. The assessment reports of the requested periodic safety update reports shall be communicated to the Pharmacovigilance Risk Assessment Committee, which shall consider whether there is a need for a single assessment report for all marketing authorisations for medicinal products containing the same active substance and inform the coordination group or the Committee for Medicinal Products for Human Use accordingly, in order to apply the procedures laid down in Article 107c(4) and Article 107e.

Article 107c

1. The frequency with which the periodic safety update reports are to be submitted shall be specified in the marketing authorisation.

The dates of submission according to the specified frequency shall be calculated from the date of the authorisation.

2. Holders of marketing authorisations which were granted before 21 July 2012, and for which the frequency and dates of submission of the periodic safety update reports are not laid down as a condition to the marketing authorisation, shall submit the periodic safety update reports in accordance with the second subparagraph of this paragraph until another frequency or other dates of submission of the reports are laid down in the marketing authorisation or determined in accordance with paragraphs 4, 5 or 6.

Periodic safety update reports shall be submitted to the competent authorities immediately upon request or in accordance with the following:

(a) where a medicinal product has not yet been placed on the market, at least every 6 months following authorisation and until the placing on the market;

(b) where a medicinal product has been placed on the market, at least every 6 months during the first 2 years following the initial placing on the market, once a year for the following 2 years and at three-yearly intervals thereafter.

3. Paragraph 2 shall also apply to medicinal products which are authorised only in one Member State and for which paragraph 4 does not apply.

4. Where medicinal products that are subject to different marketing authorisations contain the same active substance or the same combination of active substances, the frequency and dates of submission of the periodic safety update reports resulting from the application of paragraphs 1 and 2 may be amended and harmonised to enable a single assessment to be made in the context of a periodic safety update report work-sharing procedure and to set a Union reference date from which the submission dates are calculated.

This harmonised frequency for the submission of the reports and the Union reference date may be determined, after consultation of the Pharmacovigilance Risk Assessment Committee, by one of the following:

(a) the Committee for Medicinal Products for Human Use, where at least one of the marketing authorisations for the medicinal products containing the active substance concerned has been granted in accordance with the centralised procedure provided for in Chapter 1 of Title II of Regulation (EC) No 726/2004;

(b) the coordination group, in other cases than those referred to in point (a).

The harmonised frequency for the submission of the reports determined pursuant to the first and second subparagraphs shall be made public by the Agency. Marketing authorisation holders shall submit an application for a variation of the marketing authorisation accordingly.

5. For the purposes of paragraph 4, the Union reference date for medicinal products containing the same active substance or the same combination of active substances shall be one of the following:

(a) the date of the first marketing authorisation in the Union of a medicinal product containing that active substance or that combination active substances;

(b) if the date referred to in point (a) cannot be ascertained, the earliest of the known dates of the marketing authorisations for a medicinal product containing that active substance or that combination of active substances.

6. Marketing authorisation holders shall be allowed to submit requests to the Committee for Medicinal Products for Human Use or the coordination group, as appropriate, to determine Union reference dates or to change the frequency of submission periodic safety update reports on one of the following grounds:

(a) for reasons relating to public health;

(b) in order to avoid a duplication of the assessment;

(c) in order to achieve international harmonisation.

Such requests shall be submitted in writing and shall be duly justified. The Committee for Medicinal Products for Human Use or the coordination group shall, following the consultation with the Pharmacovigilance Risk Assessment Committee, shall either approve or deny such requests. Any change in the dates or the frequency of submission of periodic safety update reports shall be made public by the Agency. The marketing authorisation holders shall accordingly submit an application for a variation of the marketing authorisation.

7. The Agency shall make public a list of Union reference dates and frequency of submission of periodic safety update reports by means of the European medicines web-portal.

Any change to the dates of submission and frequency of periodic safety update reports specified in the marketing authorisation as a result of the application of paragraphs 4, 5 and 6 shall take effect 6 months after the date of such publication.

Article 107d

The national competent authorities shall assess periodic safety update reports to determine whether there are new risks or whether risks have changed or whether there are changes to the risk-benefit balance of medicinal products.

Article 107e

1. A single assessment of periodic safety update reports shall be performed for medicinal products authorised in more than one Member State and, in the cases of paragraphs 4 to 6 of Article 107c, for all medicinal products containing the same active substance or the same combination of active substances and for which a Union reference date and frequency of periodic safety update reports has been established.

The single assessment shall be conducted by either of the following:

(a) a Member State appointed by the coordination group where none of the marketing authorisations concerned has been granted in accordance with the centralised procedure provided for in Chapter 1 of Title II of Regulation (EC) No 726/2004; or

(b) a rapporteur appointed by the Pharmacovigilance Risk Assessment Committee, where at least one of the marketing authorisations concerned has been granted in accordance with the centralised procedure provided for in Chapter 1 of Title II of Regulation (EC) No 726/2004.

When selecting the Member State in accordance with point (a) of the second subparagraph, the coordination group shall take into account whether any Member State is acting as a reference Member State, in accordance with Article 28(1).

2. The Member State or rapporteur, as appropriate, shall prepare an assessment report within 60 days of receipt of the periodic safety update report and send it to the Agency and to the Member States concerned. The Agency shall send the report to the marketing authorisation holder.

Within 30 days of receipt of the assessment report, the Member States and the marketing authorisation holder may submit comments to the Agency and to the rapporteur or Member State.

3. Following the receipt of the comments referred to in paragraph 2, the rapporteur or Member State shall within 15 days update the assessment report taking into account any comments submitted, and forward it to the Pharmacovigilance Risk Assessment Committee. The Pharmacovigilance Risk Assessment Committee shall adopt the assessment report with or without further changes at its next meeting and issue a recommendation. The recommendation shall mention the divergent positions with the grounds on which they are based. The Agency shall include the adopted assessment report and the recommendation in the repository set up under Article 25a of Regulation (EC) No 726/2004 and forward both to the marketing authorisation holder.

Article 107f

Following the assessment of periodic safety update reports, the national competent authorities shall consider whether any action concerning the marketing authorisation for the medicinal product concerned is necessary.

They shall maintain, vary, suspend or revoke the marketing authorisation as appropriate.

Article 107g

1. In the case of a single assessment of periodic safety update reports that recommends any action concerning more than one marketing authorisation in accordance with Article 107e(1) which does not include any marketing authorisation granted in accordance with the centralised procedure provided for in Chapter 1 of Title II of Regulation (EC) No 726/2004, the coordination group shall, within 30 days of receipt of the report of the Pharmacovigilance Risk Assessment Committee, consider the report and reach a position on the maintenance, variation, suspension or revocation of the marketing authorisations concerned, including a timetable for the implementation of the agreed position.

2. If, within the coordination group, the Member States represented reach agreement on the action to be taken by consensus, the chairman shall record the agreement and send it to the marketing authorisation holder and the Member States. The Member States shall adopt necessary measures to maintain, vary, suspend or revoke the marketing authorisations concerned in accordance with the timetable for implementation determined in the agreement.

In the event of a variation, the marketing authorisation holder shall submit to the national competent authorities an appropriate application for a modification, including an updated summary of product characteristics and package leaflet within the determined timetable for implementation.

If an agreement by consensus cannot be reached, the position of the majority of the Member States represented within the coordination group shall be forwarded to the Commission which shall apply the procedure laid down in Articles 33 and 34.

Where the agreement reached by the Member States represented within the coordination group or the position of the majority of Member States differs from the recommendation of the Pharmacovigilance Risk Assessment Committee, the coordination group shall attach to the agreement or the majority position a detailed explanation of the scientific grounds for the differences together with the recommendation.

3. In the case of a single assessment of periodic safety update reports that recommends any action concerning more than one marketing authorisation in accordance with Article 107e(1) which includes at least one marketing authorisation granted in accordance with the centralised procedure provided for in Chapter 1 of Title II of Regulation (EC) No 726/2004, the Committee for Medicinal Products for Human Use shall, within 30 days of receipt of the report of the Pharmacovigilance Risk Assessment Committee, consider the report and adopt an opinion on the maintenance, variation, suspension or revocation of the marketing authorisations concerned, including a timetable for the implementation of the opinion.

Where this opinion of the Committee for Medicinal Products for Human Use differs from the recommendation of the Pharmacovigilance Risk Assessment Committee, the Committee for Medicinal Products for Human Use shall attach to its opinion a detailed explanation of the scientific grounds for the differences together with the recommendation.

4. On the basis of the opinion of the Committee for Medicinal Products for Human Use referred to in paragraph 3, the Commission shall:

(a) adopt a decision addressed to the Member States concerning the measures to be taken in respect of marketing authorisations granted by the Member States and concerned by the procedure provided for in this section; and

(b) where the opinion states that regulatory action concerning the marketing authorisation is necessary, adopt a decision to vary, suspend or revoke the marketing authorisations granted in accordance with the centralised procedure provided for in Regulation (EC) No 726/2004 and concerned by the procedure provided for in this section.

Articles 33 and 34 of this Directive shall apply to the adoption of the decision referred to in point (a) of the first subparagraph of this paragraph and to its implementation by the Member States.

Article 10 of Regulation (EC) No 726/2004 shall apply to the decision referred to in point (b) of the first subparagraph of this paragraph. Where the Commission adopts such decision, it may also adopt a decision addressed to the Member States pursuant to Article 127a of this Directive.

Section 3

Signal detection

Article 107h

1. Regarding medicinal products authorised in accordance with this Directive, national competent authorities in collaboration with the Agency, shall take the following measures:

(a) monitor the outcome of risk minimisation measures contained in risk management plans and of the conditions referred to in Articles 21a, 22 or 22a;

(b) assess updates to the risk management system;

(c) monitor the data in the Eudravigilance database to determine whether there are new risks or whether risks have changed and whether those risks impact on the risk-benefit balance.

2. The Pharmacovigilance Risk Assessment Committee shall perform the initial analysis and prioritisation of signals of new risks or risks that have changed or changes to the risk-benefit balance. Where it considers that follow-up action may be necessary, the assessment of those signals and agreement on any subsequent action concerning the marketing authorisation shall be conducted in a timescale commensurate with the extent and seriousness of the issue.

3. The Agency and national competent authorities and the marketing authorisation holder shall inform each other in the event of new risks or risks that have changed or changes to the risk-benefit balance being detected.

Member States shall ensure that marketing authorisation holders inform the Agency and national competent authorities in the event of new risks or risks that have changed or when changes to the risk-benefit balance have been detected.

Section 4

Urgent Union procedure

Article 107i

1. A Member State or the Commission, as appropriate, shall initiate the procedure provided for in this section, by informing the other Member States, the Agency and the Commission when urgent action is considered necessary, as a result of the evaluation of data resulting from pharmacovigilance activities, in any of the following cases:

(a) it considers suspending or revoking a marketing authorisation;

(b) it considers prohibiting the supply of a medicinal product;

(c) it considers refusing the renewal of a marketing authorisation;

(d) it is informed by the marketing authorisation holder that, on the basis of safety concerns, he has interrupted the placing on the market of a medicinal product or has taken action to have a marketing authorisation withdrawn, or that he intends to do so;

(e) it considers that a new contraindication, a reduction in the recommended dose, or a restriction to the indications is necessary.

The Agency shall verify whether the safety concern relates to medicinal products other than the one covered by the information, or whether it is common to all products belonging to the same range or therapeutic class.

Where the medicinal product involved is authorised in more than one Member State, the Agency shall without undue delay inform the initiator of the procedure of the outcome of this verification, and the procedures laid down in Articles 107j and 107k shall apply. Otherwise, the safety concern shall be addressed by the Member State concerned. The Agency or the Member State, as applicable, shall make information that the procedure has been initiated available to marketing authorisation holders.

2. Without prejudice to the provisions of paragraph 1 of this Article, and Articles 107j and 107k, a Member State may, where urgent action is necessary to protect public health, suspend the marketing authorisation and prohibit the use of the medicinal product concerned on its territory until a definitive decision is adopted. It shall inform the Commission, the Agency and the other Member States no later than the following working day of the reasons for its action.

3. At any stage of the procedure laid down in Articles 107j to 107k, the Commission may request Member States in which the medicinal product is authorised to take temporary measures immediately.

Where the scope of the procedure, as determined in accordance with paragraph 1, includes medicinal products authorised in accordance with Regulation (EC) No 726/2004, the Commission may, at any stage of the procedure initiated under this section, take temporary measures immediately in relation to those marketing authorisations.

4. The information referred to in this Article may relate to individual medicinal products or to a range of medicinal products or a therapeutic class.

If the Agency identifies that the safety concern relates to more medicinal products than those which are covered by the information or that it is common to all medicinal products belonging to the same range or therapeutic class, it shall extend the scope of the procedure accordingly.

Where the scope of the procedure initiated under this Article concerns a range of medicinal products or therapeutic class, medicinal products authorised in accordance with Regulation (EC) No 726/2004 which belong to that range or class shall also be included in the procedure.

5. At the time of the information referred to in paragraph 1, the Member State shall make available to the Agency all relevant scientific information that it has at its disposal and any assessment by the Member State.

Article 107j

1. Following receipt of the information referred to in Article 107i(1), the Agency shall publicly announce the initiation of the procedure by means of the European medicines web-portal. In parallel, Member States may publicly announce the initiation on their national medicines web-portals.

The announcement shall specify the matter submitted to the Agency in accordance with Article 107i, and the medicinal products and, where applicable, the active substances concerned. It shall contain information on the right of the marketing authorisation holders, healthcare professionals and the public to submit to the Agency information relevant to the procedure and it shall state how such information may be submitted.

2. The Pharmacovigilance Risk Assessment Committee shall assess the matter which has been submitted to the Agency in accordance with Article 107i. The rapporteur shall closely collaborate with the rapporteur appointed by the Committee for Medicinal Products for Human Use and the Reference Member State for the medicinal products concerned.

For the purposes of that assessment, the marketing authorisation holder may submit comments in writing.

Where the urgency of the matter permits, the Pharmacovigilance Risk Assessment Committee may hold public hearings, where it considers that this is appropriate on justified grounds particularly with regard to the extent and seriousness of the safety concern. The hearings shall be held in accordance with the modalities specified by the Agency and shall be announced by means of the European medicines web-portal. The announcement shall specify the modalities of participation.

In the public hearing, due regard shall be given to the therapeutic effect of the medicinal product.

The Agency shall, in consultation with the parties concerned, draw up Rules of Procedure on the organisation and conduct of public hearings, in accordance with Article 78 of Regulation (EC) No 726/2004.

Where a marketing authorisation holder or another person intending to submit information has confidential data relevant to the subject matter of the procedure, he may request permission to present that data to the Pharmacovigilance Risk Assessment Committee in a non-public hearing.

3. Within 60 days of the information being submitted, the Pharmacovigilance Risk Assessment Committee shall make a recommendation, stating the reasons on which it is based, having due regard to the therapeutic effect of the medicinal product. The recommendation shall mention the divergent positions and the grounds on which they are based. In the case of urgency, and on the basis of a proposal by its chairman, the Pharmacovigilance Risk Assessment Committee may agree to a shorter deadline. The recommendation shall include any or a combination of the following conclusions:

(a) no further evaluation or action is required at Union level;

(b) the marketing authorisation holder should conduct further evaluation of data together with the follow-up of the results of that evaluation;

(c) the marketing authorisation holder should sponsor a post-authorisation safety study together with the follow up evaluation of the results of that study;

(d) the Member States or marketing authorisation holder should implement risk minimisation measures;

(e) the marketing authorisation should be suspended, revoked or not renewed;

(f) the marketing authorisation should be varied.

For the purposes of point (d) of the first subparagraph, the recommendation shall specify the risk minimisation measures recommended and any conditions or restrictions to which the marketing authorisation should be made subject.

Where, in the cases referred to in point (f) of the first subparagraph, it is recommended to change or add information in the summary of product characteristics or the labelling or package leaflet, the recommendation shall suggest the wording of such changed or added information and where in the summary of the product characteristics, labelling or package leaflet such wording should be placed.

Article 107k

1. Where the scope of the procedure, as determined in accordance with Article 107i(4), does not include any marketing authorisation granted in accordance with the centralised procedure provided for in Chapter 1 of Title II of Regulation (EC) No 726/2004, the coordination group shall, within 30 days of receipt of the recommendation of the Pharmacovigilance Risk Assessment Committee, consider the recommendation and reach a position on the maintenance, variation, suspension, revocation or refusal of the renewal of the marketing authorisation concerned, including a timetable for the implementation of the agreed position. Where an urgent adoption of the position is necessary, and on the basis of a proposal by its chairman, the coordination group may agree to a shorter deadline.

2. If, within the coordination group, the Member States represented reach agreement on the action to be taken by consensus, the chairman shall record the agreement and send it to the marketing authorisation holder and the Member States. The Member States shall adopt necessary measures to maintain, vary, suspend, revoke or refuse renewal of the marketing authorisation concerned in accordance with the implementation timetable determined in the agreement.

In the event that a variation is agreed upon, the marketing authorisation holder shall submit to the national competent authorities an appropriate application for a variation, including an updated summary of product characteristics and package leaflet within the determined timetable for implementation.

If an agreement by consensus cannot be reached, the position of the majority of the Member States represented within the coordination group shall be forwarded to the Commission which shall apply the procedure laid down in Articles 33 and 34. However, by way of derogation from Article 34(1), the procedure referred to in Article 121(2) shall apply.

Where the agreement reached by the Member States represented within the coordination group or the position of the majority of the Member States represented within the coordination group differs from the recommendation of the Pharmacovigilance Risk Assessment Committee, the coordination group shall attach to the agreement or majority position a detailed explanation of the scientific grounds for the differences together with the recommendation.

3. Where the scope of the procedure, as determined in accordance with Article 107i(4), includes at least one marketing authorisation granted in accordance with the centralised procedure provided for in Chapter 1 of Title II of Regulation (EC) No 726/2004, the Committee for Medicinal Products for Human Use shall, within 30 days of receipt of the recommendation of the Pharmacovigilance Risk Assessment Committee, consider the recommendation and adopt an opinion on the maintenance, variation, suspension, revocation or refusal of the renewal of the marketing authorisations concerned. Where an urgent adoption of the opinion is necessary, and on the basis of a proposal by its chairman, the Committee for Medicinal Products for Human Use may agree to a shorter deadline.

Where the opinion of the Committee for Medicinal Products for Human Use differs from the recommendation of the Pharmacovigilance Risk Assessment Committee, the Committee for Medicinal Products for Human Use shall attach to its opinion a detailed explanation of the scientific grounds for the differences together with the recommendation.

4. On the basis of the opinion of the Committee for Medicinal Products for Human Use referred to in paragraph 3, the Commission shall:

(a) adopt a decision addressed to the Member States concerning the measures to be taken in respect of marketing authorisations that are granted by the Member States and that are subject to the procedure provided for in this section; and

(b) where the opinion is that regulatory action is necessary, adopt a decision to vary, suspend, revoke or refuse renewal of the marketing authorisations granted in accordance with Regulation (EC) No 726/2004 and subject to the procedure provided for in this section.

Articles 33 and 34 of this Directive shall apply to the adoption of the decision referred to in point (a) of the first subparagraph of this paragraph and to its implementation by the Member States. However, by way of derogation from Article 34(1) of this Directive, the procedure referred to in Article 121(2) thereof shall apply.

Article 10 of Regulation (EC) No 726/2004 shall apply to the decision referred to in point (b) of the first subparagraph of this paragraph. However, by way of derogation from Article 10(2) of that Regulation, the procedure referred to in Article 87(2) thereof shall apply. Where the Commission adopts such decision, it may also adopt a decision addressed to the Member States pursuant to Article 127a of this Directive.

Section 5

Publication of assessments

Article 107l

The Agency shall make public the final assessment conclusions, recommendations, opinions and decisions referred to in Articles 107b to 107k by means of the European medicines web-portal.

CHAPTER 4

Supervision of post-authorisation safety studies

Article 107m

1. This Chapter applies to non-interventional post-authorisation safety studies which are initiated, managed or financed by the marketing authorisation holder voluntarily or pursuant to obligations imposed in accordance with Articles 21a or 22a, and which involve the collection of safety data from patients or healthcare professionals.

2. This Chapter is without prejudice to national and Union requirements for ensuring the well-being and rights of participants in non-interventional post-authorisation safety studies.

3. The studies shall not be performed where the act of conducting the study promotes the use of a medicinal product.

4. Payments to healthcare professionals for participating in non-interventional post-authorisation safety studies shall be restricted to the compensation for time and expenses incurred.

5. The national competent authority may require the marketing authorisation holder to submit the protocol and the progress reports to the competent authorities of the Member States in which the study is conducted.

6. The marketing authorisation holder shall send the final report to the competent authorities of the Member States in which the study was conducted within 12 months of the end of data collection.

7. While a study is being conducted, the marketing authorisation holder shall monitor the data generated and consider its implications for the risk-benefit balance of the medicinal product concerned.

Any new information which might influence the evaluation of the risk-benefit balance of the medicinal product shall be communicated to the competent authorities of the Member State in which the medicinal product has been authorised in accordance with Article 23.

The obligation laid down in the second subparagraph is without prejudice to the information on the results of studies that the marketing authorisation holder shall make available by means of the periodic safety update reports as laid down in Article 107b.

8. Articles 107n to 107q shall apply exclusively to studies referred to in paragraph 1 which are conducted pursuant to an obligation imposed in accordance with Articles 21a or 22a.

Article 107n

1. Before a study is conducted, the marketing authorisation holder shall submit a draft protocol to the Pharmacovigilance Risk Assessment Committee, except for studies to be conducted in only one Member State that requests the study according to Article 22a. For such studies, the marketing authorisation holder shall submit a draft protocol to the national competent authority of the Member State in which the study is conducted.

2. Within 60 days of the submission of the draft protocol the national competent authority or the Pharmacovigilance Risk Assessment Committee, as appropriate, shall issue:

(a) a letter endorsing the draft protocol;

(b) a letter of objection, which shall set out in detail the grounds for the objection, in any of the following cases:

  (i) it considers that the conduct of the study promotes the use of a medicinal product;

  (ii) it considers that the design of the study does not fulfil the study objectives; or

(c) a letter notifying the marketing authorisation holder that the study is a clinical trial falling under the scope of Directive 2001/20/EC.

3. The study may commence only when the written endorsement from the national competent authority or the Pharmacovigilance Risk Assessment Committee, as appropriate, has been issued.

Where a letter of endorsement as referred to in paragraph 2(a) has been issued, the marketing authorisation holder shall forward the protocol to the competent authorities of the Member States in which the study is to be conducted and may thereafter commence the study according to the endorsed protocol.

Article 107o

After a study has been commenced, any substantial amendments to the protocol shall be submitted, before their implementation, to the national competent authority or to the Pharmacovigilance Risk Assessment Committee, as appropriate. The national competent authority or the Pharmacovigilance Risk Assessment Committee, as appropriate, shall assess the amendments and inform the marketing authorisation holder of its endorsement or objection. Where applicable, the marketing authorisation holder shall inform Member States in which the study is conducted.

Article 107p

1. Upon completion of the study, a final study report shall be submitted to the national competent authority or the Pharmacovigilance Risk Assessment Committee within 12 months of the end of data collection unless a written waiver has been granted by the national competent authority or the Pharmacovigilance Risk Assessment Committee, as appropriate.

2. The marketing authorisation holder shall evaluate whether the results of the study have an impact on the marketing authorisation and shall, if necessary, submit to the national competent authorities an application to vary the marketing authorisation.

3. Together with the final study report, the marketing authorisation holder shall electronically submit an abstract of the study results to the national competent authority or the Pharmacovigilance Risk Assessment Committee.

Article 107q

1. Based on the results of the study and after consultation of the marketing authorisation holder, the Pharmacovigilance Risk Assessment Committee may make recommendations concerning the marketing authorisation, stating the reasons on which they are based. The recommendations shall mention the divergent positions and the grounds on which they are based.

2. When recommendations for the variation, suspension or revocation of the marketing authorisation are made for a medicinal product authorised by the Member States pursuant to this Directive, the Member States represented within the coordination group shall agree a position on the matter taking into account the recommendation referred to in paragraph 1 and including a timetable for the implementation of the agreed position.

If, within the coordination group, the Member States represented reach agreement on the action to be taken by consensus, the chairman shall record the agreement and send it to the marketing authorisation holder and the Member States. The Member States shall adopt necessary measures to vary, suspend or revoke the marketing authorisation concerned in accordance with the implementation timetable determined in the agreement.

In the event that a variation is agreed upon, the marketing authorisation holder shall submit to the national competent authorities an appropriate application for a variation, including an updated summary of product characteristics and package leaflet within the determined timetable for implementation.

The agreement shall be made public on the European medicines web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004.

If an agreement by consensus cannot be reached, the position of the majority of the Member States represented within the coordination group shall be forwarded to the Commission, which shall apply the procedure laid down in Articles 33 and 34.

Where the agreement reached by the Member States represented within the coordination group or the position of the majority of Member States differs from the recommendation of the Pharmacovigilance Risk Assessment Committee, the coordination group shall attach to the agreement or majority position a detailed explanation of the scientific grounds for the differences together with the recommendation.

CHAPTER 5

Implementation, Delegation and Guidance

Article 108

In order to harmonise the performance of the pharmacovigilance activities provided for in this Directive, the Commission shall adopt implementing measures in the following areas for which pharmacovigilance activities are provided for in Article 8(3), and in Articles 101, 104, 104a, 107, 107a, 107b, 107h, 107n and 107p:

(a) the content and maintenance of the pharmacovigilance system master file kept by the marketing authorisation holder;

(b) the minimum requirements for the quality system for the performance of pharmacovigilance activities by the national competent authorities and the marketing authorisation holder;

(c) the use of internationally agreed terminology, formats and standards for the performance of pharmacovigilance activities;

(d) the minimum requirements for the monitoring of data in the Eudravigilance database to determine whether there are new risks or whether risks have changed;

(e) the format and content of the electronic transmission of suspected adverse reactions by Member States and the marketing authorisation holder;

(f) the format and content of electronic periodic safety update reports and risk management plans;

(g) the format of protocols, abstracts and final study reports for the post-authorisation safety studies.

Those measures shall take account of the work on international harmonisation carried out in the area of pharmacovigilance and shall, where necessary, be revised to take account of technical and scientific progress. Those measures shall be adopted in accordance with the regulatory procedure referred to in Article 121(2).

Article 108a

In order to facilitate the performance of pharmacovigilance activities within the Union, the Agency shall, in cooperation with competent authorities and other interested parties, draw up:

(a) guidance on good pharmacovigilance practices for both competent authorities and marketing authorisation holders;

(b) scientific guidance on post-authorisation efficacy studies.

Article 108b

The Commission shall make public a report on the performance of pharmacovigilance tasks by the Member States on 21 July 2015 at the latest and then every 3 years thereafter.'.

21. Article 111 is amended as follows:

(a) paragraph 1 is amended as follows:

(i) the first subparagraph is replaced by the following:

'The competent authority of the Member State concerned shall, in cooperation with the Agency, ensure that the legal requirements governing medicinal products are complied with, by means of inspections, if necessary unannounced, and, where appropriate, by asking an Official Medicines Control Laboratory or a laboratory designated for that purpose to carry out tests on samples. This cooperation shall consist in sharing information with the Agency on both inspections that are planned and that have been conducted. Member States and the Agency shall cooperate in the coordination of inspections in third countries.';

(ii) in the fifth subparagraph, point (d) is replaced by the following:

'(d) inspect the premises, records, documents and pharmacovigilance system master file of the marketing authorisation holder or any firms employed by the marketing authorisation holder to perform the activities described in Title IX.';

(b) paragraph 3 is replaced by the following:

'3. After every inspection referred to in paragraph 1, the competent authority shall report on whether the inspected entity complies with the principles and guidelines of good manufacturing practice and good distribution practices referred to in Articles 47 and 84, or whether the marketing authorisation holder complies with the requirements laid down in Title IX.

The competent authority which carried out the inspection shall communicate the content of those reports to the inspected entity.

Before adopting the report, the competent authority shall give the inspected entity concerned the opportunity to submit comments.';

(c) paragraph 7 is replaced by the following:

'7. If the outcome of the inspection as referred to in points (a), (b) and (c) of paragraph 1 or the outcome of an inspection of a distributor of medicinal products or active substances or a manufacturer of excipients used as starting materials is that the inspected entity does not comply with the legal requirements and/or the principles and guidelines of good manufacturing practice or good distribution practices as provided for by Union law, the information shall be entered in the Union database as provided for in paragraph 6.';

(d) the following paragraph is added:

'8. If the outcome of the inspection referred to in paragraph 1(d) is that the marketing authorisation holder does not comply with the pharmacovigilance system as described in the pharmacovigilance system master file and with Title IX, the competent authority of the Member State concerned shall bring the deficiencies to the attention of the marketing authorisation holder and give him the opportunity to submit comments.

In such case the Member State concerned shall inform the other Member States, the Agency and the Commission.

Where appropriate, the Member State concerned shall take the necessary measures to ensure that a marketing authorisation holder is subject to effective, proportionate and dissuasive penalties.'.

22. Article 116 is replaced by the following:

'Article 116

The competent authorities shall suspend, revoke or vary a marketing authorisation if the view is taken that the medicinal product is harmful or that it lacks therapeutic efficacy, or that the risk-benefit balance is not favourable, or that its qualitative and quantitative composition is not as declared. Therapeutic efficacy shall be considered to be lacking when it is concluded that therapeutic results cannot be obtained from the medicinal product.

A marketing authorisation may also be suspended, revoked or varied where the particulars supporting the application as provided for in Articles 8, 10 or 11 are incorrect or have not been amended in accordance with Article 23, or where any conditions referred to in Articles 21a, 22 or 22a have not been fulfilled or where the controls referred to in Article 112 have not been carried out.'.

23. Article 117 is amended as follows:

(a) paragraph 1 is amended as follows:

(i) point (a) is replaced by the following:

'(a) the medicinal product is harmful; or';

(ii) point (c) is replaced by the following:

'(c) the risk-benefit balance is not favourable; or';

(b) the following paragraph is added:

'3. The competent authority may, for a medicinal product for which the supply has been prohibited or which has been withdrawn from the market in accordance with paragraphs 1 and 2, in exceptional circumstances during a transitional period allow the supply of the medicinal product to patients who are already being treated with the medicinal product.'.

24. The following Articles are inserted:

'Article 121a

1. The power to adopt the delegated acts referred to in Article 22b shall be conferred on the Commission for a period of 5 years from 20 January 2011. The Commission shall draw up a report in respect of the delegated powers not later than 6 months before the end of the 5 year period. The delegation of powers shall be automatically extended for periods of an identical duration, unless the European Parliament or the Council revokes it in accordance with Article 121b.

2. As soon as it adopts a delegated act, the Commission shall notify it simultaneously to the European Parliament and to the Council.

3. The power to adopt delegated acts is conferred on the Commission subject to the conditions laid down in Articles 121b and 121c.

Article 121b

1. The delegation of powers referred to in Article 22b may be revoked at any time by the European Parliament or by the Council.

2. The institution which has commenced an internal procedure for deciding whether to revoke the delegation of powers shall endeavour to inform the other institution and the Commission within a reasonable time before the final decision is taken, indicating the delegated powers which could be subject to revocation and possible reasons for a revocation.

3. The decision of revocation shall put an end to the delegation of the powers specified in that decision. It shall take effect immediately or at a later date specified therein. It shall not affect the validity of the delegated acts already in force. It shall be published in the *Official Journal of the European Union*.

Article 121c

1. The European Parliament or the Council may object to a delegated act within a period of 2 months from the date of notification.

At the initiative of the European Parliament or the Council that period shall be extended by 2 months.

2. If, on expiry of the period referred to in paragraph 1, neither the European Parliament nor the Council has objected to the delegated act, it shall be published in the *Official Journal of the European Union* and shall enter into force on the date stated therein.

The delegated act may be published in the *Official Journal of the European Union* and enter into force before the expiry of that period if the European Parliament and the Council have both informed the Commission of their intention not to raise objections.

3. If either the European Parliament or the Council objects to the delegated act within the period referred to in paragraph 1, it shall not enter into force. The institution which objects shall state the reasons for objecting to the delegated act.'.

25. Article 122(2) is replaced by the following:

'2. Upon reasoned request, Member States shall send electronically the reports referred to in Article 111(3) to the competent authorities of another Member State or to the Agency.'.

26. Article 123(4) is replaced by the following:

'4. The Agency shall make public annually a list of the medicinal products for which marketing authorisations have been refused, revoked or suspended, whose supply has been prohibited or which have been withdrawn from the market.'.

27. In Article 126a, paragraphs 2 and 3 are replaced by the following:

'2. When a Member State avails itself of this possibility, it shall adopt the necessary measures in order to ensure that the requirements of this Directive are complied with, in particular those referred to in Titles V, VI, VIII, IX and XI. Member States may decide that Article 63(1) and (2) shall not apply to medicinal products authorised under paragraph 1.

3. Before granting such a marketing authorisation, a Member State:

(a) shall notify the marketing authorisation holder, in the Member State in which the medicinal product concerned is authorised, of the proposal to grant a marketing authorisation under this Article in respect of the medicinal product concerned.

(b) may request the competent authority in that Member State to submit copies of the assessment report referred to in Article 21(4) and of the marketing authorisation in force in respect of the medicinal product concerned. If so requested, the competent authority in that Member State shall supply, within 30 days of receipt of the request, a copy of the assessment report and the marketing authorisation in respect of the medicinal product concerned.'.

28. Article 127a is replaced by the following:

'*Article 127a*

When a medicinal product is to be authorised in accordance with Regulation (EC) No 726/2004, and the Committee for Medicinal Products for Human Use in its opinion refers to recommended conditions or restrictions as provided for in points (c), (ca), (cb) or (cc) of Article 9(4) thereof, the Commission may adopt a decision addressed to the Member States, in accordance with Articles 33 and 34 of this Directive, for the implementation of those conditions or restrictions.'.

Article 2

Transitional provisions

1. With regard to the obligation on the part of the marketing authorisation holder to maintain and make available on request a pharmacovigilance system master file in respect of one or more medicinal products provided for in Article 104(3)(b) of Directive 2001/83/EC as amended by this Directive, the Member States shall ensure that that obligation applies to marketing authorisations granted before 21 July 2011 as from either:

a) the date on which those marketing authorisations are renewed; or

b) the expiry of a period of 3 years starting from 21 July 2011,

whichever is earlier.

2. The Member States shall ensure that the procedure provided for in Articles 107m to 107q of Directive 2001/83/EC as amended by this Directive applies only to studies which have commenced after 21 July 2011.

3. With regard to the obligation on the part of the marketing authorisation holder to submit information on suspected adverse reactions electronically to the Eudravigilance database, provided for in Article 107(3) of Directive 2001/83/EC as amended by this Directive, the Member States shall ensure that this obligation applies as from 6 months after the functionalities of the database are established and have been announced by the Agency.

4. Until the Agency can ensure the functionalities of the Eudravigilance database as specified in Article 24 of Regulation (EC) No 726/2004 as amended by Regulation (EU) No 1235/2010 [1] of the European Parliament and of the Council, marketing authorisation holders shall report, within 15 days of the day on which the holder concerned gained knowledge of the event, all serious suspected adverse reactions that occur in the Union, to the competent authority of the Member State on whose territory the incident occurred and shall report all serious suspected adverse reactions that occur on the territory of a third country to the Agency and, if requested, to the competent authorities of the Member States in which the medicinal product is authorised.

5. Until the Agency can ensure the functionalities of the Eudravigilance database as specified in Article 24 of Regulation (EC) No 726/2004 as amended by Regulation (EU) No 1235/2010, the competent authority of a Member State may require marketing authorisation holders to report to it all non-serious suspected adverse reactions that occur on the territory of that Member State, within 90 days of the day on which the marketing authorisation holder concerned gained knowledge of the event.

6. During this period, Member States shall ensure that the reports referred to in paragraph 4 that relate to events that occurred in their territory are promptly made available to the Eudravigilance database, and in any case within 15 days of the notification of suspected serious adverse reactions.

7. With regard to the obligation on the part of the marketing authorisation holder to submit periodic safety update reports to the Agency as provided for in Article 107b(1) of Directive 2001/83/EC as amended by this Directive, the national competent authorities shall ensure that this obligation applies as from 12 months after the functionalities of the repository have been established and have been announced by the Agency.

Until the Agency can ensure the functionalities agreed for the repository of the periodic safety update reports, the marketing authorisation holders shall submit the periodic safety reports to all Member States in which the medicinal product has been authorised.

Article 3

Transposition

1. Member States shall adopt and publish, by 21 July 2012 at the latest, the laws, regulations and administrative provisions necessary to comply with this Directive. They shall forthwith communicate to the Commission the text of those provisions.

They shall apply those provisions from 21 July 2012.

When Member States adopt those provisions, they shall contain a reference to this Directive or be accompanied by such a reference on the occasion of their official publication. Member States shall determine how such reference is to be made.

2. Member States shall communicate to the Commission the text of the main provisions of national law which they adopt in the field covered by this Directive.

Article 4

Entry into force

This Directive shall enter into force on the 20th day following its publication in the *Official Journal of the European Union*.

Article 5

Addressees

This Directive is addressed to the Member States.

Done at Strasbourg, 15 December 2010.

For the European Parliament	*For the Council*
The President	*The President*
J. BUZEK	O. CHASTEL

[1] See page 1 of this Official Journal.

European Commission

What you Need to Know about

Biosimilar Medicinal Products

Process on Corporate Responsibility in the Field of Pharmaceuticals Access to Medicines in Europe

A Consensus Information Document

Enterprise and Industry

Disclaimer

The present document is without prejudice to any existing or future EU / national and international legislation.

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List of Acronyms

ADR	Adverse drug reaction
AIM	Association Internationale de la Mutualité
CH	Switzerland
CHMP	Committee for Medicinal Products for Human Use (EMA)
CPME	Standing Committee of European Doctors
DDD	Defined daily dose
DNA	Deoxyribonucleic acid
EEA	European Economic Area
EFPIA	European Federation of Pharmaceutical Industries and Associations
EGA	European Generic medicines Association
EMA	European Medicines Agency
EPF	European Patients Forum
EPAR	European public assessment report
EPO	Erythropoietin
ESAs	erythropoiesis-stimulating agents
ESIP	European Social Insurance Platform
EU	European Union
EV	EudraVigilance
EuropaBio	European Association for Bio-industries
G-CSF	Granulocyte colony-stimulating factor
GDP	Good Distribution Practice
GIRP	European Association of Full-line Wholesalers
GMP	Good Manufacturing Practice
GVP	Good Pharmacovigilance Practice
HGF	Human growth factor
HOPE	European Hospital and Healthcare Federation
INN	International Non-Proprietary Name
MAT	Moving annual total
MIA	Manufacturer’s and importer’s authorisation
NO	Norway
PAES	Post-authorisation efficacy studies
PAG	Policy Advisory group (EPF)
PASS	Post-authorisation safety studies
PhVWP	Pharmacovigilance Working Party
PI	Product information
PIL	Package information leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PRCA	Pure red cell aplasia
RMP	Risk management plan
SmPC	Summary of product characteristics
WDA	Wholesaler distributor's authorisation
WHO	World Health Organization

In September 2010, the European Commission launched the Process on Corporate Responsibility in the Field of Pharmaceuticals[1] focusing on, amongst others areas, non-regulatory conditions for better access to medicines following their marketing authorisation.

Under its Platform "Access to Medicines in Europe", Member States, EEA countries and relevant stakeholders were invited to a project group on biosimilar medicinal products in order to take stock of the availability of biosimilar medicinal products in European national markets, and to define the necessary conditions for an informed uptake and adequate patient access to these products.

In accordance with the project group's Terms of Reference, the group looked into topics related to improving information on the concept of biosimilar medicinal products and the science and process behind the approval. All these are relevant to decision makers including scientific societies, healthcare professionals and competent authorities, as well as patients and patient organisations.[2] All aspects related to interchangeability and/or substitution remained outside of the group's scope.

In order to provide the different target groups with adequate information on biosimilar medicinal products, the project group, in close co-operation with the Commission services, decided to prepare this information paper including a specific Question & Answer part targeting patients, physicians and payers. The European Medicines Agency contributed to the paper within their responsibilities and competence.[3]

The paper is a consensus document agreed by the project group Market Access and Uptake of Biosimilars[4] and adopted by the Steering Group of the Process for Corporate Responsibility in the field of Pharmaceuticals.

[1] Press Memo - Process on Corporate Responsibility in the Field of Pharmaceuticals - 24/09/2010

[2] For more information about the project group's other deliverables please consult our dedicated Webpage "Access to Medicines in Europe"

[3] The present information paper should not be considered as authored or endorsed by the EMA.

[4] The paper represents the consensus outcome from discussions of a multi-stakeholder subgroup (named "Information" group) and was formed by volunteers from the European Patients Forum (EPF), Standing Committee of European Doctors (CPME), European Social Insurance Platform (ESIP), Association Internationale de la Mutualité (AIM), European Generic medicines Association (EGA), European Federation of Pharmaceutical Industries and Associations (EFPIA), European Association for Bio-industries (EuropaBio) and Austria. The paper was adopted by the project group with the following members: AT, BE, CZ, DK, ES, FR, HU, IE, IT, LT, NL, NO, SE, EPF, CPME, ESIP, AIM, EGA, EFPIA, EuropaBio, European Association of Full-line Wholesalers (GIRP) and European Hospital and Healthcare Federation (HOPE). The project group was chaired by Denmark and the European Commission.

Key Messages

- A biosimilar medicinal product is a biological medicine which is similar to another biological medicine that has already been authorised for use, the "reference medicinal product".

- A biosimilar medicinal product and its reference medicinal product are expected to have the same safety and efficacy profile. Biosimilar medicinal products are authorised either for all or selected indications of the reference medicinal product on a case by case basis.

- The development and the manufacturing process of biosimilar medicinal products are more complex and expensive than generics of chemical (small molecule) products.

- Biosimilar medicinal products follow the specific provisions of EU legislation (the so-called "biosimilar pathway") which include defined high standards of quality, safety and efficacy.

- Standards of the EU Good Manufacturing Practice (GMP) apply to the manufacture of biosimilar medicinal products in the same way as for any other biological medicinal product. Compliance with the EU GMP Guidelines is verified during routine GMP inspections by the EU national competent authorities.

- Biosimilar medicinal products have been used safely in clinical practice in the European Union since 2006 and their market share has been growing at different rates across both EU Member States and product categories.

- Biosimilar medicinal products may offer a less-costly alternative to existing biological medicinal products that have lost their exclusivity rights.

- The availability of biosimilar medicinal products enhances competition, with the potential to improve patient access to biological medicines and to contribute to the financial sustainability of EU healthcare systems. Thus, their availability offers potential economic benefit to EU healthcare systems while addressing the issue of new treatment options brought about by advances in medical science.

- EMA provides detailed information on centrally authorised biosimilar medicinal product on their website.[5]

- *"The decisions on interchangeability and/or substitution rely on national competent authorities and are outside the remit of the EMA/CHMP. Member States have access to the scientific evaluation performed by the CHMP and all submitted data in order to substantiate their decisions".*[6]

[5] See dedicated EMA biosimilar medicines webpage
[6] See page 33/33 of EMA Procedural advice for users of the centralised procedure for similar biological medicinal products applications_EMA/940451/2011_March 2013

- *"For questions related to switching from one biological medicine to another, patients should speak to their doctor and pharmacist".*[7]

[7] See question: Can a biosimilar and its reference medicine be used interchangeably ? in EMA Questions and answers on biosimilar medicines (similar biological medicinal products)_EMA/837805/2011_September 2012.

1. INTRODUCTION

Biotechnology has enabled the development of treatments for a variety of serious diseases. Worldwide, many million patients have already benefited from approved biological medicines. These medicines help treat or prevent many rare and severe diseases including cancers, heart attacks, stroke, multiple sclerosis, diabetes, rheumatoid arthritis and autoimmune diseases.

Given that the first biological medicinal products produced by DNA recombinant techniques were approved in the 1980s, the exclusive rights (patents and other data protection) for several biological medicinal products have reached their expiration and many more will expire in the coming decade. Consistent with this expiry, similar biological medicinal products, or biosimilar medicinal products ("biosimilars") as they are now commonly called, are being developed and several are already available on European markets, with the first approved and marketed in 2006.

2. BIOLOGICAL MEDICINAL PRODUCTS

2.1. What are biological medicines and how do they work?

Biological medicines[8] (also called "biopharmaceuticals") are comprised of proteins such as hormones (growth hormones, insulins, erythropoietins), enzymes that are naturally produced in the human body, or monoclonal antibodies, but also blood products, immunological medicinal products such as sera and vaccines, allergens, and advanced technology products such as gene and cell therapy products. Like all medicines, biological medicines work by interacting with the body to produce a therapeutic outcome, but the mechanisms by which they do this may vary from product to product and across indications. Biopharmaceuticals can be tailor-made to fit the desired target. Therefore the role of the physicians in treatment of patients with these complex medicinal products is particularly important.

2.2. How are biopharmaceuticals produced and distributed?

Biotechnology uses living systems (plant or animal cells, bacteria, viruses and yeast) and modern technologies to produce biological medicines to treat diseases and genetic disorders in humans. Many, but not all biological medicines, are made using genetically-modified cells. Each manufacturer has its own unique cell lines and develops its own proprietary (unique) manufacturing processes. It is noted that some biological medicines are produced by non-Biotechnology methods and are therefore not necessarily authorised through the centralised procedure. This consensus information document only addresses centrally authorised biotechnology-derived medicinal products[9]. (see also 3.1)

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[8] See definition in Part I of Annex I of Directive 2001/83/EC (as amended by Directive 2003/63/EC): a biological medicinal product is a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physic-chemical-biological testing together with the production process and its control.

[9] This chapter and the whole information consensus document only focuses on biological medicinal products, including biosimilar medicinal products, that are biotechnology-derived medicines and which, since 1995, must be assessed centrally by the European Medicines Agency (EMA) and in case of a positive scientific opinion

The production of biological medicines involves processes such as fermentation and purification. The manufacturing processes for biological medicines are very sensitive and it is vital that these are precisely controlled in order to obtain consistent results and to guarantee the safety and efficacy of the final product. The production of biological medicines is a complex process which requires a very high level of technical expertise with typically about 250 in-process tests being conducted compared to about 50 tests for a small molecule medicine. Manufacturers and importers of medicines approved in the European Union, including biosimilar medicinal products, are legally obliged to hold a valid Manufacturer's and Importer's Authorisation (MIA)/ GMP certificate issued by an EU national competent authority. An MIA/GMP certificate will only be granted if the manufacturing/importing site complies with the EU Guidelines on Good Manufacturing Practice (GMP), which also include specific provisions for biological medicinal products (Annex 2 of the Volume 4 of EudraLex).

To verify compliance with GMP, manufacturers and importers in the EU are subject to regular GMP inspections by the supervisory authorities. The EU national competent authorities also inspect manufacturers located outside the EU that export to the EU. For biopharmaceuticals which are centrally assessed and authorised for marketing in the whole European Union, the EMA coordinates inspections related to the medicine's scientific assessment and conducted by the EU national competent authorities.

Importers, manufacturers and wholesale distributors are obliged to comply with Good Distribution Practice (GDP) standards. According to the GDP Guidelines, specific conditions for storage and transport (e.g. refrigeration) must be ensured. Wholesale distributors are legally obliged to hold a valid wholesaler distributor's authorisation (WDA) issued by an EU national competent authority. Wholesale distribution by manufacturers, importers and distributors is equally subject to supervision by EU national competent authorities.

2.3. How do biological medicines differ from small molecule medicines?

Biopharmaceuticals differ in many ways from small molecule medicines, including for example the manufacturing techniques, their molecular size and complexity, or their stability. Because proteins are affected by the digestive system when taken orally, most biopharmaceuticals must be administered by injection or infusion.

Small molecule medicines are typically manufactured by chemical synthesis, whereas most biopharmaceuticals are made in living systems such as microorganisms or animal cells and purified through a complex manufacturing process. Therefore their exact characteristics are subject to inherent variability and biopharmaceuticals are defined as mixtures of many different forms of the same protein. Another source of variability in certain biopharmaceuticals is the type and length of sugar or carbohydrate group attached to the protein backbone (glycosylation).

Small molecule medicines generally have well-defined chemical structures and can usually be analysed to determine all the various components. This is not the case for biopharmaceuticals, where the inherent variability in the molecules means they are

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adopted by the scientific committee, are subject to a formal decision process for marketing by the European Commission.

more difficult to characterise than small molecule medicines and most cannot be exactly reproduced, even between batches of the same product (irrespective of whether it is a reference medicinal product or biosimilar medicinal product). This inherent variability of all biopharmaceuticals is tightly controlled by manufacturers and regulators and must remain within accepted and pre-defined limits.

Biological medicines have the potential to be recognised by the body as "foreign" and therefore have the inherent potential to induce unwanted immune reactions, due to their composition and large molecular size. Chemical medicines, on the other hand, are usually too small to be recognised by the immune system.

This potential to induce an immune reaction in the body (immunogenicity) is a double-edged sword for biological medicines. Vaccines specifically exploit their immunogenic potential by provoking an immune response that recognises and "fights of" an "invader" substance. However, for some medicines based on proteins, stimulating an immune response is regarded as undesirable. Most of the immune responses that occur are mild and do not have negative effects on the patient. However in rare cases, unwanted immune reactions can lead to severe and detrimental effects on the health of a patient. An unwanted immune response in treated patients can be influenced by numerous factors such as the disease state, drug-related factors (product-and process related factors), patient-related factors (age, sex, genetic background, etc.) and treatment-related factors (concomitant drugs, route of administration, etc.).

3. REGULATION OF BIOLOGICAL MEDICINES IN EUROPE, INCLUDING BIOSIMILAR MEDICINES

3.1. What is the EU legal and regulatory pathway?

In the European Union, marketing authorisation applications for biotechnology-derived medicinal products, including biosimilar medicinal products, are by law reviewed centrally by the European Medicines Agency (EMA). The European Commission issues the Decisions concerning the authorisation of these medicinal products on the basis of the scientific opinions from the EMA. The resulting marketing authorisation is valid in all EU Member States.

The EU is the first region in the world to have set up a legal framework and a regulatory pathway for "similar biological medicinal products", more commonly called "biosimilars". The EU regulatory framework inspired many countries around the world e.g. Australia, Canada, Japan, Turkey, Singapore, South Africa, Taiwan, USA etc. as well as the World Health Organisation (WHO). The concept of a "similar biological medicinal product" was adopted in EU pharmaceutical legislation in 2004[10] and came into effect in 2005. The first biosimilar medicine was approved by the European Commission in 2006.[11]

The legislation did not introduce a definition of a biosimilar medicinal product per se. Rather it laid down the legal basis of the "biosimilar pathway". It states that "*where a*

[10] Directive 2001/83/EC, as amended by Directive 2003/63/EC and Directive 2004/27/EC
[11] Biosimilars Marketing Authorisation status as of January 2013: 22 Marketing Authorisation Applications (MAAs) reviewed (14 positive, 7 withdrawn, 1 negative); 12 biosimilar medicines currently hold a valid MA; (1 somatropin, 5 epoetin, 6 filgrastim); 5 biosimilar MAAs are currently under review (2 follitropin alfa, 2 infliximab, 1 filgrastim) - source: EMA website, Medicines under evaluation.

biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided."

Since biosimilar medicinal products are biological medicinal products, they also fall under the EU legal definition of a biological medicinal product. Consequently they have to follow the general scientific guidelines related to biological medicinal products and undergo the same rigorous regulatory assessment by the relevant regulatory authorities, like all other biopharmaceuticals.

In the course of 2012, the EMA included a definition of a "biosimilar" in an EMA procedural guidance document[12]: "*A similar biological medicinal product, also known as "Biosimilar", is a product which is similar to a biological medicine that has already been authorised, the so-called "reference medicinal product". The active substance of a biosimilar medicine is a known biological active substance and similar to the one of the reference medicinal product. A similar biological medicinal product and its reference medicinal product are expected to have the same safety and efficacy profile and are generally used to treat the same conditions."* The reference medicinal product[13], to which the application for marketing authorisation for a biosimilar medicinal product refers, "*is a medicinal product which has been granted a marketing authorisation by a Member State or by the European Commission on the basis of a complete dossier, i.e. with the submission of quality, pre-clinical and clinical data"* and in accordance with the provisions, applicable to originator medicinal products.

As mandated by law and in order to give guidance to industry, the EMA has developed overarching and product-class specific scientific guidelines on biosimilar medicines, thus providing a robust regulatory process in which to be able to grant marketing authorisations for biosimilar medicinal products. These guidelines are revised on a regular basis to reflect the experience gained with biosimilar applications and approvals, and to take into account evolving science and technology. In addition, a number of other scientific guidelines are relevant for biosimilar medicinal products, such as immunogenicity and comparability guidelines. All these guidelines are posted on a dedicated page of the EMA website.[14]

3.2. What is the scientific rationale behind approval of biosimilar medicines?

What is comparability?

Comparability between the reference and the biosimilar medicinal product is the core principle of a biosimilar development. The scientific concept of "comparability" is well

[12] See page 5/33 : EMA Procedural advice for users of the centralised procedure for similar biological medicinal products applications_EMA/940451/2011, March 2013
[13] See page 8/33 : EMA Procedural advice for users of the centralised procedure for similar biological medicinal products applications_EMA/940451/2011, March 2013
[14] See EMA biosimilar medicines webpage

established.[15] The scientific principles underlying the comparability exercise required for changes in the manufacturing process of a given biological medicinal product and for development of a biosimilar medicinal product are the same. However, as recognised by Weise et al in a scientific journal [16], data requirements for biosimilar medicinal products are higher than when assessing a process change for the same product. *"…It should be noted that a comparability exercise is also required for originator biological medicinal products when changes to the manufacturing process are made. Indeed, such changes are frequently introduced throughout a product's lifecycle (e.g., to improve the quality or to increase the yield of the product). As a consequence, the quality profile of the biological product may evolve over its life cycle but would still be considered as comparable to the product before changes were made as long as relevant impact on safety and efficacy has been excluded with sufficient confidence. The scientific principles underlying the comparability exercise required for changes in the manufacturing process of a given biological product[17] and for the development of a biosimilar product[18] are the same. Even so, data requirements for the latter are higher and, at least in the EU, always include clinical studies because, due to the completely independent manufacturing processes, some differences between the biosimilar and the reference product can be expected, and the potential impact of these differences on safety and efficacy cannot be predicted from analytical assessment alone...."*

What is biosimilarity?

"Biosimilarity" is the regulatory term used in the European Union to denote the comparability between a biosimilar and its reference medicinal product. The marketing authorisation of a biosimilar medicinal product is based upon a regulatory assessment that the applicant has demonstrated the product's similarity to the reference medicinal product by the means outlined in the Committee for Medicinal Products for Human Use (CHMP)/EMA specific "scientific guidelines on biosimilar medicines".

Biosimilar medicinal products are systematically developed to be highly similar to the reference medicinal product with regards to quality, safety, and efficacy. The biosimilar development is started with the definition of the molecular characteristics and quality attributes of the target product profile of the biosimilar medicinal product and its comparability with the reference medicinal product.

This is followed by a comparability exercise performed in several steps:

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[15] See guidelines:

- Similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues EMA/CHMP/BWP/49348/2005
- Similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues EMA/CHMP/BWP/42832/2005

For updates and ongoing revisions please go to scientific guidelines on biosimilar medicines at the EMA dedicated biosimilar medicines webpage

[16] Nature Biotechnology, Biosimilars – why terminology matters, Volume 29, Number 8, Aug. 2011, page 690

[17] Not quoted by Weise et al, but see also: ICH Topic Q5E: Comparability of Biotechnological/Biological Products: Note for guidance on biotechnological/biological products subject to changes in their manufacturing process (CPMP/ICH/5721/03)

[18] Not quoted by Weise et al, but see also guidelines:

- Similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues EMA/CHMP/BWP/49348/2005
- Similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues EMA/CHMP/BWP/42832/2005

1. first step - quality comparability (physicochemical and biological comparability)
2. second step - non-clinical comparability (comparative non-clinical studies)
3. third step - clinical comparability (comparative clinical studies)

Quality comparability is established with regard to the molecular structure as well as with regard to the functionality and must be demonstrated with comprehensive analytical characterisation, relevant receptor binding studies and bioassays, all to be performed with the biosimilar and the reference medicinal product in a rigorous comparative manner.

The non-clinical and clinical comparability then provides the confidence that any differences observed at the quality level have no impact on the safety and efficacy of the biosimilar medicinal product when compared to the reference medicinal product.

The comparability exercise is consequently based on a robust head-to-head comparison between the biosimilar and the reference medicinal product at the levels of quality, safety and efficacy.

Every biosimilar medicinal product application is assessed on an individual basis.

What is the scientific rationale for extrapolation of indications?

Biopharmaceuticals are often used in more than one therapeutic indication. Extrapolation of clinical efficacy and safety data to other indications of the reference medicine that are not specifically studied during the clinical development of the biosimilar medicine is possible based on the overall evidence of comparability provided from the comparability exercise and with adequate scientific justification. This includes at least one clinical study in the most sensitive patient population measuring the most sensitive[19] clinical endpoint(s).

If pivotal evidence for comparability is based on pharmacodynamics, and for the claimed indications different mechanisms of action are relevant (or uncertainty exists), then applicants should provide relevant data to support extrapolation to all claimed clinical indications. Biosimilar medicinal product applicants should also support such extrapolations with a comprehensive discussion of available literature including the involved antigen receptor(s) and mechanism(s) of action.

Only when quality and non-clinical and clinical comparability is achieved, is the new medicinal product accepted as a biosimilar and is it justified for the biosimilar medicinal product to cross-refer to the clinical data obtained through the extensive experience of the reference product. This is described in the relevant scientific literature and in publicly accessible health authority documents. Whether extrapolation to multiple indications is acceptable (or not) is decided on a case-by-case basis by the CHMP/EMA.

[19] Sensitive meaning most likely to show differences between the biosimilar and the reference medicine, if these exist.

3.3. Naming and identification of biological medicines, including biosimilar medicines

As required by EU law, every medicine will either have an invented (trade) name, or the name of the active substance together with the company name/trademark. The approved name, together with the batch number, is important for clear identification to support adverse drug reaction reporting and monitoring of the safe use of the medicine (see also 3.5.).[20]

3.4. Public EMA information on biosimilar medicines

As with any other medicinal product scientifically assessed by the EMA and authorised by the European Commission, the EMA publishes a defined set of official documents on its website for each biosimilar medicinal product. The dedicated webpage on biosimilar medicines can be found under Special Topics section of the EMA website.

The dedicated webpage above also contains a link to a list of all centrally authorised biosimilar medicines.

By clicking on the approved name of a biosimilar medicine on the list, a number of documents collectively known as the European public assessment report (EPAR) can be found:

- The package (information) leaflet [P(I)L] and the summary of product characteristics (SmPC) are found together in a product information (PI) that is available in all EU languages.
    - The package (information) leaflet [P(I)L] document is primarily intended to summarise information on the medicine for patients. It is also contained within each pack of the medicine.
    - The summary of product characteristics (SmPC) summarises information on the medicine for healthcare professionals and is more detailed than the package leaflet on specific characteristics of each medicine, such as pharmacokinetic, pharmacodynamic properties, preclinical and clinical data and pharmaceutical particulars.
- Assessment reports, including the reports on initial evaluation and major variations
- Summary of the European public assessment report (Summary EPAR) for the public which is a short document in lay language that explains how the Committee for Medicinal Products for Human Use (CHMP) assessed the studies performed to reach its recommendation on how to use the medicine.

[20] See content of the individual case safety report: Article 28 of Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012.
The Management and reporting of adverse reactions to medicinal products is described in the Guideline on good pharmacovigilance practice (GVP) Module VI.

3.5. Pharmacovigilance

Every pharmaceutical company must have a pharmacovigilance system in place which is used by the marketing authorisation holder to monitor the safety of authorised medicinal products and detect any change to their benefit-risk balance. This pharmacovigilance system is subject to inspections by the regulatory authorities. Every company is required to submit a risk management plan (EU-RMP) together with the marketing authorisation application. The EU-RMP describes in detail the risk management system which the company will introduce for the medicine concerned once it is marketed. The EU-RMP describes the safety profile of the medicine and outlines how the manufacturer will further monitor and fill any potential or known gaps in knowledge regarding both safety and efficacy. The EU-RMP also describes the measures the applicant intends to introduce to prevent or minimise any potential risks when using the medicinal product, including the measurement of their effectiveness in clinical practice.

Under the new EU pharmacovigilance legislation, a marketing authorisation can be granted subject to the condition to conduct post-authorisation safety (PASS) and/or post-authorisation efficacy studies (PAES).[21] Such studies will be part of the pharmacovigilance plan of the EU-RMP. The aim of a PASS is to identify, characterise or quantify a safety hazard or to confirm the safety profile of the medicine, or to measure the effectiveness of the risk management measures during its lifetime. Immunogenicity is an example of a key safety concern of any biological medicine to be addressed in the EU-RMP. PAES will be required when there are concerns relating to some aspects of the efficacy of a medicinal product which can only be resolved after the medicine has been marketed. The European Commission will, in separate delegated acts, further define the situations in which PAES may be required.

The EU-RMP for a biosimilar medicinal product is product-specific and has to be approved by the competent authorities before the medicine is marketed. Every biosimilar medicine on the market has an EU-RMP in place with information on the RMP included in the Assessment Report published on the EMA website. The EU-RMP for a biosimilar medicinal product should take into account the known safety profile of the reference medicinal product.

For all medicinal products, a standard text will be included in the summary of product characteristics and in the package leaflet encouraging healthcare professionals and patients to report any suspected adverse reaction in accordance with national spontaneous reporting systems, which should allow for different ways of reporting, including electronic reporting by means of web-based forms. For adverse reaction (ADR) reporting relating to all biological medicines including biosimilar medicines, the clear identification of the medicine is of particular importance. Therefore EU legislation requires that for every adverse reaction report of a biological medicine, the name of the medicine, as approved, and the batch number should be included in the ADR report.[22] For the same reason, and as mandated by the new EU pharmacovigilance legislation, "*the Member States shall ensure, through the methods for collecting information and where necessary through the follow-up of suspected adverse reaction reports, that all appropriate*

[21] Directive 2010/84/EU, Reg. (EU) 1235/2010

[22] A business process map in relation to the mandatory follow-up of information for the identification of suspected biological medicinal products is presented in VI. Appendix 1 of the Guideline on Good Pharmacovigilance Practice (GVP)
Module VI – Management and reporting of adverse reactions to medicinal products

measures are taken to identify clearly any biological medicinal product prescribed, dispensed, or sold in their territory which is the subject of a suspected adverse reaction report, with due regard to the name of medicinal product (…) and the batch number."[23]

The new EU pharmacovigilance legislation has also introduced a new approach which consists in publishing a list of medicines subject to additional monitoring for a set period. The EMA and the Member States will work together on this public list and further steps have been taken in the course of 2012. Medicinal products subject to additional monitoring are to be identified as such by a black symbol and an explanatory statement will be added to the summary of product characteristics and in the package leaflet. The European Commission has adopted further Implementing Measures for the new pharmacovigilance legislation and a whole set of Guidelines on good pharmacovigilance practice (GVP) have been developed and adopted by the EMA during the course of 2012.

The implementation of the new EU legislation has consequently strengthened pharmacovigilance for all medicines and increases transparency, communication and confidence.

4. ECONOMIC CONSEQUENCES

Biological medicines are an indispensable part of today's medical armamentarium for treating a variety of serious and debilitating diseases. Biological medicines are generally more expensive than small molecule medicines, and managing their use is a challenge for payers. Like the originator reference medicines, biosimilar medicines are generally more difficult and more expensive to develop than small molecule generic medicines.

The budgetary implications of biological medicines have been growing over the years and managing their use has become more and more important for payers. Biosimilar medicines may offer a less-costly alternative to existing biologic medicines which have lost their exclusivity rights (e.g. patents, data protection, etc.) and enhance competition. As a result, the availability of biosimilar medicines may improve access to biological medicines for more patients and contribute to the financial sustainability of healthcare systems. Thus, their availability offers potential economic benefit to healthcare systems while addressing the issue of new treatment options brought about by advances in medical science.

Once approved and authorised for sale, biosimilar medicines introduce an important element to existing price competition to the EU market. It should be recognized that the price differentials (at the point in time of publication of this consensus information document) between biosimilar medicinal products and their reference medicinal products have not been as substantial as experienced in the classical small-molecule generic medicine market. It remains to be seen how the future market will develop, however, it is expected that several new classes of biosimilar medicines will be approved in Europe over the next few years.

EU authorised biosimilar medicines have been launched in nearly every EU market and have thereby given European physicians and patients new treatment options. As a result, market competition has been enhanced by the addition of biosimilar medicines. Indeed,

[23] Directive 2001/83/EC, as amended; Article102, 1st paragraph, point (e)

market data from mid-2011 shows that all biosimilar medicines are growing in terms of sales and at the same time, decreasing the cost of treating patients with these medicines. Sales growth varies across EU markets and by product class indicating that market dynamics are different for each product class.[24] Overall, biosimilar medicines are starting to provide the benefits that they were expected to bring – giving physicians and patients an additional treatment option while affording payers a broader range of tools to better manage healthcare expenses.[25]

According to a study conducted in mid-2011 by the firm IMS[26], biosimilar medicines were a relatively small segment of the EU pharmaceutical market, but they have strong annual growth. It is important to note that this market data does not always show the whole picture. This is because in addition to biosimilar medicines, their reference products[27] and so-called "non-referenced" products[28], there is sometimes an additional class of products to be considered. This class comprises long acting, patent protected biological medicinal products which treat the same disease as short-acting products. These long-acting medicines are also a potential alternative to treat patients for similar diseases as biosimilar medicines and their reference medicines. It is fully expected that when the exclusivity rights of these medicines expire they too will face direct biosimilar competition.

It is important to note that biosimilar market uptake has been possible despite the fact that substitution between the biosimilar and its reference medicinal product is not practiced at the pharmacy level. The decision on whether to substitute a biological medicinal product lies outside the remit of the EMA/CHMP and is the responsibility of the relevant competent authorities within each EU Member State.[29] Since October 2011, pharmacists in Germany may substitute, within the framework of the aut idem substitution, biotechnologically manufactured products among each other which (a) have been approved with reference to the same reference product and which (b) have been produced by the same manufacturer with the same manufacturing process. The only difference between such substitutable products is their trade name.[30] At the point in time of publication of this consensus information paper, no country has explicitly authorized the substitution of biological products from different manufacturers, and a number of EU Member States have put legal, regulatory, and political provisions in place that prevent this practice.

The overall experience to date therefore suggests that the most important conditions for market uptake of biosimilar medicines are driven by factors in the commercial market

[24] The data is taken from a study commissioned by the European Commission project group Market Access and Uptake of Biosimilars. It was presented to the project group in Copenhagen on 18 April 2012 and is entitled "Biosimilar Accessible Market: Size and Biosimilar Penetration."
[25] EMINet report 2011

[26] Link to full IMS study
[27] IMS definition of reference product: Original product, granted market exclusivity at the start of its life, exclusivity is now expired and the product has been referenced (in a biosimilar application)
[28] IMS definition of non-reference(d) product : Original product, granted market exclusivity at the start of its life, exclusivity is now expired and the product has never been referenced or may have been referenced but the referencing biosimilar has not launched
[29] See page 33/33 EMA Procedural advice for users of the centralised procedure for similar biological medicinal products applications_EMA/940451/2011, March 2013

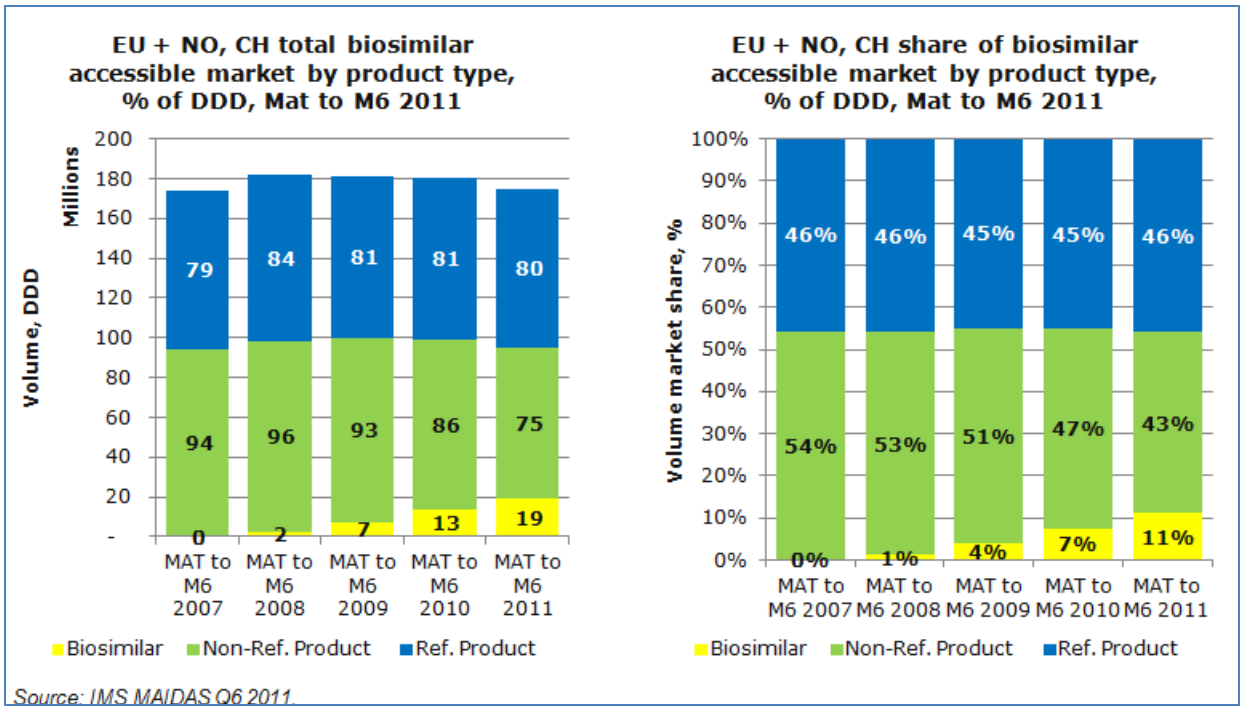
[30] Section 129, subsection 1 of the Fifth Book of the German Social Code (SGB V) in connection with the framework agreement between the National Association of Statutory Health Insurance Funds and the German Pharmacists' Association on the supply of medicinal products in the version of 1 February 2011, which is based on section 129, subsection 2 of SGB V.

place. Differences across European Member States in national healthcare systems, structures and processes impact biosimilar medicines' uptake. Such differences may be any or all of the following:

- Physician perception of biosimilar medicines
- Patient acceptance of biosimilar medicines
- Local pricing and reimbursement regulation
- Procurement policies and terms

It is thus essential that physicians and patients share a thorough understanding of biological medicines, including biosimilar medicines, and express confidence in using either type of therapy. This can be achieved by maintaining a robust regulatory framework and effective risk management, transparency with regard to biological medicinal products, and continued education on biological medicines, including biosimilar medicines.

Figure One: Biosimilars Have Steady Growth With 11 percent of Total EU Biologics Sales



Source: IMS MAIDAS Q6 2011.

- Data in the IMS report is up to the end of 2Q2011 and includes sales throughout EU countries as reported by IMS with the addition of Norway and Switzerland.

- The market data in the report shows total EU sales for the 3 classes of biosimilar products available in the EU: HGF (Human Growth Factor), EPO (short-acting erythropoetin) and GCSF (daily GCSF). Long-acting EPO and GCSF are not included in the market analysis as these medicines are still protected by their patents and supplementary protection certificates.

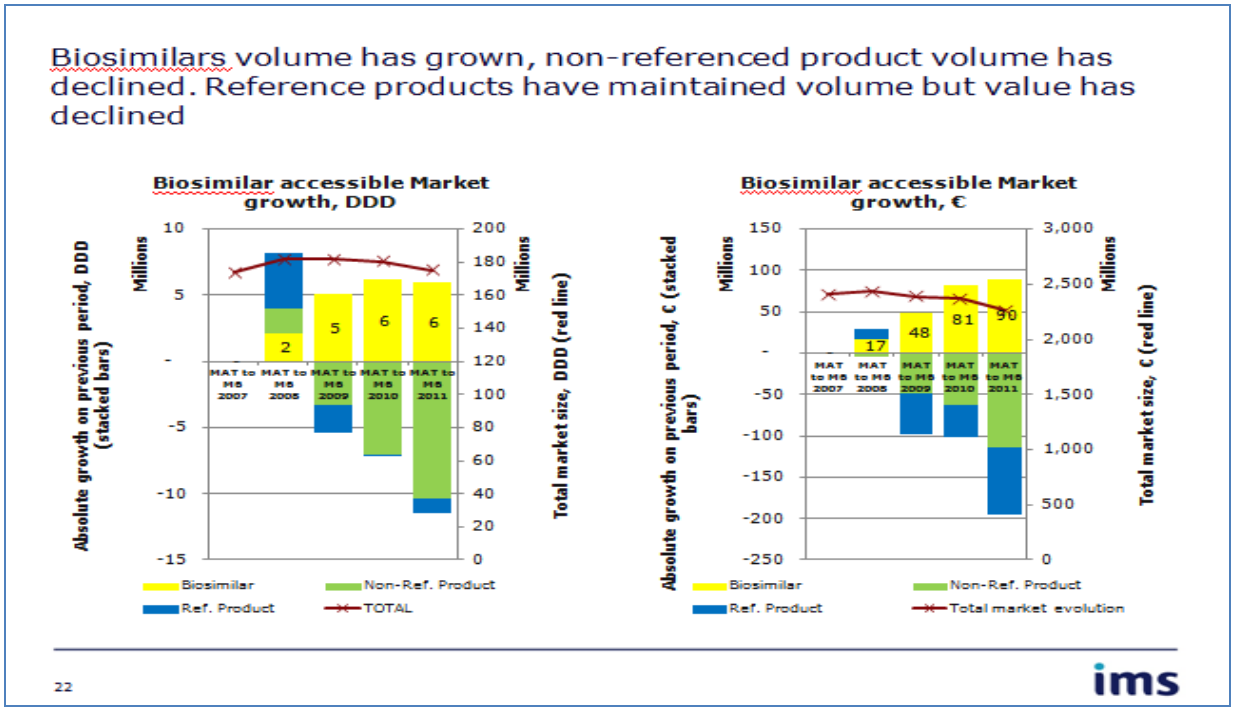
- DDD, or defined daily dose, is a World Health Organization definition that assumes average maintenance dose per day for a drug used for its main indication in adults.

- Drug consumption data presented in DDDs provide an outline estimate of consumption but this is not an exact picture of actual use.

- All figures are for the 12 month period from July 2010 to June 2011 (MAT – moving annual total – 2Q2012)

- In the 12 month period, biosimilar products represent 19 million, of a total market estimate of 175 million DDD- approximately 11 percent by total patient volume.

Figure Two: Biosimilars Have Enhanced Existing Market Competition and Helped Stabilize Health Care Costs



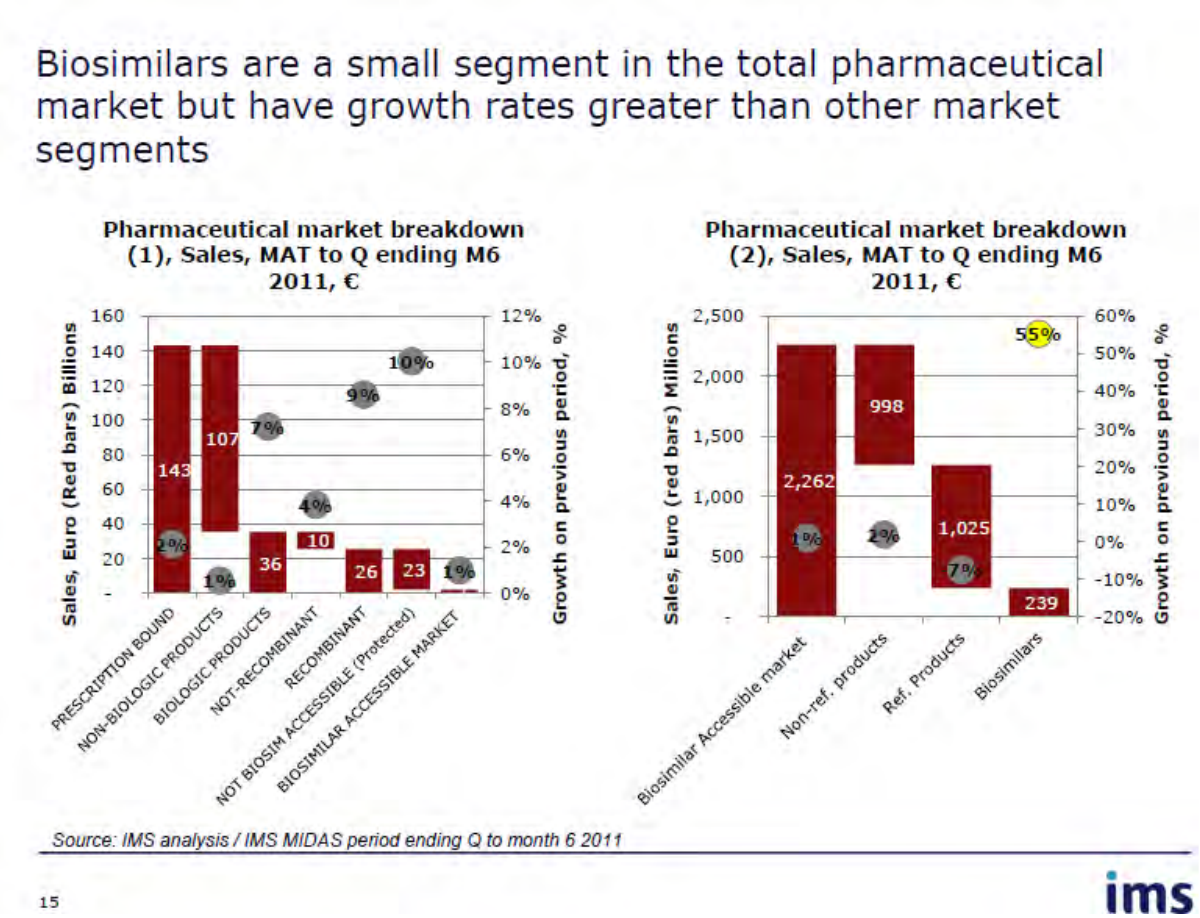
- The IMS data shows that as the number of marketed biosimilar products in Europe has increased, the total size of the market has decreased.

- The left hand chart demonstrates that, since their introduction, biosimilar products have grown steadily. At the same time there has been an increasing reduction in the DDD consumption of short-acting originator biological products, regardless of whether they have direct biosimilar competition or not.

- The right hand chart shows a gradual decline in market value (sales) as biosimilar products gain share from short-acting originator biological products, regardless of whether they have direct biosimilar competition or not.

- It is important to note that factors other than the introduction of biosimilar products may have contributed to the decline of the overall market, including safety concerns in the use of EPO in oncology patients and trends toward the use of longer acting products.

Figure Three: At This Stage Biosimilars Are a Small (but rapidly growing) Part of the EU Pharmaceutical Market



- These IMS data show total EU prescription pharmaceutical sales for the 12 month period to 2Q2011 (left chart) and total biosimilar accessible market sales for the 12 month period to 2Q2011 (right chart).

- Recombinant biological medicines account for 18 percent of total EU pharmaceutical sales.

- The majority of these sales are from biological medicines that do not yet have biosimilar competition (for example monoclonal antibody therapies) and are currently protected by patents and supplementary protection certificates.

- Sales for the 12 month period up to 2Q2012 for segment of the recombinant biological medicines market that is accessible to biosimilar products were €2.3 billion – around 8% of the total recombinant biological market.

- The "accessible market" is defined by the market of originator medicinal products which have been referenced in biosimilar applications and originator medicinal products which have lost their market exclusivity but have not yet been referenced.

- For the year to June 2011, biosimilar products accounted for ~10% of the "accessible market" with an approximate sales value of €240M of the total €2.3B. This represented a 55 percent increase from the previous period.

Q&A FOR PATIENTS

The Questions and Answers section refers only to biotechnology-derived medicines that are centrally assessed by the European Medicines Agency and authorised by the European Commission.

Introduction: questions identified from the patients' perspective

Patients' knowledge of biosimilars and biologics generally varies greatly from low to sophisticated. The questions in this document include even very basic questions that may seem obvious to an expert reader, but are real concerns based on feedback received from the EPF Policy Advisory Group.[31]

The relationship between patient and healthcare professional is key to ensuring the best treatment/care decisions and health outcomes for each patient. Patients often do not receive enough information from healthcare professionals that they understand, whereas many health professionals overestimate the amount and quality of information they provide. It is crucial that all available therapeutic options are discussed thoroughly and that healthcare professionals ensure that patients understand the options, relative benefits and risks. Prescription decisions should be based on mutual agreement (*concordance*).[32]

Patients tend to ask questions directly relevant to their own situation and in their own words, which do not always reflect medical terms and language.

The aim of the Q&A is to answer basic questions in a simple and easily understandable manner. The reader should then be able to read and understand the main paper, if they wish to have more detailed information. Other sources of good quality, understandable information, including that produced by the EMA, are given in the core document.[33]

The basics:

1. What is a biological medicine?

"*A biological medicine is a medicine that contains one or more active substances made by or derived from a biological source. Some of them may already be present in the human body. Examples include proteins such as insulin, growth hormone and erythropoietin*"[34] (hormone for producing red blood cells).

2. How are biological medicinal products made?

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[31]The EPF Policy Advisory Group (PAG) is a group of 14 representatives of different EPF member organisations (as of December 2012) .The questions included in this document were validated by the PAG. The draft answers were reviewed by a panel of 6 patient representatives, based on an open call for interest.

[32] Concordance is a term that describes the relationship between patient and prescribing doctor, and the degree to which the prescription is based on a joint agreement. Concordance means that the beliefs and preferences of both the doctor and the patient are taken fully into consideration but the patient's views take precedence. (Sources: Horne, R: Compliance, adherence and concordance: implications for asthma treatment. Chest, 2006;130;65-72; Concordance, adherence and compliance in medicine taking. Report for the National Co-ordinating Centre for NHS Service Delivery and Organisation R&D, December 2005.)

[33] Part of the wordings used in some of these questions has been 'recycled' from the EMA Questions and Answers document on biosimilar medicines (similar biological medicinal products)(EMA/83780572011) dated 27 September 2012. Where this is the case, the EMA document is cited as a reference and the text is in italic.

[34] See question: What is a biosimilar medicine? in EMA/837805/2011-27/9/2012_Questions and answers on biosimilar medicines (similar biological medicinal products)_September 2012

"Classical" medicines are typically manufactured by a process called chemical synthesis, whereas most biological medicines are made from living organisms such as genetically-modified cells. These cells have received a gene (obtained from gene banks or via a manufacturer's artificial gene production) to enable them produce a specific protein. The production of biological medicines involves processes such as fermentation and purification. Each manufacturer has its own unique cell lines and develops its own manufacturing processes.

3. How are biological medicines different from "classical" medicines?

Like all medicines, biological medicines work with the body to produce a therapeutic outcome, but the mechanisms by which they do this may be different from product to product and depending on the condition to be treated.

The active substances of biological medicines are larger and more complex than those of non-biological medicines. Only living organisms are able to reproduce such complexity. Their complexity as well as the way they are produced may result in a certain degree of variability in molecules of the same active substance, particularly in different batches of the medicine.[35] Such variability is natural for biological medicines. For more detailed information see question 4 as well as section 2.3 of the core consensus information document.

4. *What are biosimilars?*

A biosimilar medicine is a biological medicine that is developed to be similar to an existing biological medicine (the "reference medicine"). Biosimilars are not the same as generics. Generics have simpler chemical structures and are considered to be identical to their reference medicines.

"The active substance of a biosimilar and its reference medicine is essentially the same biological substance, though there may be minor differences due to their complex nature and production methods. Like the reference medicine, the biosimilar has a degree of natural variability. When approved, this variability and any differences between the biosimilar and its reference medicine will have been shown not to affect safety or effectiveness".

"*Biosimilars are usually authorised several years after the approval of the reference medicine. This is because the reference medicine benefits from a period of exclusivity, during which biosimilars cannot be authorized".*[36]

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[35] See question: What is a biological medicine? in EMA/837805/2011-27/9/2012_Questions and answers on biosimilar medicines (similar biological medicinal products)_September 2012

[36] See question: What is a biosimilar medicine? in EMA/837805/2011-27/9/2012_Questions and answers on biosimilar medicines (similar biological medicinal product)_September 2012

5. *What does "similar" mean?*

No two cell lines, developed independently, can be considered identical. This is why biotechnology-derived medicines cannot be fully copied. In recognition of this, the European Medicines Agency (EMA) has established the term "biosimilar".

A biosimilar medicine is developed to be highly similar to its reference medicine in terms of quality, safety and efficacy. "*The active substance of a biosimilar and its reference medicine is essentially the same biological substance, though there may be minor differences due to their complex nature and production methods*". [37]

"*A biosimilar and its reference medicine are expected to have the same safety and efficacy profile and are generally used to treat the same conditions".* [38]

6. *Are biosimilars generics?*

Biosimilar medicines are not generic medicines. "A generic medicine[39] is a medicine that is developed to be the same as a small-molecule (chemical) reference medicine". *"Generic medicines have simpler chemical structures."*[40] (See also question 5)

7. *What is a reference product (may also be called branded medicine)?*

The reference product is a medicine which has been granted a marketing authorisation by a Member State or by the European Commission. Marketing authorisation is granted on the basis of submitted quality, pre-clinical and clinical data, gained through laboratory studies and clinical trials. The application for marketing authorisation for a biosimilar refers to the data submitted for the reference product.[41]

8. *Are biosimilars "personalised medicine"?*

No. "Personalised medicine" is a targeted treatment approach that uses modern diagnostic tools to tailor medical care closer to the needs of individual patients. By sorting patients into subgroups of responders based on certain characteristics - such as a genetic mutation - it aims at predicting their likelihood to benefit from a specific treatment. "Personalised medicine" is also sometimes called "stratified medicine", "targeted therapies" or "personalised healthcare".

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[37] See question: What is a biosimilar medicine? in EMA/837805/2011-27/9/2012- Questions and answers on biosimilar medicines (similar biological medicinal product)_September 2012

[38] See page 5/33 of EMA Procedural advice for users of the centralised procedure for similar biological medicinal products applications_EMA/940451/2011, March 2013

[39] The legal definition of a generic medicinal product can be found under Article 10(2)(b) of Directive 2001/83/EC, as amended. The simplified definition can be found in the EMA "Questions and Answers on generic medicines" dated 17 March 2011-EMA/393905/2006 Rev. 1 and in the glossary of this consensus information document.

[40] See question: What is a generic medicine? in the "Questions and Answers on generic medicines" developed by the European Medicines Agency_EMA/393905/2006 Rev1_March 2011.

[41] See page 8/33 of EMA Procedural advice for users of the centralised procedure for similar biological medicinal products applications_EMA/940451/2011, March 2013

9. *Do biosimilars have anything to do with "parallel imports"?*

No, not specifically. Parallel import, also called parallel distribution or parallel trade, is a legal form of trade within the European Union where any pharmaceutical product that is authorised for marketing in one Member State and distributed therein may subsequently be distributed in another Member State, in which the product is also authorised for marketing. Parallel trade exists for example when there are significant price differences between Member States.

Quality and safety

10. *Is the approval process different from generic medicines? Who authorises biosimilar medicines for use in the EU?*

The legal and regulatory pathway for approval of biosimilar medicines is different from generic medicines. Since 1995, all biotechnology-derived medicines must be assessed centrally by the European Medicines Agency (EMA). In case of a positive scientific opinion adopted by the scientific committee, the European Commission makes a formal decision for marketing. Since 2003 a specific legal and regulatory pathway exists for the development and approval of biosimilar medicines. The general principles of drug development and review by the European authorities apply to biosimilar medicines in the same way as to the reference biological medicines.

11. *Is there any difference in safety between the biosimilar and the reference product?*

No, an approved biosimilar medicine and its reference medicine are expected to have the same safety and efficacy profile.

EU legislation defines the studies that need to be performed for the biosimilar medicine to demonstrate similarity in quality, safety and efficacy (therapeutic effect) in relation to its reference medicine, and that there is no significant clinical difference to the reference medicine.

Based on the information published on the EMA website, no specific safety issue has been identified for approved and marketed biosimilar medicines at the time of publication of this consensus information document.

12. *Is switching between a reference medicine and a biosimilar medicine (and vice versa) safe?*

There is relatively little published data available on the number of patients that have been switched between biopharmaceuticals in clinical practice. "*For questions related to switching from one biological medicine to another, patients should speak to their doctor and pharmacist*"[42].

[42] See question: Can a biosimilar medicine and its reference medicine be used interchangeably? in EMA/837805/2011_Questions and answers on biosimilar medicines (similar biological medicinal products)_September 2012

13. Are biosimilar medicines likely to cause more adverse reactions than the reference medicines?

No, once approved, a biosimilar medicine and its reference medicine are expected to have the same safety and efficacy profile, which includes the same level of adverse reactions.

Biological medicines in general have the potential to be recognised by the body as "foreign" and may cause unwanted immune reactions. This is called immunogenicity and it is due to their composition and large molecular size, compared to chemical medicines.[43] However, there is no evidence or scientific rationale to suggest that biosimilar medicines are likely to cause more immune reactions than their reference medicines. (see also questions 10 and 11)

14. What should I do if I suspect I have an adverse reaction to a medicine?

It is important that patients report any suspected adverse reactions; this helps in the continuing assessment of the quality and safety of medicines. Adverse drug reactions (or "side effects") can sometimes appear a long time after a person has been taking a medicine, or even after stopping it.

In the first instance, if you suspect an adverse reaction to any medicine, or if you think the medicine is not having any effect, you should speak with a healthcare professional such as your prescribing doctor or a pharmacist.

In order to report suspected reactions, your healthcare professional is expected to identify the medicine correctly, and document the trade ("brand") name of the medicine prescribed in your patient file. For the same reason you as a patient should make sure you have been given information about the trade name, the international non-proprietary name (INN)[44] of the medicine, the manufacturer's name, and the batch number of the prescribed medicine.

Under the new EU pharmacovigilance legislation, patients themselves can also report suspected side effects directly to the national authorities.[45] This is not intended to replace contact with a healthcare professional, but is of great value for the collection of data on adverse reactions. For information on medicines safety data collected by the European Medicines Agency, please visit www.adrreports.eu. (This website is not for reporting adverse reactions.)

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[43] Vaccines specifically exploit their immunogenic potential by provoking an immune response that recognises and "fights off" an "invader" substance. However, for some medicines based on proteins, stimulating an immune response is regarded as undesirable. Most of the immune responses that occur are mild and do not have negative effects on the patient; but in rare cases, unwanted immune reactions can be severe. This is why monitoring the impact of the medicine on the patient, by the patient themselves and their healthcare professional, is of crucial importance.

[44] International Non-proprietary Names identify pharmaceutical substances or active pharmaceutical ingredients. Each INN is a unique name that is globally recognized and is public property. A non-proprietary name is also known as a generic name. (Source: WHO Guidance on INN, www.who.int)

[45] More information can be found in the EPF guidance document for patient organisations on the new EU legislation

15. *Is there any difference in quality and efficacy between biosimilar medicines and their reference medicines?*

No, a biosimilar medicine and its reference medicine are expected to have the same safety and efficacy profile.[46] Biosimilar medicines are made following the same standards as other biological medicines. Before the European Commission takes a decision to authorise a biosimilar medicine to be marketed in the EU, the European Medicines Agency, through its Committee for Medicinal Products for Human Use (CHMP), evaluates whether the new biosimilar has a comparable efficacy (therapeutic effect), quality and safety profile to its reference medicine.

The studies that need to be performed for a new biosimilar medicine include comparisons on several aspects of the biosimilar and its reference medicine, such as the structure and activity of the molecules. Targeted studies are performed to show that the products are comparable. Scientific guidelines exist to determine the extent of clinical data required, and the decision is taken on a case-by-case basis. Detailed information on all biosimilar medicines approved in the EU is available on the EMA website.

16. *Is there evidence that the biosimilar medicine is at least as effective as the branded medicine in treating all the same conditions as the branded medicine? Or has this just been assumed given its high similarity?*

Biological medicines are often authorised to treat more than one condition (indication). However, the mechanism of action can be the same. Therefore, it may be possible that the biosimilar can be scientifically justified to be used in other conditions. The decision whether to extend the efficacy and safety data from a condition for which the biosimilar has been clinically tested to other conditions for which the branded product is approved is known as "extrapolation". The decision on whether to require new comparative clinical studies is taken on a case-by-case basis by the scientific committee (CHMP) at the EMA. The committee always makes its decision based on a thorough review of the scientific evidence.

The scientific basis for this extrapolation of indications is that the product has the same mode of action as its reference product; that the biosimilar and the reference medicine are proven to be comparable at the quality and biological level; and that there is conclusive evidence of similar safety and efficacy in at least one indication of the reference medicine. An authorised biosimilar medicine should be used at the same dose to treat the same conditions as the reference medicine.

17. *How is the safety of the biosimilar monitored after authorisation?*

As with all medicines, monitoring patients' response and reporting any suspected adverse reactions (unwanted negative effects) is important to ensure safety and efficacy of the treatment.

Biosimilar medicines, like all biological medicines, must be continually monitored after authorisation for adverse events. The monitoring of adverse reactions is a part of "pharmacovigilance" (the system in place for monitoring the safety and risk-benefit

[46] See page 5/33 in EMA Procedural advice for users of the centralised procedure for similar biological medicinal products applications EMA/940451/2011_March 2013

balance of authorised medicines). All manufacturers are required to set up a system to monitor side effects for their medicines.

Patients often react individually to medicines, whether chemical or biological. They themselves are often in the best position to assess the effects of a medicine on their body and their life. A patient should be able to be fully involved in the decision to take any biological medicine following a thorough discussion with their prescribing doctor of all the treatment options. They should understand the medicine and the potential reactions they may experience – both positive and negative - and be aware of the importance of taking it correctly and carefully monitoring their response. Moreover, patients need to feel confident in discussing any suspected side effects with their healthcare professional.

In order to report suspected reactions and identify the medicinal product correctly, patients on any biological medicine, including biosimilar medicines, should always have information about the trade ("brand") name of the medicine, the international non-proprietary name (INN) which is the name of the active substance, the manufacturer's name, and the batch number of the prescribed medicinal product. The patient may find this information on the package leaflet, or get it from their pharmacist or prescribing doctor.

The new EU pharmacovigilance legislation makes it mandatory for all member states to allow direct patient reporting of adverse reactions to their national authority. Ideally, patients should feel comfortable to discuss any suspected adverse reactions with their healthcare professional, but sometimes this is not the case.

The new EU pharmacovigilance legislation has also introduced a new approach which consists in publishing a list of medicines subject to additional monitoring for a set period. The European Medicines Agency and the Member States will work together on this public list and further steps have been taken in the course of 2012. An inverted black triangle symbol will identify those medicinal products which are subject to additional monitoring. An explanatory statement will be added to the package leaflet, encouraging patients to report any suspected side effects.

For information on medicines safety data collected by the European Medicines Agency, please visit www.adrreports.eu. (This website is not for reporting adverse reactions.)

18. Are biosimilars more likely to be counterfeited/falsified than any other medicine?

No. There is no evidence that biosimilar medicines are more likely to be counterfeited/falsified than any other medicines.

Use of biosimilars

19. Why have biosimilars been introduced?

Biological medicines offer treatment options for disabling and life-threatening diseases, such as cancer, infectious diseases like hepatitis, autoimmune disorders, neurodegenerative diseases and rare diseases. However, treatment with a biological medicine can be expensive compared to a "classical" chemical medicine.

Biosimilar medicines are introduced when exclusivity rights (e.g. patents, data protection, etc.) of the reference medicine have expired. They may offer a less-costly alternative to existing biological medicines and enhance competition. As a result, the availability of biosimilars may improve access to biological medicines for more patients and help the financial sustainability of healthcare systems. Thus, their availability offers potential economic benefit to healthcare systems while supporting patients' access to new treatment options brought about by advances in medical science.

20. Will I have the choice whether I will be prescribed the reference medicine or the biosimilar medicine?

It is important to have a thorough conversation with your prescribing doctor about all the available therapeutic options, their safety, benefits and risks, and the differences between the medicines, before coming to a decision concerning treatment. Policies regarding the use of biological medicines, including substitution, are the responsibility of the authorities of each EU Member State. If you have any concerns about a medicine that has been prescribed to you, you should discuss this with your doctor.

21. If the reference medicine is withdrawn from the market, will the biosimilar be withdrawn as well?

It depends on the reason for the withdrawal of the reference medicine. Each medicinal product approved on the market in the EU has its own marketing authorisation and each medicinal product is assessed independently. If the reference medicine is withdrawn for safety reasons, then that may be taken into consideration when assessing the biosimilar medicine. If there are serious safety concerns regarding the active substance of the reference medicine, the new Pharmacovigilance Risk Assessment Committee (PRAC) at the EMA will assess if other medicines with the same active substance are also concerned. Regulatory authorities investigate and take action as appropriate.

22. Can I take a biosimilar medicine in exactly the same way (after food, etc.) as the reference drug? Is there anything I should know about how to store a biosimilar medicine?

All biological medicines, including biosimilar medicines, can be less stable than chemical medicines, requiring more precautions in their production, transport and storage. When prescribing a new medicine, your doctor should advise you concerning any specific issues that should be taken into account with that particular medicine, which may be important to ensure its effectiveness and correct use.

Most biological medicines must be administered by injection or infusion, therefore except for products that must be taken with meals, such as mealtime insulins, the intake of food does not affect the product safety or efficacy. In general, a biosimilar medicine has to be taken exactly the same way as the reference medicine.

23. Where can I find more information?

- European Medicines Agency on biosimilar medicines
- European Medicines Agency on medicines safety monitoring

- Guidance document for patient organisations on the EU pharmacovigilance legislation

Q&A for PHYSICIANS

1. ***What is your responsibility as physician regarding prescription of biosimilar* medicines?**

As with prescriptions for medicinal products in general, it is the responsibility of the treating physician to take the individual patient's age, gender, stage of disease, co-morbidities and concomitant medications, as well as overall medical history into consideration when prescribing a medicinal product. In addition, as physician, you need to know that a biosimilar medicine is similar to a biological medicine that has already been authorised, the so-called "reference medicinal product". An approved biosimilar and its reference medicinal product are expected to have the same safety and efficacy profile but the biosimilar may not necessarily be authorised for all indications approved for its reference medicinal product. As with any medicine, physicians should choose carefully when prescribing.

2. ***What were the scientific steps taken to demonstrate similarity of safety and efficacy of a biosimilar to the reference medicine prior to a* marketing authorisation *being granted?***

The aim of a biosimilar development programme is to establish "biosimilarity". This is done through a stepwise "comparability exercise" in a tailor-made development programme which takes into account the safety and efficacy established for the reference medicinal product. This exercise is done in several steps: first step - quality comparability (physicochemical and biological comparability), second step - non-clinical comparability (comparative non-clinical studies) and third step - clinical comparability (comparative clinical studies). Every biosimilar application is assessed on a case-by-case basis. The comparability exercise is consequently based on a robust head-to-head comparison between the biosimilar and the reference medicinal product at the levels of quality, safety and efficacy. Comparability between the reference and the biosimilar medicine is the core principle of a biosimilar development.

3. ***Biosimilar medicines, like any biological medicine, are very sensitive to changes during their manufacturing process, transport and storage. How can a physician be sure that minor changes have not had an impact on the quality, efficacy and safety of the biosimilar medicinal product?***

The manufacturing processes for any biological medicine are very sensitive and it is vital that these are precisely controlled in order to obtain consistent results and to guarantee the safety and efficacy of the final medicinal product.

Manufacturers and importers of medicines approved in the European Union, including biosimilar medicinal products, are legally obliged to hold a valid manufacturer's and importer's authorisation (MIA)/GMP certificate issued by an EU national competent authority. An MIA/GMP certificate will only be granted if the manufacturing/importing site complies with the EU Guidelines on Good Manufacturing Practice (GMP) which also include specific provisions for biological medicinal products (Annex 2 of the Volume 4 of EudraLex).

To verify compliance with GMP, manufacturers and importers in the EU are subject to regular GMP inspections by the supervisory authorities. The EU national competent

authorities also inspect manufacturers located outside the EU that export to the EU. For biopharmaceuticals which are centrally assessed and authorised for marketing in the whole European Union, the EMA coordinates GMP inspections related to the medicine's scientific assessment and conducted by the EU national competent authorities.

Importers, manufacturers and wholesale distributors are obliged to comply with Good Distribution Practice (GDP) standards. According to the GDP Guidelines, specific conditions for storage and transport (e.g. refrigeration) must be ensured. Wholesale distributors are legally obliged to hold a valid wholesale distributor's authorisation (WDA) issued by an EU national competent authority. Wholesale distribution by manufacturers, importers and distributors is equally subject to supervision by EU national competent authorities.

4. *Where can I find updated information[47] on the pharmacokinetics, safety, immunogenicity, and interchangeability studies on biopharmaceuticals and biosimilar medicines?*

This information for each centrally authorised medicine is published by the European Medicines Agency (EMA) on their website: www.ema.europa.eu. Upon approval, a collection of documents known as the European public assessment report (EPAR) is published on the website, which contains scientific and technical information on the development of each medicinal product. Information on pharmacokinetics, efficacy and safety, as well as immunogenicity is also contained within the EPAR. Since decisions on interchangeability and substitution are not within the remit of the EMA/CHMP, and interchangeability studies are not part of the registration requirements, such information may not be included in the EPAR.

If the name of the biosimilar medicine is known, the updated EPAR can be found on the EMA homepage by going to "**Find Medicine**" and then to "**Human medicines**". Alternatively, the EPAR pages for all centrally-authorised biosimilar medicines can be found on the home page by going to "**Special topics**" and then "**Biosimilar medicines**".

5. *Are the pharmacovigilance requirements different for biological medicines than for the non-biological ones?*

In general, yes. This is because biological medicines have a higher risk of being recognised by the body as "foreign" and therefore have the inherent potential to induce unwanted immune reactions, due to their composition and large molecular size. Chemical medicines, on the other hand, are usually too small to be recognised by the immune system.

The potential to induce an immune reaction in the body (immunogenicity) is a significant safety element assessed during the exploratory and confirmatory development of an innovator biological medicinal product, and is supported in clinical trials by extensive testing and characterisation of short and long term anti-product immune responses. The results of these studies will have an impact on the design of post-authorisation follow up studies and risk management plans to ensure that rare immune-related safety issues can

[47] Please note that the "scientific discussion" document of the initial marketing authorisation reflects the data available at the time of approval and is not updated in the post authorisation phase.

be detected by collecting safety information for a longer period and from larger numbers of patients. In order to monitor long-term immunogenicity and safety, marketing authorisation holders are required to collect post-authorisation safety data for all biological medicines, including biosimilar medicines. This is part of the risk management plan (RMP) agreed at approval.

Information on risk management plans for all medicinal products approved through the EU centralized procedure (including all biotechnology-derived medicines and novel synthetic medicines) will be made accessible in line with EU Regulation 1049/2001 on access to documents. Under the same provision, the Agency will make available post-authorisation obligations e.g. registry studies, continuation of pre-approval trials and post-marketing safety studies.

The clear identification of the medicine is of particular importance for adverse reaction reporting relating to all biological medicinal products, including biosimilar medicinal products. Therefore, EU legislation requires that for every adverse reaction report of a biological medicine, the name of the medicine (trade name), as approved by the regulatory authorities, and the batch number should be included in the adverse drug reaction (ADR) report.[48]

As per the new pharmacovigilance legislation, any biological medicinal product authorised after 1 January 2011 will be included in the additional monitoring list. For all medicines on this list, marketing authorisation holders shall include in the SmPC an inverted Black Triangle symbol and the statement: "*This medicinal product is subject to additional monitoring*" together with a standardised explanatory sentence as well as a standard text asking healthcare professionals to report any suspected adverse reaction.

6. *Since the first initial authorisation of a biosimilar medicine in the EU (2006), have there been adverse effects reported following switching between the reference medicine and biosimilar medicines?*

There is relatively little data available on the number of patients that have been switched between biopharmaceuticals in clinical practice. There are several publications describing such switches, but it remains unclear how often these occur. Moreover the studies reported in the literature were generally too short to show the possible long term side effects of switching.

The European Medicines Agency (EMA) adopts a scientific opinion as a basis for a European Commission decision on the need for an update of product information (the summary of product characteristics and the package leaflet) when deemed necessary following review of reported adverse event arising from the use of any medicinal product. Safety related updates to the product information can include changes to prescribing information, additions to the list of observed side effects and additions to the precautions and warnings for use. The current versions of the product information documents are available on the EMA website, as is the history of amendments to the product information since first authorisation of the product. Review of these regulatory information resources for all currently approved biosimilar medicines to date shows that there has been no

[48] See content of the individual case safety report: Article 28 of Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012

safety related updates to their respective product information documents which have been as a consequence of reports of adverse effects following product switching or substitution.

As with all medicines, adverse event for biosimilar medicines are reported through approved pharmacovigilance mechanisms. Suspected adverse event can be obtained by searching from EudraVigilance[49] on the EMA website and in all official European Union (EU) languages. Furthermore, there is a dedicated "Patient Safety" page which lists major changes made to the authorisation of medicines, which have been recommended by the Committee for Medicinal Products for Human Use (CHMP) to improve safety for patients. From October 2009 to July 2012 there have been also monthly reports of the CHMP Pharmacovigilance Working Party (PhVWP)[50]. The cumulative Index of PhVWP Monthly Reports provides an overview of all safety concerns. No specific safety concern has been identified for approved and marketed biosimilar medicines at the time of publication of this consensus information document.

Work has been done on switches from an originator reference medicine to a biosimilar medicine that was undertaken by Skåne University Hospital (Malmö, Sweden) in 2009. Ninety-eight paediatric patients who were receiving human growth hormone were selected for a switch from a reference medicine to a biosimilar medicine, out of a larger population of 130 patients. 15 children experienced an adverse event in the course of the switch (most commonly pain at the injection site), though none were deemed "serious" by hospital personnel. Four children were switched back to the originator reference medicine.

7. Are there any studies showing differences in survival-time, efficacy and side-effects of treatment over long term?

No, but manufacturers routinely collect long term data from post-approval clinical trials, patient registry studies and long term follow up of patients who participated in the pre-approval clinical trials. For all biosimilar medicines it is a condition of authorisation that a pre-determined risk management plan (RMP) is executed which comprises some or all of the above measures. This is necessary to establish that the safety profile of a biosimilar medicine is still comparable to that of its reference medicine in a much larger patient population than has been assessed in the relatively small numbers of patients in the pre-approval clinical investigations. These larger patient numbers and longer treatment exposures allow the greater statistical sensitivity required to capture low frequency events and to enable reliable safety signal detection. It is the obligation of the manufacturers to report the findings of these RMP derived data to the EMA and to propose changes to the product information if necessary. Review of regulatory information resources at the time of publication of this consensus information document, shows that there have been no such changes required by the EMA.

8. What provisions for traceability do doctors need to follow?

[49] EudraVigilance is the EU database that holds adverse reaction reports related to all medicinal products authorised in the EU. The European Medicines Agency has launched its Website on suspected side-effect reports for medicines authorised in the European Economic Area (EEA) in all official European Union (EU) languages (http://www.adrreports.eu/)

[50] Following the implementation of the new pharmacovigilance legislation, the Pharmacovigilance Working Party (PhVWP) has been replaced by the Pharmacovigilance Risk Assessment Committee (PRAC) which is now responsible for assessing and monitoring safety issues for human medicines.

As required by EU law, every medicine will either have an invented (trade) name, or the name of the active substance together with the company name/trademark. The approved name, together with the batch number, is important for clear identification to support adverse drug reactions reporting and monitoring of the safe use of the medicine.

For example, to ensure the identification and traceability of all erythropoietin products, the EMA has taken specific steps in this area as a result of several cases of pure red cell aplasia (PRCA) that started in the nineties – prior to the approval of any biosimilar medicine. In December 2009 the Pharmacovigilance Working Party (PhVWP) within the EMA "*considered it important that accurate medication histories are maintained for patients treated with epoetins, i.e. recording the trade name or the scientific name with the name of the manufacturer in the patient file*". The identification and traceability of epoetin products used in patients will help to assess if PRCA cases and other reported cases of adverse reactions are related to any quality specifications of a certain epoetin product. As a result of the PhVWP's recommendations, the summary of product characteristics (SmPCs) for all erythropoietin products (originator and biosimilar) have been updated to include the following special warning: "In order to improve the traceability of erythropoiesis-stimulating agents (ESAs), the trade name of the administered ESA should be clearly recorded (or stated) in the patient file".

Another example is a similar statement that has been introduced in the SmPC of an originator monoclonal antibody product (containing the active substance rituximab) at time of publishing of this consensus information document.

9. Is the cost of a biosimilar medicine consistently lower than that of the reference medicine?

While in general biosimilar medicinal products are introduced to the market at a lower price than their originator reference medicinal product, price is determined through market forces, by national competent authorities, and competition between originator and biosimilar medicines' manufacturers.

10. Since the first biosimilar medicine authorised in the EU, have there been adverse effects reported following changes in manufacturing process, transport and storage?

Review of regulatory information resources for all currently approved biosimilar medicines to date shows that there have been no safety related updates to their respective product information documents which have been the consequence of reports of adverse effects following changes in manufacturing process, transport and storage.

The European Medicines Agency (EMA) updates product information (the summary of product characteristics and the package leaflet) when deemed necessary following review of reported adverse events arising from the use of any medicinal product. Safety related updates to the product information can include changes to prescribing information, additions to the list of observed side effects and additions to the precautions and warnings for use. The current versions of the product information documents are available on the EMA website, as is the history of amendments to the product information since first authorisation of the medicinal product.

11. Where can I find information for which of the biosimilar medicines' approved indications clinical trials have been done and which ones have been extrapolated?

If prescribers wish to identify which indications have been extrapolated and for which ones head to head comparative clinical trials have been performed against the reference product, this information is published by the European Medicines Agency (EMA) on their website: www.ema.europa.eu.

The relevant information can be found in the European public assessment report (EPAR) pages of each authorised medicine. If the name of the biosimilar medicine is known, this information can be found on the EMA homepage by going to "**Find Medicine**" and then to "**Human medicines**". Alternatively, the EPAR pages for all centrally-authorised biosimilar medicines can be found on the home page by going to "**Special topics**" and then "**biosimilar medicines**".

All approved indications of a medicine, whether extrapolated or not, are always approved based on scientific evidence. If questions remain regarding the approved indications of a biosimilar medicine, prescribers are reminded that the primary purpose of a biosimilar development is not to demonstrate the safety and efficacy of a known biological active substance; this has been done before for the reference medicinal product. The primary purpose of a biosimilar development programme is to demonstrate "biosimilarity" (please refer to question 2 and to the core-text).

12. Where can I find information about the clinical trials that have been conducted with the biosimilar medicine?

The EU Clinical Trials Register website contains information on interventional clinical trials on medicines. Information that appears on the EU Clinical Trials Register website is originally provided by the company or organisation responsible for the clinical trial.

Information on the assessment of the trials can be found in the European public assessment report (EPAR) pages of each authorised medicine. If the name of the biosimilar medicine is known this information can be found on the EMA homepage by going to "**Find Medicine**" and then to "**Human medicines**". Alternatively, the EPAR pages for all centrally-authorised biosimilar medicines can be found on the home page by going to "**Special topics**" and then "**biosimilar medicines**".

Q&A for PAYERS

1. Why are biosimilar medicinal products important to payers?

The availability of biosimilar medicinal products enhances competition and this potentially leads to lower prices. Lower prices may create savings for healthcare systems and payers and improved access for patients. These savings can be used to finance further advances in healthcare.

2. If biosimilar medicinal products cost less than originator medicinal products, *are they inferior?*

No, biosimilar companies have to adhere to the same high standards as originator companies in order to receive marketing authorisation. Biosimilar medicinal products can only be sold if the marketing authorisation holder has proven that their quality, efficacy and safety are similar to that of the originator medicinal products.

3. How much cheaper are biosimilar medicinal products than originator medicinal products?

Prices are not determined at the EU level and vary in the individual countries, not only in absolute amounts but also in relation to the price of the originator medicinal products. In addition, originator companies may respond to competition and prices may be subject to locally negotiated contracts. Although it is difficult to give an exact figure, biosimilar medicines have the potential to contribute to overall cost savings.

4. Originator medicinal product or biosimilar medicinal product - Who decides which brand will be dispensed?

Dispensing is not regulated at the EU level. It is up to each Member State to define who decides: doctor or pharmacist, and how patients are involved in the decision-making process. "*The EMA evaluates* biosimilar medicines *for authorisation purposes. The Agency's evaluations do not include recommendations on whether a biosimilar should be used interchangeably with its reference medicine"*.[51]

5. Is the trade name of the biosimilar medicinal product important?

The trade name of the medicinal product is not important for the efficacy of a biosimilar or originator medicinal product.

The Europe-wide marketing authorisation procedure ensures similar efficacy and safety for biosimilar medicinal products for those indications for which both the reference medicinal product and the biosimilar medicinal product have been approved. Although the route of administration must be the same for the reference medicinal product and the respective biosimilar medicinal products, different brands may have different injection devices.

However, the trade name and the batch number are important for identifying the medicinal product for administrative and pharmacovigilance purposes.

[51] See question: Can a biosimilar medicine and its reference medicine be used interchangeably? in EMA/837805/2011-27/9/2012- Questions and answers on biosimilar medicines (similar biological medicinal product)_ September 2012

Physicians, hospitals and healthcare centres have many years of experience in treating patients with different brands of biological medicinal products in the same indications. Since all products have received European Union marketing authorisation[52], additional factors may be taken into consideration when making the choice (e.g. price, ease of use, patient factors, etc.).

6. Where can I find more information about biosimilar medicinal products?

Healthcare professionals (in particular doctors and pharmacists) will answer all questions that patients have about their treatment, including the reasons for the choice of product. On the Internet, the most authoritative source of information is the European Medicines Agency (www.ema.europa.eu). National competent authorities also have websites and may have a special webpage dedicated to biosimilar medicinal products and explaining which medicinal products are reimbursed and the rules that apply.

[52] This consensus information document only focuses on biological medicinal products, including biosimilar medicinal products, that are biotechnology-derived medicines and which, since 1995, must be assessed centrally by the European Medicines Agency (EMA) and in case of a positive scientific opinion adopted by the scientific committee, are subject to a formal decision process for marketing by the European Commission.

Glossary

Active substance: Active ingredient or molecule which goes into a specific medicine and which provides this medicine with properties for treating or preventing one or several specific disease(s).

Adverse event/side effect: Any unintended or unfavourable event following the administration of a given medicine. WHO defines an adverse event as follows: “An injury related to medical management, in contrast to complications of disease. Medical management includes all aspects of care, including diagnosis and treatment, failure to diagnose or treat, and the systems and equipment used to deliver care. Adverse events may be preventable or non-preventable.”

Antibody (pl: antibodies): Antibodies (also known as immunoglobulins, abbreviated to Ig) are large proteins that are found in blood or other body fluids. Antibodies are used by the immune system to identify and neutralise foreign objects, such as bacteria and viruses.

Autoimmune disease: A disease caused by the body producing an inappropriate immune response against its own substances or tissues. Thereby, the immune system ceases to recognise one or more of the body's normal constituents as "self" and will create auto-antibodies that attack its own cells, tissues, and/or organs. Inflammation and tissue damage are common symptoms of autoimmune diseases.

Biopharmaceuticals / Biotechnology-derived medicines: A medicinal product or a vaccine that consists of, or has been produced by the use of living organisms. Often recombinant DNA (a form of DNA that does not exist naturally and which combines DNA sequences that would not normally occur together in order to establish new functions) forms the basis for biotechnologically manufactured products. Examples include therapeutic proteins such as antibodies, insulins or interleukins; but also vaccines, nucleic acid or tissues and cells. This document only refers to biotechnology-derived medicines which, since 1995, must be assessed centrally by the European Medicines Agency (EMA) and in case of a positive scientific opinion adopted by the scientific committee, are subject to a formal decision process for marketing by the European Commission.

Biosimilar medicine: A biological medicine that is developed to be similar to an existing biological medicine (the “reference medicine”). Biosimilar medicines can only be marketed following the patent expiry of the reference medicine (also called originator product in the document, for more details, please see the consensus document or the EMA Q&A on biosimilar medicines).

Biotechnology: Any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use. An example is the reproduction of human hormones like insulin.

Cell line [including master cell line]: A well-established, living system of cultured (grown in a laboratory) cells that will continue to grow and produce new cells indefinitely, so long as the cells receive nourishment and have space to develop.

Cell therapy: The infusion or transplantation of whole cells into a patient for the treatment of an inherited or acquired disease. (American Society of Gene and Cell Therapy)

Extrapolation of indications: The decision whether to extend the efficacy and safety data from an indication (a medical condition, disorder or disease) for which the biosimilar has been clinically tested to other conditions for which the branded product is approved, is known as "extrapolation".

Generic medicine: A medicine that is developed to be the same as a medicine that has already been authorised (the "reference medicine"). According to Directive 2001/83/EC "generic medicinal product" is a product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. A generic medicine can only be marketed after the loss of market exclusivity of the reference medicine (also called "originator product" in the document) (for more details, please see EMA Q&A on generic medicinal products).

Gene therapy: Gene therapy is an experimental technique for treating disease by altering the patient's genetic material. Most often, gene therapy works by introducing a healthy copy of a defective gene into the patient's cells. (Talking Glossary of Genetic Terms from the National Human Genome Research Institute)

Glycosylation: The type and length of any sugar or carbohydrate groups that are attached to a given molecule, e.g. a protein.

Immune system: The collection of mechanisms (or collection of biological substances and processes) within the body that protect against disease by identifying and killing pathogens (e.g. viruses and bacteria) and tumour cells.

Immune reaction/response: A defence mechanism by the body that leads to the production of antibodies by the human body in response to an invading substance (i.e. antigen) e.g. to viruses and substances recognized as foreign and possibly harmful.

Immunogenicity: The potential or ability of a substance or antigen to cause an immune reaction/response (see above).

Indication: A medical condition, disorder or disease.

INN: International Non-proprietary Name which identifies pharmaceutical substances or active pharmaceutical ingredients. Each INN is a unique name that is globally recognized and is public property. A non-proprietary name is also known as a generic name. (Source: WHO Guidance on INN, www.who.int)

Interchangeability: The medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative, or with the agreement of the prescriber.

Marketing authorisation: The permission granted by a regulatory authority to a company to market a medicinal product in accordance with the indications described in the product information, following the company's submission of required documentation and data in line with the regulatory and legal framework.

Molecule: The smallest particle of a substance that has all of the physical and chemical properties of that substance. Molecules are made up of one or more atoms held together by strong chemical bonds. If they contain more than one atom, the atoms can be the same (an oxygen molecule has two oxygen atoms) or different (a water molecule has two hydrogen atoms and one oxygen atom). Biological molecules, such as proteins, can be made up of many thousands of atoms.

Molecular: Of a molecule

Patent: A patent is a set of exclusive rights granted by a state (national government) to an inventor or their assignee for a limited period of time in exchange for public disclosure of its invention. Typically, however, a patent application must include one or more claims defining the invention which must be new, non-obvious, and useful or industrially applicable.

Pharmacovigilance: Science and safety control procedures to which medicines are subject before, during and after their approval by regulatory authorities with the aim of detecting, assessing and understanding the benefit: risk profile of a medicinal product. Pharmacovigilance activities cover the whole life-cycle management of medicines in relation to safety.

Protein: Large organic compounds made of amino acids arranged in a chain. Proteins are essential parts of organisms and participate in virtually every process within cells. e.g. erythropoietin is a protein.

Reference product (medicine): A medicinal product which has been granted a marketing authorisation by a Member State or by the European Commission on the basis of submitted quality, pre-clinical and clinical data, to which the application for marketing authorisation for a generic or a biosimilar product refers.

Risk management plan: A detailed description of the risk management system (see below) implemented by the manufacturer for a given medicine.

Risk management system: Set of pharmacovigilance activities and interventions which are designed to identify, characterise, prevent or minimise risks relating to a medicine, including assessment of the benefit: risk profile of a given medicine.

Side effect / adverse reaction: Any unintended or unfavourable event following the administration of a given medicine. WHO defines and adverse event as follows: “An injury related to medical management, in contrast to complications of disease. Medical management includes all aspects of care, including diagnosis and treatment, failure to diagnose or treat, and the systems and equipment used to deliver care. Adverse events may be preventable or non-preventable.”

Substitution: Practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber.

Switching: Decision by the treating physician to exchange one medicine for another medicine with the same therapeutic intent in patients who are undergoing treatment.

Vaccine: A biological preparation which is used to establish or improve immunity to a particular disease. Apart from such prophylactic vaccines, there also exist therapeutic vaccines.

What you Need to Know about Biosimilar Medicinal Products

Process on Corporate Responsibility in the Field of Pharmaceuticals
Access to Medicines in Europe

A Consensus Information Document

Cover image: Fotolia © vaso

Memorandum

Date: December 20, 2012

From: OND Therapeutic Biologics and Biosimilars Team

Subject: BLA 125427 – [xxx]-trastuzumab emtansine

To: File

FDA has determined that use of a distinguishing prefix in the nonproprietary name for Genentech's Kadcyla ([xxx]-trastuzumab emtansine), an antibody-drug conjugate submitted in a 351(a) biologics license application (BLA), will be required to distinguish the product from Herceptin (trastuzumab), a previously licensed biological product submitted in a different 351(a) BLA by Genentech that contains the unconjugated monoclonal antibody.

Kadcyla ([xxx]-trastuzumab emtansine) is a HER2-targeted antibody-drug conjugate which contains trastuzumab covalently linked to the microtubule inhibitory drug DM1 (a maytansine derivative) via the MCC linker. Emtansine refers to the MCC-DM1 complex. Kadcyla is proposed as a single agent for the treatment of patients with HER2-positive metastatic breast cancer who have received prior treatment with trastuzumab and a taxane. Herceptin (trastuzumab) is licensed for use as a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease, and in combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer. Herceptin also is indicated for adjuvant treatment of HER2-overexpressing breast cancer under specified conditions and as part of combination treatment for HER2-overexpressing metastatic gastric cancer under specified conditions.

FDA identified a potential for error between the currently marketed Herceptin (trastuzumab) and the proposed Kadcyla ("trastuzumab emtansine") due to the similarity of the nonproprietary names as well as overlapping product characteristics during review of the IND. For example, both products would be prescribed by oncologists and utilized in similar settings (infusion or cancer centers) for similar patient populations (women with breast cancer). However, the proposed dose (3.6 mg/kg) of Kadcyla is less than the recommended dose(s) of Herceptin for its approved conditions of use. Thus, if Kadcyla is confused with Herceptin, patients may experience overdose or underdose resulting in toxicity or

Reference ID: 3235478

reduced efficacy, depending on the direction of the error. Due to this concern, FDA requested that Genentech conduct a Human Factors evaluation to determine the best methods for product differentiation. The BLA submission described medication errors involving administration of the wrong drug during clinical trials that evaluated the safety and efficacy of Kadcyla. Genentech initiated a research project to understand potential areas for confusion between Kadcyla and Herceptin due to similarities between the nonproprietary names.

Due to the fact that healthcare providers may use nonproprietary names instead of proprietary names when prescribing and ordering products, and confusion has already occurred in clinical trials, FDA has determined the use of distinct proprietary names is insufficient to adequately address the Agency's safety concerns with use of "trastuzumab emtansine" as the proper name for Kadcyla. In addition, FDA has determined that the use of distinguishing labels, labeling, and warning statements together with educational programs also is not sufficient to address the concerns. For example, while distinguishing labels and labeling can help to prevent mix-ups at the point of dispensing, the potential still exists for a healthcare provider to select the incorrect product (trastuzumab vs. "trastuzumab emtansine") from a computerized drop-down menu during medication order entry.

FDA conveyed these concerns to Genentech in an Information Request dated September 7, 2012. During a teleconference between representatives of FDA and Genentech on September 28, 2012, to discuss the potential for confusion/medication error between Kadcyla and Herceptin, Genentech asked about the "potential for FDA to request a change in the established name for trastuzumab emtansine akin to that recently requested for Zaltrap as reviewed under BLA 125418" as part of its response to FDA's Information Request.

FDA has concluded that distinguishing the first word of the nonproprietary name for Kadcyla ([xxx]-trastuzumab emtansine) from Herceptin (trastuzumab) will minimize medication errors by preventing a patient from receiving a product different than what was intended to be prescribed. Additional strategies to reduce the potential for medication errors also are being considered.

To differentiate Kadcyla from Herceptin, FDA is requesting that Genentech propose a 3-4 letter prefix to be added to the nonproprietary stem, "trastuzumab emtansine," separated by a hyphen. This decision for "trastuzumab emtansine" is similar to the decision to revise the nonproprietary names for the botulinum toxin products. The nonproprietary names for botulinum toxin products were changed to emphasize the non-interchangeable potency units of each botulinum toxin product in an effort to prevent medication errors and serious adverse events. The potency units are specific to each botulinum toxin product, and the doses or units of biological activity cannot be compared or converted from one product to

any other botulinum toxin product. The new nonproprietary names (which incorporated a 3-4 letter distinguishing prefix to the "botulinumtoxinA" or "botulinumtoxinB" stem) reinforced these differences and the lack of interchangeability among botulinum toxin products. This decision for "trastuzumab emtansine" also is similar to FDA's decision to require a unique nonproprietary names for Zaltrap (ziv-aflibercept) to distinguish the product from Eylea (aflibercept), a previously licensed biological product submitted in a different 351(a) BLA that contains a similar drug substance. Among other things, Zaltrap and Eylea have different formulations, different routes of administration, and different indications.

It should be noted that the requirement to add a distinguishing prefix to the first word of the nonproprietary name for this antibody-drug conjugate is specific to this proposed product ("trastuzumab emtansine") and the potential for medication errors involving the previously licensed trastuzumab. This decision is not intended to reflect a broader change to the naming conventions for antibody-drug conjugates.

For these reasons, Kadcyla will be identified as ([xxx]-trastuzumab emtansine).

Reference ID: 3235478

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LEAH A CHRISTL
12/20/2012

Biologic product identification and US pharmacovigilance in the biosimilars era

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To the Editor:
The first approval of a biosimilar by the US Food and Drug Administration (FDA) could occur by the end of 2014 (ref. 1). Although biosimilars must demonstrate no clinically meaningful differences from their biologic reference products in terms of safety, purity and potency (per US law[2]), they are not expected to be identical because of the inherent complexity of biologics and differences in manufacturing. Therefore, the FDA recommends clinical efficacy and/or safety studies of biosimilars before approval; however, such studies may not be large enough to assess rare adverse events (e.g., as related to neutralizing antibodies)[3]. Consequently, robust post-approval surveillance of biosimilars in the United States to monitor their safety is critical. We consider that such a pharmacovigilance system requires unambiguous product identifiers that distinguish all biologics from one another to accurately trace adverse events to the correct product and to identify potential differences in safety profiles after approval. A recent case study demonstrates inconsistencies in biologic identification in the US pharmacovigilance system that limit accurate tracing of reported adverse events to the administered product when multiple manufacturers exist (see examples below)[4].

The need to rapidly and accurately identify the precise product implicated in a postmarketing safety investigation is exemplified by a case study of 246 fatal allergic-type reactions in patients on hemodialysis who received contaminated heparin[4]. In this case, the lack of manufacturer information and lot numbers in some adverse event reports was noted as hampering identification of the responsible heparin manufacturer[4]. Although heparins are glycosaminoglycans, not complex biologics or biosimilars, this example underscores the importance of distinguishable identifiers and educating the healthcare community on accurate biologic product identification for adverse event reporting, as well as the need for national pharmacovigilance systems that accurately and reliably collect this information. Other recent cases in which accurate product identification in adverse event reports was required include fatal fungal meningitis from contaminated compounded steroids, loss of antidepressant efficacy of generic bupropion and acute anaphylactic reactions to peginesatide.

When acute, adverse events occur coincident with product administration, product identification may be straightforward because primary sources of identification (e.g., product packaging) may be easily accessible. Even so, tracing adverse events associated with biologics is challenging when events occur and are reported weeks or months after administration (e.g., immune reactions) after the product packaging has been discarded. Under these circumstances, adverse event reporting likely depends on reporter memory or the patient's medical record. User-friendly drug identifiers that are easily remembered, frequently included in accessible electronic medical records and effectively distinguish products may facilitate accurate adverse event reporting and tracing[5,6].

Identifiers provide information that ranges from the nonproprietary name to details about product source (e.g., lot number or National Drug Code (NDC); **Table 1**). Brand names are the predominant product identifier used in US practice[5,7] and are often the primary identifiers for reporting adverse events. Because brand names are proprietary, they are specific to a single product and manufacturer. Product identification by brand name in adverse event reports can provide a reliable, accurate means of identifying the administered product, but including a brand name in adverse event reports is not required by federal law, and manufacturers may not specify one (e.g., for most generic small-molecule products). Lack of brand clarity has been observed in the European Union (EU; Brussels), where biosimilar companies have applied for multiple licenses for the same product, one bearing a classic brand name and another identifying the product with the nonproprietary name combined with the manufacturer's name. Although reliable if reported, brand names may not ensure accurate biologic product identification because some products lack brand names and/or brand clarity. In addition, some practitioners use the originator brand name by default for adverse event reporting for products with the same nonproprietary name, which can result in misattributing adverse events to the innovator.

The nonproprietary name (international nonproprietary name (INN)/US adopted name (USAN)) is commonly used to identify the product in an adverse event report and may be the only identifier recorded in some hospital and healthcare databases. In current practice, if a biologic was assigned the same INN/USAN as another biologic (e.g., a biosimilar the same as its reference product), adverse events could not be unambiguously traced to the correct product. Additionally, a shared INN/USAN would not allow prescriber awareness of pharmacy-level biologic substitutions. A shared INN/USAN would identify a therapeutic class rather than the specific administered biologic, unless it was complemented with additional information (e.g., brand name or manufacturer). Moreover, shared INNs/USANs could imply interchangeability, a designation that requires meeting FDA-specified criteria[2].

NDCs provide detailed information about a medication and, if accurately included in an adverse event report, would provide a reliable means of product identification. However, NDCs have substantial limitations for biologic identification. Although all approved drugs receive an NDC, the FDA requests, but does not require, its inclusion in the labeling, and some states (e.g., Florida and California) do not require it. Additionally, as 10-digit numbers, NDCs are susceptible to transcription errors; invalid or missing NDCs are common billing errors. Moreover, only 30

Table 1 General characteristics of drug identifiers

Identifier	Comment
Brand name	Unique drug identifier
	Not required by federal law
	High level of recognition/recollection by users[5]
	Lack of brand clarity (e.g., Filgrastim Hexal, Tevagrastim)
INN/USAN	Common INNs/USANs identify the therapeutic class of drugs but not the specific drug
	Intermediate level of recognition/recollection by users[5]
NDC	Unique drug identifier in the US
	Requested, but not required, on label
	Not available in most adverse event–reporting scenarios[8]
	Available only in some billing and drug safety monitoring systems[7]
	Low level of recognition/recollection by users[5]
Lot number	Unique drug identifier (if the manufacturer is known)
	Infrequently available in adverse event–reporting scenarios[6,9]
	Available only in some billing and drug safety monitoring systems[7]

of 50 databases of the FDA Sentinel Initiative (a national electronic pharmacovigilance data network) that were analyzed tracked NDCs, precluding their use in product identification[7]. In current practice, adverse event reports are unlikely to contain the NDC[5,8]. Physicians and patients are often unfamiliar with the NDC, and most adverse events are reported without access to primary packaging that may contain this code. It has been postulated that NDCs could be recovered from other databases (e.g., payer systems); however, the NDC is inconsistently collected. Furthermore, access to such databases is neither simple nor quick. For example, if the FDA wishes to investigate a series of adverse events, there is no mechanism for immediate access to private, federal or state systems or uniform system structures. Additionally, patients are anonymous in adverse event reports; queries to payer systems would be futile without first identifying each patient in the adverse event reports. These limitations introduce additional steps that can delay or halt investigations—a concern noted in the heparin case study[4].

A manufacturer's lot number identifies the precise biologic product history if the manufacturer is known. It is the only product identifier that provides information for tracing specific production batches. However, like NDCs, they are infrequently entered in adverse event reports (often in <10–20% of cases) and are susceptible to transcription errors[6,8,9].

In seeking to optimize identification of biologics, it is important to consider how current product identifiers differ in accessibility, ease of use, reporting accuracy and traceability. Among current product identifiers, brand names and INNs/USANs have been associated with a relatively high level (74%) of reporting accuracy in MedWatch[9]; such names are easier to remember and record than numeric codes[5]. Furthermore, algorithms and/or data review can usually identify a product when its name is misspelled.

Before the US approval of Granix (tbo-filgrastim; Sicor Biotech, UAB, Vilnius, Lithuania) for the treatment of severe chemotherapy-induced neutropenia in 2012, the FDA stipulated that a unique nonproprietary name was required to distinguish it from the related product Neupogen (filgrastim; Amgen, Thousand Oaks, CA, USA) to prevent medication errors and facilitate pharmacovigilance[10]. The FDA's naming approach points to the importance of identifying biologics (including biosimilars) by distinguishable INNs/USANs to avoid confusion among related biologics. The FDA noted that although it is still considering a naming approach for biosimilar and interchangeable products, it did not expect that its decision on the approach would conflict with the nonproprietary name for this product[10]. Analogous use of a prefix to distinguish related biologic products was also implemented with the US approvals of ziv-aflibercept and ado-trastuzumab emtansine, which differ in indications, dosage and other important parameters from their respective original biologics with the same root USAN. These FDA actions underscore the utility of using distinguishable INNs/USANs for all biologics, including biosimilars. Such an approach is also being considered by the World Health Organization INN committee.

Regardless of the type of patient recording method used in the US healthcare system (paper-based or electronic), there is a compelling need for a product identification approach that facilitates accurate reporting and tracing of adverse events to the suspected causative biologic product. Until a comprehensive, fully integrated electronic pharmacovigilance system is in place, an interim solution is needed to ensure unambiguous product-identifying information is collected for safety monitoring. We consider this essential for pharmacovigilance in the upcoming era of biosimilars to facilitate postapproval safety monitoring and address the need for accurate attribution of adverse events given multiple manufacturers of highly similar biologics. Because of the limitations of current identifiers, the interim solution should incorporate multiple naming mechanisms (i.e., redundancy) to support accurate adverse event attribution and accommodate the multiple sources of adverse events. A requirement for distinguishable USANs for biologics would improve the traceability of adverse events[9]; thus, we recommend a US naming policy that assigns nonproprietary names with a manufacturer-specific identifier. This approach aligns with the FDA's previous biologic-naming approach that combines a USAN with a unique prefix to optimize tracing and minimize medication errors[10,11]. Regardless of the product identification system ultimately chosen for biologics, it is essential that it have adequate redundancy so adverse events can be accurately traced to the administered product in a timely manner for patient safety.

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A divided INN crowd

To the Editor:

As Executive Vice President, Scientific and Regulatory Affairs at the Pharmaceutical Research and Manufacturers of America (PhRMA; Washington, DC), I was disturbed by your December editorial entitled 'The INN crowd'[1]. Your editorial both misrepresents the current state of the pharmacovigilance system in the United States and proposes recommendations for the naming of biosimilars that pose a serious threat to patient safety.

Because biosimilars are similar to, but not the same as, their innovative biological reference products, patients, doctors, manufacturers and regulators must be able to distinguish between all biological medicines for the purposes of effective safety monitoring, data collection and transparency. PhRMA strongly believes that distinguishable nonproprietary names for all biological products, in conjunction with clear and informative labeling of biological products, are an essential component of a robust pharmacovigilance system that prioritizes patient safety.

The need for distinguishable names has been acknowledged by the World Health Organization (WHO; Geneva), which has a well-defined mandate through the WHO International Nonproprietary Names (INN) Programme to ensure clear identification, prescribing and dispensing of pharmaceutical substances, both chemically synthesized and biological products. In 2013, the WHO held a closed meeting entitled 'Discussion on INN Proposal for Similar Biological Products (SBPs)' during which, according to the public summary, "experts felt that the best way to do this [for biosimilar products] is through nomenclature with involvement of the INN Programme in developing a unique global qualifier." In fact, innovator companies have participated with other experts and regulatory authorities in an ongoing dialog on what policies would help the WHO to facilitate the appropriate identification of medicines, including at the recent 57th Open Consultation. In referencing the WHO's now-outdated 2006 position on naming, the editorial fails to acknowledge these more current multi-stakeholder discussions that recognize the clear need to improve the INN system for biological products.

Just as biosimilars are not the same as generic medicines (and should not be treated as such), INN policies for biosimilars should not follow the same naming conventions currently used for generics. To be clear, the editors misrepresented our position: PhRMA and the innovative biopharmaceutical industry have not advocated for entirely different INNs for each product. Indeed, we agree that such a practice would lead to confusion. Our position, which is to use a distinguishable identifier in addition to the core INN, builds upon current naming practices in a logical way. This would mean that nonproprietary names would be similar to each other in structure and function; be distinguishable, but morphologically related; and have the ability to be easily recognized, remembered and reported accurately by healthcare professionals and patients. Distinguishable but related nonproprietary names would also facilitate both the accurate attribution of safety signals at the product level and the aggregation of data to detect class-wide safety issues. With appropriate education, such a naming system would provide needed clarity and therefore greater confidence in prescribing of biosimilars.

The editorial pointed to the use of the National Drug Code (NDC) as a method for tracking adverse events in the United States but failed to acknowledge that the NDC is a 10-digit numerical code that is prone to error and is not consistently included with adverse event reports. A recent study demonstrated that product name (brand or nonproprietary) is often the only meaningful product-specific information provided in the US Food and Drug Administration (FDA; Rockville, MD) Adverse Event Reporting System (FAERS) data[2]. Thus, when reporters submit adverse events identified only by shared nonproprietary names, the FDA may not be able to accurately identify the particular product associated with the report, therefore delaying or potentially making impossible the attribution of the adverse event to the correct product. Inability to accurately attribute adverse events to the correct product may undermine physician and patient confidence in all products in a class. Perhaps more importantly, it could also prevent the detection of rare safety signals from an individual company's product through dilution into an unidentified mass of adverse event reports.

With the introduction of biosimilars in the United States and the continued entry of new innovator biologic medicines into the market, treatment options for patients will expand over time. This fact makes the current policy discussion around how best to track and accurately attribute adverse drug reactions even more crucial. We have the opportunity to learn from past pharmacovigilance failures and work together toward developing a durable and robust pharmacovigilance system for all biological products. Trivializing the importance of distinguishable nonproprietary names as a means of reliably identifying products is irresponsible and potentially harmful for patients.

The recent editorial unfortunately misrepresented what should be a thoughtful, scientifically based policy debate and instead provided a false choice between patient access and patient safety. Patients deserve better.

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Evaluating the Completeness and Accuracy of MedWatch Data

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The Food and Drug Administration's MedWatch system—a voluntary surveillance program—received 600,000 adverse event reports on marketed drugs and devices in 2011. The Food and Drug Administration credits the MedWatch system with improving awareness, and expediting early detection, of drug and device risks and in illuminating the adoption of medical treatments. Reporting bias has been acknowledged as a limitation of the MedWatch system. No systematic assessment of the accuracy and completeness of adverse event reporting has been conducted, yet inaccurate adverse event reporting may lead drug safety professionals to draw incorrect conclusions, manufacturers may be wrongly forced to suspend and withdraw medications and interventions, health professionals may mistakenly alter their clinical practices, and patients may be denied safe and effective treatments. In 2011, the Tufts Center for the Study of Drug Development gathered and analyzed 10.2 million adverse event reports filed with the MedWatch system. Patient information was generally complete and accurate. Suspect product information, on the other hand, showed high levels of incomplete and inaccurate data. Start and end dates of suspect product use had 37% and 23% completion rates, respectively. Dosage level was completed only 31% of the time, and product lot numbers had only a 9% completion rate. More than 25% of the names of reported suspect products were inaccurate, and 31% of suspect product start dates were inaccurate. Higher levels of completion and accuracy were associated with reports filed closer to the date when the adverse event was observed. Implications of the results and suggested improvements are discussed.

Keywords: adverse event reporting, drug safety, postmarketing surveillance, pharmacovigilance

INTRODUCTION

With much fanfare, the Food and Drug Administration (FDA) launched the Medical Products Reporting program (MedWatch) in 1993. Dr. David Kessler, the then Commissioner of the FDA, noted at its launch that MedWatch was "developed with the enthusiastic support of the medical community, to meet 4 primary goals: (1) to make it easier for health care providers to report serious adverse events; (2) to make clear to physicians and other health professionals the specific adverse event information that the FDA wishes to receive; (3) to increase the visibility of FDA's actions that have resulted from adverse event reporting; and (4) to increase physician and other health professional understanding and awareness of drug- and device-induced disease."[1]

Since its launch, MedWatch has been used widely. Nearly 150 professional societies (eg, American Medical Association; American Dental Association; American Nursing Association; and the National Medical Association) and drug information publishers (eg, Advanstar, ePocrates, Medscape, and the Physicians' Desk Reference) promote the use of MedWatch as a single source for unsolicited, spontaneous reporting of adverse events observed outside a formal clinical research study.[2] As a standard accreditation practice, hospitals are required by the Joint Commission on the

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Accreditation of Health Care Organizations to report adverse events to the FDA.

MedWatch began as a paper-based system using mail and fax to submit adverse event reports. The FDA launched its website in 1998 to make reporting more convenient and more rapid.[3] Today, the FDA receives more than half a million voluntary, postmarketing adverse event reports on chemical entities, biologics, vaccines, and devices annually.

Health care professionals, consumers, and manufacturers can each report an adverse event using the MedWatch system. Individual reports of medication errors, product quality problems, and adverse drug reactions are either sent directly using form 3500 to the FDA, or indirectly via the product's manufacturer, who is required by law to submit a MedWatch report form 3500A upon receipt of adverse event information from a health professional or consumer.[4] According to the FDA, the majority (~75%) of reports is submitted either directly or indirectly by health professionals. Consumers and patients generate 15% of reports, and 10% of the reports are generated by manufacturers.[4]

Before 1993, the FDA primarily received nearly all reports of adverse events from pharmaceutical manufacturers.[5] Assessments in the early 1990s that helped facilitate the introduction of MedWatch demonstrated the value of empowering health professionals and consumers to act as voluntary and spontaneous postmarketing surveillance agents. One study, for example, observed a 17-fold increase in reports submitted by physicians 2 years after education and outreach among this community.[5] Under the MedWatch system, the volume of adverse event report submissions increased dramatically, as did the speed at which the reports were submitted to the agency.[5] Since 1993, the FDA has seen a quadrupling of the number of adverse event reports received annually, from approximately 140,000 in 1993 to 600,000 in 2011, an 8.4% compound annual growth rate.[6]

The FDA credits the MedWatch system with substantially improving its ability to raise awareness and accessibility of adverse event information among safety evaluators and medical officers; to improve understanding of drug and device adoption by large patient populations in various treatment settings; to expedite early detection of drug and device risks; to maintain ongoing surveillance of patients at relatively low expense; to inform health professionals and consumers of potentially harmful drug interactions; and to require manufacturers to suspend and withdraw harmful interventions from the marketplace.[4] Numerous articles published since the late 1990s in the medical and scientific literature document active mining of MedWatch safety data to identify elevated risk of serious adverse events among various patient populations and subgroups.[7–10]

The FDA and drug safety professionals have noted a number of limitations and shortcomings with the MedWatch system. These limitations and shortcomings are considered largely a function of a voluntary and spontaneous surveillance process. Specifically, recognition and acknowledgment of an adverse event is subjective. As such, determining whether a particular intervention is the root cause of an adverse reaction can be difficult and imprecise and may result in overreporting and underreporting.[4] To help address this limitation, the FDA does provide 'advice' for the individual completing an adverse event report in the narrative instructions found on the MedWatch system.

MedWatch reporting bias has been observed, and it is inversely correlated with the length of time a drug or device is on the market. Reporting on newly introduced interventions tends to peak at the end of the second year of commercialization and declines steadily thereafter. Variability in MedWatch reporting quality has also been suggested as a potential limitation, as health professionals may fail to complete certain fields in forms 3500 and 3500A.[4] No assessment, however, has been performed to date that quantitatively measures the completeness of MedWatch reporting.

The accuracy of MedWatch reporting has not been cited as a major limitation, yet this aspect of quality has profound implications for all stakeholders. Inaccurate adverse event reporting, for example, may lead drug safety professionals to draw incorrect conclusions and to make the wrong decisions. Manufacturers may be wrongly forced to suspend and withdraw medications and interventions. Health professionals may mistakenly alter their clinical practices, and patients may be denied safe and effective treatments. To our knowledge, a systematic evaluation of MedWatch reporting accuracy has never before been conducted.

To address these critical needs, in May and June 2011, Tufts Center for the Study of Drug Development (CSDD) conducted an evaluation of the MedWatch database to assess the completeness and accuracy of adverse event reporting data. It is our hope that the results of this initial analysis will prompt further inquiry and will inform the FDA of improvement opportunities in our national system of volunteer postmarketing surveillance.

MATERIALS AND METHODS

Tufts CSDD analyzed all adverse event report records files with MedWatch using forms 3500 (sections D1,

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Table 1. Completeness of MedWatch information about the patient.

Information reported	Field type	Corresponding field on the MedWatch report	Percentage complete	N
Patient age	Open—numeric	A1	75	10,242,977
Patient gender	Fixed choice	A3	96	10,242,977
Patient weight	Open—numeric	A4	47	10,242,977
Adverse event outcome	Fixed choice	B2	88	10,242,977
Date of event	Numeric	B3	82	10,242,977
Date event reported	Numeric	B4	100	10,242,977

D2, and D3) and 3500A (sections C1, C2, and C3) between January 2005 and December 2010. In total, >10.2 million adverse event reports were analyzed.

Variables about the patient—their age, gender, weight, adverse event outcome, dates event observed and reported—correspond with MedWatch form 3500/3500A fields A1, A3, A4, B2, B3, and B4 respectively. Variables about the suspect product—product name, dosage amount, start and end date of use, product lot number and expiration date—correspond with MedWatch form 3500/3500A fields D1, D2, D3, D6, and D7, respectively. Tables 1 and 2 present the variables evaluated for their completeness.

To evaluate the accuracy of the data reported, Tufts CSDD developed simple accuracy tests for each variable. Each test assessed the reasonableness of the data value reported given that the true accuracy could not be determined. As such, tests of accuracy were not rigid. Patient age, for example, was reasonable if it fell below 110 years. The date of the observed event, as another example, had to occur after the patient was born and before the adverse event was reported to MedWatch. In all, 7 data variables were evaluated for their accuracy using this method to assess their reasonableness: Patient age, patient weight, date adverse event observed, product name, start date of use of the product, date use of the product was discontinued, and product expiration data. Table 3 provides a description of the test conducted to assess the accuracy of each variable.

Tufts CSDD performed χ^2-square tests to determine whether certain independent variables—molecule size (eg, chemical vs. large molecule biologics); therapeutic area; and drug delivery forms—were associated with the accuracy of adverse event data reported. Tufts CSDD also evaluated whether completeness and accuracy improved the closer the report was filed to the date when the adverse event was observed. Specifically, this analysis assessed whether reports filed closer to the date when the adverse event was observed are generally more complete and accurate than are those reports filed after more time has elapsed.

RESULTS

Tufts CSDD observed wide variation in the level of completeness of MedWatch data reported. Overall, as indicated in Tables 1 and 2, the patient information provided on forms 3500 and 3500A was generally more complete than data reported on the suspect product. Form 3500/3500A fields containing the date

Table 2. Completeness of MedWatch information about the treatment (suspect product).

Information reported	Field type	Corresponding field on the MedWatch report	Percentage complete	N
Drug/product name	Open text	D1	100	10,242,977
Dosage	Open text or numeric	D2	31	10,242,977
Start date of use	Open—numeric	D3	37	10,242,977
End date of use	Open—numeric	D3	23	10,242,977
Lot number	Open—numeric	D6	9	10,242,977
Product expiration date	Open—numeric	D7	1	10,242,977

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Table 3. Accuracy tests of select MedWatch data.

	Test definition	Percentage accurate	N
Patient information			
Patient age	Born within past 110 yrs	100	7,711,437
Patient weight	Reasonable weight (>50 lbs) for adult age patients	100	2,744,782
Date of event	Date reported proceeds patient birth data and precedes report date	87	8,380,331
Suspect product information			
Drug/product name	Name checked with internal MedWatch list of names	74	10,242,974
Start date of use	Date proceeds patient birth date; precedes end date of use	69	3,785,717
End date of use	Date proceeds patient birth date and start date of use	94	2,317,024
Expiration data	Reasonable calendar month and day	99	142,378

the adverse event was reported and the product/drug name were 100% complete. Patient gender, adverse event outcome, the date the event was observed and the patient age had relatively high completion rates, ranging between 75% and 96% complete.

Product lot numbers were rarely reported, with only a 9% completion rate for the 10.2 million records evaluated. Only 1% of forms 3500 and 3500A contained product expiration information. Approximately one-third of all adverse event reports contained start date of suspect product use (37% completion rate); dosage level (31% completion rate) and end date of suspect product use (23% completion rate). Tables 1 and 2 provide completion rates for all variables analyzed.

Patient information reported to MedWatch also tended to contain more accurate information (Table 3) than that reported on suspect products. Patient age and weight were 100% accurate according to the tests performed. More than 25% of the names of suspect products reported were inaccurate, and approximately one-third (31%) of start dates of suspect product use were inaccurate. For example, Tufts CSDD found 868 different spellings of the common drug Tylenol (Johnson & Johnson, Fort Wayne, PA), and 747 spellings of its generic equivalent acetominophen. More than 200 different spellings were found for the drug Lipitor (Pfizer, Manhattan, NY); 240 spelling variations were found for the drug Allegra (Sanofi, Bridgewater, NJ). Approximately 1 in every 8 adverse event reports filed with the MedWatch system contained inaccurate dates for when the event was observed.

Reports filed on the MedWatch system within the first 90 days of observing an event had more complete adverse event outcome fields and more accurate start and end dates of suspect product use ($P < 0.0001$). Figure 1 shows the decline in accuracy as the time between the observed adverse event and the reporting of that event increased.

DISCUSSION

This study evaluated a very large data set of 10,242,977 adverse event reports filed on the MedWatch system between January 2005 and December 2010. Our analysis demonstrates varying levels of completeness and accuracy of the MedWatch reporting system and points to areas for more in-depth inquiry and opportunities to improve the system. In general, patient

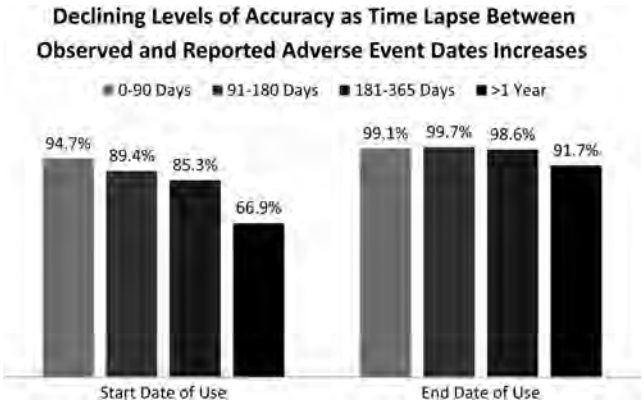

FIGURE 1. Declining levels of accuracy as time lapse between observed and reported adverse event dates increases.

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information reported on forms 3500 and 3500A tends to be more complete and accurate than the suspect product information. As such, FDA may require manufacturers to respond to adverse event reports based on incomplete and mistaken data.

The very low levels of completeness of suspect product information—in particular, dosage levels, start and end dates of use, lot numbers, and product expiration dates—are troublesome. These variables are essential to correctly identifying products that are the root cause of adverse patient reactions. Steps to improve the completion rate of this information on forms 3500 and 3500A might include awareness raising communications and web-based rules requiring field completion before allowing the individual to continue filling out the report.

Similarly, low levels of accuracy in the product name, start date of use and date of the observed adverse event may lead drug safety professionals, manufacturers, and health professionals to draw the wrong conclusions and to make incorrect decisions regarding product use and availability. Raising awareness via communication initiatives and training on the importance of the accuracy of this specific information may help improve the situation. Online validation of certain data fields, in terms of their accuracy, will also improve overall accuracy rates.

The FDA is currently upgrading the MedWatch system among its many information technology enhancement initiatives. Some of the suggested improvements proposed in the FDA's MedWatch Plus plans will help address areas of low completion and accuracy through improved data entry authentication and more rapid and interactive computing.

The recency effect found in this initial study suggests the need for FDA to encourage professionals to file adverse event reports on the MedWatch system as close to the observed date of the adverse event as possible. Communication initiatives and general awareness building of the recency effect in professional journals and in educational programs may help in this regard.

As noted earlier, a major limitation of this study is its working definition of reported data accuracy. Simple tests were performed to assess the reasonableness of the numerical values reported in the absence of actual data (eg, actual patient age, gender, and weight; actual dosage level; actual lot numbers; and dates of use). Even under these simple tests, high levels of inaccuracy were observed. Future studies might gather actual adverse event data to compare against that reported to better assess accuracy. CSDD plans to conduct more in-depth analysis of factors associated with completeness and accuracy levels.

The results of this initial study may provide constructive feedback on ways in which the MedWatch system can be improved to enhance its accuracy and utility. As the number of commercially available medicines increases—a growing proportion of them biologics, more complex therapies, and combination treatments—it is essential that the MedWatch system improve its level of completeness and accuracy to better protect public health and to provide timely and accurate information to health professionals, regulators, manufacturers, drug safety analysts, and policy makers.

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FROM THE ANALYST'S COUCH

Biosimilar competition: lessons from Europe

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Since 2005, the European Union has had a regulatory pathway through which biosimilars are approved centrally by the European Medicines Agency (EMA), as with pioneer biologics. So far, biosimilars have been approved in four separate classes: somatropins, erythropoiesis-stimulating agents (ESAs), granulocyte colony-stimulating factors (G-CSFs) and, most recently, monoclonal antibodies that are specific for tumour necrosis factor (TNF). In 2009, the US Food and Drug Administration (FDA) was given the authority to introduce a pathway for the approval of biosimilars, and draft guidance has been released; however, the pathway is not yet finalized and its potential impact on the uptake and price of biosimilars in the United States remains unclear.

Here, with the aim of understanding more about the likely future uptake of biosimilars in Europe and the United States, we analyse experiences in Europe with biosimilar products referenced to the ESA Eprex (epoetin alfa) and the G-CSF Neupogen (filgrastim) in five countries — Germany, the United Kingdom, Sweden, France and Italy — using audit data from IMS (FIG. 1). These biologics have been major products globally and so could provide a useful indication of the development of the markets for other major products for which patent protection is anticipated to expire in the next decade.

Analysis of market experience

Characteristics of the biosimilar products analysed. Erythropoietin (EPO) is a naturally occurring glycoprotein that controls erythropoiesis (red blood cell production) to treat anaemia in patients undergoing dialysis and in patients with cancer, and G-CSF is a hormone that stimulates the production of white blood cells as a treatment for neutropenia. Recombinant products are available for these natural substances in both original (Eprex and Neupogen) and longer-lasting forms (Aranesp and Neulasta), but the biosimilars approved so far are referenced only to Eprex and Neupogen. There are currently five biosimilar products approved in Europe that reference Eprex (the first of which was approved in 2007) and six biosimilar products that reference Neupogen (the first of which was approved in 2008). Entry occurred at a faster rate in the case of biosimilars referencing Neupogen. By the end of 2011, the five countries had between three and five filgrastim biosimilars available. By contrast, except for Germany (where all five ▸

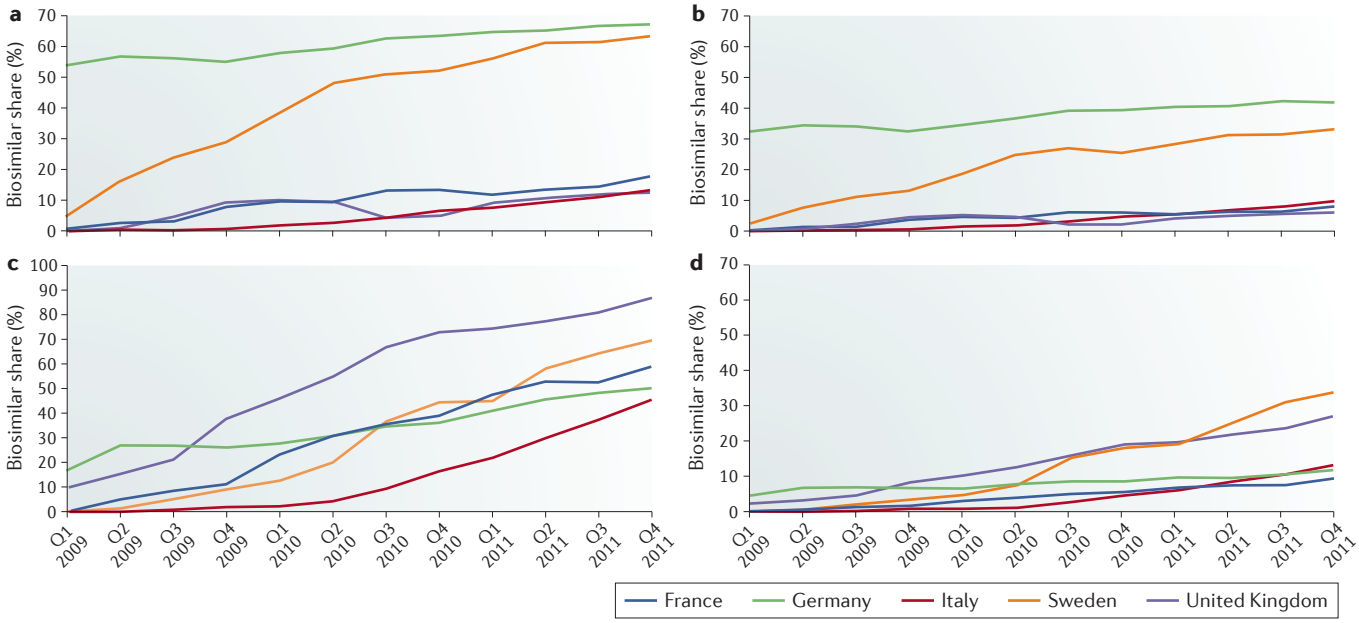

Figure 1 | **Market share for biosimilars in Europe (2009–2011).** Panel **a** shows the biosimilar share of the epoetin (Eprex) market segment, and panel **b** shows the expanded erythropoiesis-stimulating agent (ESA) market segment (also including darbopoetin alfa (Aranesp)), calculated based on daily doses. The biosimilar products are Retacrit and Binocrit in France; Epoetin Alfa Hexal, Silapo, Abseamed, Retacrit and Binocrit in Germany; Abseamed, Retacrit and Binocrit in Italy; Retacrit and Binocrit in Sweden; and Retacrit and Binocrit in the United Kingdom. Panel **c** shows the biosimilar share of the filgrastim (Neupogen) market segment, and panel **d** shows the expanded granulocyte colony-stimulating factor (G-GCSF) market segment (also including pegfilgrastim (Neulasta)), calculated based on daily doses. The biosimilar products are Zarzio, Tevagrastim, Ratiograstim and Nivestim in France; Filgrastim-Hexal, Ratiograstim, Biograstim and Nivestim in Germany; Zarzio, Tevagrastim, Ratiograstim and Nivestim in Italy; Ratiograstim and Nivestim in Sweden; and Zarzio, Ratiograstim, Nivestim, Filgrastim Teva, Tevagrastim and Filgrastim Sandoz in the United Kingdom. Source: IMS MIDAS.

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biosimilars referencing Eprex were available by early 2009), the other countries had only one to three epoetin biosimilars on the market over the 2009–2011 sample period (Supplementary information S1 (box); section 1).

Characteristics of the countries analysed. Of all the countries analysed, Germany has provided the most favourable incentives for biosimilars. In addition to a reference pricing system in place for biosimilars, Germany has specific targets or quotas for physician and sickness funds for biosimilars that vary by region (Supplementary information S1 (box); section 1). Of the other countries included in our sample, Sweden and the United Kingdom have a history of encouraging generic competition for small-molecule drugs through physician and reimbursement incentives. By contrast, France and Italy have centralized price regulation and budgetary controls, with relatively low rates of generic competition historically. However, these are large markets for biological products, so they also could be attractive markets for biosimilar producers. In contrast to the FDA, the EMA does not evaluate interchangeability, and questions of substitutability at the pharmacy level are left to member states. At this point, none of the member states allows substitution for biosimilar products.

Market experiences for biosimilars. FIGURE 1a shows the market share in units (defined daily doses; DDDs) for the biosimilars referenced to Eprex in the five European countries. The basic data source is IMS quarterly data over the 2009–2011 period with standard units converted to DDDs using information from the WHO (World Health Organization) on the DDD for each product (Supplementary information S1 (box); section 2). Biosimilars referenced to Eprex in Germany and Sweden have a market share in excess of over 60% by the fourth quarter in 2011 (FIG. 1a), whereas the other three countries have epoetin biosimilar shares of less than 20%. Shares in terms of US dollars exhibit similar outcomes across these countries (Supplementary information S1 (box); section 3).

Biosimilars referenced to Neupogen in the G-CSF market exhibit a very different pattern. In particular, there is a more rapid and extensive market penetration for biosimilars than in the case of Eprex. This is shown in FIG. 1c. Biosimilars attained shares of between 45% (Italy) and 87% (the United Kingdom) by the end of 2011. This greater acceptance of filgrastim biosimilars in the G-CSF market appears to reflect both medical considerations and reimbursement policies (Supplementary information S1 (box); section 3).

A preliminary analysis of pricing behaviour indicates that biosimilar discounts are typically less than 25%. This is generally consistent with published surveys and reimbursement information for selected European countries (Supplementary information S1 (box); section 3.) Our analysis of the pricing of biosimilars is qualified by the fact that some markets have substantial rebates to providers for both the reference product and biosimilar counterparts that are not captured in IMS data audits of invoices.

In FIG. 1b and FIG. 1d, we consider the biosimilar share of the market segment comprising both the first- and second-generation recombinant products in the overall ESA market (Eprex and Aranesp) and for the G-CSF market (Neupogen and Neulasta). The second-generation products require substantially fewer infusions over a course of treatment with potential benefits to patients and lower costs of administration. In both categories, they were introduced prior to biosimilar entry. As shown in FIG. 1b and FIG. 1d, there are substantially smaller shares in terms of this broader market segment when compared to FIG. 1a and FIG. 1c. This reflects the fact that the second-generation products have the largest overall share in most countries. In the case of the G-CSFs in particular, Neulasta had shares between 50% and 80% of this market across the five countries in the fourth quarter of 2011 (Supplementary information S1 (box); section 3).

Lessons from the European experience

One major finding is that the competitive performance of the biosimilars we analysed in Europe is mixed both across countries and products. Although the European Union has a common regulatory system for approving biosimilars, differences in reimbursement practices and incentives as well as variations in medical practices have resulted in different outcomes across countries. It is difficult to generalize across different health-care systems, but Germany and Sweden arguably provide the closest cases to the United States. Both countries have relatively high prices for innovative drug products, a history of generic utilization and a decentralized approach to drug utilization and reimbursement. This suggests that biosimilars could achieve significant shares relative to their referenced products in the United States after a transition period. At the same time, biosimilar price discounts are likely to be modest compared to generics, reflecting much greater costs of development, fewer competitors and the absence of interchangeability for the foreseeable future.

A second major finding is that cost savings from the introduction of biosimilars in the European countries analysed have been tempered by the fact that competition has been limited to the first-generation reference products in the ESA and G-CSF classes, whereas the longer-lasting second-generation versions have generally maintained leading shares in these categories. Dynamic competition through the market entry of next-generation biologics is an important consideration in analysing the market impact of biosimilars and their potential savings to the health-care system. Many of the more complex monoclonal antibody biologics, which recently experienced their first EU biosimilar approval (for the TNF antagonist infliximab), also have next-generation products under development or regulatory submission (Supplementary information S1 (box); section 4) .

Even if biosimilars gain a substantial share of sales from their referenced products, their share of overall patient treatments may be limited in the face of incremental quality advances if physicians and patients opt for next-generation products. Furthermore, many of the new firms entering the biological space appear to be focused on 'biobetters' rather than biosimilars in the recognition of these dynamic developments. It remains to be seen how competition will evolve for the more complex biological products with patent expirations as well as biosimilars and biobetters on the horizon in the case of the European and US markets.

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Competing interests statement
The authors declare competing interests: see Web version for details.

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The Effect on Federal Spending of Legislation Creating a Regulatory Framework for Follow-on Biologics: Key Issues and Assumptions

White Paper

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Executive Summary

Legislative proposals to create an expedited pathway for review of follow-on biologic drugs ("FOBs"; also called biosimilars) have generated much debate about potential cost savings, with estimates of federal budget savings over ten years of $3.6 to $14.1 billion.

This very broad range reflects substantial uncertainty about a number of critical assumptions underlying such forecasts, and policymakers should therefore proceed cautiously in assessing the potential impacts of legislation establishing an expedited pathway for FOBs.

Direct empirical evidence of rates of market share uptake and price effects due to FOBs is limited to a few recent approvals in Europe. This paper reviews currently available data on the factors that will drive pricing and utilization of FOB products and provides an economics-based perspective on these questions. In addition to data from that limited European experience, we also draw on lessons from the U.S. experience with: generic drug competition with complex small molecule products that display some key economic similarities to biologics; branded competition between products in the human growth hormone market; and market performance and competition between first generation and next-generation products in the erythropoietin stimulating agent and granulocyte-colony stimulating factor product markets.

We conclude that:

- The magnitude of the federal budgetary impact of proposed legislation is highly uncertain, as is the speed with which cost savings will be realized.
- Estimates of federal savings are very sensitive not only to the specific legislative language that emerges, but also to a range of critical assumptions about scientific, regulatory, and clinical issues, the nature of competition in markets for specific biologics, as well as future intellectual property protection, and related litigation and the development of case law.
- All of these factors are highly uncertain, and any one of them could have a substantial impact on the magnitude of potential federal savings and the speed with which they are realized.
- As a result, best available evidence and straightforward economic analysis indicates that cost savings are likely to lie at or below the lower end of the range of estimates currently before Congress.

Aggregate cost savings will reflect the impact of an expedited approval process on both prices and utilization of each affected reference biologic product. While there is considerable heterogeneity among these innovator biologics, a number of critical factors can be identified that will drive these market outcomes:

- The timing of patent expiry for these products, the nature of their intellectual property protection (more complex and more uncertain than for traditional small molecule drugs), and the associated litigation and emerging case law (assumed to permit FOB entry by

2013 to 2017 for the largest categories of federal spending on biologics approved under the Public Health Service Act)

- The time required to develop an FDA regulatory scheme, testing requirements, or product-class guidelines following passage of any legislation (two to six years, varying by therapeutic area and on the regulatory guidance approach selected by FDA)
- The time required for manufacturers to obtain regulatory approval (three to five years for pre-clinical and clinical testing, and one-and-a-half to two years for FDA review and approval) and to bring manufacturing capacity on-line (four to six years, likely developed concurrently with product development schedule)
- The evolution of utilization of currently approved biologics, driven by:
  - Demographics, disease incidence, medical practice, and regulatory and reimbursement practice
  - The pace and extent of uptake of next generation patent-protected products in markets where FOBs have entered (limiting longer-term uptake of FOBs in markets with unmet medical need)
- The nature of the competitive model in markets for biologics that experience entry by FOBs (likely to be driven by the marketing of branded, proprietary products rather than the "commodity" competition based on price alone seen among generic small molecule generic drugs), and its effect on:
  - The pace and extent of uptake of follow-on products for currently marketed branded products (likely slower and less extensive than for many small-molecule drugs, or 10 to 45% FOB share)
  - The price impact of entry by follow-on products (limited discounts of 10 to 30% off brand)

Because shorter-term budgetary savings must be balanced against longer-term interests in protecting innovation incentives in the biotech industry, we urge a cautious approach in developing and implementing a legislative framework for an expedited approval pathway for follow-on biologics. Just as the Hatch-Waxman Act fundamentally reshaped competition, pricing, and innovation for "conventional" small molecule drugs in 1984, Congressional action on a regulatory framework for follow-on biologics will have far-reaching implications, resetting the competitive and market landscape in the dynamic biotechnology industry for years to come. These changes have the potential to result in significant long-term economic realignment in the biotech and pharmaceutical industries.

Though outcomes are highly uncertain, budget savings are likely to be much smaller than suggested by some advocates. Therefore, we also urge a cautious approach in interpreting estimates of the federal budgetary impact of any regulatory framework for expedited review and approval of follow-on biologics.

1. Introduction and Context

In 1984, the Hatch-Waxman Act created a legislative framework for the expedited approval by the FDA of generic versions of drugs regulated under the Food, Drug and Cosmetic Act of 1938 ("FD&C Act"), greatly facilitating generic drug approvals and contributing to the tremendous growth of the generic drug industry. This expedited approval process does not extend to biologics approved under the Public Health Service Act ("PHS Act biologics"), where there is no such legislative authority. Several legislative proposals under consideration currently would establish an expedited pathway for the approval of follow-on biologics ("FOBs") for PHS Act biologics.[1]

There has been much debate about the likely impact on the federal budget of these or similar proposals, with estimates ranging from total federal savings over a standard ten-year scoring period of $3.6 billion (Avalere Health) to $14.1 billion (Engel & Novitt). Representatives from Express Scripts presented an estimate of $71 billion for savings to all payers, private and public.[2] Earlier estimates by Express Scripts and Engel & Novitt did not distinguish between the two types of biologics (FD&C Act biologics, which would be unaffected by the proposed legislation, and PHS Act biologics), and did not take into consideration the delay associated with new regulatory action required, intellectual property protection for on-market biologics, or the likely timing of market entry, and therefore overestimated the likely savings during the next ten years due to the legislative proposals under consideration. The later estimate by Avalere Health took these factors into consideration, and as a result arrived at a significantly lower figure.

The wide range of these estimates reflects substantial uncertainty about key assumptions and parameter values that underlie any such forecast, suggesting that policymakers should be cautious in assessing the potential impacts of legislation that establishes an expedited pathway for FOBs. The objective of this paper is to provide additional insight and perspective to policy-makers that can be used in assessing the impact on federal spending of such legislation, specifically by reviewing and summarizing the best available empirical evidence for key assumptions in an appropriate economic framework. While we do not compute a specific estimate of the budgetary impact of such legislation, this review strongly suggests that it is likely to fall in the low end of the current range of estimates presented to Congress.

In this paper we summarize the best available evidence for each of the assumptions required to estimate the budgetary impact of an expedited pathway for approval of FOBs, focusing

[1] H.R. 6257/S. 4016, H.R. 1956, S. 1505, H.R. 1038, S. 623.

[2] A Ahlstrom, R King, R Brown, J Glaudemans, D Mendelson, "Modeling Federal Cost Savings from Follow-on Biologics," Avalere Health LLC, April 2007; Engel & Novitt, LLP, "Potential Savings That Might Be Realized by the Medicare Program from Enactment of Legislation Such As The Access to Life-Saving Medicine Act (H.R. 6257/S. 4016) That Establishes a New cBLA Pathway for Follow-on Biologics,' Pharmaceutical Care Management Associates, January 2007; S Miller and J Houts, "Potential Savings of Biogenerics in the United States," Express Scripts (February 2007).

particularly on possible rates of uptake of FOBs for corresponding innovator branded biologics, as this key assumption has received less attention to-date. Estimates of federal savings are very sensitive not only to the specific legislative language that emerges, but also to a number of scientific, regulatory, clinical, market behavior, intellectual property protection, and litigation-related assumptions, all of which are uncertain, and any one of which could have a substantial impact on both the timing and magnitude of potential federal savings.

Direct empirical market evidence of share and price effects due to FOBs is limited. There are two recent examples in Europe, where two human growth hormone follow-on products have been approved, Sandoz's Omnitrope and Biopartner's Valtropin. Initial uptake has been limited, with Omnitrope accounting for only roughly a 1% share of the market thus far.[3,4] To supplement this evidence of the effects of expedited FOB entry in Europe, we review empirical evidence and market results from situations with some analogous characteristics in the U.S. that provide indirect evidence for key estimation parameters:

- Generic entry and price-based competition in the case of more complex small molecule drugs that exhibit some features that suggest they are closer to biologics than are other drugs; and

- Branded competition in the human growth hormone market.

Beyond these examples, we also examine market performance and competition by next-generation products in the erythropoetin stimulating agent ("ESA")[5] and granulocyte-colony stimulating factor ("G-CSF") markets in order to review potential longer-run implications for FOB products which will compete both against their first generation reference products, and against successive generations of products which may offer additional clinical, patient convenience, or economic benefits. We use the term "biosimilar competition" in this paper to refer to the competition between an FOB product and its reference biologic, as distinguished from competition between both of these products (i.e., an FOB product and its reference product) and future entrants which may offer additional features and benefits.

For conventional drugs with more complex characteristics we find that rates of generic uptake and generic to brand price ratios were significantly lower than for non-complex generics. These figures were generally on the order of 60% of the corresponding indicators for non-complex drugs, measured twelve months after generic entry, or a mean generic share of 45% measured

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[3] Market share as reported in A Ahlstrom, R King, R Brown, J Glaudemans, D Mendelson, "Modeling Federal Cost Savings from Follow-on Biologics," Avalere Health LLC, June 2007.

[4] '"Sales are developing with a slow uptake… there needs to be a lot of education and training for doctors and patients," says a Sandoz spokesperson.' G. Kamath, "Sticker shock: Biotech copycats are discovering the real cost of going West. And it is not cheap." http://www.businessworld.in/content/view/1394/1451/ (most recently accessed June 19, 2007).

[5] We use the term "ESA" in this paper to refer to both epoetin alfa and darbepoetin alfa products. Elsewhere these products are also commonly referred to separately as EPO, for epoetin alfa products, and DARB, for darbepoetin alfa products.

one year after generic entry (the lowest figure was only 9% for the most complex drug in the sample). This should be viewed as an upper bound estimate for the potential share impact of FOB entry for two reasons: even more complex conventional drugs may not be as complex as biologics; and because generic entrants face a more favorable set of economic incentives for uptake due to their ratings of therapeutic interchangeability (generally an AB rating) and their distribution through retail pharmacies.

For human growth hormones, we find the branded competition model employed is associated with essentially no change in average Medicaid reimbursement per prescription measures over the fifteen-year period 1991-2006.[6]

For erythropoetin and granulocyte-colony stimulating factor, we observe that dynamic competition in the form of next-generation products has a significant impact on the sales of first generation products, which have been flat over the 2000-2006 period.

This paper reviews the likely universe of projected federal expenditures on PHS Act biologics over the next ten years (the "baseline"), applying to it a framework that incorporates the following key parameters:

- Timing considerations:
  - Time required for development and promulgation of an FDA regulatory scheme following passage of any legislation
  - Timing of patent expiry and the impact of intellectual property protections
  - Timing of FOB market entry
- FOB uptake and average price effects:
  - Degree of FOB uptake and market share
  - Extent of average price effects generated by FOB entry.

With regard to timing, the first U.S. FOB entry is likely to follow the passage of legislation (assumed to be effective in 2008) by a number of years, due to: delays in developing regulations and resolving scientific issues; the expiration of complex intellectual property protection for innovator biologics; the development and regulatory approval times for FOBs, dependent on FDA requirements for establishing similarity, safety and efficacy through pre-clinical testing and clinical trials; and the need to build, license or secure manufacturing capacity. While a number of these developments will proceed in tandem, nevertheless it will likely be a number of years before significant FOB entry is likely to occur. In particular, FOB entry is problematic prior to 2013 for two of the largest categories of federal PHS Act spending (ESAs and G-CSF) due to intellectual property protections.

[6] Tev-Tropin has adopted a price-based competitive strategy with significant reductions below other products; over two years post-launch it has failed to capture more than one percent of the market. As a result of its small share, Tev-Tropin has had virtually no effect on the average level of Medicaid reimbursements per prescription for human growth hormone products.

The extent of entry will likely be much lower for FOBs than for conventional generic drugs, reflecting differences in market size and high fixed costs of entry for many biologics. Average price effects and rates of FOB uptake for innovator products are likely to be limited in the short run due to the low number and timing of entry of FOBs, limitations to perceived substitutability between innovator biologics and FOBs on the part of physicians and patients, incentives for limited price-based competition between FOBs and innovator products, and the lack of structural features of the distribution system that currently limit the rapid diffusion of generic drugs. Given the history of rapid advances for biological products, over the longer-term, dynamic competition with patent-protected next generation protein products is expected to be a more significant force than biosimilar competition between FOBs and existing original innovator products in the therapeutic areas with significant unmet medical need. Next generation biologics are expected to bring valued clinical, patient convenience, or economic benefits to the market, but will reduce the market for the first generation products that FOBs substitute for, limiting federal savings.

While a product-by-product assessment of savings is most appropriate because federal spending is concentrated on a relatively small number of products, and there are varying circumstances in each market, an aggregate view of savings is consistent with the approach used by the Congressional Budget Office ("CBO") and is adopted here. In order to populate this aggregate view with an appropriate set of assumptions, it is necessary to:

(1) project federal spending on PHS Act biologics over the bill scoring time frame, by year

(2) appropriately netting out growth due to dynamic competition over time in the form of new-branded entrants with additional features and benefits that will reduce the market for the reference innovator biologic and the associated FOB

(3) identify the likely timing of FOB entry following passage of the bill, given regulatory, intellectual property/patent, and product development and application delays

(4) identify the average price discounts that might be expected from an FOB entrant, and

(5) determine what share of the reference innovator biologics the FOB is likely to capture

These considerations can be reflected in an equation of the following form:

$$Federal\ Savings = \sum_{t=2008}^{2017} \sum_{i \in all\ products} Future\ Federal\ Spending\ on\ PHS\ biologic_{it} \times FOB\ Entry_{it} \times FOB\ Discount_{it} \times FOB\ Share_{it}$$

Where *Future Federal Spending on PHS biologic* is the projected federal spending on product *i* (a PHS Act biologic) in year *t*, appropriately netting out growth due to dynamic competition over time in the form of new-branded entrants with additional features and benefits that will reduce the market for the reference innovator biologic; *FOB Entry* is equal to 1 if there is at least one FOB entrant for product *i* in year *t* and zero otherwise; *FOB Discount* is the average price discount offered by FOB entrants for product *i* in year *t*; and *FOB Share* is the total FOB share of the reference innovator biologic product *i* that the FOB captures in year *t*.

There is considerable uncertainty surrounding these critical parameters. Federal savings from an expedited approval pathway for FOBs are therefore difficult to assess with any precision. We do not present a specific dollar estimate of likely federal budgetary savings over the next ten years, but, based on our review of the best available empirical evidence, we conclude that savings are likely to be significantly limited by delays in FOB entry, modest expected FOB price discounts, and limited FOB shares of the relevant markets. Over the longer run, dynamic competition with successive generations of branded products which may offer additional clinical, patient convenience, or economic benefits in therapeutic categories with unmet need will reduce the share of the market subject to FOB uptake.

These considerations suggest that federal budgetary savings over a ten year standard scoring period are likely to be limited, falling at or below the lower end of the range of estimates presented to Congress. In addition, given that careful consideration should be given not only to short-term budget savings but also to the appropriate balance between these benefits from enhanced price competition and longer-term interests in protecting innovation incentives in the biotech industry, caution is therefore warranted in both developing and implementing a legislative framework for an expedited approval pathway for FOBs.

SUMMARY OF KEY PARAMETERS AFFECTING THE LEVEL OF FEDERAL SAVINGS DUE TO FOBs		
Key Parameter	***Estimate***	***Estimate Based On:***
(1) Future Federal Spending On PHS Act Biologics		
- 2005 Federal Spending on PHS Act biologics	2005 Medicare Part B on PHS Act biologics: $4.3 billion 2005 ESRD program spending on ESAs:$2.0 billion	• 2005 Medicare Part B spending for PHS Act biologics among top 200 HCPCs (approximately 85% of biologics spending was for PHS Act biologics) • GAO report of ESRD spending on ESAs
- Annual Increases in Spending (Taking effects of competition with next generation products into consideration)	0% to 10% average annual increase in spending on first generation top biologics in Part B program from 2003 to 2005 Competition from next-generation entrants may limit growth of first-generation biologics (the likely targets of FOB entry)	• Average annual increase 2003-05 for older generation Part B biologics (13% decrease for ESAs and 15% increase for G-CSF)
(2) Time to first FOB Entry	2013 or later	
- Establish FDA Testing Requirements or Guidelines	2 to 6 years *May vary by therapeutic area and depends on regulatory guidance approach selected by FDA*	• Hatch-Waxman and EMEA experience • Some generics approved prior to issuance of final Hatch-Waxman regulations • Potential for moratorium to allow time for FDA to develop product-class guidances or testing requirements
- Patent Expiration	2013 to 2017 for the largest categories of federal PHS Act biologic spending	• Reported ESA and G-CSF patent expirations
- Drug Development/ Approval	3 to 5 years for pre-clinical and clinical testing 1.5 to 2 years for FDA	• Estimated development times in EMEA • 4 to 6 years required for new owned manufacturing capacity (likely developed

	application review and approval *Likely to require additional FDA resources and/or organizational realignment*	concurrently with product development schedule) • Historical BLA approval times (18 months) and EMEA approval times for FOBs (2 years) • Phase III average duration of 33 months, average approval phase time of 16 months for a sample of biologics (innovator study duration would be an upper bound for FOB required phase III studies)
(3) FOB Price Discount	10% to 30% off brand	• Analysis of hGH • Analysis of complex conventional generics • Reported Omnitrope pricing
(4) FOB Share * - Short-Term FOB Share of Reference Biologic - Longer-Term Dynamic Competition and Entry of Next-Generation Products	10% to 45% Limits FOB Market Potential	• Analysis of hGH • Analysis of complex conventional generics • Aranesp captured 11% of the ESA market within a year and 40% within four years; Neulasta captured 50% of the G-CSF market within a year and 70% within four years

* The share for FOB entrants is measured as the share of prescriptions of the reference biologic achieved by the FOB.

2. Outline of this Document

The remainder of this document is organized as follows:

- Section 3 provides a brief summary of the U.S. regulation of biologics and the relevant regulatory context for the expedited approval of follow-on biologics
- Section 4 discusses a range of estimates of projected baseline federal expenditures on PHS Act biologics over the next ten years
- Section 5 outlines factors affecting the possible timing of FOB entry
- Section 6 identifies characteristics affecting price discounts generated by FOB entry, and the degree of FOB penetration and market share
- Section 7 describes empirical analyses undertaken to estimate the extent of price discounts and FOB penetration, including analyses based on small molecule generic entry and analysis based on biologic entry in selected therapeutic areas
- Section 8 summarizes our conclusions
- Appendix A contains a table of new biopharmaceutical products approved between 1980 and 2005, with the regulatory process noted (whether approved under the PHS or FD&C Act)

3. Background: U.S. Regulation of Biologics

A. STATUTORY FRAMEWORKS FOR DRUGS AND BIOLOGICAL PRODUCTS

Currently, there are two different regulatory paths to market for biologics. While the PHS Act clearly covers certain products specifically enumerated such as blood products and vaccines, manufacturers of other biologics may have applied for market entry under the FD&C Act (under which drugs are regulated). For example, human growth hormone ("hGH"), insulin, menotropin hormone, conjugated estrogen, urokinase enzyme, and enzymes used to treat Gaucher's disease were all approved under the FD&C Act. These products would be unaffected by the proposed legislation, which would apply to PHS Act biologics only. PHS Act biologics include epoeitin stimulating agents ("ESA") Epogen, Procrit and Aranesp (for anemia related to cancer therapy or chronic kidney disease), granulocyte stimulating factors ("G-CSF") such as Neupogen and Neulasta (for inadequate white blood cell production due to cancer or other causes), interferons, and monoclonal antibodies such as Herceptin (for cancer), Enbrel, Remicade and Humira (for rheumatoid arthritis and other immunological disorders).

Under the FD&C Act, new innovator drugs apply for market entry through the New Drug Application ("NDA") process under Section 505(b)(1).[7] In 1984, the Drug Price Competition and Patent Term Restoration Act (known informally as the Hatch-Waxman Act), established a well-defined abbreviated pathway for the approval of generic versions of existing innovator drugs approved under the FD&C Act for whom patents are not otherwise a bar to entry. Under Hatch-Waxman, the Abbreviated New Drug Application ("ANDA") approval process provides that generic applicants may rely on safety and efficacy data submitted by an innovator drug and need demonstrate only bioequivalence.

Manufacturers can in some cases also apply under an alternative abbreviated NDA pathway under Section 505(b)(2), in which the FDA can rely on data from an existing comparable product when considering a new application from the same or a different manufacturer. The FDA relied on this pathway in its recent approval of Sandoz's Omnitrope application, which had the effect of approving an additional, non-therapeutically equivalent (non AB-rated) branded agent. The FDA has narrowly circumscribed the conditions under which it would consider applications under the Section 505(b)(2) pathway to those proteins that are less complex and whose mechanisms are well understood and characterized.[8] This specification includes hGH products

[7] 21 U.S.C. 321 (g)(1) <http://www4.law.cornell.edu/uscode/21/321.html - accessed on July 6, 2007>. The FD&C Act defines drugs as: "(A) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man …" and/or "(B) articles (other than food) intended to affect the structure or any function of the body of man ….".

[8] Omnitrope (somnatropin [rDNA origin]) Questions and Answers. May 30, 2006 <http://www.fda.gov/cder/drug/infopage/somatropin/qa.htm - accessed March 30, 2007>.

and would encompass other more simple biologics with NDA approvals such as insulins, but likely rules out more complex biologics.

Under the PHS Act, biologics are approved for market entry through a Biologic License Application ("BLA").[9] The majority of biologics applied under the PHS Act. The PHS Act currently provides no abbreviated pathway for the approval process. Instead, all biologics under the PHS Act, including follow-on versions, must file a BLA and undertake all required efficacy and safety clinical trials for such approval. Current proposed legislation aims to create such an abbreviated pathway, and the potential effect of such a pathway for FOB approval of PHS Act biologics on federal spending is the focus of this paper, as well as other recent estimates.

B. DIFFERENCES BETWEEN DRUGS AND BIOLOGICS

In recent years, entry of bioequivalent generics for small molecule, chemically synthesized drugs, ("conventional drugs") has resulted in substantial generic penetration and average price effects for the molecules in question. Recent examples of generic entry for conventional drugs are unlikely to present an accurate prediction of what may occur should a legislative framework be established for expedited approval of FOBs, however, due to fundamental differences between the two types of compounds:

- Conventional drugs, small molecules produced through chemical synthesis, are typically synthetic organic compounds having well-defined structures and physical and chemical characteristics. Researchers can generally assume the products' activities based on the similarity of overall chemical structures to those of other compounds and can assess safety based on standard short- and long-term toxicology studies.

- In contrast, biologics are large molecule products, often proteins, sometimes with significant glycosylation (i.e., chains of sugar molecules attached), which are either composed of, or are extracted from, living organisms. As a result, they are heterogeneous mixtures. Macromolecular by nature, determining their physiochemical characteristics is far more complex, leading them to be less well defined. They are generally immunogenic (i.e., provoking an immune response and the formation of antibodies), but the associated clinical implications might range from negligible, to loss of effective response to the therapy over time, to serious and immediate clinical reaction. Toxicology studies may require novel approaches.[10]

These differences in turn lead to important differences in the economics of discovery, development, manufacturing, and distribution for drugs and biologics. Consequently, it is

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[9] 42 U.S.C. 262 (i) <http://www4.law.cornell.edu/uscode/42/262.html - accessed June 25, 2007>. Biologics are defined as "any virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product or analogous product applicable to the prevention, treatment, or cure of diseases or injuries in man."

[10] Biologics Development: A Regulatory Overview. Third Edition. Edited by Mark Mathieu. PAREXEL International Corporation. 2004. pp. 10-1.

necessary to take account of these unique attributes when assessing the impact of expedited FOB entry on federal spending.

These differing properties pose numerous challenges to approving follow-on biologic molecules for marketing, as well as to ensuring their safe and reliable manufacturing. Policy makers will undoubtedly consider first the implications these differences have for necessary safeguards to the public health, given the demonstrated risk with even small intra-firm variations in manufacturing processes.[11,12] Given the complexity of these molecules, the FDA will consider, in each instance, whether existing analytical tools are sufficient to determine whether two products are bioequivalent: "There are unique scientific issues associated with follow-on biologics (as opposed to generic small-molecule drugs), including how to ensure safety and efficacy, how to measure sameness, and immunogenicity of products. There are additional market and public policy implications for specific types of products, such as vaccines and blood products. At present, the science does not exist to adequately protect patient safety and ensure product efficacy through an abbreviated follow-on pathway for all biologic products, and questions exist whether some products, such as vaccines or blood products, would ever lend themselves to such a pathway"and elsewhere in the same letter from Secretary of Health and Human Services Michael Levitt to Senator Kennedy, "(t)here is a spectrum of scientific complexity for protein products, from relatively simple peptides to large proteins with highly complex structures. Scientific understanding and technology (e.g., available analytical techniques) does not currently support the approval of larger and more complex protein products under an abbreviated process such as section 505(j) of the FDCA."[13] Because the quality, safety, and potency of biologics can be very sensitive to changes in manufacturing conditions, the FDA will need to consider these factors. As Dr. Janet Woodcock (2007), Chief Medical Officer of the FDA, emphasizes, "Even well-characterized, highly purified recombinant proteins may exhibit minor degrees of structural variability from lot to lot resulting from variants in the manufacturing process. The quality and nature of natural source products can vary depending on the condition of the source material, processes used to extract and purify the product and other factors."[14] Woodcock provides several examples of the case-by-case approach that the FDA has used in the past when evaluating

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[11] In 2002, Johnson & Johnson (J&J) made a change to its Eprex erythropoietin manufacturing processes to eliminate the use of human serum albumin due to concern by health authorities about the potential transmission of Creutzfeldt-Jakob disease. While the resultant product did not exhibit any detected differences from J&J's original product some patients developed pure red blood cell aplasia, an immunologic response due to which red blood cells fail to develop. Patients' bodies rejected both natural and recombinant erythropoietin, the lack of which leads to failure to develop red blood cells. The suspected cause of the problem was a minor formulation change and potential reaction with rubber stoppers.

[12] Woodcock, J., *Follow-on Protein Products*, Statement before the Committee on Oversight and Government Reform, U.S. House of Representatives, March 26, 2007.

[13] Letter from Secretary of Health and Human Services Michael O. Leavitt to The Honorable Edward M. Kennedy, Chairman, Committee on Health, Education, Labor and Pensions, United States Senate, June 26, 2007.

[14] Ibid.

follow-on and second-generation biologics, and illustrates the reliance and challenges to scientific reasoning when extrapolating findings from one biologic product to a similar one.[15]

The markets for biologics also differ substantially from small molecule, chemically synthesized drugs. The size of typical biologic product markets, capital structure and the importance of venture capital for early stage development programs, the structure of distribution systems, and economic incentives for substituting follow-on products for innovator products all differ from conditions in small molecule markets. Together, these differences will likely result in FOBs having a less significant impact on market outcomes than has been observed in the case of generic drugs.

[15] Woodcock, J. "The FDA's Assessment of Follow-on Protein Products: A Historical Perspective," *Nature Reviews Drug Discovery*, 6: 437-442, June 2007.

4. Baseline Federal Expenditures on PHS Act Biologics

Key Assumptions: *Projected Federal Spending on PHS Act Biologics**	*Estimate Based On:*
• $4.3 billion in Part B PHS Act biologic spending in 2005	• 2005 Medicare Part B spending for PHS Act biologics among top 200 HCPCs (approximately 85% of biologics spending was for PHS Act biologics)
• $2.0 billion in ESRD spending on ESAs in 2005	• GAO report of ESRD spending on erythopoetin stimulating agents (ESAs)
• 0% to 10% annual increase in spending on first generation top biologics in Part B program	• Average annual increase 2003-05 for older generation Part B biologics (13% decrease for ESAs and 15% increase for G-CSF) • Spending growth on first generation products may be limited or negative due to dynamic competition with successive generations of new products

* Excludes Veterans Administration/Department of Defense purchases, federal portion of Medicaid program spending on PHS Act biologics.

A. CURRENT BASELINE: MEDICARE PART B FEDERAL SPENDING FOR PHS ACT BIOLOGICS

Total U.S. sales of biologics have been elsewhere estimated at $32 billion in 2005, whether funded by individual out-of-pocket, or federal, state and private third-party spending. This total includes spending on both FD&C Act and PHS Act biologics. Based on a review of allowable charges for the top 200 HCPCS codes, we estimate that approximately $5.0 billion of this total represented spending under the Part B program on biologics, $4.3 billion of which was for PHS

Act biologics, or approximately 85% of the total. This figure corresponds with other estimates of the portion of total spending on biologics associated with PHS Act biologics.[16] Another $2.0 billion was spent by the end stage renal disease ("ESRD") program on Epogen, Amgen's erythropoietin stimulating agent.[17,18] These figures represent the majority of federal spending, but exclude Veterans Administration/Department of Defense purchases, the federal portion of Medicaid program spending on PHS Act biologics, and Part D federal payments for self-injectable biologics. They also excludes PHS Act biologics with less than $20 million in 2005 Medicare Part B reimbursements; these smaller drugs are less likely to be targets of FOB entry due to their limited market size.

Care must be given in any calculation of savings to the federal budget not to "double count" savings already anticipated from other proposals. In this case, a change to the current ESRD reimbursement system in which payment for drugs such as Epogen are separately billed to one in which reimbursement would be bundled with all other ESRD services is also under active consideration and development. One anticipated outcome of this proposal is to reduce spending on separately billed drugs. Because specific details on the contents of the bundle, its implementation, and the structure of periodic adjustments to its reimbursement level over time are unavailable, we focus here instead on the implications of FOBs for the Part B program. To the extent that FOB entry provides additional savings to the ESRD program above and beyond that resulting from transition to a bundled payment system, focusing solely on savings to the Part B program would underestimate federal savings from FOB entry.

A list of biologics and whether they entered the market under the PHS or FD&C Act appears in Appendix A.

B. PROJECTED FUTURE INCREASES IN BASELINE FEDERAL SPENDING FOR PHS ACT BIOLOGICS

Increases in spending on PHS biologics over this baseline figure will reflect increases in both average prices and utilization, for both existing and for new products. While increases in sales for the entire category of biologics have recently totaled 20%[19], these increases reflect price and utilization effects from both existing products and new entrants. As calculated in Section 7, all of the growth between 2001 and 2006 in sales of erythropoietin stimulating agents and

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[16] See, for instance, the estimate by Ahlstrom et al. that 86% of total spending on biologics from 2005 IMS data for all payers is due to products for which there is not currently an abbreviated application pathway.

[17] United States Government Accountability Office, "Report to the Chairman, Committee on Ways and Means, House of Representatives. End-Stage Renal Disease: Bundling Medicare's Payment for Drugs with Payment for All ESRD Services Would Promote Efficiency and Clinical Flexibility." November 2006. Available on-line at: http://www.gao.gov/new.items/d0777.pdf.

[18] This figure includes the 20% coinsurance due by beneficiaries.

[19] IMS Health Inc., "IMS Reports U.S. Prescription Sales Jump 8.3 Percent in 2006, to $274.9 Billion." March 8, 2007. Available on-line at: http://www.imshealth.com/ims/portal/front/articleC/0,2777,6599 3665 80415465,00.html. (accessed most recently June 20th,2007)

granulocyte-colony stimulating factor biologics is due to next-generation products, with sales of first generation products remaining level or having declined. While there would be potential savings associated with future follow-on biologics for recent or new market entrants, these savings would accrue many years in the future, beyond the ten-year scoring window. A growth rate for existing, first generation biologics should be calculated in order to arrive at an appropriate adjusted baseline federal spending figure for those biologics that are likely to be the target of FOB entry during the scoring window.

Isolating the increases in spending just for existing products with patent protection that would be expiring over the next several years and therefore be the focus of FOB entry, the average annual increases between 2003 and 2005 vary:[20]

- a 6% increase for all erythropoietin stimulating agents reflects a 13% decline for first generation products Epogen and Procrit and a 36% increase for Aranesp[21]
- an average growth rate of 46% for combined first and second generation granulocyte-colony stimulating factors reflects a 15% increase for first generation product Neupogen and a 62% increase for second generation product Neulasta.[22]

Future savings are sensitive to the assumption selected for rates of future growth in the absence of a new regulatory pathway for PHS biologics, and to the level of future dynamic competition assumed. For example, assuming federal spending on PHS Act biologics of $4.3 billion in 2005, a 5% straight line annual growth rate yields forecast baseline federal spending of $5.0 billion in 2008, increasing to $7.8 billion in 2017. The corresponding figures are baseline federal spending of $5.7 billion in 2008, increasing to $13.5 billion in 2017 if one assumes a 10 percent straight line annual growth rate. Logistic "S" curve patterns of growth are generally preferred for longer term projections, however, and should also be considered.

C. MEDICARE PART B SPENDING FOR TOP PHS BIOLOGICS

Table 1 summarizes Part B reimbursements for top biologics (i.e., all those biologics appearing in the top 200 HCPCs codes). In addition to 2005 reimbursement totals for these biologics, two factors affecting the timing of FOB market entry are also included. The assumed dates of patent expiration, where readily available, are listed. We also present a proxy measure for the complexity of the task of establishing comparability and therefore whether the biologic may be

[20] Monoclonal antibodies (for whom data for both years are available) experienced growth of 12%

[21] Future federal spending growth on ESAs may be reduced by new Medicare coverage and reimbursement policies for ESA products. CMS has begun a national coverage review that could restrict the list of indications that are covered under the program. To the extent that CMS finalizes a decision that significantly restricts coverage, the pool of potential savings from FOBs would also be correspondingly reduced.

[22] Federal spending on combined first and second generation G-CSF products increased 12% between 2004 and 2005, but a very high growth rate in pegfilgrastim (Neupogen) federal spending between 2003 and 2004 drives up the overall G-CSF growth rate estimate for 2003 to 2005.

subject to earlier, rather than later, entry by indicating whether a product-specific annex guideline has already been issued by the European Medicines Agency ("EMEA"). If EMEA guidance has not been issued, indicating greater scientific and regulatory complexity in establishing comparability for those biologics, FOB entry is likely to occur later.

The existence of EMEA guidance has been a useful indicator for successful FOB applications in Europe. Manufacturers may submit an application to EMEA without the existence of a product-specific annex, but so far FOB approvals have been limited to areas with product-specific annexes. In addition to its approval of two applications for FOBs for human growth hormones (somatropin and valtropin), EMEA rejected an application by BioPartners for its interferon-alpha product, a therapeutic area for which a product-specific annex had not been issued (one is now under development). Erythropoetin stimulating agents and granulocyte-colony stimulating factor are the only classes of PHS biologics for which EMEA has already established product-specific annex guidelines. Recently, the advisory committee to the EMEA has recommended approval of Novartis's FOB application for erythopoetin alfa, referencing Eprex.[23,24] In addition to serving as a measure of the complexity of the scientific and regulatory task involved in review of a manufacturer's application, it may be the case that, depending on the reference product selected, some of the trials conducted for EMEA applications may be accepted in a U.S. application.[25] The issues relating to the timing of FOB market entry are discussed in the following section.

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[23] Three related applications, for Binocrit from Sandoz, Epoetin alfa from Hexal, and Abseamed from Medice Arzneimittel Puetter, were recommended for approval. Sandoz and Hexal are Novartis subsidiaries and Medice arzneimittel Puetter is a Novartis licensing partner.

[24] "Committee for Medicinal Products for Human Use June 2007 Plenary Meeting Monthly Report," EMEA/267656/2007, 29 June 2007, <http://www.emea.europa.eu/pdfs/human/press/pr/26765607en.pdf> accessed June 29, 2007. Hirschler, B. "Update 2-EU Experts back Novartis Biosimilar Anemia Drug," Reuters, June 22, 2007, <http://yahoo.reuters.com/news/articlebusiness.aspx?type=health&storyid=nL22860315&WTmodLoc=HybArt-R2-IndustryNews-3&from=business>, accessed June 29, 2007. Eprex is an epoietin alfa product distributed by Johnson & Johnson in Europe.

[25] Based on the number of patients and duration of clinical trials submitted by Sandoz in both the FDA and EMEA applications for its human growth hormone Omnitrope, the same trials may have been relied upon in both approvals.

Table 1: 2005 Medicare Part B Spending on PHS Act Biologics

Therapeutic Area	Description	Allowed Charges (in millions) 2005	2004	2003	CAGR 2003-2005	Patent Expiration	EMEA Guidance
EPO	Aranesp (Darbepoetin alfa)	$962	$911	$523	36%	2016	✓
EPO	Procrit and Epogen (Epoetin alpha)	$772	$984	$1,017	**-13%**	2013	✓
MAB	Rituxan (Rituximab)	$761	$595	$570	16%		
MAB	Remicade (Infliximab)	$539	$544	$487	5%		
G-CSF	Neulasta (Pegfilgrastim)	$523	$504	$200	62%	2017	✓
MAB	Avastin (Bevacizumab)	$282	not ranked	not ranked	NA		
G-CSF	Neupogen (Filgrastim)	$159	$106	$120	**15%**	2013-2015	✓
MAB	Herceptin (Trastuzumab)	$125	$95	$88	19%		
MAB	Erbitux (Cetuximab)	$112	not ranked	not ranked	NA		
Other	Botox (Botulinum toxin a)	$65	$56	$53	11%		
Interferon	Intron A (Alfa-2b interferon)	$21	$30	$33	-20%	Expired	
Interferon	Avonex (Beta-1a interferon)	$20	$21	$12	29%	Expired	
Total PHS Act Biologics		$4,341	$3,846	$3,103	18%		
EPO	All EPO	$1,734	$1,895	$1,540	6%	2013-2016	✓
G-CSF	All G-CSF	$682	$610	$320	46%	2013-2017	✓
MAB	All MABs with complete data (2003 to 2005)	$1,425	$1,234	$1,145	12%		

Notes:

- Procrit and Epogen are first generation ESA biologics, with Aranesp being a next-generation product. Similarly, Neupogen is a first generation G-CSF biologic, with Neulasta being a next-generation product.
- Data are allowed charges for reimbursed physician services for the 200 most expensive level II HCPCS codes including all products, supplies, and services not included in the physician service reimbursement (i.e., CPT) codes, which encompass all biologics covered under Medicare Part B, excluding drugs for end stage renal disease. Source: http://www.cms.hhs.gov/MedicareFeeforSvcPartsAB/04_MedicareUtilizationforPartB.asp, accessed June 6, 2007.

5. Timing of Follow-on Biologic Entry

Even after passage of legislation creating an abbreviated approval pathway for FOBs under the PHS Act, it will likely be a number of years before the first FOB market entry based on that pathway. Prior to market entry of a specific follow-on biologic, a number of additional steps must occur, including:

- Development and promulgation of an FDA regulatory scheme
- Expiration of patent protection for an innovator product
- Development, required pre-clinical testing and clinical trials, manufacturing scale-up, and FDA review/approval

While a number of these developments will proceed in tandem, nevertheless, it will likely be a number of years before significant FOB entry is likely to occur.

A. DEVELOPMENT OF FDA REGULATORY FRAMEWORK

Key Assumptions: *Development and promulgation of FDA regulations*	*Estimate Based On:*
• 2 to 6 years *May vary by therapeutic area and depends on regulatory guidance approach selected by FDA*	• Likelihood of FDA case-by-case approach[26] • Other FDA regulatory development examples from non-biologics: 4 years from passage of Hatch-Waxman Act to final FDA regulations (although some drugs approved prior to issuance of final regulations) • 4 to 6 years for issuance of overarching EMEA guidelines and product-specific annexes for insulin, somatropin, G-CSF, ESAs • Potential for two to five year moratorium in some proposals to allow time for FDA to develop guidance[27]

[26] See discussion in J Woodcock, et al., "The FDA's assessment of follow-on protein products: a historical perspective," *Nature Reviews Drug Discovery* 6:, 437-442. June 2007.

[27] Senator Kennedy staff discussion draft, as reported in K Cacciatore et al., "Nothing Generic About Generic Biologics," Cowen and Company. June 2007.

There would likely be a significant period of time required following passage of legislation establishing an abbreviated pathway for FOB entry until the finalization of regulatory guidelines establishing the required procedures for FOB review and approval. The timing of FDA regulation development and promulgation, and the impact of this timing on FOB entry, may vary by therapeutic area and depends on a number of factors, including: whether or not the FDA elects to adopt an overarching set of regulatory guidances supplemented by product-specific annexes, as is the case in Europe, or review applications on a case-by-case basis without such regulatory structure, whether FOB manufacturers wait for regulations to be in place before submitting applications, and whether a moratorium on such applications or similar provision is included in legislation. It is possible that such a framework would follow a similar path as adopted by the EMEA, which first developed general overarching guidance, then developed specific guidance for a limited number of biologic product areas and case-by-case reviews. Alternatively, the FDA could elect to follow a "case law" approach which is developed through reviewing and responding to specific individual manufacturer applications.

This period could range from 2 years (optimistic) to 6 years (pessimistic), depending on the specific approach adopted by the FDA (i.e., whether a case-by-case approach similar to that adopted for Europe by EMEA), the scope of the therapeutic areas for which guidelines are initially developed (product-specific annexes have been issued for insulins, somatropin/human growth hormone, growth colony stimulating factor, and erythropoietin stimulating agents, in Europe), and the legal and scientific issues that were identified but not resolved during the FDA's public hearing process. In a June 26, 2007 letter to Senator Kennedy, Secretary of Health and Human Services Michael Leavitt advocates for a "guidance approach":

> "The Administration believes that the legislation should be amended to require a predictable and public product-class guidance process prior to acting on any follow-on applications. It should ensure that FDA receives expert and public scientific and technical advice, but should include flexibility for FDA to adjust the process to meet its scientific needs with respect to data requirements and other matters. This guidance process would signal to stakeholders which product classes FDA considers appropriate for follow-on applications and data elements that might allow review and approval of a follow-on product. Such a process will ensure the agency has optimum information regarding safety and efficacy considerations for follow-on products; enhance transparency of decision-making; establish a level-playing field for all follow-on applicants; and encourage follow-on applications by describing Agency expectations for application content."[28]

We assume that even after four years, there would be a number of biologic therapeutic areas where specific guidelines would not have been developed or the scientific and regulatory issues

[28] Letter from Secretary of Health and Human Services Michael O. Leavitt to The Honorable Edward M. Kennedy, Chairman, Committee on Health, Education, Labor and Pensions, United States Senate, June 26, 2007.

fully resolved, given the complex and contentious issues involved. In some biologic therapeutic areas, there may be some FOB manufacturers willing to undertake drug development and testing "at risk", in advance of FDA regulations being promulgated. In these areas, development and pre-clinical and clinical testing may proceed in tandem with the development and promulgation of regulations or guidance documents, although there may be few manufacturers with sufficient tolerance for risk to pursue this route given the magnitude of clinical testing investments potentially involved. In the case of generic entry under the ANDA procedures established by Hatch-Waxman, several firms submitted applications to the FDA and received approval prior to the issuance of specific regulations, one notable example being for diazepam (Valium).[29]

In the past, development of general guidance for similar regulatory frameworks both in the US and Europe has taken four to five years. In the US, approximately four years passed from the passage of the Hatch-Waxman Act to the issuance of the first set of specific regulations that allowed for imitator entry.[30] In Europe, the EMEA published its first overarching guidance in October 2005, four years after beginning an analysis in 2001. This was followed by further clarifications of the general clinical, non-clinical and quality issues for biosimilars, as well as product-specific guidelines for hGH, insulin, ESAs, and G-CSF in June of 2006. As of 2007 (six years following passage of legislation), EMEA guidance is restricted to these four therapeutic areas (guidance for interferon-alpha is under development).

Of these four areas, only ESAs and G-CSF are PHS Act biologics; hGH and insulin biologics received FDA approval under the FD&C Act and would be unaffected by the proposed legislation.[31] The experience gained in Europe in developing guidelines and in reviewing FOB applications may inform the FDA's review, but the FDA may be likely to adopt a case-by-case evaluation of the requirements for clinical studies establishing the safety and efficacy of FOBs for the U.S. Woodcock notes with respect to evaluating the scientific issues of determining safety and efficacy of FOB products, next generation innovator biologics, and changes in the manufacturing process for innovator biologics, "The FDA has addressed the scientific challenges

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[29] H.G. Grabowski and J.M. Vernon, "Brand Loyalty, Entry, and Price Competition in Pharmaceuticals After the 1984 Drug Act," *Journal of Law and Economics* 35 (1992): 331-350.

[30] The FDA published regulations pertaining to the Hatch-Waxman Act on March 7, 1988 – 21 C.F.R. Part 60, < http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=60> accessed June 26, 2007.

[31] Biologics approved under the FD&C Act would not be affected by legislation establishing an abbreviated pathway for FOB approval of PHS Act biologics, and should not be included in the calculation of potential federal savings from such legislation. Abbreviated pathways for biologics approved under the FD&C Act under sections 505(j) and 505(b)(2) already exist. We have assumed, consistent with the position advocated by Secretary Leavitt in a June 26, 2007 letter to Senator Kennedy, that there would be no ex post transfer of authority for products (such as insulins) currently regulated under section 505 of the FD&C Act to section 351 of the PHS Act. If such a provision is included in legislation, but is not effective for ten years following enactment, any effects would be beyond the standard ten year scoring window. Further, unless any new pathway resulted in lower costs and barriers to entry than the existing pathways, no savings would be associated with the legislation even beyond the scoring window.

presented by these types of evaluations on a case-by-case basis."[32] This suggests that the FDA is likely to evaluate future FOB applications on a case-by-case basis as well.

B. TIMING OF EFFECTIVE PATENT EXPIRATION

Key Assumptions: *Expiration of patent protection*	*Estimate Based On:*
• Epoetin and Procrit – 2013 to 2015	• Expiration of U.S. process (2012), product claims (2013), pharmaceutical compositions (2013), production cell (2015) patents[33]
• G-CSF – 2013 to 2017	• Expiration of Amgen U.S. patents: claimed sequence – 2013 pegylated versions – 2017 method of preparation – 2015 method of treatment – 2013

Even once an FDA regulatory framework is in place, FOB entry will face delays because many biologics will continue to be protected by existing patents. The patent estate is generally more complicated for a biologic than a conventional drug. In addition to patents on the compound, the composition, and the method of treatment such as those that protect conventional drugs, biologics may also be protected by patents on the research and manufacturing tools used (e.g., host cells, expression systems, process of making), with the potential for multiple such manufacturing process patents, as well as component patents, for a single biologic.[34] In addition, the data generated during clinical trials may be proprietary, and trade secrets with respect to the manufacturing of some biologics may further limit FOB entry even after effective patent protection has expired. Finally, the ownership of intellectual property rights may be much more complex, particularly for upstream methods and tools, with universities, individuals, and firms all having some relevant patent rights. Changes in the intellectual property environment due to evolving case law and new legislation are possible, which could have a significant impact on FOB entry and therefore on potential federal savings.

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[32] J. Woodcock, "The FDA's Assessment of Follow-on Protein Products: A Historical Perspective," *Nature Reviews Drug Discovery* 6: 437-442. June 2007.

[33] U.S. Patent Office, as summarized by K Cacciatore et al., "Nothing Generic About Generic Biologics," Cowen and Company report, June 2007.

[34] J. Kushan, presentation to American Enterprise Institute, June 11, 2007. Available on-line at: http://www.aei.org/events/eventID.1535,filter.all/event_detail.asp (last accessed June 20, 2007).

In line with several security analysts, we have assumed for purposes of analysis that Epoetin and Procrit (two of the largest PHS Act biologics in terms of federal spending) will be protected in the U.S. by patents on the compound until 2013, precluding U.S. FOB applications for approval until that time.[35] Although some key European patents and the U.S. patent for DNA and host cells expired in 2004, there are other patents on the compound that would extend the effective U.S. patent life of Epoetin and Procrit to 2013.[36] Security analysts also indicate that the next generation darberythropoietin biologic Aranesp (Epoetin and Procrit are first generation ESAs) is protected in the U.S. by patents until 2016.[37] There is uncertainty around this assumption, and litigation is likely. In addition, the ability of potential entrants to "invent around" existing methods patents in order to bring FOBs to market is unknown.

G-CSF drugs similarly have U.S. patent protection till at least 2013 and possibly extending till 2017 for some versions. For Amgen's G-CSF drugs, U.S. patents on sequence, method of preparation, and method of treatment extend to 2015, and patents for the pegylated versions extend further to 2017. These assumptions are also subject to uncertainty around whether the patents are likely to hold, or may be invented around to permit entry without infringement. The specific patent situation for each significant biologic will differ and need to be evaluated individually in order to accurately assess potential federal savings due to the legislative proposals under consideration.

[35] K Cacciatore et al., "Nothing Generic About Generic Biologics," Cowen and Company report, June 2007.

[36] Interviews with pharmaceutical company representatives.

[37] K Cacciatore et al., "Nothing Generic About Generic Biologics," Cowen and Company report, June 2007.

C. TIMING OF DRUG DEVELOPMENT, PRE-CLINICAL TESTING, CLINICAL TRIALS, MANUFACTURING SCALE-UP, AND FDA REVIEW / APPROVAL

Key Assumptions: Development, required pre-clinical testing and clinical trials, manufacturing scale-up, and FDA review/approval	*Estimate Based On:*
• 3 to 5 years for development, pre-clinical testing and clinical trials	• Estimated development times in EMEA: 1-2 years for cell biology, 1 year for process/analytics, 2-4 years for clinical trials[38] • Historic drug development times (DiMasi, 2003) • DiMasi and Grabowski (2007) Phase III average duration of 33 months for a sample of biologics[39]
• 3 (contracted) to 7 (in-house, more complex new construction) years for manufacturing capacity development (whether owned or contracted)	• Estimated cell culture facility development times[40]
• 1.5 to 2 years for marketing application review and approval	• Historic drug approval times of 18 months (DiMasi, 2003) • Average approval phase time of 16 months for a sample of biologics (DiMasi and Grabowski, 2007) • EMEA experience of approximately 2 years for Omnitrope and Valtropin

[38] E. Schafer, CEO BioGeneriX "Opportunities for FOBs in Europe – A Risk Benefit Analysis with EPO" (Presentation at the Institute for International Research Follow-on Biologics forum, Washington, D.C., April 2005).

[39] J.A. DiMasi and H.G. Grabowski, "The Cost of Biopharmaceutical R&D: Is Biotech Different?" *Managerial and Decision Economics*, June 2007.

[40] Interviews with manufacturing consultants and biotech companies summarized in K Cacciatore et al., "Nothing Generic About Generic Biologics," Cowen and Company report, June 2007.

Following the development of FDA guidelines and once patent protection is no longer effective for a specific branded innovator biologic, an FOB manufacturer will still need to complete required pre-clinical testing and clinical trials of the drug, secure approvable manufacturing capacity for the drug, and obtain FDA approval of its application for the FOB prior to market entry.

As opposed to the case for generic drugs, where only approximately $1-2 million in cost and only approximately two years are necessary to demonstrate bioequivalence[41], FOB development and trials will likely take 3 to 5 years, and obtaining FDA approval another one and a half to two years. Obtaining approvable manufacturing capacity may take 3 to 7 years, depending on whether the facility will rely on bacterial fermentation or mammalian cell lines, and whether the manufacturer has existing experience or partnerships in place. Some of these activities can be pursued in parallel, particularly the development or securing of manufacturing capacity. As a result, these delays should not be interpreted as additive.[42] We have assumed that any FOB legislation will contain a "Safe Harbor" provision allowing for FOB drug and manufacturing development to begin prior to patent expiration for the innovator drug. Lack of experience on both the part of manufacturers and the FDA will likely result in longer development and approval times for the first potential FOBs to come to market, which then may decrease over time, all other factors being equal.

1. Clinical Trials and Approval for FOBs

We assume that, given concerns around establishing true bioequivalence between innovator drugs and FOB applicants, and the potential for immunogenicity, clinical trials will be required for all PHS Act biologics. We anticipate that the extent of clinical trials for FOBs required by the FDA will vary by therapeutic area, and that those therapeutic areas requiring more extensive trials will experience greater delays to entry.

a) EMEA Experience

As a benchmark, EMEA product-specific annexes present pre-clinical and clinical testing requirements that increase with increasing molecular complexity:[43]

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[41] H. Grabowski, "Patents and New Product Development in the Pharmaceutical and Biotechnology Industries," *Georgetown Public Policy Review* 8, no. 2 (2003): 7-24.

[42] It is unknown whether the FDA could allow FOB manufacturers to rely on trials already undertaken for approval in other jurisdictions with reference products relevant to the U.S., thereby expediting their FDA approval process.

[43] EMEA product-specific annexes, as summarized by Citigroup "A Global 'Generics Biologic' Guidebook," November 6, 2006.

- Insulin: Comparative in vitro bioassays; no in vivo pharmacodynamics study; no clinical efficacy studies needed; 6 month comparative immunogenicity study; pharmacovigilance program

- Somatropin (human growth hormone): Comparative in vitro bioassays; at least one *in vivo* pharmacodynamic rodent study; one randomized clinical efficacy study needed; 12 month immunogenicity study; pharmacovigilance program

- G-CSF: Comparative in vitro bioassays; at least one *in vivo* pharmacodynamic rodent study; at least one two- or three-arm clinical efficacy study needed; immunogenicity study with one year follow-up for chronic administration; pharmacovigilance program

- ESAs: Comparative in vitro bioassays; at least one *in vivo* pharmacodynamic rodent study; at least one randomized clinical efficacy studies needed (separate studies for pre-dialysis and dialysis patients, and for subcutaneous and IV administration); 12 month immunogenicity study; pharmacovigilance program

G-CSF and ESAs have the greatest requirements placed on them by EMEA guidelines and are also likely to face substantial requirements in an FDA regulatory framework, resulting in lengthy development and approval times.

Development times have been estimated in EMEA at a total of five to eight years, from beginning development to market approval: [44]

- one to two years for cell biology

- one year for process/analytics

- two to four years for clinical trials

- one year for approval

Omnitrope's application included several non-clinical tests, three clinical combined pharmacokinetic and pharmacodynamic studies, one Phase III comparative clinical efficacy study with 89 patients for 9 months (patients continue to be followed for up to 24 months), and one Phase III open label non-comparative clinical safety study with 51 patients for 12 months (study is still ongoing beyond the 12-month data submission). Actual approval times for Omnitrope and Valtropin were closer to two years.

[44] E. Schafer, CEO BioGeneriX "Opportunities for FOBs in Europe – A Risk Benefit Analysis with EPO" (Presentation at the Institute for International Research Follow-on Biologics forum, Washington, D.C., April 2005).

b) Innovator Biologic Experience

A recent analysis by DiMasi and Grabowski (2007) examined the R&D costs and times for a data set of recombinant proteins and monoclonal antibodies, and compared them to corresponding figures for development of new drugs (DiMasi et al., 2003), making appropriate adjustments for the difference in the time periods studied.[45] The authors assembled drug-specific R&D cost and duration data by development phase for a sample of seventeen biologics, and integrated them with a larger database on transition probabilities and development times for new biologics. Mean development times for innovator biologics were longer than clinical development times for drugs (ninety-eight months versus ninety months). Clinical development and approval times for this sample of innovator biotech drugs and the larger sample of drugs are presented in Figure 1.

Of most interest are the average Phase II and Phase III development times:

- Average duration of the biotech innovator's Phase II program was 29 months
- Average duration of a full Phase III program for biotech innovators were calculated to be 33 months (approximately the same as the corresponding figure for new drug development programs).
- The corresponding mean actual out-of-pocket cost figure was $96 million (Phase III) for an investigational biopharmaceutical compound.

While FOB applicants are unlikely to have to repeat the innovator's full clinical testing investments, it is likely that some clinical testing will be required, varying with the complexity of the molecule at issue. Even if full Phase III trials of the same magnitude and duration are not required, abbreviated trials with a few hundred patients would still cost tens of millions of dollars and take several years to complete.

2. Timing of Development of Manufacturing Capacity

In addition to obtaining FDA approval, an FOB manufacturer will need to develop or secure manufacturing capacity to produce the biologic for market. Because biologics are inherently unstable, they are sensitive to even minute changes in manufacturing parameters such as temperature, pH, and pressure. As a result, manufacturing requires highly specialized assets and time-tested expertise. Firms may elect to develop in-house capacity or to partner with a contract manufacturing organization (CMO). The CMO market has increased over the years, reaching an estimated 66% of the more straightforward microbial manufacturing capacity and 25% of

[45] J.A. DiMasi and H.G. Grabowski, "The Cost of Biopharmaceutical R&D: Is Biotech Different?" *Managerial and Decision Economics*, June 2007.

mammalian cell manufacturing capacity.[46] While contracted manufacturing reduces the level of capital investment required, it also reduces profit margins.

Estimates of the time and cost to develop new construction vary, but generally total at least $250 million, and potentially much higher, depending on the specific nature of the capacity required:

- Interviews with manufacturing consultants and biotech company representatives conducted by investment analysts peg the cost and timing of cell culture facilities at $250 to $300 million and approximately 5 to 7 years[47]

- A Deloitte Consulting report describes the costs of setting up a plant at typically about $400 million and models the expected time to build an average biologics plant for self-manufacture at 4 years [48]

- Genentech describes costs ranging from $200 million to $800 million, with a timeline of 4 to 6 years[49]

- An industry director of biologics production describes the typical timeline for an antibody project new production facility as being over 4 years from design to start of production[50]

- Molowa described the timeline to develop a large scale mammalian cell culture manufacturing plant as taking 4 to 5 years and $250 to $400 million (2001 figures)[51]

For new construction, Molowa outlines the primary steps in the process of developing capacity and the average time to complete each step, for an overall total of 5 years (assuming some overlap across steps).

- Conceptual/preliminary engineering (1.5 years)

- Detailed engineering (1 year)

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[46] Citigroup report, "Lonza Group AG." September 2005.

[47] Interviews with manufacturing consultants and biotech companies summarized in K Cacciatore et al., "Nothing Generic About Generic Biologics," Cowen and Company report, June 2007.

[48] C Chao and J Lakshmikanthan, "For biologics production, contract manufacturing organizations can bring real economic benefits," available online at: http://www.deloitte.com/dtt/article/0,1002,sid%253D2218%2526cid%253D123912,00.html (last accessed June 21, 2007).

[49] "Genentech Manufacturing," available online at: http://www.gene.com/gene/news/kits/corporate/pdf/manufacturing-backgrounder.pdf (last accessed June 21, 2007).

[50] G Welch, "Regulatory and Economic Challenges in Biotechnology Manufacturing," presentation, November 2003.

[51] Molowa DT . 2001 *The State of Biologics Manufacturing*. JP Morgan Securities, February 16th.

- Construction (2 years)
- Start-up and validation (1.25 years)
- Filing, plant inspection and regulatory review (1 year).

Welch (2003) alternately describes the steps as consisting of: design; construction; commissioning and validation; and start of production. He arrives at similar overall estimates for a typical timeline for a new antibody production facility of over 4 years. In the case of contracting for manufacturing capacity, Welch notes that a manufacturing strategy needs to be in place typically prior to Phase III studies, in order that registration batches and ultimate market launch material can be produced from the same facility. An additional challenge to potential FOB firms without existing biologics manufacturing capacity is that the market for biologics manufacturing is highly concentrated, either among a small number of CROs (microbial manufacturing) or a mix of in-house manufacturers and CROs (mammalian cell manufacturing). Potential FOB entrants without either existing capacity or close relationships with CROs may find it difficult to secure manufacturing capacity without expensive guarantees to lock in committed capacity in advance of demonstrated market demand for the product.

3. Timing of FDA Review and Approval of FOB Application

Standard FDA review times for innovator biologics are approximately 16 months on average (18.2 months for conventional drugs).[52] EMEA review times for Omnitrope and Valtropin were each approximately two years. We anticipate that the initial FOB applications will take a comparable period of time for the FDA to review and reach an approval decision, or between one and a half and two years. Both firm and FDA reviewer inexperience with a new process, involving the review of complex molecules, with greater clinical risks and relatively new clinical requirements will result in longer review times. Over the long-term, review periods may decrease, all other factors being equal, depending on in-market actual clinical experience.

[52] DiMasi, Joseph A., and Grabowski, Henry G. The Cost of Biopharmaceutical R&D: Is Biotech Different? *Managerial and Decision Economics*, June 2007.

6. Follow-on Biologic Pricing and Rates of Uptake

Once FOB entry occurs, savings resulting from that entry will depend on: (1) FOB price discounts compared to the brand; (2) the level of uptake of the FOB product; and (3) dynamic competition over time in the therapeutic area with other branded products which may offer improved clinical and patient convenience benefits. Various factors will affect FOB pricing and share, including the number of FOB entrants in any given product market, the competitive model adopted by FOB manufacturers (i.e., whether primarily price-based, or based on product feature differentiation and brand value), and the behavior of other stakeholders and economic agents in a position to influence the rate of FOB uptake or level of price discount achieved.

FOB uptake assumptions over time involve a complex interaction between competition from biosimilars based on the rate of uptake of the FOB for the branded reference product in the short run, and *dynamic competition* considerations of the share that either the branded reference product or the FOB will achieve of all treatment in the therapeutic area. The latter includes the effect over time of successive generations of new therapies which may offer additional clinical, patient convenience, or economic benefits. Some dynamic competition effects may be triggered by FOB entry; innovators may respond to anticipated FOB entry by developing and releasing next generation products that supplant the use of the first generation biologics subject to FOB competition.

The main factors determining FOB pricing and share results for any biologic include:

- The extent of FOB entry, which affects both FOB price and share and is primarily determined by:
  - Market size
  - Fixed costs of entry
- Other factors affecting FOB price discounts:
  - FOB product marketing and competitive strategy (i.e., whether primarily price-based or based on product feature differentiation and brand value)
- Other factors affecting FOB share:
  - Physician, patient, and payer acceptance of FOB products as substitutes for the branded innovator product
  - Dynamic competitive responses by innovator manufacturers
  - Structure of the distribution system and set of economic incentives for FOB uptake

This section includes a discussion of these issues and summary of relevant findings from the published literature. In the next section we present empirical evidence from two potential competitive model outcomes:

- a branded competition model (using observations from branded competition in the human growth hormone market); and
- a generic competition model (using data from generic entry and competition in the more complex conventional drugs that share some features with biologics).

A. EXTENT OF FOB ENTRY

Potential federal savings depend not only on FOB entry occurring, but also on the price discounts and level of uptake of the FOB for its branded counterpart that are achieved. Existing economic analyses of the conventional drug market find that the number of entrants is strongly related to both the generic price discount (i.e., the generic to brand price ratio) and the extent of generic share (i.e., the generic share of the molecule) and we expect that these relationship will also hold true for the biologics market.

For some biologics, the markets are too small and the expected fixed costs of entry too high to encourage any FOB entry. For larger market biologics, such as ESAs and G-CSF, the magnitude of potential development and clinical trial costs may constrain entry to only a few entrants. There is already some evidence in Europe that development programs in this area are undergoing some consolidation, as a result of the expected fixed costs of entry implied by the EMEA product-specific annex.[53] There are currently only two approved FOB hGH entrants in Europe. In the U.S., five companies serve the bulk of the innovator hGH market (Genentech's Nutropin and the older generation somatrem Protropin, Eli Lilly's Humatrope, Novo Nordisk's Norditropin, Pfizer's Genotropin, and Serono Labs's Saizen, Serostim and Zorbtive). Teva Pharmaceuticals's somatropin product Tev-Tropin recently entered the market, but as of Q1 2006 has achieved negligible sales. Other FOB markets with less well-characterized proteins or smaller markets may see fewer entrants. The pace of FOB approvals in Europe may increase as regulators review additional FOB applications and as manufacturers are better able to anticipate what types of clinical trials will be required and design programs that will pass regulatory muster. The advisory committee to the EMEA has recently recommended approval of Sandoz's FOB version of Eprex.[54,55]

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[53] See, for instance, analysis by PipelineReview.com at http://www.pipelinereview.com/pipeline_samples/biogenerics_bfm.pdf (most recently accessed June 14, 2007).

[54] "Committee for Medicinal Products for Human Use Summary of Positive Opinion for Binocrit," EMEA/CHMP/236267/2007, 21 June 2007, <http://www.emea.europa.eu/pdfs/human/opinion/23636707en.pdf> accessed June 26, 2007.

[55] The recent recommendation of an expert panel for the EMEA in favor of approval of three FOBs whose reference product was the ESA Eprex were closely related applications – Sandoz and Hexal are Novartis subsidiaries and Medice Arzneimittel Puetter is a licensing partner of Sandoz. There is unlikely to be direct competition between these applicants, therefore.

Two key factors affecting the extent of FOB entry are the potential market size and the fixed costs of entry. Saha, Grabowski, et al. (2006), Reiffen and Ward (2005), and Grabowski, Ridley, and Schulman (2007) all find that the number of entrants strongly determines both the generic price discount and the extent of generic share for conventional drugs.[56] The sales and growth rate of sales for the innovator drug prior to FOB entry is generally a good measure of the potential market available to an FOB entrant. The fixed costs of entry can depend on many factors, but will likely be closely tied to the cost of obtaining manufacturing capacity and the extent of clinical trials that the FDA requires for FOB approval in each therapeutic area. Therapeutic areas requiring more extensive trials are likely to see lower levels of FOB entry, all other factors held equal.

1. Market Size

The speed of entry and number of FOB entrants for a specific biologic drug depends on the potential market size for FOB therapies in that category. Firms will only enter if expected revenues are sufficient to cover the fixed costs of entry, with an appropriate risk premium, as well as the variable costs of each unit sold after entry. Saha, Grabowski, et al. (2006) found that for conventional drugs, the level of brand sales prior to generic entry is a key determinant of the subsequent number of generic entrants.[57] Reiffen and Ward (forthcoming) also found that the hypothetical market size was a major determinant of generic entry.[58] A number of biologic markets are smaller than conventional drug markets and have higher fixed and variable costs, all of which will limit entry compared to conventional drugs. As is the case for conventional drugs, the sales distribution for biologics is highly skewed, with a few biologics accounting for a disproportionate share of sales and profits. In an analysis of thirty new biologics introduced between 1982 and 1994, Grabowski (2003) finds that the top 20% of biologics accounted for approximately 70% of 2002 sales.[59] We expect these biologics to be the primary targets of FOB manufacturers.

Anecdotal evidence also supports this analytical conclusion. For example, STADA/Bioceuticals note that they abandoned an interferon-beta FOB development project because the "marketing opportunities do not justify the high expenditures for the completion of the project."[60]

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[56] Saha, A., Grabowski, H., Birnbaum, H., and Greenberg, P., "Generic Competition in the U.S. Pharmaceutical Industry," *International Journal of the Economics of Business* 13, no. 1 (2006): 15–38; Reiffen, D. and Ward, M., "'Branded Generics' as a Strategy to Limit Cannibalization of Pharmaceutical Markets," *Managerial and Decision Economics*, (forthcoming); Grabowski, H., Ridley, D., and Schulmann, K., "Entry and Competition in Generic Biologics," *Managerial and Decision Economics* (forthcoming).

[57] Saha, A., Grabowski, H., Birnbaum, H., and Greenberg, P., "Generic Competition in the U.S. Pharmaceutical Industry," *International Journal of the Economics of Business* 13, no. 1 (2006): 15–38

[58] D. Reiffen and M. Ward, "'Branded Generics' as a Strategy to Limit Cannibalization of Pharmaceutical Markets," *Managerial and Decision Economics*, (forthcoming).

[59] Grabowski HG 2003. "Patents and New Product Development in the Pharmaceutical and Biotechnology Industries," *Georgetown Public Policy Review* 8 (2): 7-24.

[60] <http://www.stada.de/english/about/profile/leadership.asp>, accessed June 14, 2007.

2. Fixed Costs of Entry

The fixed costs of developing an FOB drug and bringing it to market also strongly affects the number of likely FOB entrants for that biologic. The higher the fixed costs of entry for any given biologic, the fewer FOB manufacturers there are that will find it profitable to enter (for any given market size). Clinical trials will comprise a major component of these fixed FOB costs of entry and the extent of these trials and costs will depend on FDA requirements. For example, whether the FDA requires that an FOB demonstrate bioequivalence to the branded product and safety with limited trials, or more extensive phase III clinical trials, could mean a difference of tens of millions of dollars. Post market entry pharmacovigilance requirements can also be important forms of fixed costs, since provision for them may need to be made in advance of any market performance experience.

a. Biologic Drug Development Costs

DiMasi and Grabowski (2007) found total out-of-pocket R&D costs for a sample of new biologic introductions to be $198 million in the preclinical period, $361 million in the clinical testing period, for a total of $559 million.[61] Taking into account opportunity costs, using a real cost of capital of 11.5%, overall capitalized costs for the representative new biological entity are $1.24 billion.[62, 63] While the development costs for FOBs will be smaller than for new innovator biologicals, they are still likely to substantially exceed the estimate of $600,000 to $2,000,000 associated with the development of generic small-molecule drugs.[64]

Actual out-of-pocket phase III trial costs for the sample of innovator biotech drugs averaged $96 million for investigational biopharmaceutical compounds.[65] While FOB applicants are unlikely to have to repeat the innovator's full clinical testing investments, it is likely that some clinical testing will be required, varying with the complexity of the molecule at issue. Even if full Phase III trials of the same magnitude and duration are not required, abbreviated trials with a few hundred patients would still cost tens of millions of dollars and take several years to complete.

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[61] DiMasi, J. A. and Grabowski, H. G., "The Cost of Biopharmaceutical R&D: Is Biotech Different?" Managerial and Decision Economics (forthcoming).

[62] Assuming a historical rate of inflation of 3 to 3.5%, the corresponding nominal cost of capital would be approximately 15%. The cost of capital estimate is based on a capital asset pricing model analysis for a small set of biotech firms with a history of profitability based on multiple marketed products. These companies also had an extensive portfolio of new biological product candidates over the period 1990-2003. (DiMasi and Grabowski, 2007)

[63] Grossman, M. (2003) estimates that biotechnology firms without a marketed product but with one or more drug candidates in phase II or III trials have an average nominal cost of capital of 27.4%. He also estimates a nominal cost of capital for biotechnology firms with at least one drug approved have of 18.l7%. Grossmann, M. 2003. *Entrepreneurship in Biotechnology*, Physica-Verlag New York.

[64] Reiffen, D. and Ward, M., "'Branded Generics' as a Strategy to Limit Cannibalization of Pharmaceutical Markets," *Managerial and Decision Economics*, (forthcoming).

[65] Grabowski, H., Ridley, D., and Schulmann, K., "Entry and Competition in Generic Biologics," *Managerial and Decision Economics* (forthcoming); DiMasi JA and Grabowski HG. The Cost of Biopharmaceutical R&D: Is Biotech Different? *Managerial and Decision Economics* (forthcoming).

Elsewhere, the cost of development, including abbreviated Phase III studies has been estimated at $30 to $50 million.[66]

Fixed costs will vary by therapeutic area, depend on the trials required, and be higher in the short-run due to firm inexperience. There will be costs to the firm due to learning, on both the part of the regulators and the firms submitting FOB applications, because of the uninsurable uncertainty in the regulatory process.

Even the relatively simple and well characterized human growth hormone Omnitrope was required to undertake substantial testing to gain EMEA approval, including: several non-clinical tests, three clinical combined pharmacokinetic and pharmacodynamic studies, one Phase III comparative clinical efficacy study with 89 patients for 9 months (patients continue to be followed for up to 24 months), and one Phase III open label non-comparative clinical safety study with 51 patients for 12 months (study is still ongoing beyond the 12-month data submission).[67,68] Sandoz's U.S. application for Omnitrope through the FD&C Act Section 505(b)(2) pathway reflected four multi-center phase III clinical trials demonstrating safety and efficacy.

b. Manufacturing and Other Costs

Additional costs that would need to be considered for any entry decision include the costs of building manufacturing facilities, variable costs, and the costs of post-marketing surveillance. A new manufacturing plant can take three to five years to build, and can cost $200 million to as high as $800 million, with most estimates ranging from $200 million to $450 million (see earlier discussion on delays to entry). In the alternative, contract manufacturing solutions can be sought, but come at the price of margin reductions and can present challenges to secure. Variable costs of manufacturing are higher for biologics due to higher input costs and higher costs of manufacturing in the biological versus conventional drug manufacturing process. Post marketing surveillance costs for FOBs may be substantial as well, considering the potential for significant side effects associated with even seemingly minimal modifications to a biologic.

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[66] Interviews with manufacturing consultants and biotech companies summarized in K Cacciatore et al., "Nothing Generic About Generic Biologics," Cowen and Company report, June 2007. Earlier, Biogenerix estimated these costs at $20 to $80 million. E. Schafer, CEO BioGeneriX "Opportunities for FOBs in Europe – A Risk Benefit Analysis with EPO" (Presentation at the Institute for International Research Follow-on Biologics forum, Washington, D.C., April 2005).

[67] Omnitrope European Public Assessment Report, http://www.emea.europa.eu/humandocs/PDFs/EPAR/Omnitrope/060706en6.pdf

[68] A second Phase III safety study was required due to the initial batch of Omintrope used in the first study containing a high concentration of impurities causing 60 percent of the patients in that study to develop non-neutralizing antibodies to Omintrope (compared to 2 percent in the reference product). Wang, E. J. Jerman, P. Heldman, A. Swanson, "A Global 'Generic Biologics' Guidebook," *Citigroup Equity Research*, November 6, 2006. This highlights some of the difficulties in manufacturing even a relatively simple biologic such as hGH.

B. OTHER FACTORS AFFECTING FOB AVERAGE PRICE DISCOUNTS

As in the market for conventional drugs, average price discounts for FOBs are expected to reflect the number of FOB entrants, with greater numbers of entrants resulting in greater price reductions, but can also be influenced by other factors such as the strategy that the FOB manufacturer assumes in marketing the follow-on drug. Given the high fixed costs of development, non-negligible risks (regulatory risk, product liability risk, risk of protracted intellectual property litigation), and uncertain acceptance by physicians and patients, rather than compete solely on price, FOB manufacturers may have incentives to follow a branded competition model in order to fund the marketing and sales investments that may be necessary to maximize market success of the FOB product.

In that case, the FOB would be marketed in a similar manner to a branded biologic, potentially generating greater economic rents (and reflecting the fact that FOBs are unlikely to receive an A rating, reflecting therapeutic substitutability for the corresponding branded innovator product). The incentive to pursue a non-price competition strategy would increase with the level of safety and efficacy data required in the regulatory review process. Significant marketing and sales force investments may be needed in order to achieve acceptance among often brand-loyal specialist physicians, who often require more intensive and focused educational marketing spend than primary care physicians (although they are fewer in number). Margins will need to be sufficient to support higher levels of marketing spend (prices for generic conventional drugs, by contrast, do not need to support marketing, promotion, or sales force investments, as sales forces need only call on a small handful of major retail pharmacy chains and sales are driven by "demand pull" from payers and pharmacists rather than "marketing push" by manufacturers). Such marketing oriented, branded competition strategies are likely to result in limited reduction in the average price for the biologic therapy, depending on other factors, and therefore limited federal savings from FOB entry.

C. OTHER FACTORS AFFECTING FOB UPTAKE

Factors other than the extent of FOB entry that could substantially affect the level of uptake achieved by the FOB for the corresponding branded innovator product include two major hurdles that the FOB needs to overcome: (1) the need to convince often brand-loyal and time-pressed physicians and clinically vulnerable patients that the FOB is substitutable for the innovator biologic; and (2) the lack of a mature set of distribution system incentives favoring rapid and deep FOB uptake.

1. Physician, Patient, and Payer Acceptance

The level of FOB uptake will be strongly influenced by the degree to which physicians and patients accept the substitutability of innovator and FOB therapies and perceive them to be of equal safety and efficacy. Delays or limitations in physician use of FOBs due to lack of familiarity, and perceived or actual differences between the FOB and innovator drug, will be in part determined by the amount of clinical evidence establishing the FOB's safety and efficacy.

FOBs are unlikely to be rated as interchangeable with their branded innovator counterparts and switching studies may be required in order to demonstrate that FOBs have similar clinical results. Physician and patient comfort with "tried and true" products is unlikely to be matched at least initially by the FOB, which may be emphasized in innovator marketing messages.

If the FOB is required to complete significant phase III clinical trials and switching studies, then physicians and patients may be more willing to accept the FOB as a substitute for the innovator drug. However, extensive trials raise the fixed costs of FOB entry, reducing the number of FOBs entrants and raising price. Reduced FOB entry could result in lower FOB price discounts and limited federal savings from FOB entry.

2. Dynamic Competitive Responses by Innovator Manufacturers

The perceived substitutability of the FOB and innovator drug is likely also to be influenced by the marketing approach adopted by the follow-on manufacturer and the dynamic competitive behavior of the innovator and other manufacturers in the market (e.g., investment in differential messaging, and follow-on products which may offer value-added features and benefits by the innovator and other manufacturers). In addition to marketing responses to differentiate the existing innovator biologic from the FOB, competition within therapeutic classes is dynamic and products are subject to competition not just from FOBs, but also from new branded products with the same general mode of action but which may offer enhanced efficacy, safety, patient convenience, or economic features and benefits. The degree to which next generation products affect the rate of uptake or eventual share achieved by FOBs is a function, among other factors, of how significant these enhanced features and benefits are to clinicians, patients and payers, as compared with the features and benefits offered by the FOB reference product. All other factors being equal, if the next generation product offers only modest, incremental improvements in a therapeutic area with needs that are largely met, the expected impact of the next generation product on uptake of the FOB would be modest, and conversely, the expected impact of the FOB on uptake of the next generation product would be substantial. On the other hand, all other factors being equal, if the next generation product offers significant improvements in a therapeutic area with significant unmet need, the expected impact of the next generation product on uptake of the FOB would be substantial, and the expected impact of the FOB on uptake of the next generation product would be modest.

Innovator manufacturers will have incentives to invest in product improvements and next generation products that will increase consumer welfare, but will reduce FOB market shares. These next generation products are less likely to be priced at a discount to current on-market products. As a result of these two factors, federal savings may be limited.

The rate at which new drugs are subject to such competition has increased over time, with DiMasi and Paquette (2004) showing that the number of first-in-class drugs that do not face competition has declined strongly since the 1970s, reflecting a decline in the barriers to entry for new molecules within established classes. DiMasi and Paquette cite a number of structural

factors for this phenomenon, including supply side factors such as enabling technological advances in basic biomedical research.[69]

3. Structure of the Distribution System and Economic Incentives for FOB Uptake

The rapid generic penetration for many conventional drugs that we observe today reflects a mature system of economic incentives encouraging generic substitution by pharmacists in the retail sales channel that took time to develop. "Autopilot" factors such as state generic substitution laws, higher retail pharmacy margins on generics than on branded products, and public and private insurer benefit structures (including higher copays or coinsurance on non-preferred drugs) all play an important role in the rapid generic substitution observed for many products today. FOBs are unlikely to be rated as fully therapeutically substitutable, and therefore FOB demand would not be driven to the same degree by these policies. This position is reflected in a letter from Secretary of Health and Human Services Michael Leavitt to Senator Kennedy:

> "Because of the variability and complexity of protein molecules, current limitations of analytical methods, and the difficulties in manufacturing a consistent product, it is unlikely that, for most proteins, a manufacturer of a follow-on product could demonstrate that its product is identical to an already approved product. Technology is not yet sufficiently advanced to allow this type of comparison for more complex protein products … For many follow-on protein products, there is a known significant risk in repeatedly switching between products and a resulting negative impact on both patient safety and/or effectiveness. While there may be the possibility of determining interchangeability in the future, pharmacies or patients might substitute biological products determined to be biosimilar, but not determined to be interchangeable for one another, possibly resulting in serious injury or death. Therefore, in light of the current scientific limitations on the ability to make determinations of interchangeability, and because it is critical to protect patient safety, the Administration believes that patients should not be switched from the innovator biologic product to a follow-on biologic product (or vice versa) without the express consent and advice of the patient's physician, and legislation should not allow for determinations of interchangeability at this time." [70]

Even if legislation allows for interchangeability, such a determination by the FDA would likely require patient crossover studies. The pathway to interchangeability would therefore be much more challenging than for generic drugs.[71,72]

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[69] DiMasi JA and Paquette c. 2004. "The Economics of Follow-on Drug Resarch and Development," *PharmacoEconomics*, Vol. 22, Suppl. 2, pp 1-14.

[70] Letter from Secretary of Health and Human Services Michael O. Leavitt to The Honorable Edward M. Kennedy, Chairman, Committee on Health, Education, Labor and Pensions, United States Senate, June 26, 2007.

[71] Proposed Biologics Price Competition and Innovation Act of 2007.

[72] Remarks of Scott Gottlieb at AEI symposium "What Should Congress Do About Generic or Follow-On Biologic Drugs?", Washington D.C., June 11, 2007. See also S. Gottlieb presentation at: http://www.aei.org/publications/pubID.25967,filter.all/pub_detail.asp.

In addition, many biologics are currently managed as medical, rather than pharmacy, benefits in commercial third party insurance plans. As a result, the well-developed and often complex system of patient and provider economic incentives and requirements favoring generic substitution would not apply. From an expenditure management perspective, while biologic therapies might be significant as compared with pharmaceutical expenditures, they are much less significant in comparison with medical expenditure such as hospitalizations.

In some therapeutic areas, managed care controls may be limited by liability concerns, depending on the severity of the indication, the payer's leverage over the specialty physicians administering the drug, and the perception of safety issues involved in substituting the innovator product for the FOB. The ability of the managed care organization to negotiate with manufacturers on price will be based on the applicability of the above, the level of physician outcry, and related concerns about safety and plan liability. To the degree that FOBs are not therapeutically equivalent and therefore not substitutable by retail pharmacists for the reference branded innovator product, the financial incentive due to higher retail pharmacy margins on generic than on branded drugs that help drive generic substitution in the case of conventional drugs will be muted. In many cases, retail pharmacies may not be involved in the distribution of biologics, although specialty pharmacy vendors may be a force for FOB uptake. However, as biologics represent a greater share of insurance plan spending, and as their management becomes integrated with the management of pharmacy budgets, public and private sector managed care payers will have an increasing interest in FOB uptake. Specialty drug tiers and coinsurance are emerging and may be applied in order to encourage FOB uptake.

7. FOB Pricing and Uptake – Evidence

Key Assumptions: *FOB Price and Share*	*Estimate Based On:*
FOB Price Discount: *10% to 30% off brand*	• Empirical analysis of generic entry for non-biologic drugs with complex characteristics • Empirical analysis of Medicaid reimbursements for hGH (somatropin recombinant) biologics • Reported Omnitrope pricing
Short-Term FOB Share of Reference Biologic: *10% to 45%*	• Empirical analysis of generic entry for non-biologic drugs with complex characteristics • Empirical analysis of Medicaid reimbursements for hGH (somatropin recombinant) biologics
Longer-Term Dynamic Competition and Entry of Next-Generation Products: *Limits FOB Market Potential*	• Empirical analysis of next generation ESAs - Aranesp captured 11% of the ESA market within a year and 40% within four years • Empirical analysis of next generation G-CSF drugs - Neulasta captured 50% of the G-CSF market within a year and 70% within four years

Both *biosimilar* and *dynamic* competition affect the actual level of uptake of an FOB for an innovator biologic product (and consequently the level of potential federal savings):

- **Biosimilar competition effect**: When FOB entry occurs, there will be some uptake of the FOB rather than the innovator product. Key considerations in the case of biologics beyond the level of price discount offered alone are the behavioral and structural barriers to uptake (e.g., physician and patient acceptance of substitutes, lack of economic incentives and mature systems for uptake).

- **Dynamic competition effects**: FOB products will not only compete with their reference innovator products, but also dynamically with next generation products which may offer additional features, offsetting short-term uptake effects to some degree. A large part of the growth in biologic spending is due to the introduction of next-generation products that target areas of unmet need. FOBs will compete with first generation products, and so the potential market for FOB use is likely to grow much more slowly than the overall biologic market.

We review evidence relevant to both the FOB potential share of the reference product sales and dynamic market measures incorporating the impact of product improvements on FOB and reference product share of total therapy in a given therapeutic area. Federal savings are affected by both biosimilar and dynamic competition factors. For example, even in the case where an FOB captures a large share of the sales of the reference biologic product, if next-generation products enter and quickly largely displace the older generation reference product and the FOB, then federal savings from FOB entry will be small.

Limited direct empirical market evidence of uptake and price effects due to follow-on biologics is available. Only two human growth hormone follow-on products have been approved in Europe, both recently. Omnitrope, an FOB version of Pfizer's hGH biologic Genetropin has been marketed for the past year in Europe and somewhat longer than that in Australia. Anecdotal reports typically cite Omnitrope being available at a 20 to 25 percent price discount in Germany and a 10 to 20 percent price discount in Australia.[73] Uptake of Omnitrope has been limited to only approximately 1%, with a Sandoz spokesperson stating that, "[s]ales are developing with a slow uptake… there needs to be a lot of education and training for doctors and patients."[74]

To supplement this limited empirical experience with FOBs in Europe, we present empirical evidence from several situations with some analogous characteristics:

- price-based competition in the form of generic entry of more complex conventional drugs that share some features suggestive of biologics;
- branded competition in the human growth hormone market; and
- dynamic competition with entry of next generation products in the ESA and G-CSF markets.

[73] Pisani, J. and Bonduelle, Y., "Opportunites and Barriers in the Biosimilar Market: Evolution or Revolution for Generics Companies?" PricewaterhouseCoopers LLP; and Pipelinereview.com <Http://www.pipelinereview.com/joomla/content/view/10955/286/ -- accessed June 22, 2007.

[74] <Http://www.businessworld.in/content/view/1394/1451/> -- accessed June 19, 2007.

A. PRICE-BASED COMPETITION: EVIDENCE FROM GENERIC ENTRY OF COMPLEX CONVENTIONAL DRUGS

While many conventional drugs experience rapid price declines and substantial generic shares following generic entry, this experience does not hold for all conventional drugs. Some drugs have characteristics that begin to approximate the features of biologics:

- black box warnings
- a narrow therapeutic index[75]
- use by specialists rather than primary care physicians
- use in oncology
- a manufacturing technology available to only a limited number of firms.

We find that these more complex products experienced much lower levels of generic penetration and price discounts than did other conventional drugs. For example, at one year following initial generic entry, the share of generic Coumadin (a drug with a narrow therapeutic index) was 9 percent, while the share of generic Prozac was ten times higher, or 89 percent. Even four years after initial generic entry the share of generic Coumadin had reached only 20 percent. Because generic drugs benefit from economic and structural incentives for substitution, even complex drugs may achieve levels of generic penetration in excess of those which FOBs might achieve when pursuing a strategy of competing on price.

1. Generic Substitution Among More Complex Drugs

We analyzed price and quantity data from IMS for 35 conventional (i.e., non-biologic) drugs that experienced generic entry between 1997 and 2003. We then determined whether the characteristics listed above that begin to approximate some of the features of biologics were associated with each of the 35 drugs, and compared rates of generic substitution and generic price discounts for drugs with and without these characteristics. We found that they are associated with lower levels of generic share and price discounts. Generic share is substantially lower for drugs having an FDA-required black box warning on the drug label, a narrow therapeutic index, an oncology indication, a delivery technology possessed by few generics manufacturers, or one that is used primarily by specialist physicians.

Figure 2 compares the average generic share over time for drugs with two or more of the above complex characteristics to drugs with one or none of these characteristics. At one year following initial generic entry, the mean generic share for drugs with two or more complex characteristics is 45%, while drugs with one or no complex characteristics had a mean generic share of 78% (1.7

[75] Drugs with a narrow therapeutic index are those drugs that exhibit the desired therapeutic effect at a dose level close to the toxic dose level for that drug. As a result, small deviations from the appropriate dosing level could have significant harmful effects.

times higher).[76] Among drugs with two or more of the above characteristics, the rate of generic share erosion was lowest for Coumadin, a narrow therapeutic index drug, where one year following initial generic entry, generic erosion totaled only 9%.

While these data from conventional generics cannot be directly applied to estimate FOB shares following market entry in the biologics market, they suggest that FOB uptake will be significantly lower than observed in the case of generic drugs. Even more complex generic drugs are nevertheless rated therapeutically equivalent (i.e., have an A rating) and therefore benefit from some "automatic" substitution. In order to avoid substitution, physicians need to specify in "do not substitute" orders that prescriptions are to be dispensed as written. FOBs will not be rated therapeutically equivalent and therefore will not be subject to "automatic" substitution. Further, to the degree that distribution occurs through physicians' offices and similar settings under a "buy and bill" system, historically there have been incentives for higher, rather than lower priced products. These factors, together with additional factors related to specialist brand loyalty, clinically vulnerable patient populations, and physician conservatism in switching stable patients to new therapies, are likely to reduce rates of FOB uptake below levels observed in these more complex drugs.

2. Prices

Figure 3 compares the generic price discounts from the brand over time for drugs with two or more of the above complex characteristics to drugs with one or none of these characteristics. At one year following initial generic entry, the generic price discount for drugs with two or more complex characteristics is 35%, while drugs with one or no complex characteristics had a generic discount of 58% (1.6 times higher).[77]

Results are summarized in the table below. In each case, the mean value of the variable shown for drugs with two or more complex characteristics is roughly 60% of the value of that variable for drugs with one or no such characteristics. The lower mean levels of generic shares and price discounts for drugs with two or more complex characteristics are also reflected in a lower number of generic entrants. On average, drugs with two or more characteristics faced 2.5 generic entrants one year following initial generic entry, while drugs with one or no characteristics faced an average of 8.5 generic entrants.

[76] The difference in mean generic shares measured twelve months after generic entry for drugs with two or more characteristics and drugs with one or no characteristics is statistically significant at the 99% confidence level.

[77] The difference in mean generic price discounts measured twelve months after generic entry for drugs with two or more characteristics and drugs with one or no characteristics is statistically significant at the 98% confidence level.

Generic Share and Generic Price Discounts from Brand One Year After Generic Entry		
	Average Generic Share of the Molecule	**Generic Price Discount from the Brand**
Drugs with Two or More Complex Characteristics: – Mean – Minimum (Coumadin)	45% 9%	35% 0%
Drugs with One or No Complex Characteristics	78%	58%
Ratio for Drugs with Two or More Characteristics to Those with One or None	0.6	0.6

B. BRANDED COMPETITION AMONG HUMAN GROWTH HORMONE BIOLOGICS

As biologics themselves, human growth hormones may provide a useful approximation of FOB entry and competition for some PHS Act less complex biologics.[78] Most human growth hormones are derived from the same molecule, somatropin recombinant, chemical variations are minimal and are well understood, and competition takes place between branded products on multiple dimensions including price, promotion and delivery features (e.g., cartridge and pen systems).[79] As a result, the entry of new somatropin recombinant biologics may provide a baseline for estimating the potential effects of FOB entry in other biologic therapies, should manufacturers adopt a branded competition model of market behavior.

[78] In addressing concerns regarding the approval process for Omnitrope, a FOB to Pfizer's Genotropin, the FDA stated that "[a]mong other things, human growth hormone (hGH) has several characteristics that enable one hGH product to be adequately compared to another for purposes of approval…hGH is well characterized…[t]he primary structure of hGH is known…hGH's mechanism of drug action is known, and its human toxicity profile is well understood," *Omnitrope (somnatropin [rDNA origin]) Questions and Answers*, May 30, 2006, http://www.fda.gov/cder/drug/infopage/somatropin/qa.htm (accessed June 1, 2007).

[79] According to the FDA, human growth hormones, hGHs, are well characterized and non-glycosylated (that is, sugar molecules are not added to the protein, which minimizes the complexity of a protein and makes it easier to compare the structures from one version of the protein to another using standard tools such as mass spectrometry). The primary structure of hGH is known, and physicochemical tests exist for the determination of an hGH product's secondary and tertiary structures (how the protein folds upon itself). Clinically relevant bioassays and qualified biomarkers are available for hGH, and hGH has a long and well documented history of clinical use as a replacement for endogenous growth hormone deficiency. The mechanism of hGH drug action is known, and its human toxicity profile is well understood. Omnitrope (somnatropin [rDNA origin]) Questions and Answers. May 30, 2006. http://www.fda.gov/cder/drug/infopage/somatropin/qa.htm. Accessed on March 30, 2007.

We collected Medicaid state drug utilization data from 1991 through the first quarter of 2006 on all somatropin recombinant hGH products. This molecule comprises the vast majority of hGH sales. While these Medicaid reimbursement data may not be directly indicative of the effects on Part B federal expenditures, the Medicaid data are complete and provide a substantial time horizon for analysis, and may be generally indicative of outcomes for public payers in similar markets with multiple entrants in more highly substitutable biologics markets where there is both price-based and non-price based competition.

1. Average Reimbursements per Prescription

Between 1991 and 2006, the number of separate somatropin recombinant biologics increased from 1 to eight products.[80] Despite this substantial increase in the number of biologics, the average market reimbursement per Rx for somatropin recombinant biologics was not significantly affected, excluding Serostim, as illustrated in Figure 4. Two products, Serostim and Protropin, exhibit characteristics that are not shared by other products: Serostim is the only hGH product was an indication for use in AIDS Wasting Syndrome (and so the pricing and sales of this product may reflect a separate market from the other hGH products); and Protropin is an entirely different molecule, a recombinant somatrem rather than a recombinant somatropin. For these reasons, we compare results for the remaining more closely related products.

All of the somatropin recombinant products were similarly priced (excluding Serostim). Products have largely chosen to compete on dimensions other than price, such as delivery system and dosing convenience. All of the major branded products have pen or needle-free delivery systems. One exception is the product Tev-Tropin, introduced by Teva Pharmaceuticals in February 2005 without the dosing and delivery convenience features of other competitors (Tev-Tropin is delivered with a conventional needle system, as is Omnitrope). Despite a price discount of roughly 40% from other somatropin products, over two years later, in April 2007, Tev-Tropin had failed to capture more than 1% of all somatropin prescriptions[81] (less than 1% of Medicaid prescriptions in the time period we examined) and therefore had a negligible effect on overall Medicaid spending.

Most manufacturers have chosen not to compete on price despite the fact that all of the drugs are derived from somatropin and may share many common attributes. This suggests that non-price competition may be a desirable strategy for potential FOB entrants in PHS Act biologic markets. In the one case where an hGH product, Tev-Tropin, appears to have selected a strategy of competing on price it has failed to capture much of the market.

2. Rate of Uptake

We also observe that as new somatropin recombinant biologics enter they do not substantially affect the trend in prescriptions for existing products, as seen in Figure 5. The prescription path for Serostim is unique, reflecting its indication for AIDS Wasting Syndrome and substantial sales in that market, which likely expanded the overall market for somatropin.

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[80] We combined products such as Nutropin, Nutropin AQ, and Nutropin Depot into a single biologic when generating these counts of unique biologics

[81] K Cacciatore et al., "Nothing Generic About Generic Biologics," Cowen and Company report, June 2007.

As noted, Protropin also exhibits a unique prescription path reflecting its position as an older generation somatrem recombinant (rather than a somatropin recombinant) product. The manufacturer of Protropin, Genentech, subsequently released the somatropin recombinant product Nutropin.

Even excluding Serostim, the size of the hGH market has grown substantially, fueled by new entry. A similar dynamic may be observed in the markets for some PHS Act biologics, with additional entrants expanding the market, due to marketing and product differentiation, rather than leading only to share effects on other innovator drugs. A more complete analysis would go beyond these descriptive observations and carefully control for factors which may affect share such as delivery system unique features and level and mix of marketing spending and tactics in order to isolate the determinants of share and to estimate the degree to which new entrants expanded the total market.

C. DYNAMIC COMPETITION WITH SUCCESSIVE GENERATIONS OF PRODUCTS: EVIDENCE FROM ESA AND G-CSF BIOLOGICS

Dynamic competition through market entry of products which may offer additional features is an important consideration when investigating the impact of FOB entry on federal spending. To the extent that innovator manufacturers introduce new products with features not available in the FOB, then the size of the market available to the FOB may be reduced over time. Even if the FOB gains a large share of sales from the benchmark innovator biologic, the FOB's share of overall treatment may decline or remain limited. This is likely to be particularly true in markets with substantial unmet need, where physicians and patients may readily adopt new products with additional patient convenience or clinical efficacy and side effect benefits. Conversely, in more established therapeutic areas, where current drugs are highly effective and side effects minimal, FOBs may achieve higher levels of uptake. Further, the prospect of FOB entry will provide innovator manufacturers with additional incentives to develop and introduce these next-generation products.

1. ESA

In 2002 Amgen began marketing the next generation ESA drug Aranesp. Prior to that time the market for ESAs was served largely by the drugs Epogen and Procrit in the U.S., identical drugs marketed under two names depending on the clinical indication. Aranesp is approved for both renal failure and chemotherapy related anemia, allowing use of Aranesp as an alternative for both biologics. Aranesp's less frequent dosing schedule has given it an advantage in the ESA market. Figure 6 illustrates the growth in ESA sales since the introduction of Aranesp is entirely due to Aranesp sales, while the sales of Epogen and Procrit have remained relatively unchanged. Aranesp captured 11% of the ESA market in the first year following its release and 40% within four years. An FOB for Epogen and Procrit will face a segmented ESA market.[82]

[82] Other factors may also affect the pattern of share uptake between these similar biologics, such as marketing approach and tactics. This brief discussion is not intended to be a comprehensive discussion of market interactions between the ESA products, but rather a suggestion that successive generation biologic products can have significant impacts on market outcomes for first generation biologics and their FOBs, even when they are very similar (CMS treats Aranesp/DARB as functionally equivalent to EPO from a reimbursement point of view).

Other factors could also affect the total size of the ESA market in future years and the likely share that an ESA FOB might capture, including the unknown resolution of certain cardiovascular and oncology concerns that could result in changes to current dosing practices, and future competition from other products (such as Roche's CERA) and other entirely new therapies in development including oral agents.

2. G-CSF

Also in 2002, Amgen began marketing the next generation pegylated G-CSF drug Neulasta. Prior to that time the market for G-CSF was served largely by its drug Neupogen. As a result of the structural change, Neulasta does not have to be administered as often as Neupogen. Figure 7 displays the change in Neupogen sales over the 2000 to 2006 period, which have declined, with sales of Neulasta, which have increased substantially. Neulasta captured 50% of sales in the first year following its release and 70% of sales within four years. An FOB entrant based on Neupogen would face significant challenges in competing with Neulasta.

8. Conclusion

Just as the Hatch-Waxman Act fundamentally reshaped competition, pricing, and innovation for "conventional" small molecule drugs in 1984, Congressional action on a regulatory framework for follow-on biologics will have far-reaching implications, resetting the competitive and market landscape in the dynamic biotechnology industry for years to come. These changes have the potential to result in significant long-term economic realignment in the biotech and pharmaceutical industries. Elsewhere, we have discussed the need for careful consideration in structuring the appropriate balance between long-term interests in protecting innovation incentives in the biotech industry and shorter-term interests in enhanced price competition.[83] We have also examined the importance of setting an appropriate data exclusivity period that reflects the demand and supply side characteristics of this market: early stage research concentrated in start-up companies typically financed by venture capital firms and partnerships; long, costly and risky R&D in which most candidate molecules never reach the market; and market sales distributions that are highly skewed, with long payoff periods to profitability.[84]

This paper examines in greater detail the key assumptions which will drive market outcomes, specifically the likely timing and magnitude of federal savings due to the creation of a regulatory framework for follow-on biologics under the Public Health Service Act. Although some industry observers have suggested that market outcomes for follow-on biologics may closely parallel those observed in the case of generic drug entry after the implementation of the Hatch-Waxman Act, we find that similar outcomes are unlikely due to significant differences between the two situations and sets of therapies that will result in different market outcomes.

We summarize the best available evidence for each key assumption, focusing particularly on the potential effects of biosimilar competition (i.e., possible rates of uptake of FOBs in cases where the corresponding innovator branded biologics would otherwise have been used) and competition with future next generation biologic products, as these key assumptions have received less attention to-date. Direct market evidence of share and price effects due to FOBs is limited, and largely confined to recent experience in Europe. Therefore, we also review the available empirical market data on outcomes in the most closely analogous situations in the U.S., including generic entry for more complex small molecule drugs, and branded competition in the human growth hormone market, as well as experience with competition between first and succeeding generation biologic products. Each of these examples suggests modest savings in the short run, consistent with potential FOB price discounts of between 10% and 30%, and FOB shares of 10% to 45%, and market entry for the most significant products in 2013 or later.

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[83] H.G. Grabowski, I. Cockburn and G Long, "The Market for Follow-On Biologics: How Will It Evolve?", *Health Affairs* 25 (5)L 1291-1301.

[84] H.G. Grabowski, "Data Exclusivity for New Biological Entities," Duke University Department of Economics Working Paper, June 2007.

In addition, we conclude that estimates of federal savings are very sensitive not only to the specific legislative language that emerges, but also to a range of critical assumptions about scientific, regulatory, and clinical issues, the nature of competition in markets for specific biologics, as well as future intellectual property protection, and related litigation and development of case law. All of these factors are highly uncertain, and any one of them could have a substantial impact on the magnitude of potential federal savings and the speed with which they are realized. Nonetheless, our review of the relevant evidence, combined with considerations of the structure of competition and economic incentives, suggests that such savings are likely to fall at the lower end of the very wide range of estimates that have been put forward. As a result, we recommend a cautious approach in developing and interpreting estimates of the federal budgetary impact of any regulatory framework for expedited review and approval of follow-on biologics.

Acknowledgments

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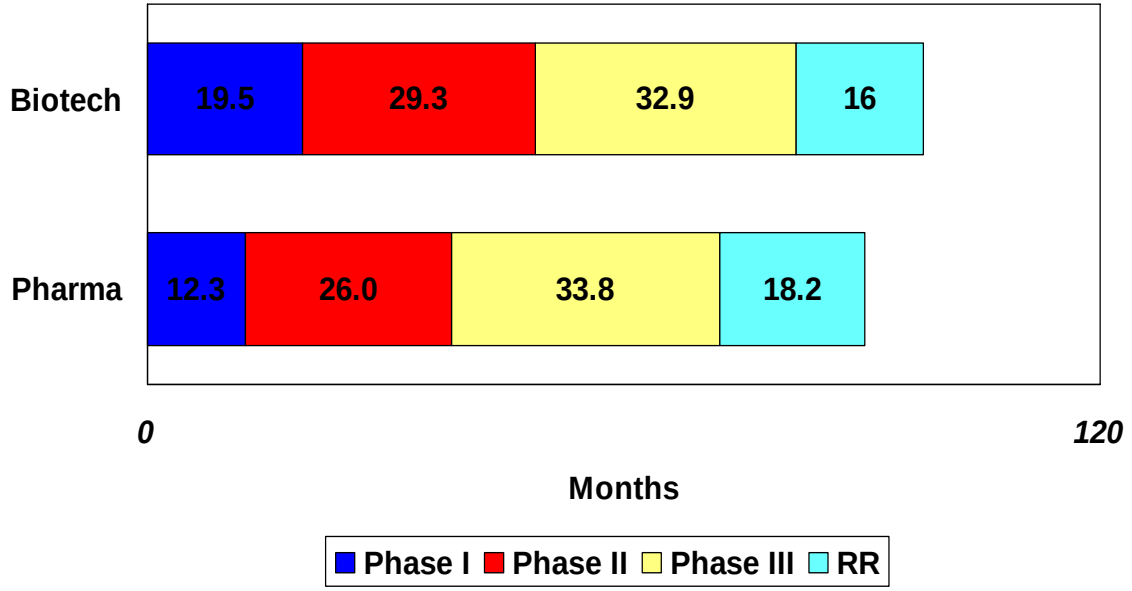
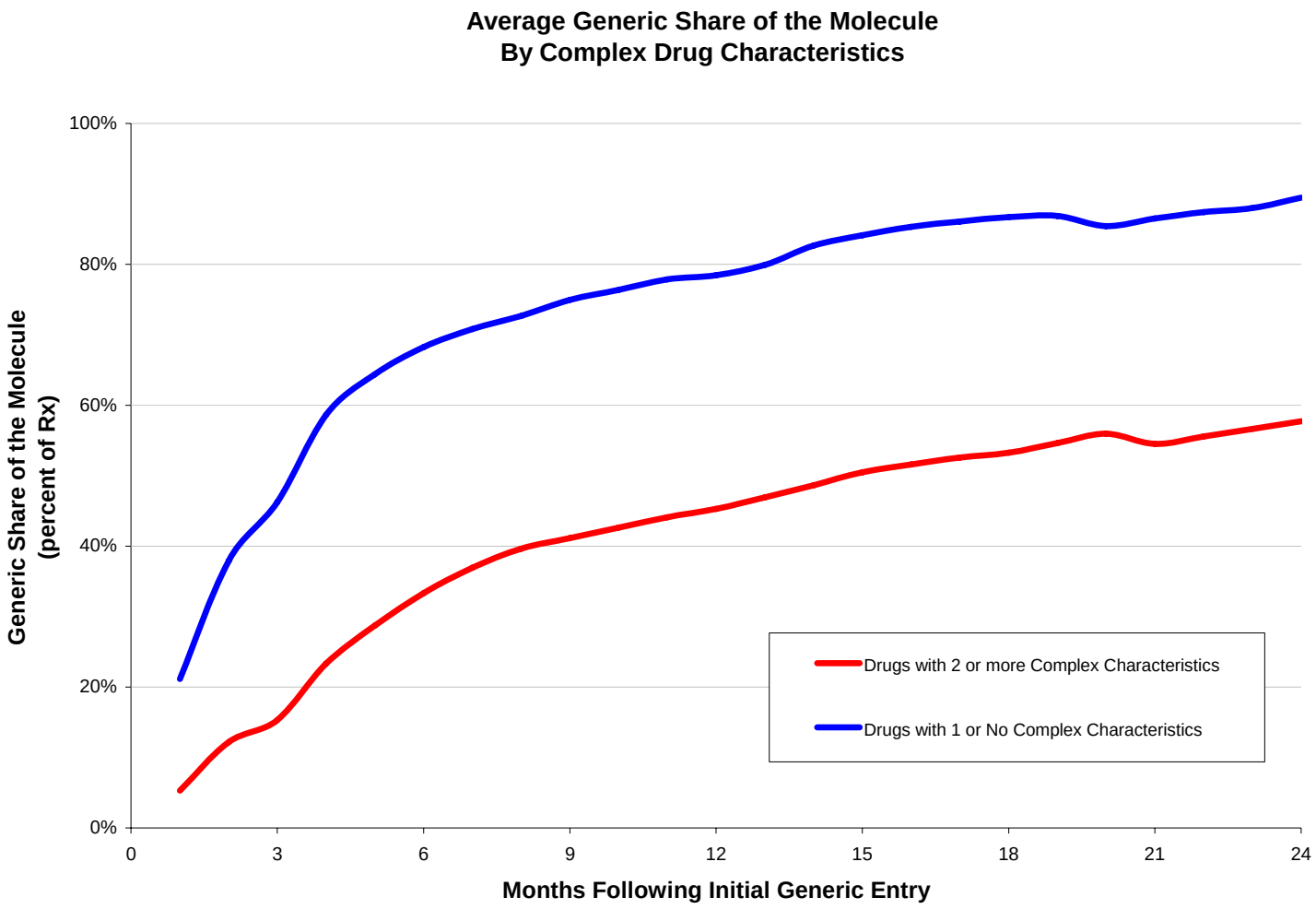
Figure 1: Clinical Development and Approval Times: Biotech and Pharma



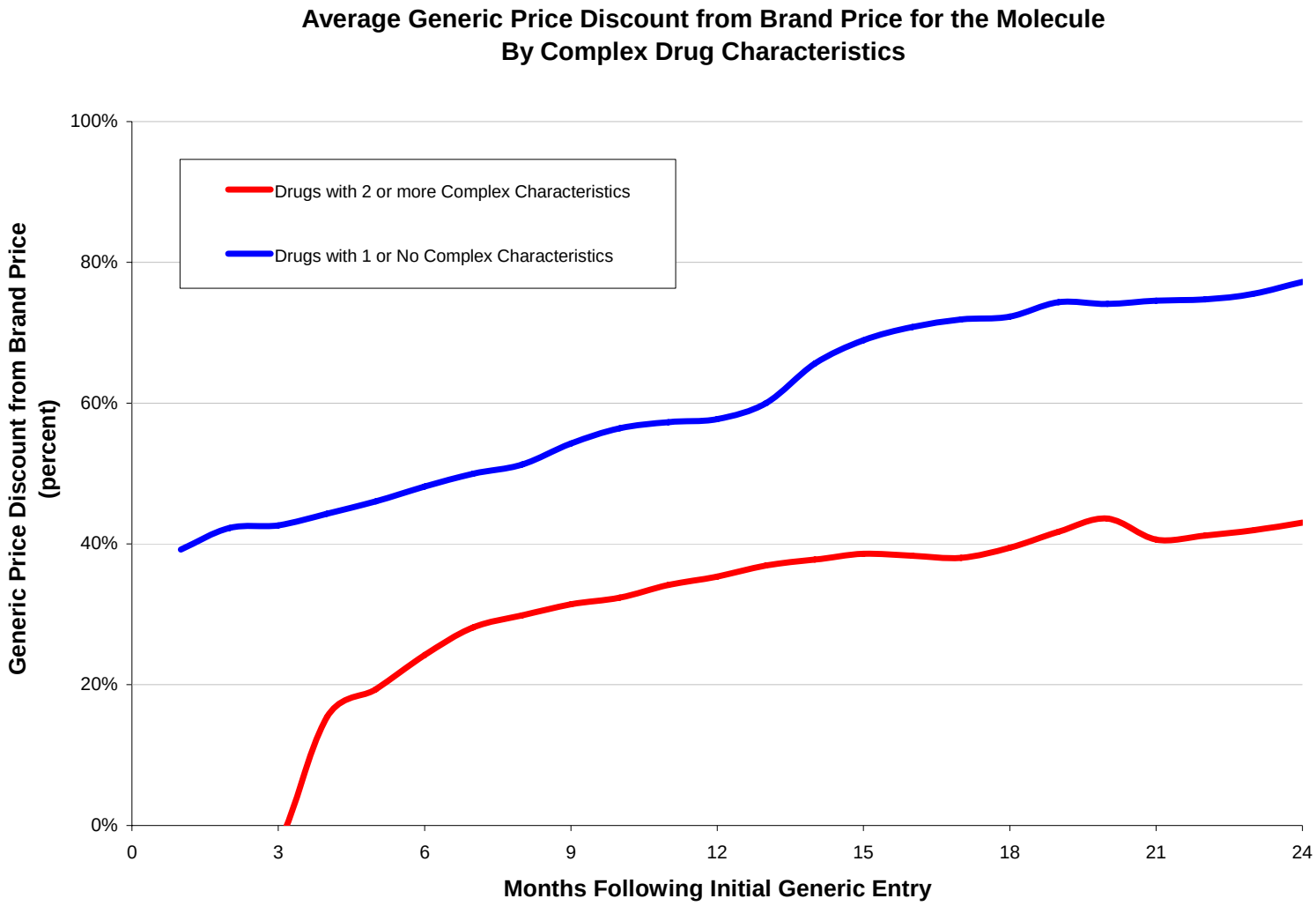
Source: DiMasi, Joseph A., and Grabowski, Henry G. The Cost of Biopharmaceutical R&D: Is Biotech Different? *Managerial and Decision Economics*, June 2007.

Figure 2: Generic Share of Molecule for Drugs with and without Multiple Complex Characteristics



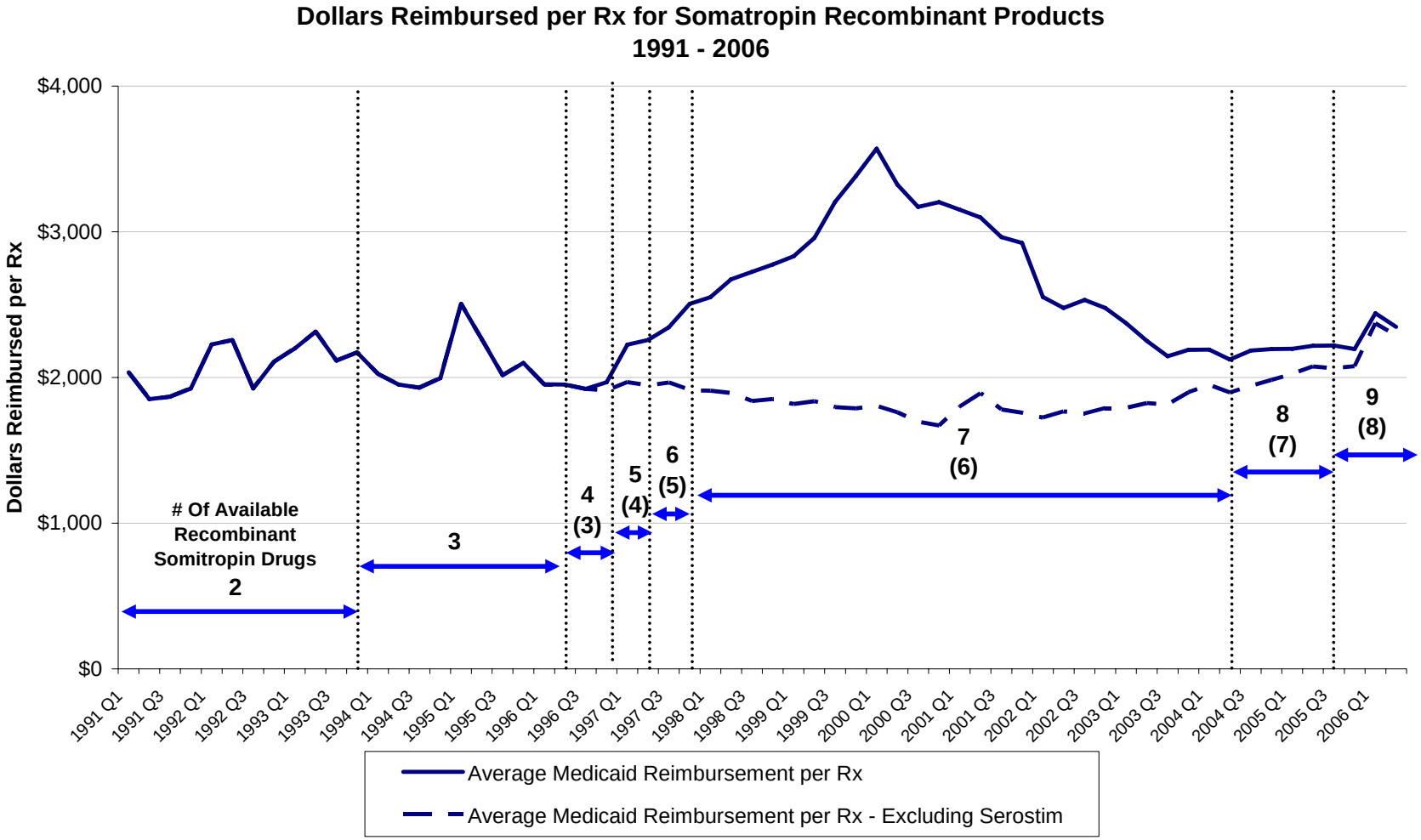
Source: Authors' calculations from a sample of 35 drugs experiencing generic entry between 1997 and 2003.

Figure 3: Generic Price Discounts for Drugs with and without Multiple Complex Characteristics



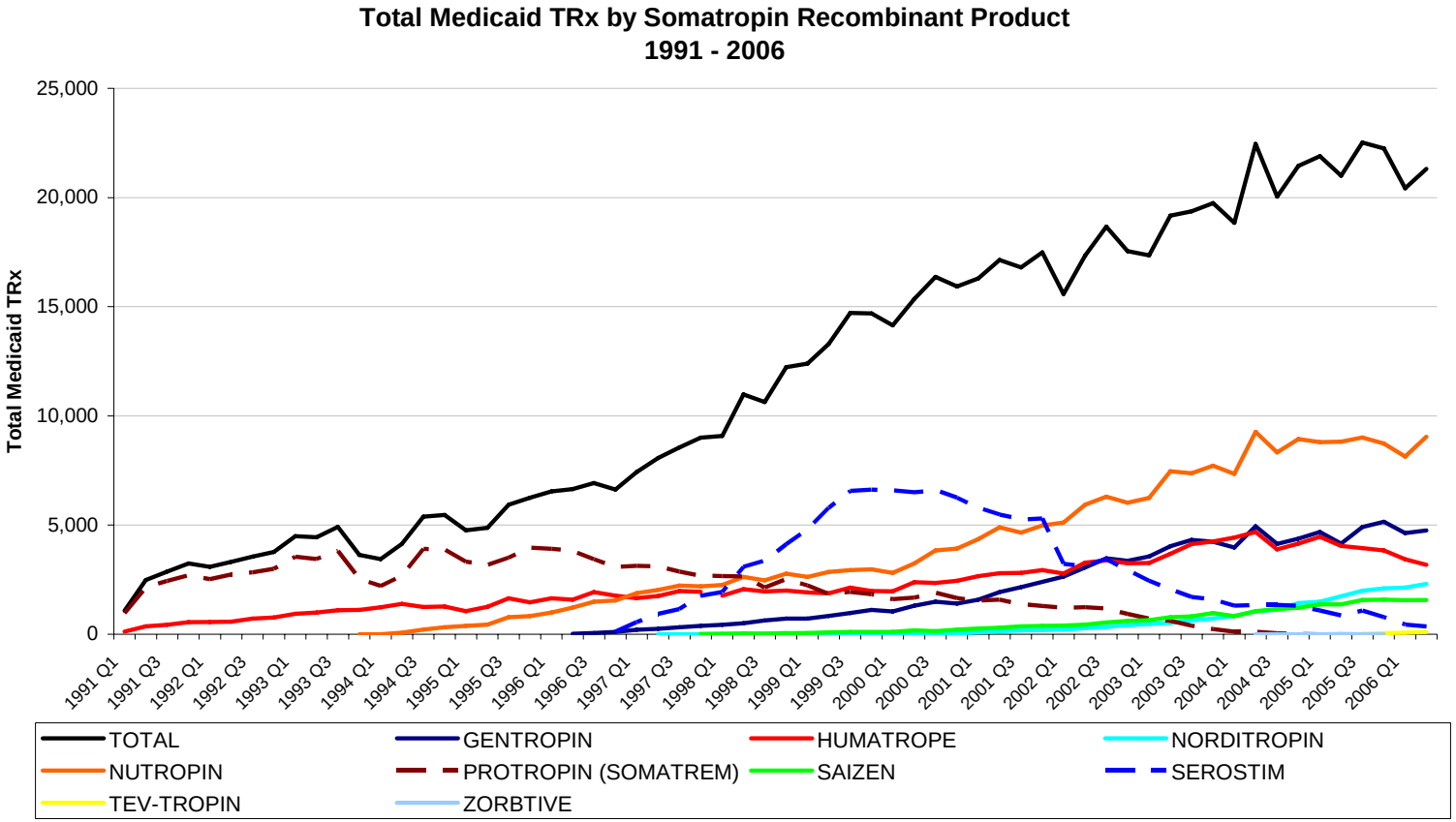
Source: Authors' calculations from a sample of 35 drugs experiencing generic entry between 1997 and 2003.

Figure 4: Average Amount Reimbursed per Prescription for Somatropin Recombinant Products



Notes: 1) Calculations based on products derived from Somatropin Recombinant.
2) Variations of a brand product are not counted separately in # of available Somitropin Drugs (e.g., Nutropin, Nutropin AQ, and Nutropin Depot only count as one drug).
3) Serostim is the only HgH indicated for AIDS Wasting and therefore many of its sales may be in a separate market from the other HgH drugs.
Source: Medicaid SDUD data.

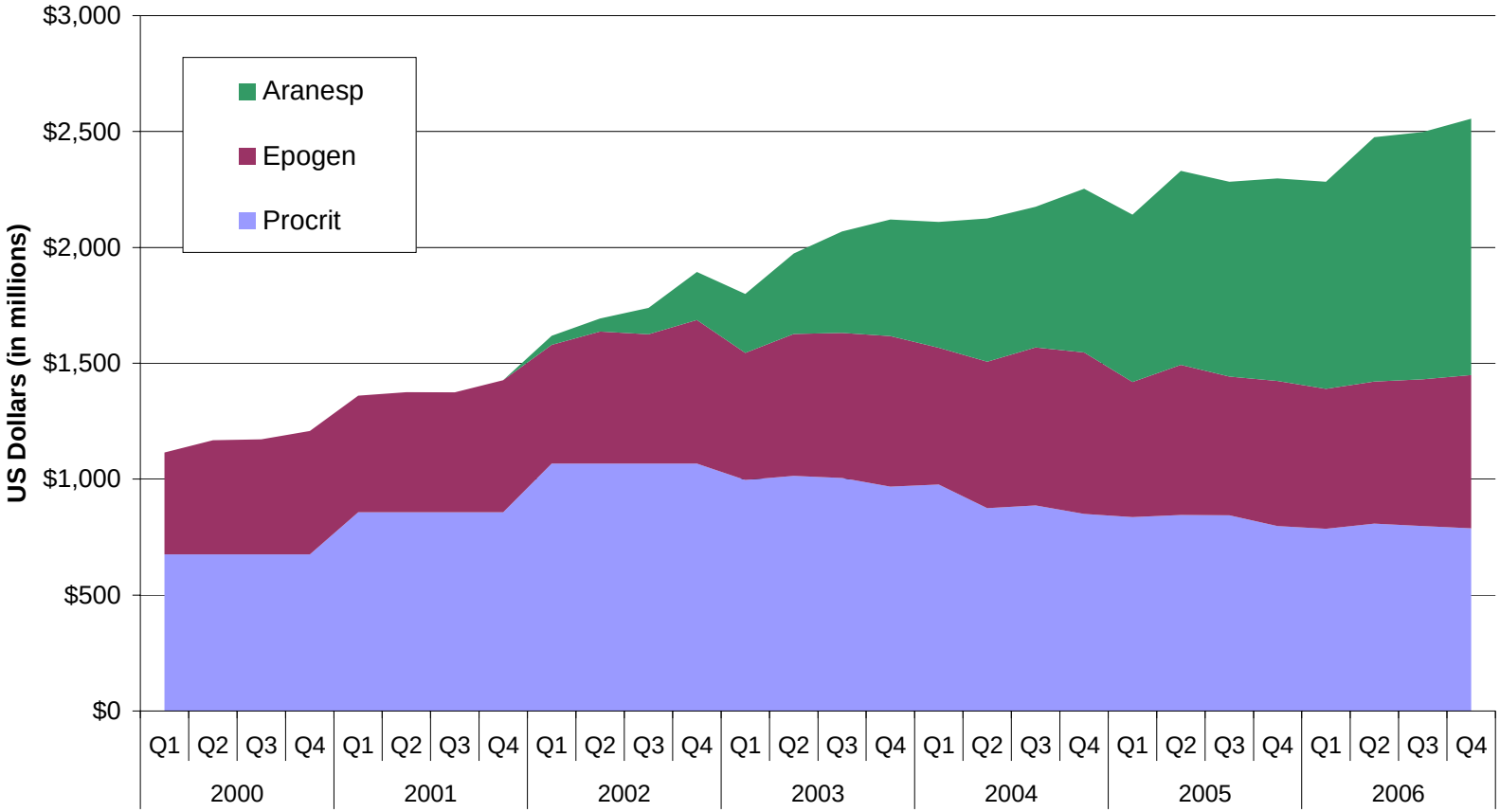
Figure 5: Prescriptions of Somatropin Recombinant Products



Notes: 1) All products shown are derived from Somatropin Recombinant.
2) Products include all variation of the brand name (e.g., Nutropin includes, Nutropin, Nutropin AQ, and Nutropin Depot).
3) Serostim is the only HgH indicated for AIDS Wasting and therefore many of its sales may be in a separate market from the other HgH drugs.
4) Manufacturers corresponding to the listed biologics include: Genentech – Protropin and Nutropin; Eli Lilly – Humatrope; Novo Nordisk – Norditropin; Pfizer – Gentropin; Serano Labs – Saizen, Serostim, and Zorbtive; and Teva Pharmaceuticals -- Tev-Tropin.

Source: Medicaid SDUD data.

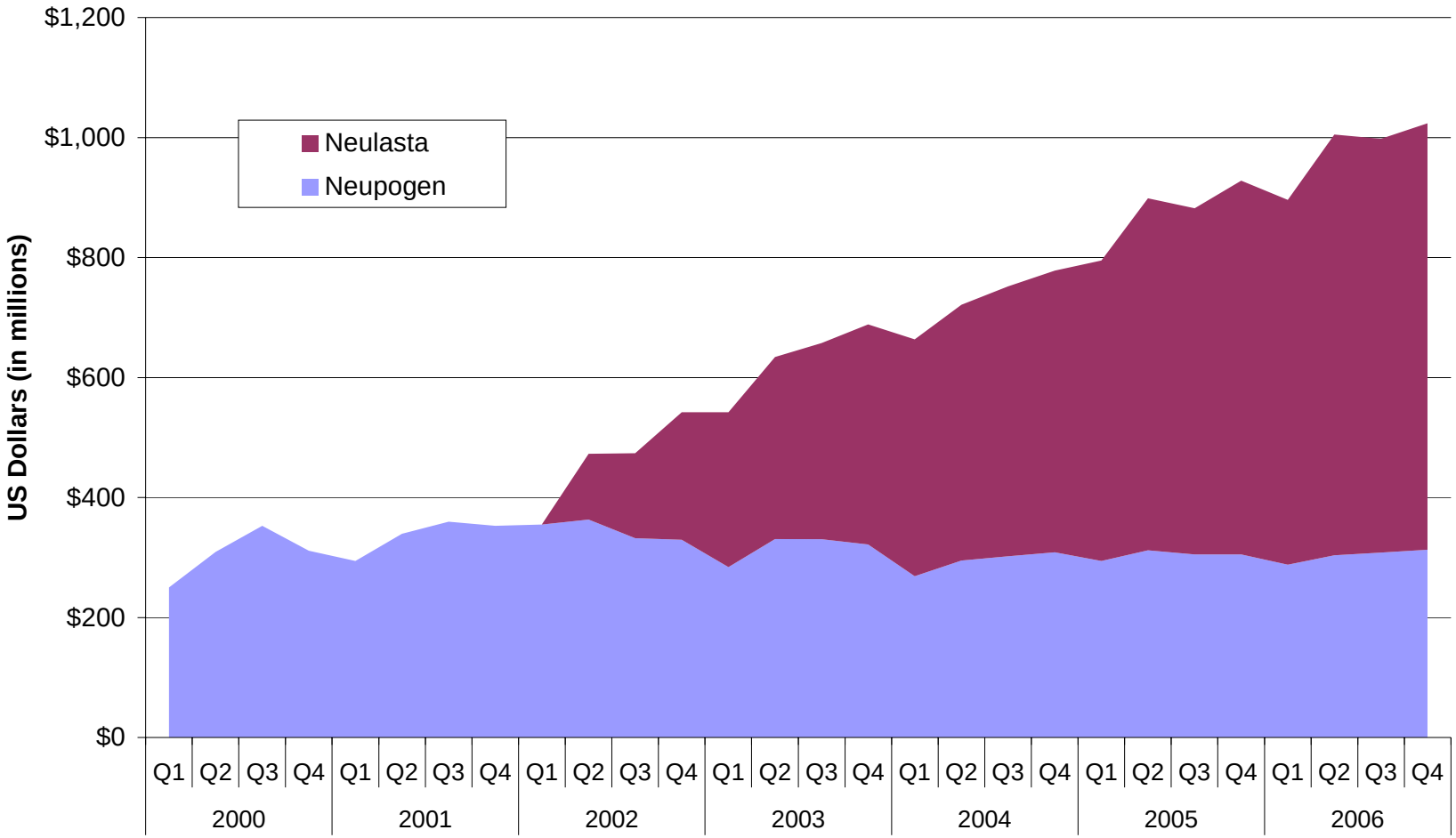
Figure 6: Sales of First Generation (Procrit/Epogen) and Next-Generation (Aranesp) ESA Products



Sources: Amgen 10-K (2000 - 2006), Amgen 10-Q (2000-2006), Johnson & Johnson 10-K (2001-2006), Johnson & Johnson 10-Q (2003-2006), and Tsao, A., "J&J's Rx for the Anxious Investor," *Business Week* , June 27, 2001.

Note: Quarterly sales were estimated for Procrit in 2000, 2001, and 2002 by dividing annual sales by 4 (quarterly sales were unavailable in these years).

Figure 7: Sales of First Generation (Neupogen) and Next-Generation (Neulasta) G-CSF Products



Sources: Amgen 10-K (2000 - 2006) and Amgen 10-Q (2000-2006).

Appendix A. Approved Biologics by Pathway

Product	Company	FDA Approval Date	Approval Pathway
Factor Products			
Advate (Recombinant antihemophilic factor produced without any added human or animal plasma proteins and albumin)	Baxter Healthcare Corp.	July 2003	NDA
BeneFix™ (coagulation factor IX)	Wyeth	February 1997	BLA
Bioclate™ (antihemophilic factor)	Aventis Behring	December 1993	BLA
Helixate® (antihemophilic factor)	Aventis Behring	February 1994	BLA
Kogenate®FS (antihemophilic factor)	Bayer Corp.	September 1989	BLA
NovoSeven® (coagulation factor VIIa)	Novo Nordisk	March 1999	BLA
Recombinate® rAHF/ (antihemophilic factor)	Baxter Healthcare Corp.	February 1992	Unknown
ReFacto® (antihemophilic factor)	Wyeth	March 2000	BLA
Hormone Products			
GenoTropin® (human somatropin)	Pharmacia	August 1995	NDA
Humatrope® (somatotropin)	Eli Lilly and Company	December 1996	NDA
Norditropin®/Norditropin Nordiflex® (somatropin [rDNA])	Novo Nordisk	May 1995	NDA
Nutropin Depot™ (sustained-release formulation of somatropin)	Alkermes, Inc., and Genentech, Inc.	December 1999	NDA
Nutropin® (somatropin)	Genentech, Inc.	October 1985	NDA
Protropin® (somatrem)	Genentech, Inc.	October 1985	NDA
Saizen® (somatropin)	Serono S.A.	October 1996	NDA
Zorbtive™ (Serostim®) (Somatotropin)	Serono S.A.	August 1996	NDA
BioTropin™ (human growth hormone)	Biotech General	May 1995	NDA
Follistim™ (follitropin beta)	Organon (unit of	September 1997	NDA

	Akzo Nobel)		
Gonal-F® (follitropin alfa)	Serono S.A.	September 1998	NDA
Thyrogen® (thyrotropin alfa)	Genzyme	December 1998	NDA
Insulin Products			
Humalog® (insulin)	Eli Lilly and Company	June 1996	NDA
Humulin® (human insulin)	Eli Lilly And Company	October 1982	NDA
Lantus® (insulin glargine)	Aventis	April 2000	NDA
Levemir® (insulin detemir [rDNA origin] injection)	Novo Nordisk	June 2005	NDA
Novolin L® (insulin; zinc suspension;)	Novo Nordisk	June 1991	NDA
Novolin N® (insulin; isophane suspension)	Novo Nordisk	July 1991	NDA
Novolin R® (insulin, regular;)	Novo Nordisk	June 1991	NDA
Novolin® (insulin;)	Novo Nordisk	October 1982	NDA
Novolin® 70/30 (70% insulin isophane suspension and 30% regular insulin)	Novo Nordisk	June 1991	NDA
NovoLog® (insulin aspart)	Novo Nordisk	May 2000	NDA
Velosulin® BR (insulin; buffered formulation)	Novo Nordisk	July 1999	NDA
Vaccine Products			
Comvax™ (Haemophilus B conjugate [meningococcal conjugate] and hepatitis B [recombinant] vaccine)	Merck & Co., Inc.	October 1996	BLA
Engerix-B® (hepatitis B vaccine)	GlaxoSmithKline	September 1989	BLA
Pediarix™ (diphtheria and tetanus toxoids and acellular pertussis adsorbed, hepatitis B [recombinant] and inactivated polio-virus vaccine combined)	GlaxoSmithKline	December 2002	BLA
Recombivax-HB®/Recombivax HB Dialysis Formulation (hepatitis B vaccine)	Merck & Company, Inc.	July 1986	BLA
Twinrix® (hepatitis A inactivated and hepatitis B [recombinant] vaccine)	SmithKline Beecham Biologicals (unit of GlaxoSmithKline)	May 2001	BLA

Monoclonal Antibodies

Avastin™ (bevacizumab)	Genentech	February 2004	BLA
BEXXAR® (Tositumomab and I-131 tositumomab; monoclonal antibody targeting the CD20 antigen and radiolabeled version of the antibody)	GlaxoSmithKline	June 2003	BLA
Campath® (alemtuzumab)	Ilex Oncology, Inc., Millennium Pharmaceuticals, Inc., Genzyme and Berlex Laboratories, Inc.	May 2001	BLA
CEA-Scan® (acritumomab; technetium-99 labeled)	Immunomedics, Inc.	June 1996	BLA
Erbitux™ (cetuximab)	ImClone Systems Inc.	February 2004	BLA
Herceptin® (trastuzumab)	Genentech, Inc.	September 1998	BLA
HUMIRA™ (adalimumab)	Cambridge Antibody Technologies and Abbott Laboratories	December 2002	BLA
Mylotarg™ (gemtuzumab ozogamicin)	Celltech Pharmaceuticals and Wyeth	May 2000	NDA
Orthoclone OKT3® (muromomab-CD3)	Ortho Biotech, Inc. (subsidiary of Johnson & Johnson)	June 1986	Unknown
ProstaScint® (indium In 111 capromab pendetide)	Cytogen Corp.	October 1996	BLA
RAPTIVA™ (Efalizumab; selective, reversible T-cell blocker [subcutaneous injection; self-administered])	Xoma, Ltd. and Genentech, Inc.	October 2003	BLA
REMICADE® (infliximab)	Centocor, Inc. (subsidiary of Johnson & Johnson)	August 1998	BLA
ReoPro™ (abciximab)	Centocor, Inc. (subsidiary of Johnson & Johnson) and Eli Lilly and Company	December 1994	BLA
Rituxan™ (rituximab)	Biogen Idec and Genentech, Inc.	November 1997	BLA
Simulect® (basiliximab)	Novartis Pharmaceutical Corp.	May 1998	BLA
Synagis™ (Palivizumab; recombinantly produced, humanized monoclonal antibody)	MedImmune, Inc.	June 1998	BLA
TYSABRI® (formerly ANTEGREN®) (natalizumab)	Biogen Idec and Elan Corp.	November 2004	BLA

Xolair® (Omalizumab; recombinant DNA-derived humanized monoclonal antibody targeting immunoglobulin-E [subcutaneous])	Genentech, Tanox, Inc. and Novartis Pharmaceuticals	June 2003	BLA
Zenapax® (daclizumab)	Hoffmann-La Roche, Inc., and Protein Design Labs	December 1997	BLA
Zevalin™ (ibritumomab tiuxetan)	Biogen Idec	February 2002	BLA
Interferons			
Actimmune® (interferon gamma-1b)	InterMune Pharmaceuticals, Inc.	December 1990	BLA
Alferon N® (interferon alfa-N3, human leukocyte derived)	Interferon Sciences, Inc	October 1989	BLA
Avonex® (interferon beta-1a; recombinant)	Biogen Idec	May 1996	BLA
Betaseron® (Interferon beta-1b)	Berlex Laboratories and Chiron Corporation	August 1993	BLA
Infergen® (interferon alfacon-1)	InterMune Pharmaceuticals, Inc., and Amgen	October 1997	BLA
Intron A® (alpha-interferon)	Schering-Plough Corp.	June 1986	BLA
Pegasys® (peginterferon alfa-2a)	Roche and Nektar Therapeutics, Inc.	October 2002	BLA
PEG-Intron™ (pegylated version of interferon alfa-2b)	Enzon, Inc., and Schering-Plough Corp.	January 2001	BLA
Pegasys® (peginterferon alfa-2a)	Roche and Nektar Therapeutics, Inc.	October 2002	BLA
PEG-Intron™ (pegylated version of interferon alfa-2b)	Enzon, Inc., and Schering-Plough Corp.	January 2001	BLA
Rebetron™ (combination of ribavirin and alpha interferon)	Schering-Plough Corp.	June 1998	Unknown
Rebif®/Rebif® Titration Pack (interferon beta 1-a)	Serono S.A., and Pfizer, Inc.	March 2002	BLA
Roferon-A® (interferon alfa-2a)	Hoffmann-La Roche, Inc.	June 1986	BLA
All Other Products			
Activase®/Cathflo® Activase® (alteplase; tissue	Genentech, Inc.	November 1987	BLA

plasminogen activator)			
Aldurazyme® (laronidase)	BioMarin Pharmaceuticals Inc. and Genzyme	April 2003	BLA
Amevive® (Alefacept; recombinant, dimeric fusion protein; targets CD45RO+ T-cells)	Biogen Idec	January 2003	BLA
Aranesp™ (darbepoetin alfa)	Amgen	September 2001	BLA
Cerezyme® (imiglucerase; recombinant form of beta-glucocerebrosidase)	Genzyme	May 1994	NDA
Elitek® (rasburicase)	Sanofi-Synthelabo	July 2002	BLA
ENBREL® (etanercept)	Amgen and Wyeth	November 1998	BLA
Epogen® (epoetin alfa)	Amgen	June 1989	BLA
Fabrazyme® (algasidase beta)	Genzyme	April 2003	BLA
FORTEO® (teriparatide)	Eli Lilly and Company	November 2002	NDA
FORTICAL® Nasal Spray (calcitonin salmon)	Unigene Laboratories Inc.	August 2005	NDA
GEM 21S® (GEM 215 is composed of the tissue growth factor, recombinant human Platelet-Derived Growth Factor (rhPDGF-BB), and a synthetic bone matrix, Beta-tricalcium phosphate.)	BioMimetic Therapeutics Inc.	November 2005	Unknown
Geref®	Serono S.A.	October 1997	Unknown
GlucaGen® (glucagon)	Novo Nordisk	June 1998	NDA
Hylenex™ (recombinant human hyaluronidase)	Halozyme Therapeutics Inc.	December 2005	NDA
Increlex™ (mecasermin)	Tercica Inc. Genentech Inc.	August 2005	NDA
INFUSE™ Bone Graft/LT-CAGE™ (device utilizing recombinant human bone morphogenetic protein [rhBMP-2-]/absorbable collagen sponge)	Wyeth and Medtronic Sofamor Danek	July 2002	Unknown
IPLEX™ (mecasermin rinfabate [rDNA origin])	Insmed Inc.	December 2005	NDA
Kepivance (palifermin)	Amgen	December 2004	BLA
Kineret™ (anakinra)	Amgen	November 2001	BLA
Leukine®/Leukine® Liquid (granulocyte macrophage colony-stimulating factor)	Berlex Laboratories	March 1991	BLA
Luveris (lutropin alfa for injection)	Serono	October 2004	NDA

LYMErix™ (OspA lipoprotein)	SmithKline Beecham Biologicals (subsidiary of GlaxoSmithKline)	December 1998	Unknown
Myobloc™ (botulinum toxin type B)	Elan Corp.	December 2000	BLA
Naglazyme™ (galsulfase)	BioMarin Pharmaceuticals	May 2005	BLA
Natrecor® (nesiritide)	Scios, Inc.	August 2001	NDA
Neulasta™ (pegfilgrastim)	Amgen	January 2002	BLA
Neumega® (oprelvekin)	Wyeth	November 1997	BLA
Neupogen® (filgrastim)	Amgen	February 1991	BLA
NeutroSpec™ (formerly LeuTech®) (Technetium [99m Tc] fanolesomab)	Palatin Technologies and Mallinckrodt Imaging (Tyco Healthcare)	July 2004	BLA
Ontak® (denileukin diftitox)	Ligand Pharmaceuticals, Inc.	February 1999	BLA
Orencia™ (abatacept, fully human soluable fusion protein)	Bristol-Myers Squibb Company	December 2005	BLA
Procrit® (epoetin alfa)	Ortho Biotech, Inc.	December 1990	BLA
Proleukin, IL-2® (aldesleukin)	Chiron Corp.	May 1992	BLA
Pulmozyme® (dornase alfa)	Genentech, Inc.	December 1993	BLA
Refludan® (lepirudin)	Berlex Laboratories	March 1998	NDA
Regranex® Gel (gel becaplermin)	Ortho-McNeil and Chiron Corp.	December 1997	BLA
Retavase™ (reteplase)	Centocor, Inc. (subsidiary of Johnson & Johnson)	October 1996	BLA
SOMAVERT® (pegvisomant)	Nektar Therapeutics and Pfizer, Inc.	March 2003	NDA
TNKase™ (tenecteplase)	Genentech, Inc.	June 2000	BLA
Xigris™ (drotrecogin alfa)	Eli Lilly and Company	November 2001	BLA

Note: Unknown approval pathway indicates that there was no relevant listing at the Drugs@FDA website; (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/)

Sources: Approved Biotechnology Drugs, BIO, available at http://bio.org/speeches/pubs/er/approveddrugs.asp

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Generic Medicines: Essential contributors to the long-term health of society

SECTOR SUSTAINABILITY CHALLENGES IN EUROPE

Generic Medicines: Essential contributors to the long-term health of society

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EXECUTIVE SUMMARY

Sustainability has been defined as the capacity to withstand, endure, nurture and prolong over time. An ability to continue that should not be confused with simply surviving, but rather maintaining the vitality and strength to build on, enhance, and thrive.

Today, generic medicines play an essential role in treating disease by increasing the accessibility and affordability of modern day pharmaceuticals in global healthcare systems. The sustainability of the generic medicines sector is vital to ensure that these benefits accrue into the future and essential medicines continue to be made available to as many patients as possible without deference to cost.

The benefits of a healthy and dynamic generic medicines industry – historically and in the future - are evident. Currently over half of the volume of medicines are supplied as generics medicines but this represents just 18% in value terms. The EGA have estimated that, to date, generics medicines in the EU have generated savings in the order of €30 billion, excluding those made from the stimulation of competition with the pharmaceutical sector as a whole. However, with the expansion of the European Union to 27 member states, the accrued savings could certainly be projected to double this figure. Any activity that curbs the role of generic medicines could have disastrous consequences, not only for generics manufacturers but also, more especially, for patients, as well as governments, payers and all other stakeholders involved in the delivery of healthcare.

The long-term sustainability of the generic medicines sector relies on fair prices and a level playing field. Acceptable margins across the entire generic medicines supply chain will be essential if their full value is to be realised. The recent paper '*How to Increase Patient Access to Generic Medicines in European Healthcare Systems*' from the EGA Health Economics Committee highlights the importance of increasing patient access to generic medicines and the benefits to be gained from their faster uptake[1]. Treating them solely as a cost-saving mechanism will serve only to stifle their ability to deliver continued benefits long-term.

In certain countries, particularly where the generic medicines market is well developed, there are a high number of generic medicines companies, thus ensuring healthy competition. Often there is a mix of large international players and local producers. This is a key benefit for smaller generic medicines markets which rely on a local presence to ensure a supply of medicines that would not otherwise be available from outside the country due to low volumes or other issues.
Europe is becoming increasingly dependent on a high percentage of imported generic medicines. Without the appropriate level of control and monitoring, this could easily lead to shortages and problems with supply continuity in those smaller markets.

Globalisation of the generic medicines industry will bring new challenges to Europe which must be met if the sector is not to be marginalised with respect to both pricing and supply.

Innovation has been traditionally perceived as the domain of the research-based originator companies. However, generic medicine companies often spend significant sums on innovating – improving formulations, enhancing delivery systems and finding solutions to patient compliance issues. In 2007, 7% of revenues from the generics medicine industry were spent on research and development alone. Furthermore, sector investments in manufacturing and development facilities have created a solid base of employment (150,000 direct employees in the EU[2]) yielding societal benefits that go beyond the realms of healthcare.

The potential benefits of the generics medicine industry will not be maximised if the focus is on the lowest price alone. There is a need to increase the volume of generic medicines penetration in the EU market and optimise such key areas as competition with in-patent medicines, co-payment policies, time to market, and ready supply. A generic medicine treatment is now available within many of the major therapeutic classes and this is often the 'gold standard' option for specific diseases. Opportunities exist to recommend schedules that encourage initiation of treatment with these 'gold standard' generic medicines. This is a positive sign which should increase the uptake of these drugs and potentially generate long-term savings through the use of a safe and effective therapy at an affordable price.

THE RISING COSTS OF HEALTHCARE IN EUROPE

The provision of an effective and efficient healthcare system in any country is a complex equation balancing appropriate levels of patient care with resources available. Within this lies the need for infrastructures to support both primary and secondary care as well as associated services such as social welfare.

Making direct comparisons of costs and best practices across EU member states is difficult; inherent political differences give rise to highly variable systems. No one country is the same. However, one element that is common to all and often the focus of attention is the cost of medicines.

[1] How to Increase Patient Access to Generic Medicines in European Healthcare Systems: A Report by the EGA Health Economics Committee. Frank Bongers, Hugo Carradinha, June 2009. [2] EGA.

Although medicines generally constitute only around 10% of a country's total healthcare budget (with generic medicines only comprising between 1-2%) they are a prime target for cost savings - despite being arguably the most cost-effective part of the healthcare solution. However, even here, the lack of coherent policies and variations in pricing and reimbursement systems, socio-demographics and the management of healthcare within each EU member state make comparisons difficult. What works in one country may be totally inappropriate in another.

One thing is certain, the ageing population and changes in lifestyle automatically bring an increased demand for healthcare and consequent escalation of costs. Pharmaceutical expenditure has been growing at comparable rates across all the major Western markets (Figure 1), with the developing markets exhibiting greater growth due to expanding access to medicines.

FIGURE 1. Top 10 markets pharmaceutical sales and growth. Audited markets in MAT Mar 2009.

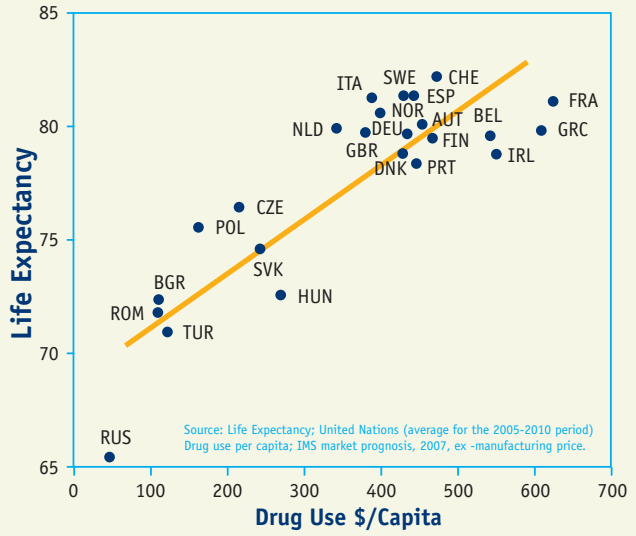
COUNTRY	US$bn 2009	% Mkt Shr 2009	% Growth Const US$ 2009	CAGR 04-08
10 Key Markets	$560.6	77.7%	3.8	5.9
United States	288.5	40.0	2.4	6.3
Japan	71.6	9.9	3.0	3.0
France	41.0	5.7	2.1	5.4
Germany	40.1	5.6	4.2	4.1
Italy	25.7	3.6	3.9	4.1
Spain	22.0	3.0	7.7	8.0
United Kingdom	20.9	2.9	4.1	3.1
China	20.8	2.9	25.2	22.0
Canada	18.0	2.5	5.8	8.1
Brazil	12.0	1.7	11.9	11.6

Source: IMS Health, MIDAS, MAT Mar 2009

Prolonged life expectancy in diseases previously associated with high mortality is also extending the use of longer-term chronic therapy treatments, further increasing the burden on healthcare providers. It is a fundamental principle in medicine that pharmaceuticals can delay or even prevent the need for costly hospitalisation in some patients. Therapies to improve quality of life in patients with terminal diseases are also playing a growing role in the physicians' armamentarium.

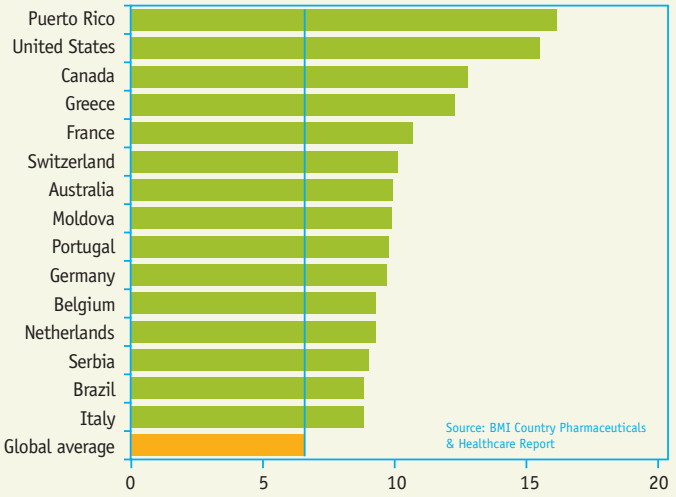
Against this background, it is possible to draw a correlation between life expectancy and pharmaceutical consumption as shown in Figure 2.

FIGURE 2. Link between drug use and life expectancy in an ageing Europe (2005-2010).



Pharmaceuticals undeniably play an essential role in improving and maintaining health, but managing and controlling cost remains a major challenge for society, including governments and payers. Although the percentage of GDP spent on healthcare is fairly consistent in the major EU countries (Figure 3), the absolute amounts available are straining to deliver the desired levels of healthcare.

FIGURE 3. Top 15 Countries According To Healthcare Spending in 2008 as a % of GDP.



COST AND AFFORDABILITY

A successful and innovative pharmaceutical industry brings many benefits. However, these have to be balanced with affordability and external competitive forces in order to provide the appropriate standards of healthcare. It can be argued that the majority of illnesses now have gold standards of therapy available with which patients can be adequately, and successfully, managed. However, there still remain significant unmet clinical needs where the search for new or improved medicines continues.

Certain clinical challenges require medicines based on biotechnologies, which are associated with higher research and development costs. In order to recoup the increased investment, and in part because they are generally intended for a smaller population base, these medicines are often associated with a premium price.

At the same time, development costs for the generic medicines industry are also rising, due to both the increasing complexity of the molecules that are losing protection and the rising burden of regulatory requirements.

It is vital that patients have access to the most appropriate medicines available in order to avoid the longer-term morbidity issues that can arise from non-treatment. Improved access to medicines through affordable generic medicines provides a solution in many therapeutic areas, and policies should be based not only on cost but also on clinical value.

Generic medicines not only offer cost savings but also the ability to ensure that patients continue to receive those gold standard treatments at affordable prices post patent expiry.

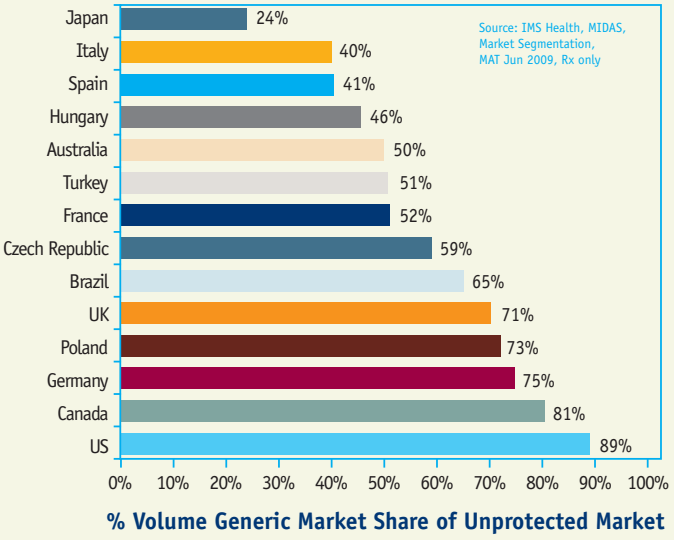
The growing cost of healthcare is unavoidable in today's climate; drug expenditure is forecast to increase by around 5% annually over the next 3-5 years. A long-term approach involving increased utilisation of generic medicines could compensate for some of this rising expenditure without compromising outcomes. In his 2006 paper on sustaining generic medicines markets in Europe[3], Prof. Dr. Steven Simoens underscored the necessity for policy intervention to secure the development of a competitive generic medicines market. However, different measures will need to reinforce each other and be part of a coherent generic medicines policy. For this to happen, strategies must be planned and implemented now.

ROLE AND CONTRIBUTION OF THE GENERIC MEDICINES SECTOR

The role of generic medicines has been to provide essential medicines that are both high quality and affordable throughout the EU. There can be no doubt that their use has increased patient accessibility to medicines and provided significant savings for EU healthcare systems – savings that can, among other things, be deployed to cover the costs of newer, innovative, and generally more expensive medicines that truly add increased clinical benefit if managed effectively.

Due to the differences already noted in pricing and reimbursement systems across Europe it is difficult to accurately project the savings from generic medicines. To a large extent, the magnitude is dependent on the level of utilisation in each country (Figure 4) and the price differentials between them and the originator brand. In the USA, for example, where the use of generics is almost 90% within the off-patent (unprotected) market, savings from their use in 2008 alone totalled US$121 billion. It can be argued that potential savings in many European countries are not fully exploited due to lower utilisation of generic medicines in key therapy areas.

FIGURE 4. Utilisation of generic medicines within the unprotected markets.



The significant contribution arising from the efficient use of generic medicine policies within certain countries cannot be denied. The scope for further savings is dependent on a sustainable generic medicines industry and policy supported by governments, stakeholders and patients.

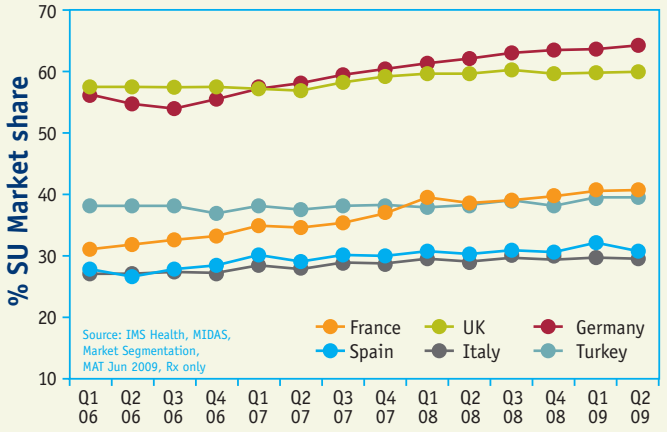
[3] Professor Dr Steven Simoens, Sustaining Generic Medicines Market in Europe, Katholieke Universiteit Leuven, April 2006.

VOLUME PENETRATION AND PATIENT ACCESS

When considered as a proportion of total pharmaceutical consumption within a given country, the volume consumption of generic medicines in the EU is at an even lower level, and highly variable across countries (Figure 5). In the most developed generic medicines markets, such as the UK and Germany, their volume use represents more than half of the total market. However, in less mature generic medicines markets, such as Spain and Italy, volumes remain low. Thus, in order to deliver the full benefits of generic medicines, greater importance must be placed on increasing volume use rather than focusing simply on price. Introducing educational programmes for prescribers, dispensers and patients, to demonstrate the benefits of treatment regimens incorporating generic medicines, could be one useful way of achieving this.

Reducing the price of generic medicines in low volume markets can severely challenge the sector's sustainability. In these countries the cost of maintaining the essential infrastructure related to registration costs, pharmacovigilance and other legal requirements will not be covered by the revenues generated. More affordable and lower-priced treatments will be a natural result of increasing the demand for generic medicines and will raise the level of competition in all markets.

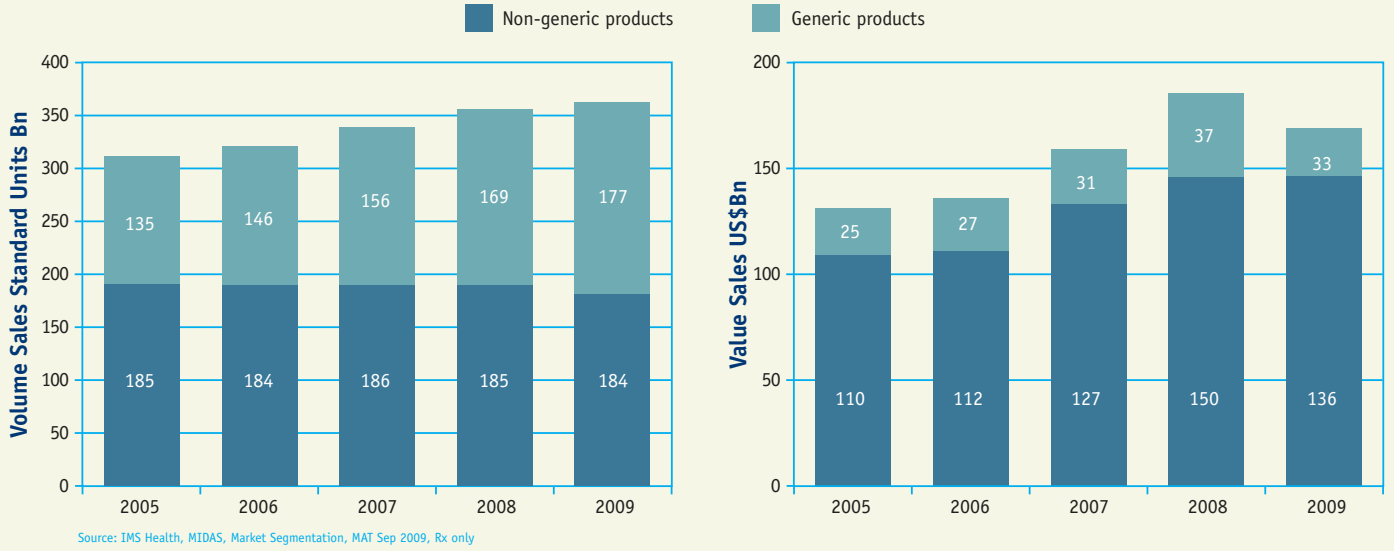
FIGURE 5. Contrasting generic medicines volume penetration in key countries.



VALUE GROWTH AND AFFORDABILITY

Although generic medicines now fulfil over 50% of the demand for medicines in Europe, they still only represent 18% of the total medicines bill. Value growth in the sector is the result of new generic medicines entering the market following patent expiries in the absence of any price increases. Indeed, significant price decreases on many molecules in the major markets, arising from competition or enforced pricing policy changes, has countered value growth each year (Figure 6).

FIGURE 6. In Europe, generics make up almost one half of volume sales, but merely a fraction of value sales.



[4] Final report on the EU Pharmaceutical Sector Inquiry 2008/09. Accessed http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/communication_en.pdf

KEY FACTORS FOR AN EFFICIENT GENERIC MEDICINES MARKET

To maximize the contribution of generic medicines to the affordability and sustainability of the healthcare system, the generic medicines industry must be able to operate within a sustainable, competitive and efficient market model. In order to derive the maximum benefit from a generic medicine it must be available from day one following patent expiry. This may seem obvious. However, in certain markets, generic medicine entry is often delayed, partly by the need to gain pricing and reimbursement approval. Depending on the sales value of the originator product, lost savings can amount to tens of millions of Euros within the first year. In its final report on the EU Pharmaceutical Sector Inquiry (2008/9) the European Commission suggested that the additional savings on the 219 prescription medicines investigated could have been as much as 20% higher if there had been no delays to entry[4].

As noted earlier, pricing systems in each country vary widely. Some directly link the price of the generic medicine to the originator price whereas others have 'dynamic freedom' of pricing and leave it to competitive market forces to dictate prices. Whatever the system, the potential savings are significant; accrued benefits over the years from generic medicines are estimated to be in excess of €100 billion in the major EU markets.

HEALTHY COMPETITION

Stimulating competition between generic manufacturers not only means lower costs for patients but also drives product improvements, distribution efficiencies and improved access to all medicines. Whereas an originator product usually comes from a single source, generic medicines are typically multi-sourced, with several generic medicine manufacturers producing the same product. This generally assists continuity of supply for particular medicines which can be important at times of increased demand, such as unexpected requirements for anti-infectives during an influenza epidemic.

SUPPLY CONTINUITY

A further benefit of generic medicines arises from the sector's continual provision of products many years after the patent has expired. The originator may have exited from the market for several reasons after loss of patent protection but invariably because of low volume demand leading to limited commercial opportunity. It is often the generic medicine that remains on the market, meeting the needs of patients for whom there may be no suitable therapeutic alternative for their particular condition.

ESSENTIAL INVESTMENT

Investment and employment within the generic medicines sector is vital for some member states. It is estimated that the European generic medicines industry consists of more than 700 companies directly employing around 150,000 people. Research from the largest generic medicines employer in Germany has shown that although they 'only' employ 1,300 staff, by doing so they create a further 2,000 jobs locally and in the region of another 1,400 jobs nationally. In economic terms, through direct spending, they generated "value-added" benefits in 2008 of approximately €140 million locally or about €243 million nationwide. A careful extrapolation of this value would indicate that the European generics industry represents significant economic value within the community.

In some cases, it is the local generic medicines industry that sustains employment in a country's pharmaceutical manufacturing sector as originator products are often imported from a central manufacturing site. Consolidation within the generic medicines industry is threatening this position but countries with low-cost manufacturing potential may benefit, as well as those companies that are able to identify niche or local country-specific opportunities.

CHALLENGES TO THE EUROPEAN GENERIC MEDICINES INDUSTRY

Some of the major challenges to the generic medicines industry in Europe arise from increasing costs in a market undergoing constant price erosion, unsustainable policies and an unequal playing field compared to other geographical regions with regard to taxes, regulations and incentives. All of these limit the competitiveness and sustainability of the European generics sector.

LIMITATIONS ON PRE-EMPTING PATENT EXPIRY

The introduction of the Bolar provision in Europe[5] has now enabled European manufacturers to develop generic medicines within Europe prior to patent expiry. Previously, this could only happen in certain countries where different patent positions or non-observance or non-existence of patents made it possible.

Notwithstanding this advance, certain restrictions still inhibit such development within Europe - the main one being the manufacture of commercial batches within the EU prior to patent expiry. As a result, products developed and manufactured in those 'non-patent' position countries can be on the market earlier than any product manufactured in Europe – a position that is achieved by importing finished product on the day of patent expiry having already gained approval for its release using samples from the commercial batches. For European generic medicine companies this has meant continually having to develop many key molecules

[5] Directive 2004/27/EC: An exception to patent infringement for obtaining EU marketing authorization of a generic or similar medicinal product.

outside the EU – including manufacturing which must take place in the same country as product development to meet the day one launch.

Generally speaking, products are manufactured where they are developed because of the need to link the regulatory dossier with the site of manufacture. Although not a barrier this does add a further hurdle of complex logistics.

Allowing the manufacture of commercial quantities in the EU prior to patent expiry, ready to launch on day one following loss of exclusivity, would encourage the development and manufacture of more generic medicines within Europe – and avoid the delays and missed opportunities for manufacturers and healthcare providers.

IMPORTATION

Importation into Europe poses few major hurdles for overseas generic medicines manufacturers. Conversely, exporting into these markets is often far less favourable given the strong incentives that exist for the local industry - including export subsidies, tax breaks and grants for building production or development facilities. Indeed, many European companies are starting to take advantage of these benefits to the detriment of investments in Europe.

INCREASINGLY STRINGENT REGULATIONS

The generic medicines industry also faces an increasing regulatory burden such as pharmacovigilance requirements, periodic safety updates (PSURs) and the introduction of Braille packaging. Rising costs in quality assurance, anti-counterfeit measures and product security are also a major challenge and must all be absorbed without the ability to counter them with price adjustments. Regulatory authorities gather around 70% of their income from generic medicine manufacturers, reflecting not only the multiplicity of submissions for the same molecule but also the numerous variations they are required to submit.

COSTS AND PRICING

In most instances, manufacturing cost levels for generic medicines are the same as those for an originator product. Often, the only flexible parameter for reducing costs lies within the price of the active pharmaceutical ingredient (API) which may fall over time as API manufacturers face their own competition. All other costs tend to be fixed, with little room for manoeuvrability. This is the reason why any downward pricing adjustment by an originator company prior to generic entry creates problems for the generic medicines manufacturer. In this instance, any price linkage requiring the generic medicine to be set at a permanent fixed percentage discount to the originator will seriously disadvantage its introduction and financial viability.

Initial price linkage may be necessary but should not be continued throughout the lifecycle of a generic medicine as it can be a major barrier for products with high development costs and relatively slow product uptake. This includes, for example, biosimilars or products with a 'narrow therapeutic index'. As prices sink ever lower, the sustainability of some molecules in certain markets becomes increasingly questionable.

In most countries, legislation only allows reimbursement prices to go down and this becomes an issue with infrastructure costs such as salaries and energy costs increasing year-on-year. In this event the conflict becomes self-perpetuating.

Pharmaceutical markets in the EU are national, each with their own drivers and systems. Some member states are taking steps to learn from other healthcare systems with a view to adopting them in their own country. However, it is important to remember that what works in one country may not yield the same benefits in another. Systems are not always compatible with the basic healthcare infrastructures in other countries. If all countries were to adopt the lowest price approach, sustaining the current supply of generic medicines in all countries would be a major challenge.

TENDERING

In this respect, one major threat to the generic medicines industry is a change in the procurement method for generic medicines. Fragile systems have been disturbed since elements of tendering were adopted in Denmark, Germany and the Netherlands, producing what may only be considered as some short-term savings. This has also had some unsettling financial effects regarding the stability of some pharmacists and wholesalers as well as problems with continuity of supply as seen in the Netherlands and Germany

From the generic medicines manufacturers' position the impact of tendering in the long-term could lead to major changes in the industry, including reduced investment in not only the more complex molecules and biosimilars but all prospective new generic medicines - especially more traditional molecules which may have a lower market value. Few companies could afford to run the risk of committing large sums only to find themselves unable to recoup their investments or left with large inventories if they are not awarded a supply contract upon approval.

There is continued interest in the European generic medicines market from the Indian and Chinese-based industry. These countries see Europe as an opportunity to fully utilise their manufacturing capacity for finished dose forms and APIs at marginal cost. This places the European-based industry at a severe disadvantage as it is often the low cost overseas players that are able to drive down prices and maximise their market share through tendering, which requires little European infrastructure.

BIOSIMILARS

The next category of products considered most likely to generate significant savings will be biosimilar medicines. Products derived from biotechnology are among the fastest-growing medicines and often considered expensive. If savings are to be generated, there is a need for early clarification of the regulatory approval pathway for biosimilar products. Although Europe is seen to lead the way here, there is still uncertainty around complex, large molecules e.g. monoclonal antibodies. More transparent requirements would not only speed their development but also encourage more companies to invest, raising competition in this very important market sector.

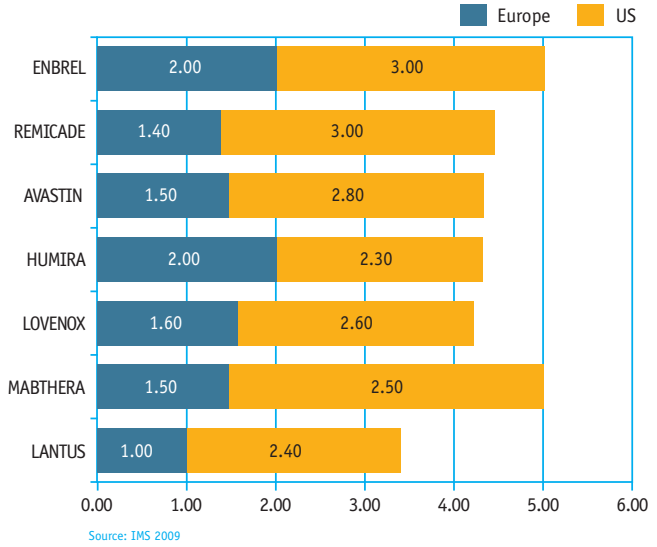
Biosimilar approvals are based on stringent submission requirements, including substantial clinical studies. Accordingly, their associated development costs are significantly higher than for small molecule generic medicines; estimates range up to US$150 million for each molecule. Additional high-cost risk management plans must also be produced and implemented. Global development programs for biosimilar products are also a must; not even large, financially healthy companies can afford to duplicate such expensive pre-clinical and clinical studies in each country or region in the world. There is also a clear need to develop a consistent scientific global approach to regulating these products.

As a novel segment, biosimilar medicines are proving a challenge to bring to market. In addition to the high costs of development, unfamiliarity with the product class and misinformation has created a significant need for promotion. Furthermore, with lack of clarity around their inter-changeability and substitution with the originator reference product they have been generally slow to gain market share.

The ability of the biosimilar medicines' company to recoup this investment is vital to secure the development of second generation biosimilars and achievement of the full value and savings they can bring.

Products based on biotechnology are indeed significant contributors to the rising cost of the drugs bill in all countries. Savings from traditional generic medicines will not be able to compensate for this escalation in drug expenditure, with the resultant inability of payers to control costs. Increased competition and market penetration of biosimilar medicines provide a major opportunity to control the costs and availability of biopharmaceutical medicines. It is estimated that a 20% price reduction could result in savings in excess of €1.8 billion.

FIGURE 7. Biopharmaceuticals with High Biosimilar Market Potential – Top 6 Biopharmaceuticals, in bn USD (2009).



DELAYING TACTICS

The recent EU Pharmaceutical Sector Inquiry highlighted the issue of practices employed to delay or even block the entry of generic medicine competition. Instruments used by the originator companies concerning the products reviewed were found to have delayed entry by more than seven months post loss of exclusivity (LoE).

The use of patent clusters - allowing a medicine to be protected by up to 1,300 patents or patents pending - leads to a lack of transparency for the generic medicine developer. The ensuing litigation can take several years (on average 2.8 years in the Inquiry report) and be a costly exercise for the generic medicine company. This cost will eventually have to be passed on to the payer or patient through pricing, which again erodes the potential saving from the generic medicine. Furthermore, in 75% of the European Patent Office opposition cases started by generic medicine companies, patents are revoked or restricted. Interventions before competent authorities, based on patent linkage or claims of minor quality, have delayed the generic medicines market entry on average by four months.

Generics won 62% of the 149 litigations that proceeded to trial. Of the 700 total started litigations, 223 were settled, with 50% of those settlement agreements containing what the Commission consider to be a limitation on generic entry. Some were associated with a direct payment from the originator company or a license and distribution agreement.

The threat of litigation is, for some smaller generic medicines companies, a major deterrent. For the larger companies it involves not only cost but lengthy use of legal resources that could be utilised elsewhere. Clearly, patents and intellectual property should be defended. However, the results of the Inquiry surely indicate that defence is often initiated from weak ground in many cases. The existence of a 'community' patent and a single European patent litigation system would go a long way to removing some of these commercially inspired defensive patent strategies. Whatever the consequences, the emphasis should now be on a quick implementation of the recommendations in order to bring transparency to what is often a delicate area for all concerned.

BIOEQUIVALENCE

Some originator companies continue to imply that generic medicines may be less safe and effective than the branded counterpart. This is considered to be an unfounded claim. Indeed, a recent review and meta-analysis looking at the clinical equivalence of generic and brand-name drugs used in cardiovascular disease showed no superiority of the originator medicine over the generic medicine[6]. In the absence of sound clinical data, the use of a 'fear factor' in misinforming the public by the originator company should be prevented.

PATENT LINKAGE

Delays to generic medicine entry are sometimes caused by regulations in certain countries with regard to pricing approval following marketing or price and reimbursement authorisation. Further delays may then be encountered whilst waiting for reimbursement status, as shown in Figure 8.

Interpretation of the regulations in some countries may even delay granting of the marketing authorisation through a mechanism known as 'patent linkage'. In Portugal there are currently 140[7] law suits before the administrative courts using a specific provision of the Portuguese constitution to delay entry.

Originators have alleged that granting a marketing authorisation constitutes a violation of their process and product patents. This is despite EU legislation which states that the granting of a marketing authorisation should be based solely on quality, safety and efficacy data and not on other criteria such as economic factors. The administrative courts have even ignored claims from the generic medicines companies that their products do not infringe the patents. They have recently suspended the granting of marketing authorisations and pricing and reimbursement approval for a wide range of key molecules including atorvastatin, clopidogrel, escitalopram and others. These actions deprive patients in Portugal access to affordable medicines and delay potential savings for the payers (Figure 9 overleaf).

The Transparency Directive 89/105/EEC lays down maximum time-limits of three or six months for pricing and reimbursement decisions. This does not preclude Member States from establishing quicker decision making procedures where deemed appropriate.

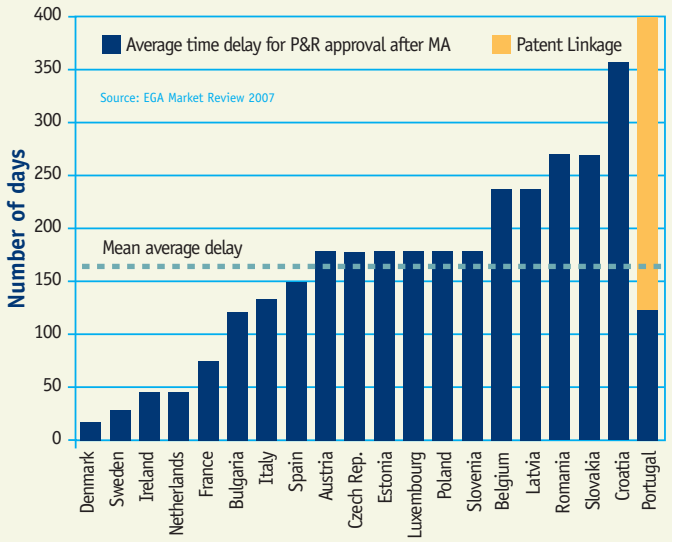
FIGURE 8. Time delays by country for price and reimbursement approval

COUNTRY	Austria	Belgium	Bulgaria	Croatia	Czech Rep.	Denmark	Estonia	France	Ireland	Italy	Latvia	Luxembourg	Netherlands	Poland	Portugal	Romania	Slovakia	Slovenia	Spain	Sweden	Total Yes	Total No	Total
Average Time Delay for Price Approval	180	90	90	180	90	14	90	75	45	135	120	30	N/A	180	21	90	120	15	75	30			
Average Time Delay for Reimbursement Approval	180	180	30	180	90	14	90	75	45	135	120	180	45	180	90	180	150	180	75	30			
Are the Applications for P&R of generic medicine's simultaneous?	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	No	Yes	No	Yes			
Average Time Delay for P&R Approval after MA	180	240	120	360	180	14	180	75	45	135	240	180	45	180	111	270	270	180	150	30			

Source: EGA Market Review 2007

[6] Clinical Equivalence of Generic and Brand-Name Drugs Used in Cardiovascular Disease: A Meta-Analysis. Kesselheim AS, Misono AS, Lee JL, et al. JAMA, 2008; 300(21):2514-26.
[7] Apogen, 7th December 2009

FIGURE 9. Time delay for price and reimbursement approval for a generic medicine after granting market authorisation.



Commenting on this issue, the EU Pharmaceutical Sector Inquiry recommended amendments to policies in those countries where delays have occurred. The Commission even went as far as to invite Member States to consider the granting of automatic/immediate pricing and reimbursement status to generic medicines where the corresponding originator product already benefitted from reimbursement based on a higher price. They concluded that this would considerably alleviate the administrative burden for all concerned and lead to faster access of generic medicines. This should happen sooner, not later.

The Inquiry was also critical of other delaying tactics such as 'settlement agreements' between originators and generic companies, abuses of a dominant market position and defensive patenting strategies.

THE GENERIC MEDICINES MARKET AND KEY DYNAMICS

The global pharmaceutical market is currently valued at US$720 billion, growing at 5% per year (MAT, March 2009). In Europe, the market is estimated at US$236 billion, growing at 5.8% per year, with a forecasted increase of a further US$45 billion in the time period 2008 to 2013.

Based on IMS MIDAS Market Segmentation data, the generic medicines market has an estimated value of €57 billion in the top 8 global markets with growth of around 8% in 2009, up from 3% in the prior twelve months. In Europe, the EGA estimate that the generic medicines market size is €31 billion and growing at rate of approximately 6% per annum. However, growth figures can be misleading for payers because they often overlook the fact that for each €1 increase in the value of the generic medicines sector, almost €3 on average are saved on total pharmaceutical expenditure. This reflects the lower price of the generic medicine used when compared to the price of the originator product, had this been prescribed. Thus, the higher the growth in the generic medicines market, the greater the savings that are made.

PRICING DYNAMICS

Pricing policies, reimbursement levels and generic medicines substitution are key dynamics in the generic medicines market. In some countries, such as Italy and France, the price of the generic medicine is directly linked to the price of the originator product whereas in other markets, such as the UK, there is relative freedom of pricing with competitive forces setting the price.

The pricing level in each country therefore varies considerably but generic medicines prices are always lower than the originator price, hence the potential for savings. While it is impossible to have one system throughout, for all the reasons we have mentioned, it is important to have coherent systems that create room for competition. The French system, for example, stimulates competition without destroying prices, thus delivering significant savings to the medicines bill yet maintaining adequate margins within the supply chain to provide the required service levels.

It should be noted, however, that if the price of generic medicines is very low, the incentive for pharmacists to dispense them is minimal since part of their remuneration is frequently based on the value of each item dispensed. Unless they are compensated for this loss in another way, pharmacists may not give full support to any generic medicines initiative. Noting the financial disincentives to dispense generic medicines that exist in many EU countries, Prof. Dr. Simoens in his paper goes on to show that where companies offer discounts to pharmacists, healthcare payers and patients do not capture the potential savings from generic medicines. Thus, price and reimbursement levels for generic medicines are important for all parties.

GENERIC SUBSTITUTION

Where patient co-payment policies are in place, generic medicines offer a lower financial burden for the patient but may be less attractive for the pharmacist to dispense. This depends on the regulations governing pharmacist reimbursement. For example, where the pharmacist receives a percentage of the price there is actually a negative incentive to dispense a generic as generics are always priced lower. This is where substitution rules may become important. Compulsory substitution for a prescribed originator medicine requires the pharmacist to dispense a generic medicine in order to be reimbursed. Optional substitution can be less effective as it allows the physician to specifically request that a particular product is not substituted. Some substitution rules include a price element whereby only generic medicines within a certain price band may be used as the substituted product.

The degree of generic medicine penetration and utilisation therefore also varies widely from country to country because of the local dynamics on the supply and demand side.

CHANGES IN PROCUREMENT

To date, the main focus around generic medicines has been on cost. Indeed, when governments see the growth in this sector they all too often assume that it is thriving and successful. In reality, many smaller generic medicine companies are struggling to stay in business; even the major ones deliver less than half the net income of the originator companies. Enforced price reductions, international reference pricing and procurement through tendering put the long-term future of the generic medicines industry at risk.

If 'tendering' is to remain then tenders for new generic molecules should only be considered after a period of time following launch, to enable a competitive position to be established. Generally speaking, tendering currently results in selection of the lowest priced product and for reasons explained earlier, supplies will then likely be sourced from manufacturers outside of the EU. Tendering currently predisposes to a monopoly supply position leaving exposure to all the threats and consequences associated with such a strategy.

Multi-sourcing of generic medicines within Europe is one of the competitive forces that ensure low prices, choice and continuity of supply. Complex logistics can further increase risks to continuity of supply especially if demand increases unexpectedly. Potentially a non-supply situation could arise if alternative sources of the product are no longer available in certain countries. Stock-outs with generics are inevitable at some point in time for a variety of reasons. Even if payers can contractually recoup costs from the manufacturer in the event of inability to supply, this may still lead to a patient being unable to access his usual medicine. Thus, tendering for generic medicines could in the long-term lead to an increase in costs as players withdraw from the market; indeed experience in the Netherlands has already seen manufacturers withdrawing certain molecules. Tendering also selects the lowest priced product on offer, ignoring all other attributes, which may be to the long-term detriment of the patient.

Tendering will certainly encourage consolidation which may or may not be in the interest of certain countries or players.

The 'Sunset' clause associated with market authorisations[7] could also lead to issues for manufacturers in the event of being unable to find a market for their products.

DISTRIBUTION

One key element in the market is the changing role of distributors in the generic medicine supply chain. Vertical integration (wholesaler acquisition of pharmacies) has seen wholesalers moving over time from logistics providers to customers. Some have even adopted their own private label supply of generic medicines. However, the major issue is the margin that generic medicines can offer to wholesalers and this has been exacerbated with the move by originator companies to a direct-to-pharmacy or customer approach. This has limited access to certain products for some wholesalers as well as squeezing margins, meaning that distribution costs for generic medicines as part of their overall business are causing financial issues. Where the fee for distribution is a fixed percentage of the medicine's price then the cost of distributing a product which cost just a few cents a pack is not financially viable. The challenge for distributors is compounded when you consider the extremely low prices resulting from tendering of generic medicines in some markets.

Proposals for a fee for each pack of generic medicines delivered have been suggested but, as already indicated, there is little margin within the price of a generic medicine to cover this additional cost in the absence of a price increase. This will only further discourage the supply of generic medicines in a market unless an equitable solution for both manufacturer and distributor can be found.

[8] EC 726/2004: Marketing authorisation lapses if the product is not placed on the market within three years of being granted authorisation or if it was previously on the market and has not been for a period of three consecutive years.

Rules and Incentives															
Market Rules	Mandatory price reduction	✓	✓					✓		✓	✓				✓	
	Patient co-pay		✓	✓			✓			✓	✓	✓	✓		✓	
	Price referencing			✓	✓	✓	✓		✓		✓	✓	✓	✓		
	Pharmacy-level substitution				✓	✓				✓	✓		✓	✓		✓
Market Incentives	At the pharmacy				✓	✓			✓	✓	✓		✓	✓		✓
	With the health insurers						✓			✓						
	With wholesalers										✓					
	With payers	✓	✓			✓										
	Favouring brands							✓				✓				
	Favouring generics	✓		✓			✓		✓		✓			✓	✓	✓

FIGURE 10. Differing rules & incentives for use of generic medicines across EU markets leads to different market forces.

MARKET RULES AND INCENTIVES

Market forces vary across the EU depending on whether the healthcare system in place focuses attention on physicians, pharmacists, wholesalers or payers (Figure 10).

Some degree of substitution, whether automatic or optional, exists in most EU countries which encourages generic medicine utilisation.

Only a few EU countries actively support the generic medicines industry publicly. Italy and Portugal are among the main proponents with public campaigns focused on increasing generic medicine consumption and changing physicians and pharmacists prescribing and dispensing habits, as well as increasing patient acceptance of and demand for generic medicines.

GENERIC MEDICINES: MARKET IMPACT

The generic medicines sector is dependent on a thriving R&D-based industry launching and developing a rich pipeline of innovative medicines.

With development costs for new medicines rising (particularly in the field of biotechnology), greater regulatory hurdles and tougher market conditions, fewer new products are being launched and those attaining 'blockbuster' sales of over US$1 billion are declining. The introduction of a generic medicine at the time of patent expiry puts further pressure on the R&D-based companies. Brand share erosion or switching to a generic medicine, generally now occurs quicker than ever before, with the UK and Germany being the fastest. However, in certain countries, such as Spain and Italy, erosion not only takes longer but also ensures that the level of switching is kept low (Figure 11).

Some R&D-based companies are finding it difficult to replace sales lost to generic medicines with sales generated from new products. This has led to many companies diversifying or consolidating while at the same time stimulating true innovation in the search for new medicines.

One thing is certain, in today's environment the R&D-based industry can no longer depend on the historical business models delivering the same levels of return.

FIGURE 11. Degree of generic erosion following loss of exclusivity.

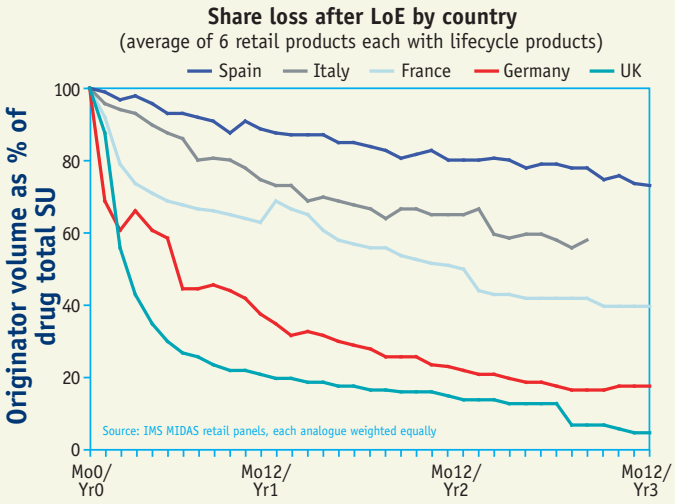
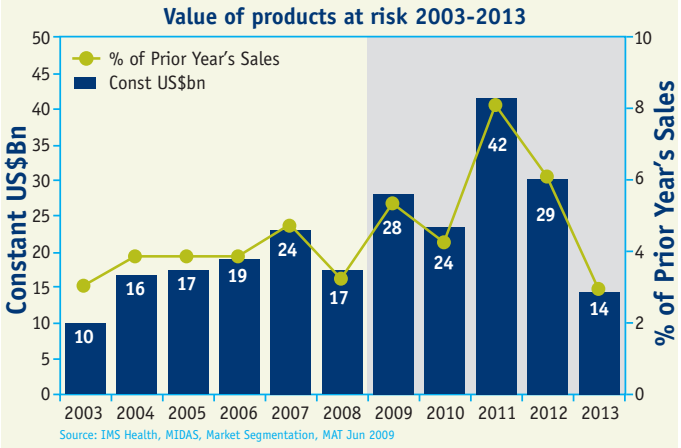


FIGURE 12. Medicines with a value of $137 billion are losing patent protection in 8 key markets (Canada, France, Germany, Japan, Italy, Spain, UK and US) through 2013.



Over the next five years, medicines with a value of over US$137 billion will lose protection in the eight major world markets, bringing further challenges to the R&D-based industry (Figure 12).

Utilisation of generic medicines in place of these patented medicines in the future offers a huge potential for savings.

With each new generic launched, additional pressure is brought to bear on originator products as Health Technology Assessments (HTAs) focus on cost of therapy. Their demands for ever increasing amounts of data on cost benefits leaves 'Me Too' products with little space in today's markets.

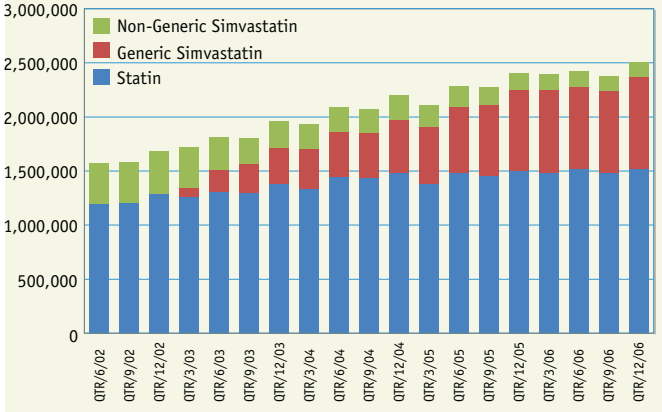
EXTENDING MARKET MONOPOLY BY LIFECYCLE STRATEGIES

The threat of significant revenue losses from patent expiries has led originators to develop enantiomers or different polymorphs or salts of blockbuster products in order to prolong the lifecycle of the brand.

Molecules such as omeprazole, citalopram and loratidine have been replaced by esomeprazole, escitalopram and desloratidine, respectively. Despite comments that they offer only limited advantages, if any, over the original medicine, in many instances, supported by large advertising and promotional expenditure, they have successfully switched physician prescribing from the original brand to the 'new' product. This has resulted in the loss of significant savings for payers and indeed continuing growth in expenditure for these molecules through the extended patent life of the new alternative.

[9] Generic Bulletin, 2008

FIGURE 13.
C10A Cholest&Trigly Regulator market - Volume.



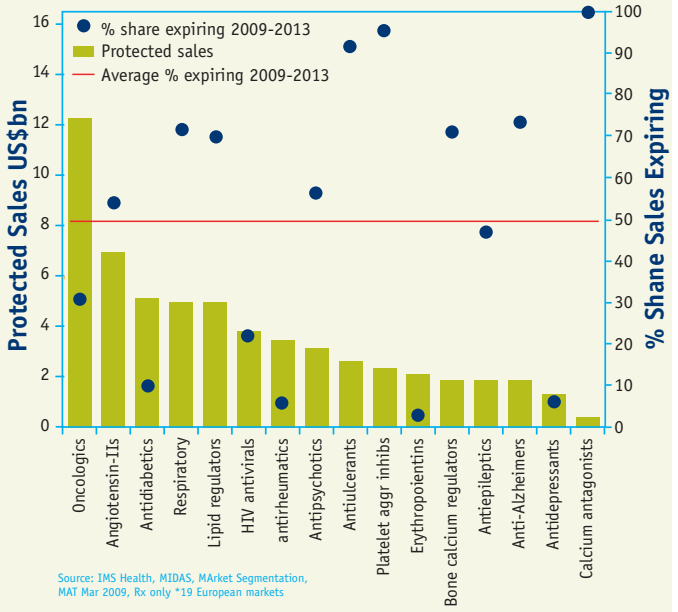
More recently, the pharmaceutical firm Servier was accused by the Danish generics industry (IGL) association of using the practice of evergreening in Denmark to extend the life-cycle of their product Coversyl©, an antihypertensive product, by introducing onto the market a "therapeutically identical" version of Coversyl©, called Coversyl Novum©. As reported in the industry press: "By promoting Coversyl Novum—which contains perindopril arginine rather than the original tertbutylamine salt—at different strengths to the original, Servier is attempting to protect its monopoly on the ACE-inhibitor...."

The costs of Coversyl Novum© to the Danish healthcare system in 2007 was €10.7 million. According to the IGL, the use of the generic formulation could potentially have saved the authorities €8.1 million.[9]

Generic entrants have the potential to impact a whole therapeutic category as evidenced when a gold standard therapy loses patent protection. The launch of a generic medicine version of the leading anti-ulcer drug omeprazole made the drug affordable for use in less serious conditions such as gastro-oesophageal reflux, in addition to the savings in ulcer therapy. A similar effect was shown when generic simvastatin entered the market. A lower, affordable price supported with positive clinical data expanded the statin therapy category, opening up lipid treatment for a whole new population of patients (figure 13).

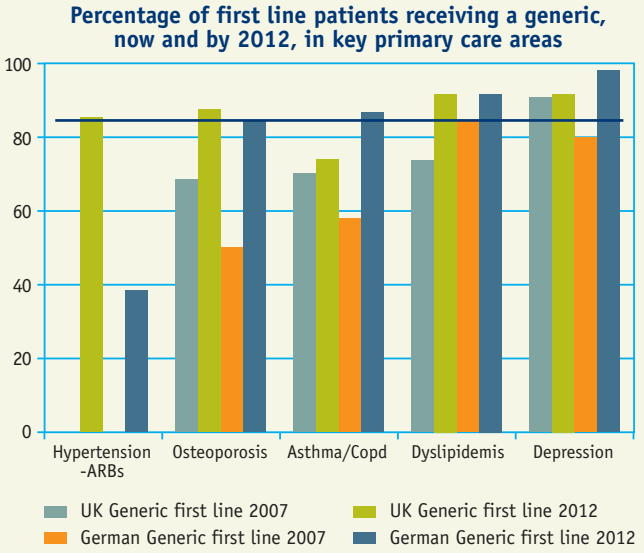
The potential for greater savings will continue as a range of products lose patent protection in many therapy areas over the next five years (Figure 14 overleaf). It is for this reason that most R&D-based companies are focused on delaying or preventing the entry of a generic medicine; as soon as it is launched the continuing existence of the brand is under threat.

FIGURE 14. Key therapy classes face significant generic exposure in Europe* in the next five years.



Source: IMS Health, MIDAS, MArket Segmentation, MAT Mar 2009, Rx only *19 European markets

FIGURE 15. Potential exists for Payers to recommend a generic medicine as first line therapy in key primary care areas.



Source: IMS Disease Analyser Germany, UK, 1st line use defined as new to pharmacotherapy – ARBs=Angiotensin II receptor antagonists (antihypertensive class)

Whatever it takes, the generic medicine industry should not be subject to unfair practices which either reflect abuse of a dominant position or disincentivise the use of generic medicines by R&D-based companies. This may be applicable if the originator companies find that the risk to their business of lost patent protection on major products over the next three years is sufficiently high to warrant new pricing strategies or changes to the way patients access these medicines.

OPPORTUNITIES ARISING FROM INCREASED USE OF GENERIC MEDICINES

DRIVING FIRST-LINE USE

One alternative to focusing on the price of generics could be a treatment regimen approach for some of the major indications where generic medicines represent the gold standard therapies. The opportunity to commence first-line therapy with a generic medicine exists in many of the most common disease areas (Figure 15).

This formulary-style approach would give confidence in using the appropriate medicine whilst at the same time providing a sound basis for calculating future costs of therapy in these selected areas. Competition between generic medicine manufacturers would still remain as they have duplicate product portfolios, and continuity of supply would not be an issue. Adequate reimbursement schemes could then be formulated for pharmacists to ensure profitability and confidence in dispensing generic medicines.

INCENTIVISING INNOVATION

The development expertise within the generic medicines industry is recognised as being innovative. Indeed, it is the level of skill in chemistry and process development that has driven the successful introduction of so many generic medicines. Furthermore, there is an understanding within the industry of patient and pharmacist needs in relation to patient-oriented packaging, arising from the production of a wide range of products across many countries. Certain generic medicine companies have produced packaging specifically designed to help patients and minimise pharmacy dispensing errors. Others have developed fixed combinations of routinely co-prescribed off-patent medicines such as diuretic/potassium conserving and non-steroidal/proton pump inhibitor combinations to aid patient compliance. If the pressure is only on costs without any incentive for advancements in this area then the potential will never be manifested.

Once an originator product loses exclusivity, most research is terminated; in fact it may cease well before this time as the period to recoup any additional research costs will be limited. Many older generic medicine molecules never maximised their therapeutic potential for this reason. In some instances, new indications or uses did appear but much later than might have been expected had the appropriate level of research continued. Unless rewarded, opportunities for further development will never be pursued and yet the benefits to patients could be significant.

ENCOURAGING INVESTMENT

The European generic medicines sector has to compete on a global scale, which includes competition from manufacturers with facilities outside of Europe. Lack of flexibility in regulatory procedures and financial incentives has sent European-based pharmaceutical development and manufacturing into a decline. Although a positive move, the Bolar provision does not go far enough to level the playing field for European-based generic medicines manufacturers.

The existence of grants and low interest loans for building production facilities and export incentives with tax breaks in non-European countries produces cost advantages which cannot be obtained within the EU.

The opportunity exists for governments and payers to incentivise the European generics medicine sector in order to generate a sustainable generics medicine industry which can deliver cost savings through good patient management with gold standard therapies at affordable prices.

CONCLUSIONS

The generic medicines industry is now an essential and integral part of healthcare delivery across Europe, supplying over half the volume demand for medicines but representing less than 18% in cost terms. Its contribution to savings in pharmaceutical expenditure and broader access to medicines has secured the provision of quality healthcare across the region. Without the presence and availability of affordable generic medicines it is doubtful whether governments and payers could have sustained the growing demand for medicines.

The potential savings in the major markets from utilisation of generic medicines in place of those originator brands losing exclusivity over the next four years is projected at around US$100 billion, the highest ever level. Beyond this period, the number and nature of opportunities for savings diminishes as products from biotechnology replace small molecule medicines. With generic medicines unable to compensate for the growth arising from innovative products, pharmaceutical expenditure will escalate.

The savings arising in the next four years should be used to formulate a longer- term plan for the utilisation of generic medicines.

The gold standards of many therapies in the treatment of cardiovascular disease, CNS disorders, GI problems and many other chronic ailments are available now (and certainly will be in the near future) as generic medicines. Initiation and continuation of therapy through treatment schedules in these disease areas should involve the use of a generic medicine as first-line therapy. This would generate sustainable savings allowing for the use of truly innovative medicines in those diseases requiring such therapy.

Attempts to control medicine expenditure using price as the sole parameter not only puts the generics industry at risk but also all the players involved in healthcare delivery, including pharmacists and distributors. Enforced and unpredicted price cuts cause serious damage across the industry, having a destabilising effect and making planning impossible. This will be to the detriment of any healthcare system in the longer-term.

The varied nature of healthcare systems within Europe means that what is successful in one country may not be applicable in another. Importing one aspect of healthcare from another country could have major consequences.

The generic medicines industry is perceived as a threat to the R&D-based sector. However, recent examples of diversity witnessed within originator companies reflect the changing dynamics and will lead to increased competition across all markets. This should be to the benefit of healthcare providers and ensure sustainable business models for the pharmaceutical industry.

What should not be allowed to happen is any abuse of a dominant position by the R&D-based companies that leads to unfair competition or use of delaying tactics that cannot be defended. Swift implementation of the EU Pharmaceutical Sector Inquiry recommendations will be essential to removing hurdles to the timely introduction of new generic medicines, specifically in the area of pricing and re-imbursement.

Sustainability of the generic medicines industry is one of the key elements in ensuring the continuity of broad access to medicines. To meet the rising demand from more patients who are living longer lives, requiring chronic therapy and expecting an improved quality of life, generic medicines offer established treatment at an affordable price. There is no other single, simple solution.

KEY TAKEAWAYS

GENERIC MEDICINES:

- Provide an affordable, gold standard medication for many major illnesses
- Allow access to medicines for a greater proportion of the population
- Stimulate healthy competition with the branded sector
- Deliver savings to national health bills
- Enable future long-term savings in the expanding role of medicines vs hospitalisation
- Are high quality products

IMS Health and the EGA have worked closely and collaboratively over a number of years on issues relating to the generic medicine industry.

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IMS HEALTH

Operating in more than 100 countries, IMS Health is the world's leading provider of market intelligence to the pharmaceutical and healthcare industries. With US$2.3 billion in 2008 revenue and more than 50 years of industry experience, IMS offers leading-edge market intelligence products and services that are integral to clients' day-to-day operations, including product and portfolio management capabilities; commercial effectiveness innovations; managed care and consumer health offerings; and consulting and services solutions that improve productivity and the delivery of quality healthcare worldwide. Additional information is available at http://www.imshealth.com

EGA

The EGA is the official representative body of the European Generic medicines and Biosimilar medicines pharmaceutical industry, which is at the forefront of providing high-quality affordable medicines to millions of Europeans and stimulating competitiveness and innovation in the pharmaceutical sector.

Formed in 1993, the EGA represents generic pharmaceuticals companies and their subsidiaries from throughout Europe, either directly or through national associations. Companies represented within the EGA provide approximately 150,000 jobs in Europe. Cost-effective generic medicines save EU patients and healthcare systems over €30 billion each year, thus helping to ensure patient access to essential medicines and providing urgently needed budget headroom for the purchase of new and innovative treatments.

The EGA plays an important consultative role in European healthcare policy-making. The EGA and its members work with the European national governments and the EU institutions to develop affordable solutions for pharmaceutical care and to increase Europe's competitive strength in the global pharmaceutical medicines market.

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Perspective

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Developing the Nation's Biosimilars Program

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Biologic products developed over the past three decades and approved by the Food and Drug Administration (FDA) now provide important therapeutic options for a variety of serious clinical conditions (see graph). Therapeutic biologics such as genetically engineered recombinant proteins and monoclonal antibodies represent a large portion of newly approved therapies for conditions such as chronic inflammatory diseases and cancer. Biologic enzyme-replacement therapies provide clinical benefits in previously untreatable genetic disorders. Although typically more structurally complex than the small-molecule drugs more prevalent in today's market, biologics vary in complexity from cellular therapies to small, highly purified proteins. Unfortunately, access to such products may be limited, not infrequently because of their cost.

To improve access, Congress passed the Biologics Price Competition and Innovation (BPCI) Act of 2009, authorizing the FDA to oversee an "abbreviated pathway" for approval of biologics that are "biosimilar" to already-approved products.[1] Utilizing knowledge from the reference products, the abbreviated pathway will eliminate unnecessary (and therefore unethical) testing of biosimilars in animals and humans.

Since 1984, U.S. laws regulating nonbiologic products have allowed an abbreviated approval pathway, permitting the rapid approval of thousands of less expensive generic drugs based on comparisons to reference drugs and dramatically increasing medicines' affordability. In 2009, almost 75% of small-molecule prescriptions dispensed in the United States were for generics, and the approval of a generic drug resulted in average savings of 77% of the product's cost within 1 year. Although cost reductions for biosimilars probably won't be as large, the Federal Trade Commission predicts that their availability will significantly reduce biologics' cost and increase their accessibility.[2]

Reconciling the science of biosimilar development with the new regulatory framework required by the BPCI Act presents the FDA with numerous challenges. First and foremost, the agency must establish scientific criteria that address the key question: how similar is similar enough when it comes to the substitution of complex biologic drug products in clinical practice? The complex structures of biologic products

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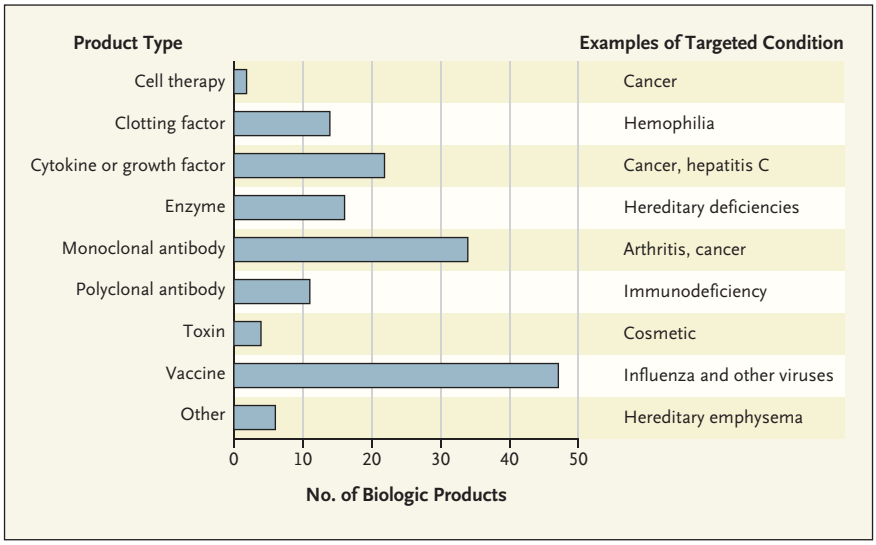

Numbers of FDA-Approved Biologic Products of Various Types Available for Treating or Preventing Various Conditions.

The numbers are based on proper names for therapeutics from the Drugs@FDA Web site and the Center for Biologics Evaluation and Research list of biologics (www.fda.gov). The examples of targeted conditions are general, and specific product indications should be based on product labels.

are usually not easily characterized (see diagram). Generally, therapeutic proteins must have a specific set of structural features (e.g., amino acid sequence, glycosylation, protein folding) essential to their intended effect, and slight modifications can affect their performance in humans. In addition, inadvertent chemical modifications can affect their immunogenicity.

Fortunately, progress in the characterization and understanding of biologics now permits demonstration that some products are highly similar to a reference product. Furthermore, the FDA's experience with biologics provides important relevant knowledge. Since the mid-1990s, for example, physicochemical and functional assays have been used to characterize changes in manufacturing processes for some biologics, and then animal or clinical studies are used to resolve any remaining uncertainties about the comparability of the products created before and after such changes and to provide sufficient confidence that safety and efficacy are not diminished. The FDA also has extensive experience with abbreviated applications for proteins that are regulated as drugs.[3] Moreover, the agency is carefully scrutinizing lessons from the European Medicines Agency (EMA), which published general guidelines on biosimilars in 2005[4] and approved its first biosimilar in 2006. Initial EMA guidance has suggested product-specific requirements for structural, animal, and clinical studies. Given the complex nature of biologics, it's unlikely that a "one size fits all" systematic assessment of biosimilarity can be developed. Instead, FDA scientists will need to integrate various types of information to provide an overall assessment that a biologic is biosimilar to an approved reference product.

The FDA has traditionally relied on integrating various kinds of evidence in making regulatory decisions. Such a "totality of the evidence" approach can also be applied to assessing biosimilars, since it seems possible to exceed a current state-of-the-art analytic characterization by evaluating more attributes and combinations of attributes at greater sensitivities with multiple complementary methods. There may be strategies that allow a "fingerprint"-like identification of very similar patterns in two different products. Such strategies were used in supporting the approval of a generic low-molecular-weight heparin product, enoxaparin — which, though it differs from proteins in important ways, is structurally complex. Although additional animal and clinical studies will generally be needed for protein biosimilars for the foreseeable future, the scope and extent of such studies may be reduced further if more extensive fingerprint-like characterization is used.

The totality-of-the-evidence approach faces several challenges. Developers of biosimilars who intend to match reference products more closely will, for example, need to select appropriate source materials and tune their processes carefully. Current approaches to manufacturing process design and improvements in process analytics may be useful.

To help ensure that any additional animal and human testing is appropriately targeted and that biosimilar development plans are optimally streamlined, studies assessing biosimilarity must be carefully tailored to address residual uncertainty. The recent EMA draft guideline on biosimilar monoclonal antibodies[5] introduces concepts relevant to the design of biosimilarity studies, including the use of populations,

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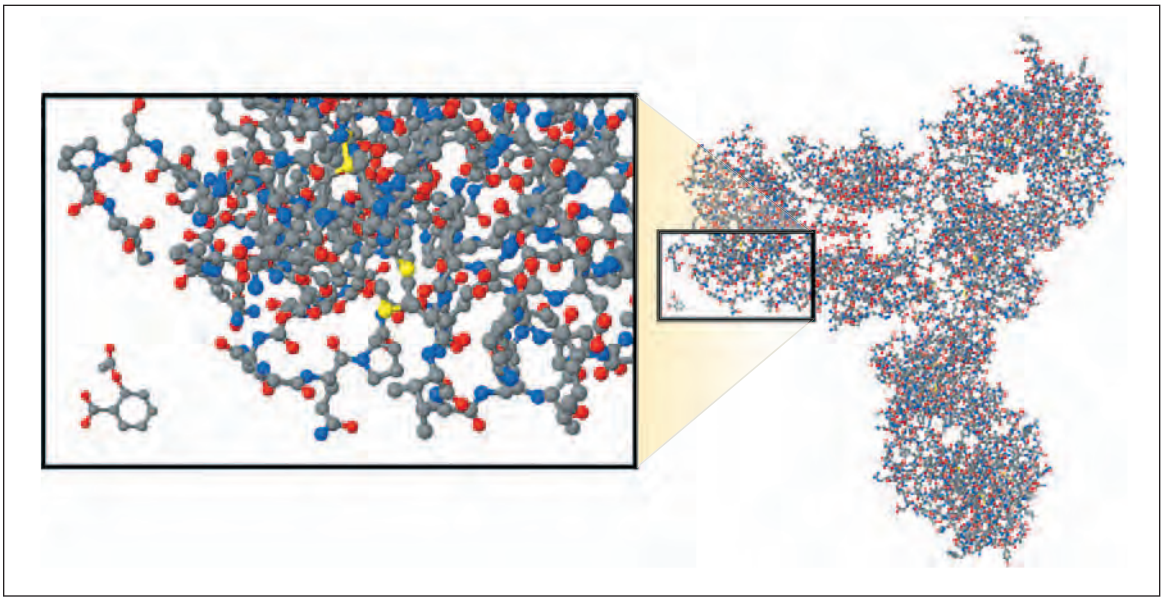

Comparison between a Biologic Monoclonal Antibody and an Aspirin Molecule.

An approximately 800-fold difference in size necessitates magnifying the boxed area to clearly identify the aspirin molecule on the lower left. The antibody structure was taken from the RCSB Protein Data Bank and has the identifier 1HZH.

pharmacodynamic markers, and end points that are sensitive to the potential differences between products. The guideline thus suggests an increasing alignment with the totality-of-the-evidence approach favored by the FDA. This approach, along with the FDA's experience with fingerprint-like characterization of complex products, will be essential in designing a U.S. biosimilars policy that encourages development of biosimilars, emphasizing the use of innovative technologies.

The new pathway will require a new paradigm for sponsor–FDA interactions. To provide the best advice on the scope of any required animal and human studies, the FDA should already have completed an in-depth review of comparative analytic characterization and in vitro data. Although the agency frequently meets with sponsors before they submit investigational new drug applications, a more extensive product review will be required to determine how much additional data are needed for a biosimilar. The FDA is currently considering how such interactions might be structured and how they will affect the user-fee program that Congress has mandated for biosimilars.

The FDA evaluation of biosimilarity must consider the product's complexity, its formulation, its stability, and the usefulness of biochemical and functional characterizations and incorporate these factors into a risk-based approach. The mechanistic understanding of the clinical effect of a biologic and the level of clinical information available about it will also affect the evaluation of risk, and the manufacturing processes may introduce potential variants or impurities that could affect risk. Evaluating biosimilarity with a risk-based approach is scientifically appropriate and familiar to the FDA, whose decisions are commonly based on reducing residual uncertainty to an acceptable level in any given clinical setting.

Immunogenicity remains a critical factor when assessing biosimilarity, and the FDA will evaluate immunogenicity in a risk-based manner. For example, aggregation of proteins may be associated with higher risks of immunogenicity, and the risks related to an immune response are greater with products that stimulate immunity to nonredundant self-proteins, such as erythropoietin.

The FDA process for biosimilars must include product-specific safety monitoring. History suggests that pharmaceutical companies will make manufacturing-related changes to biologics periodically throughout their lifecycles, and even small changes could affect safety or efficacy. Tracking adverse events associated with the use of reference and biosimilar products will be difficult if the specific product

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or manufacturer cannot be readily identified, and appropriate strategies must be developed to ensure the implementation of robust, modern pharmacovigilance programs for biologics.

Under the BPCI Act, biosimilars will also have the opportunity to meet a higher standard of similarity to a reference product — "interchangeability," reflecting an FDA assessment that pharmacists can make substitutions between biologics without the prescriber's intervention. A biologic will be considered interchangeable with a reference product if the developer demonstrates that it can be expected to produce the same clinical result in any given patient and that the risk associated with alternating or switching between the two products is not greater than that involved in continuing to use the reference product.

The FDA will carefully consider what data will be necessary for this purpose and translate that assessment into effective regulatory standards. The agency will also develop standards to ensure that products not deemed interchangeable are not inadvertently substituted for a reference product without the prescriber's consent. But even without interchangeability, recognition that two products are biosimilar will give clinicians far more information than the mere knowledge that they were developed for the same indication.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Redesigning Employee Health Incentives — Lessons from Behavioral Economics

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Buried as Section 2705 of the Patient Protection and Affordable Care Act (ACA) is a provision of potentially momentous importance. Beginning in 2014, employers may use up to 30% of the total amount of employees' health insurance premiums (50% at the discretion of the secretary of health and human services) to provide outcome-based wellness incentives. Such rewards can "be in the form of a discount or rebate of a premium or contribution, a waiver of all or part of a cost-sharing mechanism (such as deductibles, copayments, or coinsurance), the absence of a surcharge, or the value of a benefit that would otherwise not be provided under the plan."

This provision represents an attempt to rein in health care costs, to which health conditions associated with unhealthy behaviors, such as smoking, overeating, and not exercising, are major contributors. Projections that the provision would reduce costs arose, in part, from claims that Safeway Supermarkets had achieved flat health care costs from 2005 to 2009 by tying employees' health insurance premiums to outcome-based wellness incentives.[1] It later became clear, however, that Safeway's program began in 2008 — too late to deserve credit for flat costs starting in 2005.[2]

Although it may seem obvious that charging higher premiums for smoking (or high body-mass index, cholesterol, or blood pressure) would encourage people to modify their habits to lower their premiums, evidence that differential premiums change health-related behavior is scant. Indeed, we're unaware of any health insurance data that have convincingly demonstrated such effects.

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Biosimilar Naming: How Do Adverse Event Reporting Data Support the Need for Distinct Nonproprietary Names for Biosimilars?

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Biosimilar Naming: How Do Adverse Event Reporting Data Support the Need for Distinct Nonproprietary Names for Biosimilars?

I. INTRODUCTION

The Biologics Price Competition and Innovation Act (BPCIA), which was enacted in 2010 as a part of healthcare reform, grants the U.S. Food and Drug Administration (FDA) the authority to approve biosimilars, biological products that are "highly similar" to previously approved, innovative biological products (reference products). The BPCIA did not, however, include provisions regarding the naming of biosimilars. Accordingly, FDA, like many regulatory agencies around the world, is grappling with whether a biosimilar should be required to have a nonproprietary name that is distinguishable from that of its reference product and from that of other biosimilars citing the same reference product.

The adverse events associated with biologics can have significant clinical consequences, and some adverse events may be rare and difficult to detect in any reasonable premarket testing program. Moreover, because biosimilars will be only "highly similar" to (not the "same as") their reference products[2] and will be approved on the basis of abbreviated clinical data packages, important information about their efficacy and safety profiles — including how those profiles actually differ from their reference products — could emerge after their approval. And differences between the products also could emerge after approval as the individual manufacturers introduce manufacturing changes. For these reasons, to be effective the U.S. pharmacovigilance system must ensure all individual post-market adverse events are accurately attributed to the particular biological product associated with the event. As discussed in this article, however, adverse event reporting in practice suffers from widespread product misattribution and gaps in information that hinder traceability.

This paper describes an analysis of adverse event reporting for non-biological drugs that found that adverse events are often attributed to the innovative product when in fact the patient likely took a generic product with the same nonproprietary name. In addition, this analysis found that meaningful product-identifying information (beyond product brand or nonproprietary name) is usually not included in information provided by reporters. These findings support the need for distinctive names for biosimilars, which will help to ensure that adverse events are traced to the correct product and that FDA, sponsors, healthcare professionals, and patients can rely on timely and more accurate adverse event data to make critical decisions regarding the use of biologics.

POLICY RECOMMENDATIONS

To facilitate robust and accurate pharmacovigilance for biologics, FDA should require distinct nonproprietary names for biosimilars. Specifically, the Agency should:

- Require that each biosimilar label bear a nonproprietary name that distinguishes the product from the reference product and from other biosimilars that cite the same reference product.
- Issue guidance on the process through which FDA will work with biosimilar sponsors to assign distinct nonproprietary names.
- Work with the World Health Organization and national regulatory agencies around the world to help develop consistent naming policies for biosimilars.

II. BACKGROUND

The BPCIA grants FDA the authority to approve biosimilars — biological products that are "highly similar" to reference biological products "notwithstanding minor differences in clinically inactive components" and that have no "clinically meaningful differences" from those reference products in terms of safety, purity, or potency.[3] In addition, FDA has the authority to deem a biosimilar as "interchangeable" with its reference product. This designation means that the product "may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product."[4] To obtain this status, an applicant must establish that the product "can be expected to produce the same clinical result as the reference product in any given patient." For products that are administered more than once, the sponsor must meet an additional requirement: "the risk in terms of safety or diminished efficacy of alternating or switching between" the proposed interchangeable biosimilar and the reference product must not be "greater than the risk of using the reference product" alone.[5]

Although early versions of biosimilar legislation contained provisions relating to naming,[6] the final legislation remained silent on this issue. The agency's residual authority over drug naming thus applies to biosimilars. This includes section 502 of the Federal Food, Drug, and Cosmetic Act (FDCA), which deems a drug (including a biological drug) "misbranded" if the labeling is false or misleading "in any particular" or if the label fails to bear the drug's "established name" as defined in section 502(e)(3). It also includes section 508, pursuant to which FDA may unilaterally designate an official (nonproprietary) name, though it rarely does so. In practice, the vast majority of drug nonproprietary names are selected by the United States Adopted Name (USAN) Council, which comprises representatives from the American Medical Association (AMA), the United States Pharmacopeial (USP) Convention, the American Pharmacists Association, and FDA, as well as one

member at-large. A drug sponsor also typically applies for an international nonproprietary name (INN), which is assigned by the World Health Organization (WHO). A drug's USAN and INN are the same in almost every case.

Since the beginning of serious stakeholder discussions on enactment of a biosimilar pathway, FDA officials have repeatedly signaled that the agency may support the use of distinct names for biosimilars, primarily out of concern for our pharmacovigilance system. For example, in June 2007, the Secretary of Health and Human Services sent a letter to Senator Kennedy stating that any biosimilar legislation should require distinct nonproprietary names for biosimilars.[7] In 2008, FDA reiterated this view to Congress, stating that the agency "believes that legislation should recognize the potential impact on pharmacovigilance and prescribing and require that [biosimilars] be assigned a distinguishable, nonproprietary name for safety purposes."[8] After the BPCIA was enacted, FDA stated in an October 2010 *Federal Register* notice that it "must be able to distinguish between a reference product, . . . a biosimilar product, and an interchangeable product." The agency therefore asked stakeholders to submit comments on whether "a distinguishing prefix or suffix" should be added to the nonproprietary name for a biosimilar or interchangeable biologic.[9] Finally, in 2011, several FDA personnel stated that "[t]racking adverse events associated with the use of reference and biosimilar products will be difficult if the specific product or manufacturer cannot be readily identified, and appropriate strategies must be developed to ensure the implementation of robust, modern pharmacovigilance programs for biologics."[10]

Some stakeholders have also suggested that the agency's use of distinguishing prefixes in the nonproprietary names of biologics recently approved under section 351(a) of the Public Health Service Act indicates that the agency will use similar prefixes for biosimilars. When FDA approved Teva's follow-on version of Amgen's innovative product Neupogen (filgrastim), for example, the agency assigned a distinct nonproprietary name to Teva's product, tbo-filgrastim:

> FDA has concluded that a nonproprietary name for Teva's product that is distinct from Amgen's product will help to minimize medication errors by (1) preventing a patient from receiving a product different than what was intended to be prescribed and (2) reducing confusion among healthcare providers who may consider use of the same nonproprietary name to mean that the biological products are indistinguishable from a clinical standpoint. FDA also has concluded that unique nonproprietary names will facilitate postmarketing safety monitoring by providing a clear means of determining which "filgrastim" product is dispensed to patients. Due to the fact that health care providers may use nonproprietary names instead of proprietary names when prescribing and ordering products, and pharmacovigilance systems often do not require inclusion of proprietary names, the use of distinct proprietary names is insufficient to address these concerns.[11]

To date, however, FDA has not publicly issued any guidance (formal or informal) regarding its intended approach for the nonproprietary names for biosimilars. The agency also has yet to receive any biosimilar applications, so it may be some time before stakeholders receive such guidance.

III. ISSUES IN DISPUTE

Stakeholders supporting the use of distinct names for biosimilars argue that effective pharmacovigilance for biologics cannot be achieved without the ability to trace adverse events to the correct product, which, in turn, cannot be accomplished without distinct nonproprietary names.[12] Unlike a generic drug, which is the "same" as its reference product, a biosimilar will be only "highly similar" to its reference product and, therefore, could have a subtly different clinical profile. This issue may be compounded by the abbreviated testing programs that biosimilars will undergo. It may not be possible to fully elucidate the safety profile of a biosimilar during pre-market testing. Accordingly, important information about the biosimilar may be available only through post-market adverse event reporting. If an adverse event cannot be reliably attributed to the biosimilar causing the adverse event, however, this information may not be readily available to the sponsor, FDA, or other stakeholders. Moreover, an adverse event associated with a biosimilar (or the innovative biologic) could be inappropriately attributed to the therapeutic class as a whole. This could lead to difficulty in detecting new safety trends with a specific product.

In contrast, some other stakeholders suggest that distinct nonproprietary names will discourage the use of biosimilars, thereby limiting market competition and potential price reductions. They contend that such a naming convention would suggest to healthcare professionals and patients that a biosimilar is significantly different from its reference product. In addition, these stakeholders argue that adverse events can be adequately tracked using a product's national drug code (NDC) [13] and lot number, and that existing nonproprietary names shared among biologic and biologic-like products (e.g., somatropin) have not resulted in any known concerns. Finally, some stakeholders argue that distinct nonproprietary names are not necessary for biologics because these products are often administered by a healthcare professional, thereby reducing the risk that an adverse event cannot be traced to the responsible product.[14]

Many stakeholders on both sides of the naming debate have expressed concerns regarding the inconsistency in approaches taken by regulatory authorities around the world. Some biosimilars approved in the European Union (EU) share the same nonproprietary name as their reference product, while others do not. All biosimilar products in the EU, however, have distinct product names (either brand names like Omnitrope or a product name consisting of a combination of the nonproprietary name plus the manufacturer, such as Tevagrastim). Remsima (infliximab), a monoclonal antibody biosimilar approved by the Korean Food and Drug Administration in July 2012, has the same nonproprietary name as its reference product, Remicade (infliximab). Japan requires that both the proprietary and nonproprietary names indicate the status of the product: "Follow-on 1" (or 2, 3, etc.) must be added as a suffix to the nonproprietary name, and "BS" should be added to the end of the biosimilar's brand name.[15] The WHO currently recommends only that a biosimilar use a distinct brand name.[16] Recently, however, the WHO International Nonproprietary Names Group acknowledged that the WHO's current approach to INNs may not be viable in the long-term and announced that it is considering recommending that biosimilars have unique nonproprietary names.[17]

IV. RESEARCH

To assess how adverse event reporting practices might affect the need for distinct names for biosimilars, Covington and AbbVie, Inc., (AbbVie) worked with BDO Consulting (BDO) to analyze adverse event reporting patterns for eight innovative (branded) non-biological drugs.[18] As discussed in more detail below, the analysis found that adverse event reporters often incorrectly attribute adverse events — i.e., assume the event is associated with the innovative product, when in fact the patient likely took a generic product with the same nonproprietary name. Moreover, meaningful product-identifying information (beyond product brand or nonproprietary name) is usually not included in FDA's adverse event report database or included in information provided by reporters.

A. Analysis Methodology

FDA's Adverse Event Reporting System (FAERS) data from 2004 to 2012, which was made publicly available on the agency's website, was the primary source of data for this assessment.[19] FAERS is a database that "contains information on adverse event and medication error reports submitted to FDA . . . for drug and therapeutic biologic products."[20] These adverse events (FAERS) are collected from drug manufacturers (mandatory reporters) and consumers, healthcare professionals, lawyers, etc. (voluntary reporters). FAERS data available for the following drugs were included in this assessment:

Brand Name	Nonproprietary Name	Dosage Form(s)[21]
Ambien	zolpidem tartrate	oral tablet
Ambien CR	zolpidem tartrate	extended release oral tablet
Catapres TTS	clonidine	extended release transdermal film
Lamictal[22]	lamotrigine	oral tablet & chewable dispersible tablet
Zocor	simvastatin	oral tablet
Zoloft[23]	sertraline hydrochloride	oral tablet & oral concentrate
Zyprexa	olanzapine	oral tablet & intramuscular injectable
Zyrtec[24]	cetirizine hydrochloride	oral tablet & oral syrup

Covington and AbbVie selected these drugs based on the following criteria, without regard to product manufacturer or therapeutic area: (1) the drug became subject to generic competition between 2005 and 2011[25]; and (2) the drug experienced significant sales before the introduction of generic competition.[26] Although Catapres TTS did not experience sales as significant as some of the other selected drugs, it was selected because it is a narrow therapeutic index drug that was subject to generic competition in the relevant years.

After employing quality control measures and removing duplicate and outdated records,[27] the numbers of prescriptions dispensed for the eight products were compared against the number of adverse event reports associated with these products over time. Monthly prescription data (both new prescriptions and refills dispensed) purchased by AbbVie from IMS Health Incorporated were used for this portion of the analysis. (As discussed in further detail below, the de-duplicated FAERS

data for all drugs and biologics from 2004 to 2012 were also analyzed to gain further insight into the robustness of data submitted to FAERS).

Depending on the specific information submitted by an adverse event reporter, the FAERS data may contain one or more of the following product-identifying details concerning a reported adverse event: the drug's "trade" name (which can be populated with either a brand or nonproprietary name); the name and/or unique numerical identifier of the manufacturer submitting the report[28]; the drug's marketing application (new drug application or biologics license application) number; and the drug's lot number. There is no data field provided in the FAERS database for an NDC number. This information, however, does appear to be captured in a few hundred records (less than .01% of the de-duplicated records), primarily as part of the lot number field.

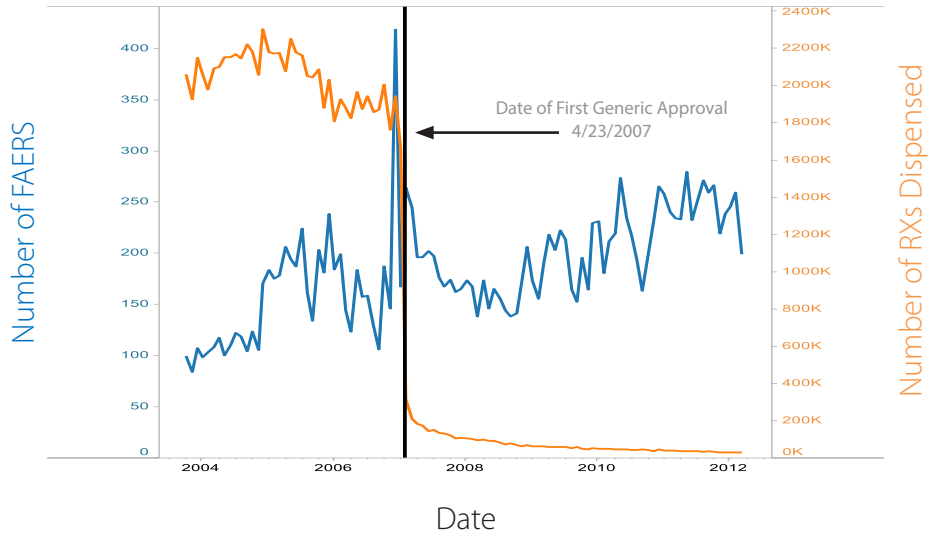
The analysis included only those reports associated with an innovative "Valid Trade Name;" that is, only those reports that included an analyzed product's brand name as approved by FDA (no typos, etc.).[29] The adverse event reports were analyzed according to the date the manufacturer first received information concerning an adverse event. The vast majority (93%) of total de-duplicated adverse event reports analyzed for the selected eight products include this date, and the date would presumably be reasonably close in time to the date an adverse event took place.

B. Results

The following graphs present the results of this analysis.

Ambien (zolpidem tartrate) (oral tablet)

Monthly Number of De-Duplicated FAERS v Monthly Number of Prescriptions Dispensed

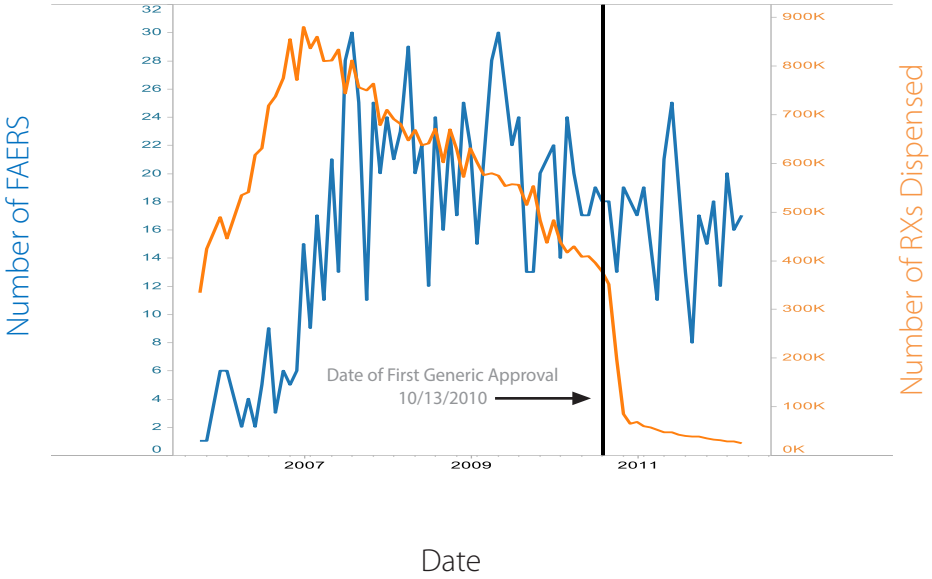


Legend: ● Number of FAERS ● Number of RXs Dispensed[30]

30. This information is an estimate derived from the use of information under license from the following IMS Health Incorporated information service: IMS Health NPA (NRX, TRX, EU NRX, EU TRX) and NSP (NSP Total Dollars, NSP Extended Units) for the period 2004 to 2012. IMS expressly reserves all rights, including rights of copying, distribution and republication.

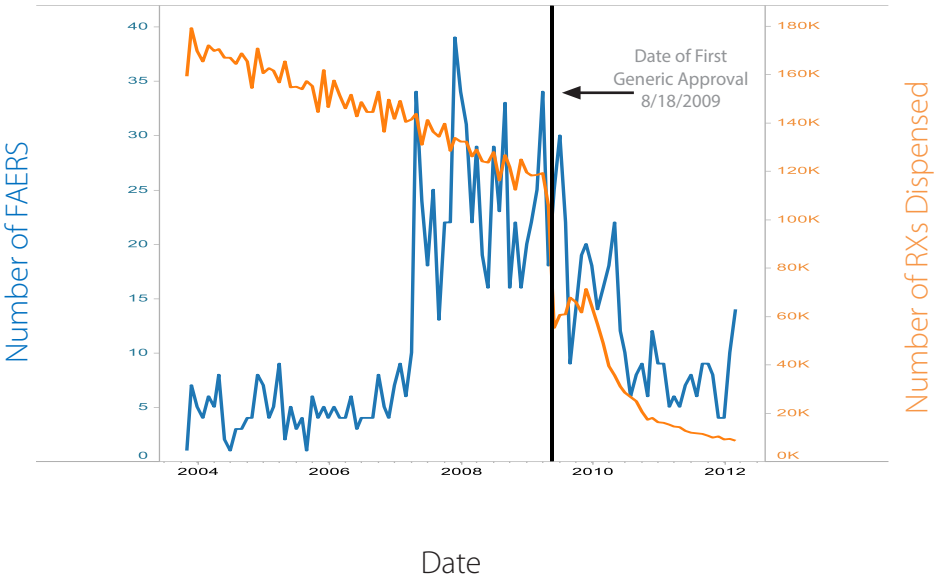
Ambien CR (zolpidem tartrate) (extended release oral tablet)

Monthly Number of De-Duplicated FAERS v Monthly Number of Prescriptions Dispensed



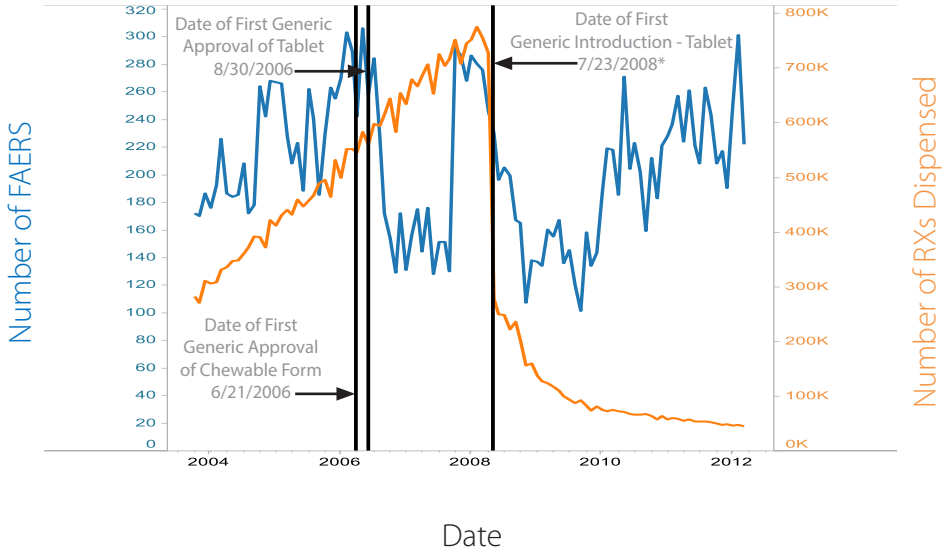
Catapres TTS (clonidine) (extended release transdermal film)

Monthly Number of De-Duplicated FAERS v Monthly Number of Prescriptions Dispensed



Lamictal (lamotrigine) (oral tablet & chewable dispersible oral tablet)

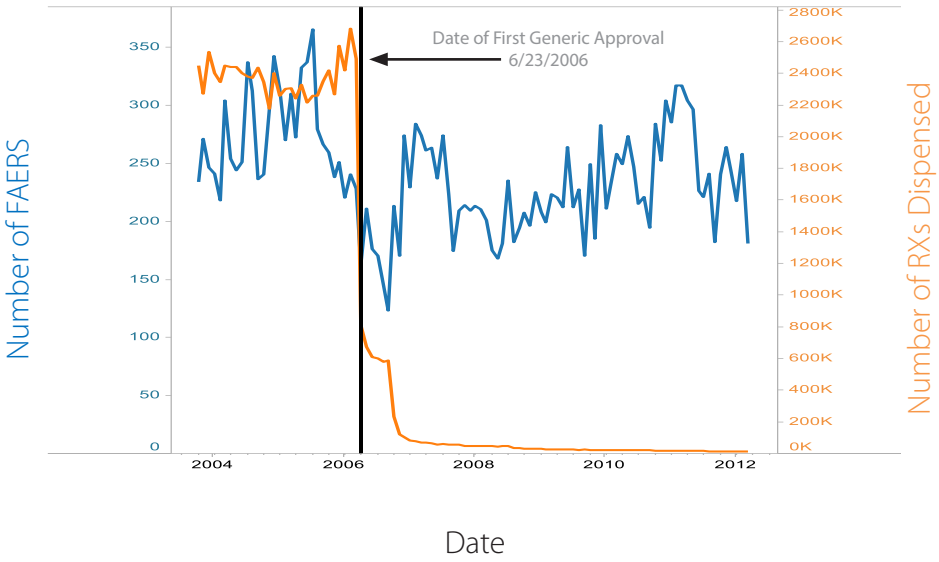
Monthly Number of De-Duplicated FAERS v Monthly Number of Prescriptions Dispensed



*Although the actual market entry date for the generic lamotrigine oral tablets was delayed until 7/23/2008, it appears that Teva marketed the chewable dispersible oral tablets immediately after approval.

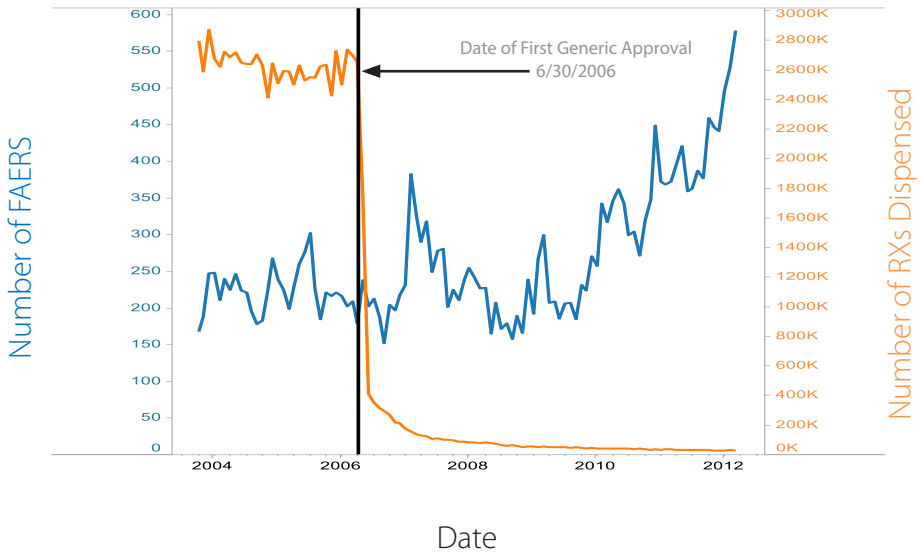
Zocor (simvastatin) (oral tablet)

Monthly Number of De-Duplicated FAERS v Monthly Number of Prescriptions Dispensed



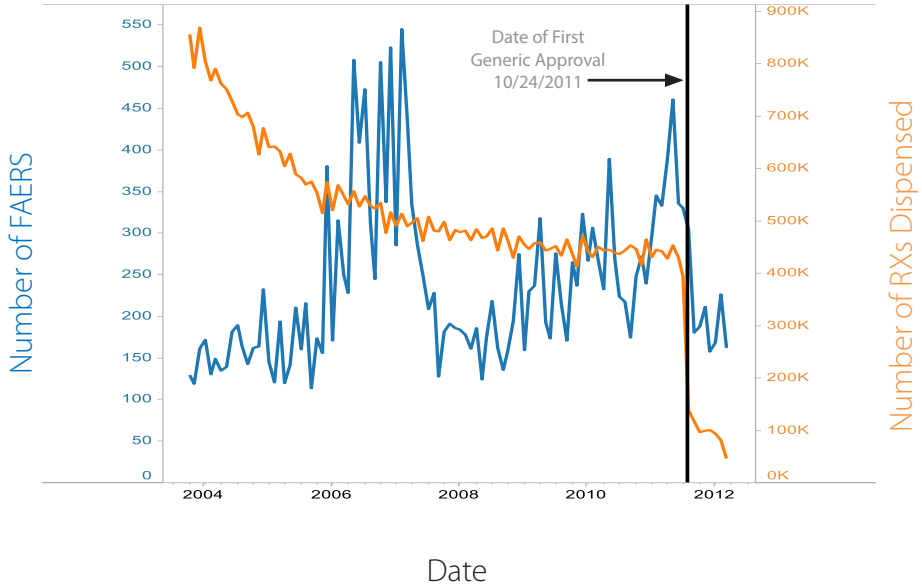
Zoloft (sertraline hydrochloride) (oral tablet & oral concentrate)

Monthly Number of De-Duplicated FAERS v Monthly Number of Prescriptions Dispensed



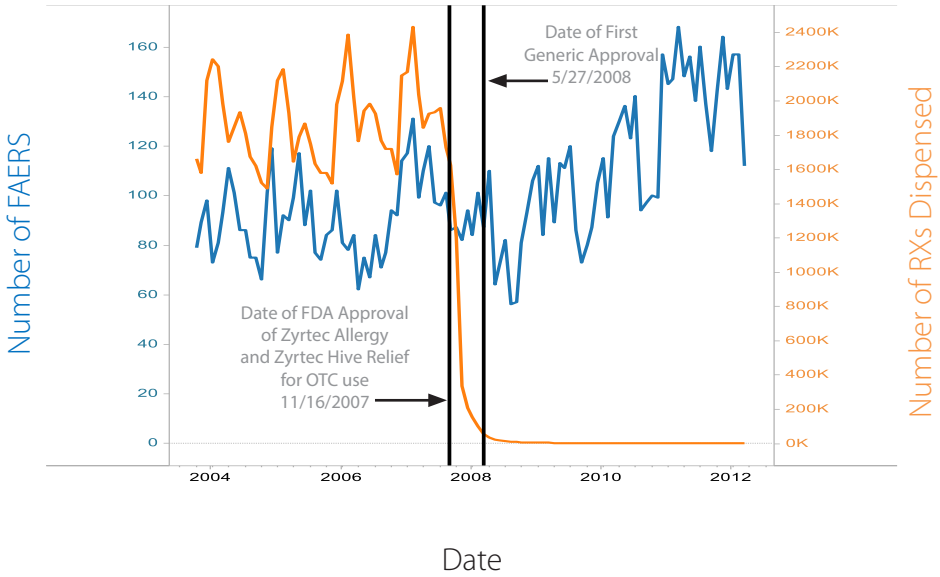
Zyprexa (olanzapine) (oral tablet & intramuscular injection)

Monthly Number of De-Duplicated FAERS v Monthly Number of Prescriptions Dispensed



Zyrtec (cetirizine hydrochloride) (oral tablet & syrup)

Monthly Number of De-Duplicated FAERS v Monthly Number of Prescriptions Dispensed



As shown in the chart below, the increase in the rate of adverse event reports to prescriptions dispensed after generic introduction ranged from 4.69 times the rate of pre-generic introduction (for Lamictal) to over 411.23 times the rate of pre-generic introduction (for Zyrtec). In other words, for Zyrtec — for example — prior to generic introduction one adverse event report was submitted for every 19,507.95 prescriptions dispensed. After the introduction of generic competition, one adverse event report was submitted for every 47.44 prescriptions dispensed. This is a post-generic introduction rate of 411.23 times the pre-generic introduction rate.

Drug Name	Number of prescriptions per each FAER pre-generic introduction [A]	Number of prescriptions per each FAER post-generic introduction [B]	Increase in rate of prescriptions per each FAER pre- v. post-generic introduction [C] = [A]/[B]
Ambien	14,468.73	372.08	38.89
Ambien CR	71,021.71	5,089.53	13.95
Catapres TTS	29,818.84	2,564.43	11.63
Lamictal	2,604.80	555.33	4.69
Zocor	8,875.40	477.63	18.58
Zoloft	12,010.78	655.16	18.33
Zyprexa	2,664.69	488.77	5.45
Zyrtec	19,507.95	47.44	411.23

Moreover, an analysis of the product-identifying information included in all de-duplicated adverse event reports (not just those concerning the eight products analyzed) found serious limitations in the information contained in the reports. For example, less than a quarter (23%) of adverse event reports have the marketing application field (i.e., NDA or BLA number) populated. Only 10% of adverse event reports have the lot number field populated. At least 95% of adverse event reports include the date the manufacturer first received information concerning an adverse event, meaning that the vast majority of adverse events are reported by manufacturers to FDA, and the reporting manufacturer is associated with the report by default (regardless of whether the adverse event reporter has misattributed the adverse event to the innovative product). FDA's mandatory adverse event reporting form, FDA Form 3500A (Regulated Industry and User Facilities), does not include a prompt requesting the identity of the manufacturer of the drug that is the subject of the report. The manufacturer receiving the report is thus presumed to be the manufacturer of the drug at issue.

C. Limitations of Analysis

The above analysis was limited by a number of factors. For six of the eight products analyzed (all but Zocor and Zoloft), there are other drugs in the same "family" (i.e., other drugs marketed by the same manufacturer that have a variation of the same brand name). For example, in the "Lamictal family," there are distinct products named Lamictal, Lamictal ODT, and Lamictal XR.[31] BDO observed that for these six products, a number of FAERS identify the product by name but refer to an NDA number that corresponds to that of a related product, thus suggesting that these FAERS are attributed to the wrong drug within a "family." For example, the NDA number for Ambien is 019908, and the NDA number for Ambien CR is 021774. The FAERS data, however, contain 303 records with the drug name "Ambien," but with the NDA number of Ambien CR, 021774. Conversely, there is only one record with the drug name Ambien CR and the NDA number of Ambien. For records where the NDA number is not provided, which is the vast majority of the de-duplicated records (approximately 78%), the impact of this potential for over-attribution of adverse events to the shortest branded product name was not analyzed. The analyzed data, however, suggest that there may be a tendency for FAERS to over-attribute adverse events to the shortest product name (e.g., "Ambien" rather than "Ambien CR" or "Lamictal" rather than "Lamictal XR"). Where the product with the longer brand name was subject to generic competition after the product with the shorter brand name (which is the case with Lamictal and Lamictal XR, for example), a small number of the adverse events inappropriately reported to the product with the shorter brand name may have actually been associated with the other brand name product, instead of being associated with the generic product, as the analysis would otherwise suggest.

For all eight products, there are instances where the drug name is correct, but the NDA number provided is neither for that product nor for a related product. In addition, extensive cleanup is required to fully analyze FAERS data. FAERS data contain numerous duplicate or outdated records. Additionally, drug names (including generic and brand names) are allowed to be submitted in free text format, resulting in numerous misspellings and extraneous information in the name field (e.g., dosages, manufacturers). As noted above, this analysis included only those FAERS that contained Valid Trade Names and where the NDA number either was blank or was the correct number. Many components of the FAERS data are incomplete. For example, the FAERS database has a field for

route of administration, yet over 50% of all de-duplicated FAERS do not have this field populated. In addition, the FAERS database has a field for dose, yet 65% of all FAERS do not have this field populated. Furthermore, for those records where dose is populated, it is an open text field, which provides inconsistent information that is difficult to analyze without extensive clean-up efforts, as noted above. The effects of these quality problems on the trends seen in this analysis are unclear.

The analysis does not explain the reason for the apparent widespread misattribution of adverse events observed. In our view, a variety of factors, in addition to shared nonproprietary names, may contribute to this phenomenon in the small molecule context.[32] It is possible that after the introduction of biosimilar competition in the United States, adverse event reporters will take greater care to appropriately attribute adverse events to the dispensed biologic.[33] And because biosimilars may have brand names (unlike most generic drugs) and may not be deemed interchangeable (making it less likely they would be automatically substituted for prescribed innovative biologics), and many biologics are administered in hospitals, clinics, or physician offices, physicians and patients may be more likely to be aware of — and able to report — the particular biological product dispensed.

V. POLICY IMPLICATIONS

A number of conclusions were drawn from the results of this analysis:

First, of the eight products analyzed, seven experienced a substantial drop in monthly prescriptions dispensed on or about the time of the introduction of generic competition.[34] The one outlier is Zyrtec. Its sales began declining substantially when its manufacturer introduced two over-the-counter versions of the product, about six months before the introduction of generic competition.[35] All of the products experienced continued low sales in the years after generic introduction.

Second, for six of the eight products analyzed, the number of adverse event reports on a monthly basis did not appreciably decrease after the introduction of generic competition, despite the fact that the monthly prescriptions dispensed decreased substantially. This suggests that adverse event reporters incorrectly attribute adverse events to innovative products (by brand name), when in fact the patients took generic products with the same nonproprietary name. This misattribution conceals the identity of the individual product in fact associated with an adverse event. The two outliers are Zyprexa and Catapres TTS. Zyprexa does not yet have enough post-generic introduction data to permit drawing a conclusion. Catapres TTS, in contrast, does not appear to follow the same pattern as the other products analyzed. After the introduction of generic competition, there does appear to be a rough correlation between Catapres TTS prescriptions dispensed and adverse events reported. Why the Catapres TTS data follow a different pattern is unclear. Catapres TTS also had little consistent correlation between prescriptions dispensed and adverse events attributed to Catapres TTS *prior* to the introduction of generic competition, so the drug appears to be an outlier on all accounts.

Third, for each of the eight products analyzed, there was an increase in the rate of adverse event reports to prescriptions dispensed after the introduction of generic competition (or, conversely put, a decrease in the number of prescriptions dispensed per adverse event report submitted).

Fourth, product name (brand or nonproprietary) is often the only meaningful product-specific information provided in the FAERS data. Thus, where reporters report adverse events only by nonproprietary name, researchers (including regulators) may not be able to identify the particular product associated with the report. This results in the pooling of data for products that share the same nonproprietary name.

VI. IMPACT OF POLICY RECOMMENDATIONS

The ability to trace an adverse event to an individual biologic will be especially important after biosimilars are introduced to the market. As discussed above, a biosimilar will be approved on the basis of an abbreviated clinical data package and, unlike a small molecule generic drug, will be only highly similar to — not the same as — its reference product. Biological products are extremely sensitive to changes in starting materials and manufacturing processes, and seemingly minor differences in manufacturing processes can result in clinical differences between the biosimilar and its reference product.[36] It is thus expected that critical information about a biosimilar's efficacy and safety (including immunogenicity) profiles, and the ways in which these profiles differ from those of the reference product, will continue to be gained after approval. Further, the timely detection of safety signals associated with an individual biological product is vital. The immunogenicity risk presented by biologics is greater than that associated with small molecule products,[37] and immunogenicity often has the potential to have significant adverse clinical consequences.[38] And the adverse events associated with biosimilars, even when increased relative to the innovative product, may nevertheless remain rare, making accurate adverse event data on an individual product basis imperative.

Shared nonproprietary names for biosimilars and their reference products would significantly impede efforts to identify the particular product(s) associated with adverse event reports. First, as this analysis suggests, adverse event reporters may incorrectly attribute to an innovative product — by brand name — adverse events in fact associated with a different product that shares the same nonproprietary name as the innovative product. This misattribution effectively pools data and conceals the identity of the responsible product. Second, this analysis demonstrates that adverse event reporters rarely report a marketing application number or lot number; in the vast majority of cases NDC number information is not provided in the FAERS database; and the manufacturer name in the FAERS database is the name of the manufacturer submitting the report (which, as noted, often is not the manufacturer of the product at issue). Thus, where reporters report an adverse event by nonproprietary name, it will often be impossible to identify the specific product involved. This results in the pooling of data for products that share the same nonproprietary name. Both types of data pooling may mask new safety signals, obstruct the search for root causes, and delay or preclude implementation of corrective actions.

Even if the misattribution effect observed with non-biological drugs would not occur to the same extent in the biologics context after the introduction of biosimilar competition, distinct nonproprietary (in addition to brand) names for biosimilars remain essential for a robust pharmacovigilance system. Distinct names would eliminate the forced pooling of adverse events that occurs when adverse events are reported by a drug's nonproprietary name alone. They would also reduce the misattribution (in whatever amount it would have otherwise occurred) of adverse event reports associated with a biosimilar to the innovative product. With distinct nonproprietary names, patients, physicians, and pharmacists would more readily know (or be able to learn) what specific product was dispensed.[39]

Moreover, distinct nonproprietary names would enhance traceability without requiring a sea change in dispensing information provided or in adverse event reporting habits. Physicians currently do not prescribe by NDC number, and the NDC number is not usually found on dispensed pharmacy prescriptions.[40] Specific lot numbers may be challenging for reporters to identify. In addition, achieving consistent reporting of NDC numbers, marketing application numbers, lot information, or manufacturer name would require an overhaul of adverse event reporting practices. And even if this information were provided on a more regular basis, it could confuse as well as clarify. When this information is currently provided in FAERS data, for example, it often does not match the name of the reported drug.

To address these concerns, FDA should require that each biosimilar use a nonproprietary name that distinguishes it both from the reference product and from other biosimilars citing the same reference product, whether through a distinguishing suffix or prefix or other means. The agency should create a system for working with biosimilar sponsors in order to impose consistent naming conventions. Once FDA has established its own standards, it should seek to work with other regulatory authorities, such as the WHO and the European Medicines Agency, to ensure that biosimilar naming practices are consistent around the world. This would help to reduce stakeholder confusion and prevent potential medication errors.

VII. CONCLUSION

As the analysis shows, adverse event reporting in practice has suffered from substantial product misattribution and gaps in information that impede traceability. Distinct nonproprietary names (in addition to distinct brand names) for biosimilars would promote, in an immediate and consistent manner, the traceability of biologics after biosimilars enter the market.

ENDNOTES

1. The views expressed herein are solely those of the authors and do not necessarily reflect the views of the firm or its clients or consultants.

2. *Compare* Public Health Service Act (PHSA) § 351(i)(2)(A) *with* Federal Food, Drug, and Cosmetic Act (FDCA) § 505(j)(2)(ii).

3. PHSA § 351(i)(2).

4. *Id.* § 351(i)(3).

5. *Id.* § 351(k)(4).

6. *See, e.g.,* H.R. 5629, 110th Cong. (2008) ("The Secretary shall ensure that the labeling and packaging of each [biosimilar] bears a name that uniquely identifies the biological product and distinguishes it from the reference product and any other biological products licensed under this subsection following evaluation against such reference product."); H.R. 1038, 110th Cong. (2007) ("If, pursuant to section 508 of the Federal Food, Drug, and Cosmetic Act, the Secretary determines that designation of an official name for a comparable biological product is necessary or desirable in the interests of usefulness or simplicity, the Secretary shall designate the same official name for the comparable biological product as the Secretary designated for the reference product.").

7. Letter of Michael O. Leavitt, Sec'y of HHS, to Sen. Kennedy (June 26, 2007).

8. Letter of Frank M. Torti, M.D., M.P.H., to Rep. Pallone, Chairman, Subcomm. on Health, H. Comm. on Energy & Commerce (Sept. 18, 2008).

9. Approval Pathway for Biosimilar and Interchangeable Biological Products; Public Hearing; Request for Comments, 75 Fed. Reg. 61,497, 61,499 (Oct. 5, 2010).

10. Steven Kozlowski et al., *Developing the Nation's Biosimilar Program, 365* New Eng. J. Med. 385, 387-88 (2011).

11. Memorandum, Biological Product Naming Working Group re. BLA 125294 - [xxx]-filgrastim (Aug. 2, 2012), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/125294Orig1s000NameR.pdf. Similarly, when FDA approved Zaltrap (ziv-aflibercept), a product that shares some similarities with another innovative biologic, Eylea (aflibercept), FDA required a distinguishing prefix in order to reduce potential confusion. ZALTRAP Administrative and Correspondence Documents, Memorandum from Melanie Pierce dated July 17, 2012 ("FDA concluded that a different nonproprietary name would minimize the possibility of medication errors and reduce confusion among healthcare practitioners who may consider use of the same nonproprietary name to mean the biological products are indistinguishable."). FDA also assigned a distinguishing prefix when it approved Kadcyla (ado-trastuzumab emtansine) in order to prevent medication errors. Summary Review for Regulatory Action, BLA 125427 Kadcyla (ado-trastuzumab emtansine) (2013), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/125427Orig1s000Sumr.pdf.

12. Other potential benefits of distinct names include preventing inappropriate automatic substitution of biosimilars that have not met the interchangeability standard.

13. The NDC number is a unique, three-segment identifier that FDA assigns to every human drug product marketed in the United States. These numbers are published in the NDC Directory, an online searchable database, *available at* http://www.accessdata.fda.gov/scripts/cder/ndc/default.cfm. Each approved drug or biologic typically has numerous NDC numbers based on different dosage strength, dosage form, pill count or doses available in a package, etc.

14. *See, e.g.,* Comments to Docket FDA-2010-N-0477-0062 (CVS Caremark Corp.) (Dec. 31, 2010).

15. Japan Ministry of Health, Labor and Welfare, Guidelines for the Quality, Safety and Efficacy Assurance of Follow-on Biologics (Notice to Directors, Health Bureaus, Prefectural Government) (Mar. 2009).

16. WHO Expert Committee on Biological Standardization, Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs) § 12 (2009).

17. According to the WHO, "[t]he current INN policy for biosimilars follows two different approaches, one for those that are glycosylated and one for those that are not. Non-glycosylated biosimilars are considered to have highly similar post-translational modifications and receive the same INN, whilst those that are glycosylated are considered comparable but distinct; they get the same INN name but are further qualified by a Greek letter suffix." *See* 55th Consultation on International Nonproprietary Names for Pharmaceutical Substances Geneva, 16-18 October 2012, Executive Summary (February 2013), *available at* http://www.who.int/medicines/services/inn/55th_Executive_Summary.pdf.

18. BDO Consulting, a Division of BDO USA, LLP, provides litigation, investigation, restructuring, valuation, and risk advisory services to major corporations, law firms, insurance companies, financial service entities, and government organizations. Pursuant to a contract with AbbVie Inc. and Covington & Burling LLP, BDO professionals analyzed the number of prescriptions dispensed relative to the number of adverse event reports submitted to the U.S. Food and Drug Administration (FAERS) in the United States for eight products before and after the introduction of a generic version of each product for the period January 2004 – June 2012. The products and time period for the analysis were selected by AbbVie and Covington & Burling, LLP. BDO drew no conclusions from the data analysis.

19. *See* "The FDA Adverse Event Reporting System (FAERS)," at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082193.htm.

20. *See* "FDA Adverse Event Reporting System (FAERS) (formerly AERS)," at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm. Not all adverse event reports are entered by FDA into FAERS. In particular, a nonserious periodic report for a new molecular entity that has been on the market for more than three years is not entered if the report was submitted on paper forms. *See* "Reports Received and Reports Entered into AERS by Year," at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070434.htm.

21. Data for more than one dosage form were combined for the analysis of Lamictal, Zoloft, Zyprexa, and Zyrtec data. FAERS data do not capture, and therefore do not permit a researcher to consistently distinguish among, product dosage forms (tablet, capsule, syrup, etc.) that use a common brand name.

22. The generic entry dates for the two dosage forms were less than three months apart. Both dosage forms share the name Lamictal. *See supra* note 21.

23. A combined analysis of pre- and post-generic introduction trends was possible for the Zoloft and Zyprexa dosage forms because these dosage forms faced generic competition on the same day.

24. Only the Zyrtec syrup dosage form ever faced generic prescription competition (because the other forms were switched to over-the-counter status). Because the prescribing data for Zyrtec combine the syrup with the tablets, however, these dosage forms were combined for purposes of the analysis.

25. At the time of the analysis, FDA had made publicly available FAERS data for January 2004 through June 2012. Selecting drugs that became subject to generic competition between 2005 and 2011 ensured that some pre-generic competition and post-generic competition data could be analyzed.

26. Covington and AbbVie believed this enhanced the likelihood that robust prescribing and adverse event information would be available.

27. There are outdated records in the FAERS data due to the same report being provided in electronic and paper format, as well as instances where one case has initial and follow-up reports. BDO confirmed its de-duplication process by comparing the results of its de-duplication process to results published in an article in the *International Journal of Medical Sciences*, which employed de-duplicated FAERS data from 2004 to 2009. *See* "Platinum Agent-Induced Hypersensitivity Reactions: Data Mining of the Public Version of the FDA Adverse Event Reporting System, AERS," INT. J. MED. SCI. 2011, 8. A comparison of the publication's de-duplicated record count to BDO's de-duplicated record count for the same time period determined BDO's count to be 99.99% of the publication's count.

28. For adverse event reports submitted to FDA by voluntary reporters, the FAERS data do not identify the name of the manufacturer of the drug that is the subject of the report, even though FDA's voluntary reporting form includes a prompt requesting this information. *See* Form FDA 3500 (Voluntary Reporters), at § D.

29. In the full de-duplicated FAERS data analyzed by BDO, 78% of drugs have the "Valid Trade Name" field populated. Although the title of the field refers to a drug's "Trade Name," the field itself may be populated with either a brand or nonproprietary name. The analysis did not include records where the new drug application (NDA) number matched the NDA number of the analyzed innovative drug, but the drug name was not a Valid Trade Name or was a Valid Trade Name that did not match that of the analyzed innovative drug. Also excluded from the analysis were records where the drug name matched that of an analyzed innovative drug but the NDA number provided was not that of the analyzed innovative drug.

30. (See text page 6 for citation.)

31. GSK originally proposed a brand name of Lamictal CD (lamotrigine) Chewable Dispersible Tablets. During review of the application, FDA requested that GSK remove the "CD" from the brand name. GSK agreed to do so. *See* Supervisory Review of Sponsor's Response to Approvable Letter Memorandum (NDA 20-764) (Aug. 19, 1998), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/98/020764a_admindocs_corres_P2.pdf. Accordingly, the approved brand name for both the regular tablet and the chewable dispersible tablet is Lamictal. The use of the Lamictal CD brand name was nevertheless widespread (including at Drugs @FDA and in the *Orange Book*). The IMS sales data in the analysis covers both dosage forms (the tablet and the chewable tablet). BDO pulled FAERS data using the Lamictal brand name. It is therefore possible that the number of adverse events is somewhat under-reported (given that some events may have been reported under the incorrect brand name Lamictal CD).

32. For example, reporters may make less of an effort to correctly identify the small molecule product involved in an adverse event given their assumption that the adverse event profile of a generic product is the same as that of the innovative product. Also, because the innovator is responsible for maintaining the package insert on which a generic product relies, reporters may have little incentive to associate an adverse event with a generic product. In addition, because a prescribed innovative small molecule product may be automatically substituted with a generic product at the pharmacy, it often may be difficult for physicians or patients to know or remember what product (innovative or specific generic)

was dispensed in any given case. Further, patients and prescribers often refer to the brand name of the drug, even once a generic becomes available.

33. This could be a result of physicians' limited experience with use of biosimilars, the fact that biosimilars will be highly similar to (rather than the same as) their reference products, and the desire of reporters to help ensure that safety information is added to a biosimilar's labeling when appropriate.

34. Lamictal has three dates noted: 6/21/2006 (Generic Approval of Chewable); 8/30/2006 (Generic Approval of Tablet); and 7/23/2008 (Generic Introduction - Tablet). The generic approval and introduction of the chewable were both on 6/21/2006; however, the chewable represents approximately 1% of the sales of Lamictal, and thus Lamictal is included as one of the products that is considered to have experienced a drop in the monthly prescriptions dispensed on or about the time of the introduction of the generic.

35. *See* Approval Letter, Application Nos. 19-835/S022, 21-621/S005, at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/019835s022_021621s005_APPROV.pdf.

36. *See, e.g.,* Schellekens, H., "Biosimilar therapeutics — what do we need to consider?," Neph. Dial. Trans. Plus 2(Supp. 1):i28 (2009) ("The molecular size and complexity of biopharmaceuticals and their production in living cells makes the final product very sensitive to changes in production conditions."); Declerck, P.J., "Biotherapeutics in the era of biosimilars: What really matters is patient safety," Drug Safety 30(12):1088 (2007) ("Small distinctions in the cell line, the manufacturing process or in any step from the cell line stage through to administration to the patient can make a major difference in effects observed during treatment"); & Kozlowski, S., and Swann, P., "Current and future issues in the manufacturing and development of monoclonal antibodies," Adv. Drug Delivery Rev. 58:710 (2006) ("[manufacturing c]hanges that perturb the process [of manufacturing monoclonal antibodies] have had unforeseen consequences on the product").

37. *See, e.g.,* Jelkmann, W., "Biosimilar epoetins and other 'follow-on' biologics: Update on the European experiences," 85 Am. J. Hematol. 771, 773 (2010) ("Because of their structural complexity and potential contaminants, biopharmaceuticals have a greater immunogenic potential than small chemical drugs.").

38. For some biologics, immunogenicity has been associated with reduced or lost therapeutic efficacy (of the given drug or of an entire product class), adverse events (such as immune complex disorders and injection site and infusion reactions), and/or neutralization of the body's naturally occurring protein.

39. If biosimilars share the same nonproprietary names as their reference products, in contrast, physicians (and possibly patients) might not be aware of the specific product dispensed if physicians prescribe by nonproprietary name.

40. Form FDA 3500 (Voluntary Reporting), at 10.

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FDLI's Food and Drug Policy Forum provides a marketplace for the exchange of policy ideas regarding food and drug law issues. The Forum welcomes articles on cutting-edge state, national and international policy issues related to food and drug law.

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Normalized names for clinical drugs: RxNorm at 6 years

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ABSTRACT

Objective In the 6 years since the National Library of Medicine began monthly releases of RxNorm, RxNorm has become a central resource for communicating about clinical drugs and supporting interoperation between drug vocabularies.

Materials and methods Built on the idea of a normalized name for a medication at a given level of abstraction, RxNorm provides a set of names and relationships based on 11 different external source vocabularies. The standard model enables decision support to take place for a variety of uses at the appropriate level of abstraction. With the incorporation of National Drug File Reference Terminology (NDF-RT) from the Veterans Administration, even more sophisticated decision support has become possible.

Discussion While related products such as RxTerms, RxNav, MyMedicationList, and MyRxPad have been recognized as helpful for various uses, tasks such as identifying exactly what is and is not on the market remain a challenge.

INTRODUCTION

RxNorm is a standard nomenclature developed by the United States National Library of Medicine (NLM) in the field of medications. By choosing to represent medications at the level of 'clinical drug,' defined as ingredient(s), strength(s), and dose form, it provides normalized names for these clinical drugs, and related drug names, and links its names to other commonly used drug vocabularies. Normalized names are formed by editors using a set of business rules and validations to create names in a standard way, based on the three elements of clinical drugs. The RxNorm system then assigns named distinct relationships linking various concepts (eg, from clinical drugs to the ingredients) algorithmically, and represents associated information such as the Food and Drug Administration's National Drug Codes (NDC) as attributes of the concepts. The most recent RxNorm dataset includes more than 61 000 non-obsolete unique RxNorm drug names (RxNorm January 2011 release). The RxNorm vocabulary is available at no cost from http://www.nlm.nih.gov/research/umls/rxnorm/.

Typical uses of RxNorm include navigating between names and codes among drug vocabularies, exchanging standard RxNorm names and codes, and using information available within RxNorm to assist with medication-related clinical decision support.

The creation of RxNorm was motivated by the need for a single, standard, multipurpose terminology for representing medications. Many clinical information tasks can benefit from the use of a standard terminology for representing drug information, including creation of electronic medical records (EMR), automated decision support, quality assurance, healthcare research, reimbursement, and mandatory reporting.[1] The NDCs have not proved suitable for such use. They lack many of the desirable characteristics for controlled terminologies.[2 3] For example, the identifiers are not meaningless, but are composed of identifiers for the manufacturer or packager, the product, and the package size. While usable for tracking products, these codes are not suitable for aggregating products for the uses mentioned above. Various drug terminologies, while working well on their own, present a barrier when medical information systems containing these varying names and codes need to be cross-linked or reconciled.[4]

In 1998, the HL7 Vocabulary Technical Committee created a subcommittee to explore possible sharing of terminologies among pharmacy system knowledge base vendors. They proposed a hierarchical model for representing drug terms that includes a specification for creating formal definitions.[5] A key concept in the model was the notion of a clinical drug—a drug as it appears in a provider's medication order, comprised of active ingredient, strength, and dose form.[6] Various efforts followed to investigate the validity of such a model. Cimino *et al* mapped clinical drug terms (53% for overall match) against three leading pharmacy system knowledge base vendors.[7] Nelson *et al* parsed 70% of the entries in the Veterans Administration National Drug File algorithmically into the semantic normal forms (normalized names) of clinical drugs.[8] These observations and findings led to the development of RxNorm, a terminology that is intended to represent drug terms in a formalized fashion and support interoperability among various drug terminologies.

RxNorm is built upon what is already available—various drug vocabularies commonly used in pharmacy management and drug interaction software. It is built by creating normalized drug names based on the information and names in the contributing source vocabularies. It has a limited and controlled scope—the domain of medications expressible as clinical drugs. Medical devices or medical supplies are thus not within its scope, whereas non-prescription, over-the-counter medications are included. With the release by the FDA of the labels for over-the-counter products, the number of clinical drugs in RxNorm increased considerably.

RxNorm started in 2002 as an investigational project within the larger Unified Medical Language

Glossary

API
Application Programming Interface - A particular set of rules and specifications that a software program can follow to access and make use of the services and resources provided by another particular software program that implements that API.
CCD
Continuity of Care Document - An XML-based markup standard intended to specify the encoding, structure, and semantics of a patient summary clinical document for exchange. The CCD specification is a constraint on the HL7 Clinical Document Architecture (CDA) standard.
CDA
Clinical Document Architecture - An XML-based markup standard intended to specify the encoding, structure, and semantics of clinical documents for exchange.
Clinical Drug
A name specifying ingredient, strength, and form of a medication.
CUI
Concept Unique Identifier - A meaningless number representing a set of names whose meanings are considered equivalent for a given purpose.
HITSP
Health Information Technology Standards Panel - A combined public private advisory committee on health information technology standards.
HL7
Health Level 7 - A standards development organization influential in health information technology.
IN
Ingredient - The term type (TTY) indicating that this name is that of the substance represented in an RxNorm name responsible for the medicinal activity. Also, the name and the substance.
MIN
Multiple Ingredients - The TTY indicating that this name is that of the ingredients of a combination product represented in an RxNorm name, where those ingredients are responsible for the medicinal activity. Also, the name and the substances.
NDC
National Drug Code - A coding system established by the Food and Drug Administration to track packaged products.
Normalized Name
A name created by a set of formal rules and logic. In RxNorm, the normalized name allows linking of multiple names at a given level of abstraction.
PIN
Precise Ingredient - The TTY indicating that this name is that of the substance, expressed more precisely as a salt or ester of the ingredient, represented in an RxNorm name. Also, the name and the substance expressed precisely.
SBD
Semantic Branded Drug - The TTY indicating that this name is the normalized name created for a branded clinical drug. The name consists of ingredient, strength, and dose form, followed by a brand name in square brackets. Also, the name and the product.

Systems (UMLS) project. After it was demonstrated that it was feasible both in terms of cost and structure to proceed, the NLM based team (see Appendix below for additional members) developed an independent editing and production database. In November 2004, RxNorm was first released as an independent terminology, and established a monthly release schedule. In October 2008, weekly releases were introduced as additions to the corresponding monthly release. Over the past 6 years, source vocabularies included in RxNorm have grown from 5 to 11, its data size has increased fivefold, and its adoption has grown substantially.

Today, RxNorm continues to evolve as a standard for clinical information exchange. Any source vocabulary included in RxNorm can be used to achieve compliance with the 'Meaningful Use' requirements for electronic health records (EHR); such designation establishes an important bridge to full RxNorm adoption.[9] Recommended by the Healthcare Information Technology Standards Panel (HITSP), RxNorm is the designated vocabulary to represent 'Medication Brand Name,' 'Medication Clinical Drug Name,' and 'Allergy/Adverse Event Product' (if the product causing the adverse event is a medication).[10]

CONTENT WITHIN RXNORM

No single drug vocabulary provides complete and interoperable drug names, codes, and relevant information. RxNorm takes the multiple drug names, using them to complement each other and reconcile the conflicts among them. By aggregating and organizing content from various source drug vocabularies, RxNorm can derive a more complete and consistent representation of drug names, codes, and relevant information.

Unique identifiers and normalized names

Unique identifiers and normalized names are the primary mechanism to group together semantically equivalent terms and codes from various source vocabularies. Different names and codes can be mapped to each other if they share the same RxNorm Concept Unique Identifier (RxCUI). Table 1 shows an example grouping of terms and codes.

Multiple levels of description and relationships

Multiple levels of description and relationships enable RxNorm to represent drugs from multiple purposes or various perspectives. A physician may find the description in the form of a clinical drug useful when he writes medication orders. At the same time, he may find descriptions at the ingredient level helpful for clinical decision support such as drug–drug interaction checking or drug–allergy checking. A pharmacist may find brand names and relationships linking branded names to generic names more helpful when substituting a branded drug with a generic one. A patient sometimes enters a medication for his personal record at the brand name or ingredient level if he doesn't remember the exact strength or dose form. To accommodate these various needs and contexts, RxNorm assigns term types (TTY) to organize various levels of description, representing drugs not only at the clinical drug level (SCD) {ingredient+strength+dose form}, but also at levels of ingredient, which includes single ingredient (IN), multiple ingredients (MIN), and precise ingredient (PIN), clinical drug component (SCDC) {ingredient+strength}, clinical drug dose form (SCDF)

Table 1 Example grouping of terms and codes

RxCUI	Source vocabulary	String
309304	RxNorm	Ciprofloxacin 2 mg/ml injectable solution
309304	SNOMED CT	Ciprofloxacin 100 mg/50 ml intravenous infusion
309304	MDDB	Ciprofloxacin IV Soln. 0.2%
309304	MTHSPL	Ciprofloxacin 400 mg in 200 ml intravenous injection

Table 2 Descriptive names of medications across various levels of abstraction

Term type	Descriptive name	Ingredient	Strength	Dose form
IN	Diazepam	✓		
SCDC	Diazepam 5 mg	✓	✓	
SCDF	Diazepam oral tablet	✓		✓
SCD	Diazepam 5 mg oral tablet	✓	✓	✓

{ingredient+dose form}, and pack (multiple clinical drugs or clinical drugs designed to be administered in a specified sequence) as well. Named, reciprocal relationships link a drug among levels of descriptions. These relationships can facilitate clinical decision support or data entry. Table 2 shows the descriptive names of medications across various levels of abstraction. Figure 1 shows the relationships linking an example drug at any various levels of abstraction.

Attributes

Attributes are relevant information about a drug at an appropriate level of abstraction. This relevant information indicates various aspects of a drug, including those that may be of clinical interest, such as related codes including NDC and Unique Ingredient Identifier (UNII), the new drug application number (NDA), and the abbreviated new drug application number (ANDA). These attributes provide additional information, other than names and codes, about a drug that may be useful for various purposes. While some attributes are listed as those attached to RxNorm names, others are listed as attributes of a given source vocabulary term. This distinction allows the determination if a license is necessary to use that attribute in a system, and allows RxNorm to represent faithfully the data from the source vocabularies it has received.

The National Drug File Reference Terminology (NDF-RT)

The National Drug File Reference Terminology (NDF-RT) was integrated into RxNorm as a source vocabulary beginning with the RxNorm June 2010 monthly release. NDF-RT is a resource developed by the Department of Veterans Affairs (VA) Veterans Health Administration, as an extension of the VA National Drug File.[11] The inclusion of NDF-RT has provided RxNorm with an additional type of information. Besides drug names and codes, providers now can find within the RxNorm data the clinical properties associated with certain drugs, such as the possible clinical use, the pharmacologic properties such as the

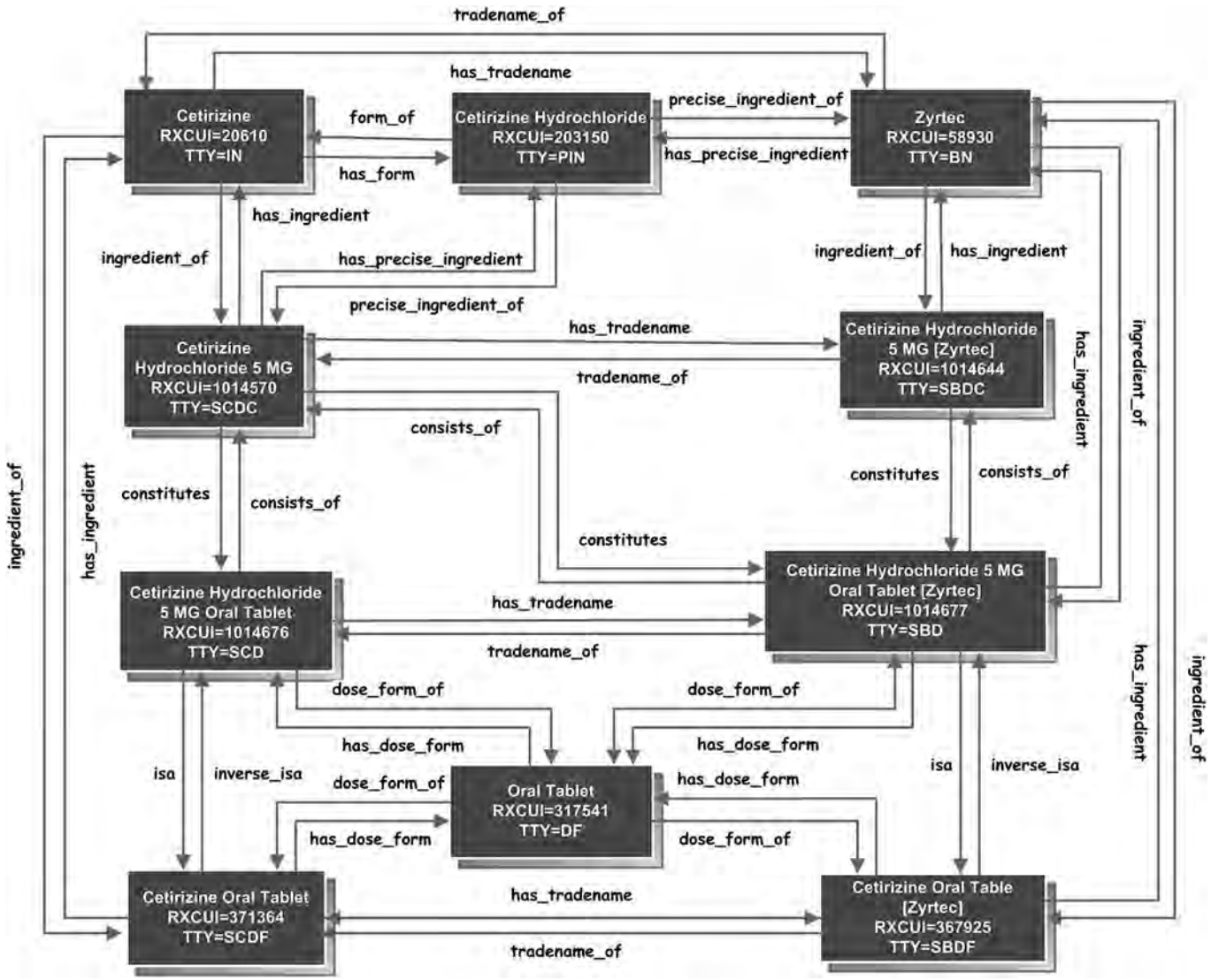

Figure 1 Relationships linking an example drug at various levels of abstraction.

mechanism of action or physiologic effect, chemical structure, contraindications to use, or possible interactions. These clinical properties of a drug may help providers with better decision support. NDF-RT associates clinical properties via named relationships. Table 3 shows the relationships and the represented clinical properties. Table 4 shows the clinical information associated with cetirizine.

Source content

Source content, if provided to the NLM and indicated as releasable, is present in RxNorm release files. Users wishing to use a source vocabulary integrated with RxNorm may find that, at times, content from a particular source is not available in released RxNorm for a given drug. This can happen for the following reasons:

(a) The source vocabulary does not cover such content at that time. For example, when a drug is approved by the FDA, RxNorm may be the first to create its name and code. Thus, RxNorm would be the only source for this drug when no other source vocabularies have included the new drug in their database and provided that information to RxNorm.

(b) Although the source vocabulary covers the content, such content has not been provided to the NLM. The brand names maintained by Medispan are an example of content that is not provided to the NLM. To obtain these brand names, users would have to consult the source vocabulary provider directly.

(c) The source vocabulary covers the content and provides it to the NLM, but the content is not releasable within RxNorm. Such information includes FirstDataBank's MEDIDs and branded drug names. Additionally, the Center for Medicare and Medicaid Services (CMS) may provide information to the NLM about products not currently covered by other sources, but which need to be represented in RxNorm. As the CMS information is not a true source vocabulary, but simply ad hoc information, it is not released as a source vocabulary. Rather, the normalized names are created de novo by the editors based on the information provided by CMS.

TYPICAL USES OF RXNORM

We have observed a steady and fast growth in the use of RxNorm over the past few years, manifested by the increasing number of RxNorm downloads and the vibrant user community activities. Monthly RxNorm downloads averaged about 350 in 2010. There are currently 89 subscribers to the RxNorm listserv begun in January 2010. In addition, we frequently receive inquires, comments, and suggestions from RxNorm users. Typical uses of RxNorm include using RxNorm standard names and codes to capture drug product information in EHR, cross mapping among disparate drug vocabularies, and facilitating medication-related clinical decision support.

RxNorm names and codes

RxCUIs and corresponding names are being included in the CMS Formulary Reference File (FRF) as of the calendar year 2010. RxCUIs are now used in the FRF to represent drug products, replacing proxy NDC codes that were used for the same purpose previously. As each unique RxCUI can represent multiple NDCs of the same drug product, use of RxCUIs can streamline the formulary submission process. Accordingly, Part D sponsors are required to use RxCUIs for formulary submissions.

Recommended by HITSP, RxNorm is the designated vocabulary to represent 'Medication Brand Name,' 'Medication Clinical Drug Name,' and 'Allergy/Adverse Event Product' (if the product causing the adverse event is a medication). RxNorm names and codes are used to represent medication names in the Continuity of Care Document (CCD). CCD is a Clinical Document Architecture (CDA) Release 2 implementation that maps the Continuity of Care Record (CCR) elements into a CDA representation, harmonizing CCR and CDA into a common framework.[12] CCD is a content standard for patient summary records.[9] For easier understanding, an example CCD medication section with RxNorm names and codes and other relevant information is illustrated in detail in figure 2. The medication section contains a narrative block (1) wrapped by the <text> element that renders human readable content and several coded CCD entries (2) for automatic processing purposes. The example document indicates that the patient is currently taking 'Celebrex 200 MG Oral Capsule,' identified by RxCUI: 213469 in RxNorm (3). This medication was started on February 4, 2009 (4). Dose is '1 capsule' (5) and frequency is 'once a day' (6). The generic counterpart of this drug is 'Celecoxib 200 MG Oral Capsule' (7). This medication was prescribed February 4, 2009 by Dr John Jose (8). Number of refills is 5 (9) and quantity dispensed is 90 (10). Note that the branded medication and the corresponding generic drug are represented by RxNorm names and codes.

Table 3 Clinical properties and corresponding relationships

Pharmacologic class	isa
Therapeutic intent	may_treat, may_diagnose, may_prevent
Contraindications	drug_contraindicated_for
Mechanism of action	mechanism_of_action_of
Physiology	has_physiologic_effect
Metabolism	metabolic_site_of, metabolizes, pharmacokinetics_of
Drug-drug interactions	contraindicated_with

Table 4 Clinical properties associated with cetirizine

drug_contraindicated_for	Drug allergy
may_treat	Rhinitis, allergic, perennial
may_treat	Urticaria
has_mechanism_of_action	Histamine H1 antagonists
has_physiologic_effect	Decreased histamine activity

Semantic interoperability

RxNorm has been used in the patient data exchange between the VA and the Department of Defense (DoD).[13] By mapping from VUID (VA Unique IDentifier) or NCID (Numeric Concept ID used by DoD) to RxCUI, real-time bi-directional encoded data exchange between the two agencies is enabled. Vendors have developed products that support their customers for drug terminology interoperability as well. Some products exploit mappings available in RxNorm as well as those not included in RxNorm. For example, FirstDataBank RxNorm Cross Reference Module provides mapping between RxNorm and NDDF Plus identifiers.[14]

Medication-related decision support

Standard drug names and codes, and cross-mapping among various drug terminologies can be considered as a necessary first step toward medication-related decision support. That is, correct identification of medications is essential. Based on this, more advanced decision support can be achieved via relationships and attributes in RxNorm. For example, relationships linking the clinical drug and branded drug can be used to discover the unintended duplicate therapy of a branded drug and its generic equivalent. NDCs associated with a drug can be used for dispensing and for inventory checking.

```
<section>
 <templateId root="2.16.840.1.113883.10.20.1.8"/>
 <code displayName="History of medication use"
codeSystem="2.16.840.1.113883.6.1" code="10160-0"/>
 <title>Medications</title>
 <text>
  Take Celebrex 200 MG Oral Capsule Once a Day.          ①
 </text>
 <entry>
  <substanceAdministration moodCode="EVN">
   <templateId root="2.16.840.1.113883.10.20.1.24"/>     ②
    <effectiveTime xsi:type="IVL_TS">
     <low value="20090204"/>
    </effectiveTime>                                     ④
   <effectiveTime xsi:type="PIVL_TS"
institutionSpecified="true">
   <period value="24" unit="h"/>                         ⑥
  </effectiveTime>
  <doseQuantity value="1" unit="1"/>                     ⑤
  <consumable>
   <manufacturedProduct>
    <templateId root="2.16.840.1.113883.10.20.1.53"/>
    <manufacturedMaterial>
     <code displayName="Celecoxib 200 MG Oral Capsule"
codeSystemName="RxNorm"
codeSystem="2.16.840.1.113883.6.88" code="205323">      ⑦
      <originalText>Celecoxib</originalText>
      <translation displayName="Celebrex 200 MG Oral
Capsule" codeSystemName="RxNorm"
codeSystem="2.16.840.1.113883.6.88" code="213469"/>    ③
     </code>
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   </manufacturedProduct>
  </consumable>
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     <repeatNumber value="5"/>                           ⑨
     <quantity value="90"/>                              ⑩
     <author>
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      <assignedAuthor>
       <telecom value="301-123-4567"/>
        <assignedPerson>
         <name>
          <family>Jose</family>
          <given>John</given>
          <suffix>MD</suffix>
         </name>
        </assignedPerson>
       </assignedAuthor>
     </author>
   </supply>
   </entryRelationship>
  </substanceAdministration>
 </entry>
</section>
```

Figure 2 An example medication section in the Continuity of Care Document body (with prescription history).

Furthermore, recent inclusion of NDF-RT within RxNorm has made more sophisticated decision support possible. With the drug classification information, medications can be organized into categories and thus what may be duplicate drug therapies within the same class can be identified. Based on the drug indications, a patient problem list can be approximately inferred from his/her medication list. The organization and presentation of patient medication data into drug classes and diseases can facilitate decision support as well as cognitive support.

Users should be aware that while medication related decision support can render many benefits, it can also have significant limitations. For example, drug—drug interaction checking or drug—allergy checking can improve patient safety and lower medication-related cost when combined with computerized provider order entry (CPOE), but it may result in excessive alerting and disrupt clinical workflow.[15]

NLM-PROVIDED RXNORM-RELATED SERVICES

To facilitate the use of RxNorm, the NLM has provided a few additional services, mainly developed as research projects, including RxNav, RxTerms, MyMedicationList, and MyRxPad. These services can help users with better understanding of the RxNorm model and content, easier access/retrieval of the RxNorm data, as well as integration of RxNorm into their personal health record (PHR) or EHR systems.

RxNav, the RxNorm Navigator, was originally primarily a browser for RxNorm.[16] It is a software application that displays RxNorm names and codes and the relationships among them based on a user's search input. It serves as a supplemental tool to help users browse through RxNorm in a visually friendly and interactive manner. The RxNav Application Programming Interface (API), which was originally developed for RxNav, was made public in 2008. The API serves as an interface to an RxNorm database and provides access/retrieval of the RxNorm data. The API has multiple implementations, including SOAP and REST, making it platform or program language independent. Today, RxNav serves as both a browser and an application programming interface for RxNorm.

RxTerms[17] is a drug interface terminology derived from RxNorm to facilitate CPOE. It reorganizes RxNorm names and codes into a two dimensional representation tailored for prescription writing; it eliminates certain drug names that are less likely to be needed in a prescribing environment as well. RxTerms de-normalizes drug descriptions at different levels into an SCD or semantic branded drug (SBD) centric view, associating ingredient, brand name, route, strength, and other related information to the corresponding SCD or SBD. Rather than linking drug descriptions at different levels via named relationships, such association is achieved by organizing a SCD or SBD and its related information into rows of records within a single table of named columns.

MyMedicationList (MML) is an application that helps patients create, update, and save their medication lists.[18] MyRxPad is a prototype application that is intended to help prescribers lower some of the e-prescribing adoption barriers and encourage an early positive experience of e-prescribing.[19] Both MML and MyRxPad use standard RxNorm names and codes for data entry and recording and save medication or prescription information in the standard CCD format, illustrated in figure 2. They also extract information from RxNorm for medication related decision support, such as auto-completion, over-dose checking at the ingredient level, and linking to prescribing information available at DailyMed (http://dailymed.nlm.nih.gov/). These applications demonstrate the applicability of RxNorm in a PHR or EHR setting. Certain functionalities implemented in MML and MyRxPad can be desirable for other systems, including CPOE with standard RxNorm names and codes, medication or prescription information in the standard CCD format, and some medication-related decision support capabilities.

In addition, MML, together with MyRxPad, can serve as an alternative approach to medication reconciliation. A patient uses MML to maintain and update his medication list and shares his medication list (brought in on a USB drive or emailed beforehand) with prescribers. Prescribers use MyRxPad to open the patient medication list, write new or refill prescriptions, and make necessary changes on the patient medication record. Accordingly, the patient obtains an updated medication list that might include refilled medications and other medication

adjustments. The patient can then use MML to add the new prescriptions to his 'current medications' without manually entering the medication names. As the patient carries along the medication list to various prescribers, the evolving and updated list serves as the integrated medication data across disparate providers. As aggregating medication histories from multiple sources may often be difficult,[20–22] this patient-centric, participatory approach can address this challenge. MML and MyRxPad provide an alternative approach to medication reconciliation across points of care as illustrated in figure 3. After the initial demonstration phase, more users and organizations are trying out MML and MyRxPad. Researchers at Oregon Health & Science University are using MyRxPad for their research effort to facilitate the access of patient medication records across doctors' offices, long term care facilities, and pharmacies. The WorldVista groups are working to adopt MML and MyRxPad, and use RxNorm for their EMR applications.

PRODUCTION AND RELEASES

While source content in RxNorm is presented 'as is,' RxNorm is not a simple accumulation of the source vocabularies. Source content is integrated into RxNorm through an inversion, insertion, editing, and production life cycle.[23] First, content from source vocabularies is converted to a common format which can be processed by the RxNorm system. Second, converted source vocabularies are inserted into RxNorm using various matching algorithms. Third, human editors review all the content that was inserted, creating normalized names where needed. Finally, after the quality assurance process, RxNorm content is released. During this RxNorm data life cycle, semantically equivalent names and codes are grouped, RxNorm unique identifiers, normalized names, relationships, and attributes are generated and assigned, and source content is preserved.

Quality assurance is a major concern in the production of the RxNorm releases. While minimizing requirements for keyboard entry during RxNorm data production keeps typographical errors to a minimum, review of consistency of relationships and other internal checks help assure the quality of the release. One step in the assurance cycle is reviewing where two sources with the same NDC code are linked to different RxNorm names. Reviewing and reconciling these errors provides an important check on consistent creation of RxNorm names and the RxNorm model.

RxNorm is released in full on the working day coinciding with or following the first Monday of each month. Each release

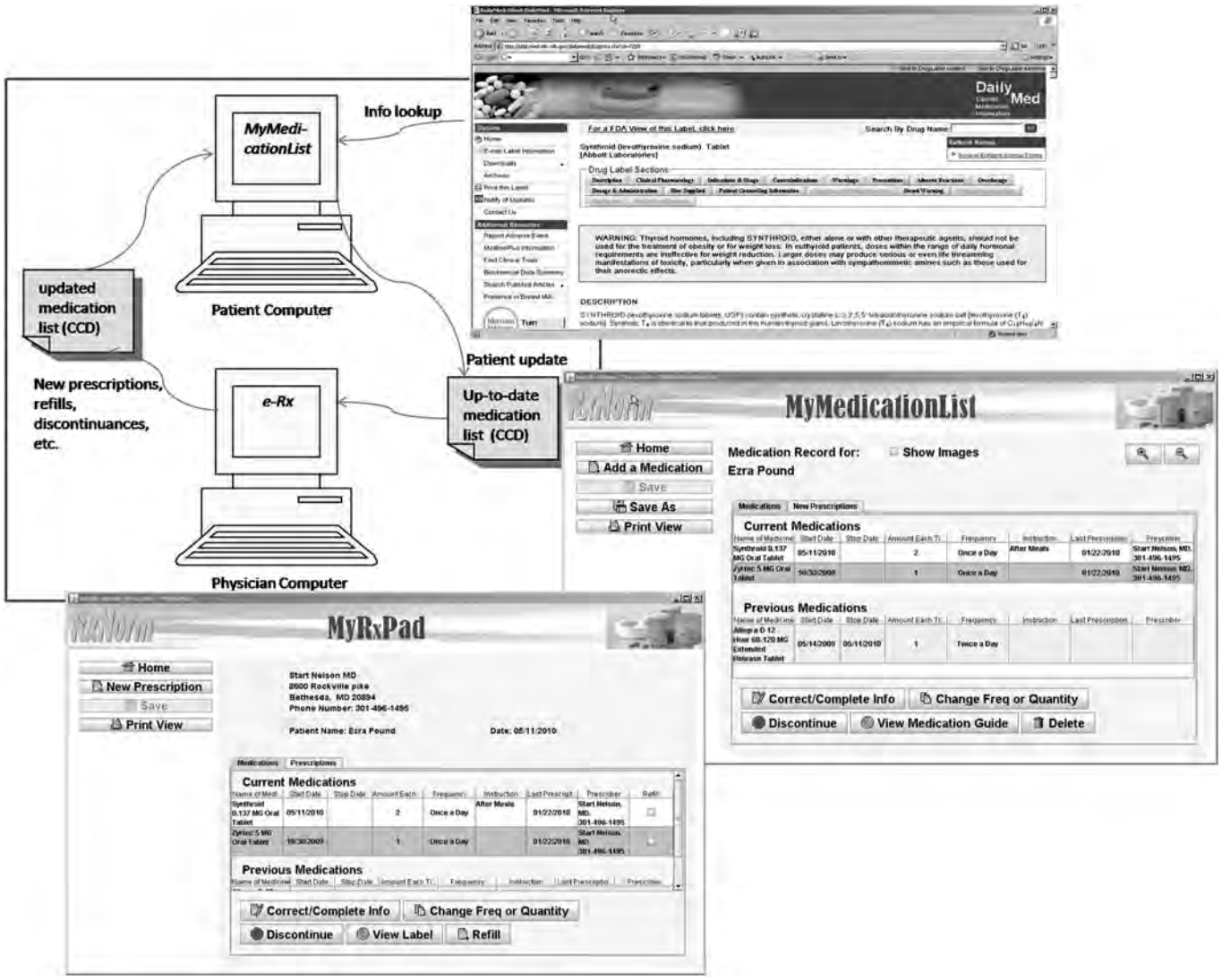

Figure 3 MyMedicationList and MyRxPad: an alternative approach for medication reconciliation across points of care. CCD, Continuity of Care Document.

follows the rich release format of the UMLS Metathesaurus, and, where references to concepts in the Metathesaurus occur, they refer to the current extant version of the Metathesaurus. Twice a year the releases of the Metathesaurus and RxNorm are scheduled to occur simultaneously, in which case the references in RxNorm are to that release of the Metathesaurus. Weekly releases of RxNorm were begun to keep up with new medications and new formulations when they appear on the market. Most of the information for these additions to RxNorm comes from the Structured Product Labels (SPL) submitted to DailyMed. The weekly release consists of only new material, linked by codes to older material if necessary. Changes in concept structure, such as moving a source atom from one RxNorm concept to another, take place only in the monthly releases, which are full releases.

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The RxNorm file can be obtained at no cost from the NLM RxNorm website (http://www.nlm.nih.gov/research/umls/rxnorm/). The downloadable zip file contains several RxNorm content files which are bar-delimited text files, as well as load scripts that can be used to import the content files into MySQL or Oracle databases. At the same web site, users can find related information, including the RxNorm overview and technical documentation.

To obtain the RxNorm file, users need to complete a UMLS license agreement, which permits uses of public domain content in perpetuity. Certain content of RxNorm is freely available, including RxNorm names and codes. Other content contains copyrighted proprietary information. For use of that proprietary content, users need to contact the source vocabulary contributor for specific terms of use or licenses.

To be informed about the upcoming RxNorm changes, users can subscribe to the RxNorm announcement at rxnorm-announces-l@list.nih.gov. Inquires, comments, or suggestions can be directed to rxnorminfo@nlm.nih.gov.

FUTURE WORK

Over the past few years, RxNorm has evolved to be an emerging standard for clinical information exchange. RxNorm names and codes have gained wide recognition. Users often use RxNorm names and codes to record drug names, and RxNorm attributes for various purposes in their PHR or EMR applications. For these specific uses, users may find names and codes from sources other than RxNorm less relevant. Thus, a pre-processed RxNorm subset that contains only data that are pertinent to users' needs seems desirable. The subset can also facilitate the adoption of RxNorm as providers prepare themselves to meet the requirements for 'Meaningful Use' Stage 2 when full adoption of RxNorm is expected.

At the time of this paper, the RxNorm team is working on an RxNorm e-prescribing subset. The subset intends to provide a comprehensive nomenclature that includes all prescribable clinical drugs and packs on the market for use in e-prescribing systems. The subset would include Federal Medication Terminologies components (RxNorm, UNII, NDC, NDF-RT classes) as well as important attributes in RxNorm. Not included in the list would be drugs not sold in the US and those sold only for veterinary purposes.

We believe the e-prescribing subset will encourage providers to use standard RxNorm names and codes to enter medication orders electronically. Increasing CPOE use is a core objective specified by the 'Meaningful Use' regulation. Only when providers enter orders electronically can the computer help improve decisions by applying clinical logic to those choices in light of all the recorded patient data.[24] E-prescribing is a starting point to realize the true potential of EHRs and thus we have named the subset an e-prescribing subset. The use of the subset, however, is not limited to e-prescribing only. The subset also can be applied throughout EHRs when medication information is captured. For example, patients can use the subset to enter medications on their medication lists and pharmacies can use the subset to record the medications dispensed.

Several challenges remain in constructing such a subset. One obstacle is to identify drugs that are on the market. There is no reliable complete and accurate listing of all the drugs that are currently on the market in the USA. We consider the information from the SPLs in DailyMed to be a reliable source for what is on the market. Pending the full listing of SPLs, our approach is to interpret and reconcile source data which provide information on whether a drug is currently on the market. We identify current drugs algorithmically and have editors review the information.

By eliminating names and codes from sources other than RxNorm, the subset size will be much smaller than the RxNorm full release. The smaller file size is desirable for data management and access, as well as for mobile applications.

Like RxNorm, the information included in the RxNorm e-prescribing subset includes not only RxNorm names and codes, but also RxNorm attributes that could assist with medication-related clinical decision. However, both RxNorm and its e-prescribing subset remain as a terminology, not necessarily a complete drug knowledge base. Therefore, certain knowledge is not within its scope, such as formulary information or drug pricing information. Although such knowledge is not included in RxNorm, as more drug knowledge bases are incorporating RxNorm codes, users can choose to interface with certain knowledge bases via these names and codes.

While the basic structure, mission, and uses of RxNorm are well established, additional features and developments continue to be made. Additional drug classification information, allergy and adverse reaction classes, and other grouping information may be included over time.

CONCLUSION

RxNorm was built with the idea that uses of it might provide substantial benefits including standard names and codes for drug product representation, semantic interoperability across disparate drug vocabularies, and medication-related clinical decision support. At this point it appears that RxNorm is a compliant vocabulary for medications to support 'Meaningful Use'; incorporation of RxNorm may be needed for health information system certification and for incentive payments.

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The work of maintaining the documentation, inverting and inserting multiple sources into RxNorm, as well as distribution of the RxNorm vocabulary and maintenance of the RxNorm website is done by the Office of Computer and Communications Systems (OCCS) of the National Library of Medicine.

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Supplement

NCCN Biosimilars White Paper: Regulatory, Scientific, and Patient Safety Perspectives

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Key Words

Biosimilars, follow-on biologics, health policy

Abstract

Biologics are essential to oncology care. As patents for older biologics begin to expire, the United States is developing an abbreviated regulatory process for the approval of similar biologics (biosimilars), which raises important considerations for the safe and appropriate incorporation of biosimilars into clinical practice for patients with cancer. The potential for biosimilars to reduce the cost of biologics, which are often high-cost components of oncology care, was the impetus behind the Biologics Price Competition and Innovation Act of 2009, a part of the 2010 Affordable Care Act. In March 2011, NCCN assembled a work group consisting of thought leaders from NCCN Member Institutions and other organizations, to provide guidance regarding the challenges health care providers and other key stakeholders face in incorporating biosimilars in health care practice. The work group identified challenges surrounding biosimilars, including health care provider knowledge, substitution practices, pharmacovigilance, naming and product tracking, coverage and reimbursement, use in off-label settings, and data requirements for approval. (*JNCCN* 2011;9[Suppl 4]:S1–S22)

Executive Summary

The use of biologics is widespread and has become an essential element in cancer treatment and supportive care management; based on current patterns of drug development, the increased use of biologics in cancer is inevitable. Patents for older biologics will soon expire, and the United States is developing a regulatory process for the approval of similar biologics (biosimilars). Therefore, the safe and appropriate incorporation of biosimilars into clinical practice for patients with cancer is important to consider. Biologics are complex to develop and manufacture, and therefore are often high-cost components of cancer treatment. The potential for biosimilars to provide cost competition and reduce the cost of biologics was the impetus behind the Biologics Price Competition and Innovation Act of 2009 (BPCI Act), a part of the 2010 Affordable Care Act. As the FDA implements elements of the BPCI Act, stakeholders must actively engage in discussions to ensure biosimilars are safe and effective for the treatment of patients with cancer.

To provide guidance regarding the challenges health care providers and other key stakeholders face in incorporating biosimilars in health care practice, NCCN assembled a Work Group consisting of thought leaders from NCCN Member Institutions and other organizations external to NCCN. These multidisciplinary thought leaders represented providers (physicians, pharmacists, and nurses), patients, manufacturers, payors, and government. The NCCN Biosimilars Work Group was convened in order to advise oncology practitioners and key stakeholders regarding challenges and recommendations concerning biosimilars in oncology. The

content of this White Paper represents the work of NCCN and may not necessarily reflect the opinions of the external work group members or the organizations with which they are affiliated.

Incorporating Biosimilars Into Oncology Practice: Challenges in the United States

The NCCN Biosimilars Work Group recognized that substantial differences exist between biologics (i.e., drugs produced by living systems) and traditional small-molecule drugs (i.e., chemical drugs) in terms of basic chemical structure, molecular weight, and manufacturing processes. Generic small-molecule drugs can be replicated in an exact way so that they are atomically identical to their reference drug. Therefore, because generic versions of small-molecule drugs are completely identical, they can be manufactured, marketed, and used in clinical practice with relative ease compared with biosimilar products. However, because biologics are complex products produced by living systems, they will inherently exhibit some physiochemical differences in addition to the varying production processes that will also modify the products (e.g., purification methods), and therefore biosimilars can be close or "similar" to the innovator products but will not be identical. This can also occur with manufacturing separate lots of biologics, whether innovator or biosimilar, but is controlled for with tightly managed in-process controls. The science, regulatory processes, and pharmacovigilance mechanisms for these complex biologics are still developing. The fundamental differences between biosimilars and small-molecule generic drugs are key drivers of the identified challenges listed in Table 1.

Key Recommendations

- Clinical trials are expected to be required, and, at minimum, these clinical trials should include

Table 1 Challenges for Incorporating Biosimilars Into Oncology Practice in the United States

Topic	Challenge, Consensus Statement, or Recommendation
Use of biosimilars for off-label indications	• In oncology, the use of biologics for off-label indications is common.
	• Although the FDA is expected to determine whether the use of a biosimilar can be extrapolated to all labeled indications based on the data submitted, the challenge for clinicians, payors, and other stakeholders will be to decide whether the data (and therefore use of a biosimilar) can be extrapolated to off-label indications.
Biosimilar economics and diffusion	• Biosimilar development costs are relatively high (compared with small-molecule generics), and therefore on a percentage basis, cost savings from biosimilars may be more modest compared with small-molecule generic drugs.
	• However, because biologics are expensive therapies, any cost savings have the potential to be meaningful.
	• Questions exist for how biosimilars will be covered, reimbursed, and dealt with by United States payors. Additionally, coverage and reimbursement policies have the potential to positively or negatively affect patient access and uptake.
Clinical trial enrollment	• Potential barriers exist to enrolling patients in clinical trials for biosimilars.
	• For example, physician interest in enrolling patients in clinical trials involving biosimilars and patient interest in participating in these trials may be low.
Biosimilar safety, product specific tracking, and naming	• Pharmacovigilance will be important to show that biosimilars exhibit a comparable safety profile to the reference product.
	• Although many large institutions have the infrastructure to track the use of a specific product back to a given patient, this system is less common in community settings.
	• Therefore, in an environment in which multiple sources of individual biologic entities are available (i.e., multisourced environment), a particular challenge exists in tracking the source of a biologic administered in the community setting.
Substitution practices	• Differences in substitution practices may be seen between small-molecule drugs and their generic versions versus biologics and their corresponding biosimilars.
	• Substitution practices may vary among states but should only be considered if the FDA determines a biosimilar to be interchangeable with its corresponding biologic.
Health care provider education	• Preliminary data from an NCCN Trends Survey indicate that health care providers require education on biosimilars.

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clinical end points that are most sensitive to show a difference (if any difference does exist) between the reference and biosimilar products.

- The FDA should provide guidance as soon as possible to define "highly similar" quality attributes and "no clinically meaningful differences in efficacy and safety."
- The NCCN Guidelines Panels should evaluate recommendations regarding the use of biosimilars where available. This will provide guidance to both institutional Pharmacy and Therapeutics (P&T) Committees and practitioners who do not routinely practice under the auspices of a P&T Committee (e.g., those in community practice).
- Biologics and biosimilars are complex, and education regarding the basic scientific principles about biologic manufacturing processes and pharmacovigilance efforts should be disseminated to health care practitioners, including physicians, pharmacists, nurses, and mid-level practitioners (e.g., physician assistants, nurse practitioners).

The NCCN Work Group consensus statements and recommendations are summarized in Tables 2 and 3.

Overview and Background

On March 23, 2010, President Obama signed into law the Patient Protection and Affordable Care Act. The Affordable Care Act contains the BPCI Act that establishes an abbreviated approval pathway for biological products that are shown to be "biosimilar" to, or further shown to be "interchangeable" with, an FDA-licensed biological product. The BPCI Act states that in order for a biologic product to be considered biosimilar to a reference product, the biological product must be proven to be biosimilar to a reference product based on data derived from analytical, animal, and clinical studies. The BPCI Act[1] defines "biosimilar" or "biosimilarity" as a 2-part demonstration that 1) the proposed biosimilar product is "highly similar to the reference product notwithstanding minor differences in clinically inactive components," and 2) "no clinically meaningful differences" exist between the proposed similar product and the reference product in terms of "safety, purity, and potency." Additionally, it must be proven that the proposed,

> biosimilar product and reference product utilize the same mechanism or mechanisms of action for the

Table 2 NCCN Biosimilars Work Group Consensus Statements

Category	Consensus Statement
Importance, access, and affordability	• The overall goal of biosimilars is to increase affordability and access to biologic medications for patients, which are often important therapies for cancer care.
	• The NCCN Work Group believes that biosimilars are important to oncology care, and is supportive of defining a biosimilars approval pathway (characterized in the Biologics Price Competition and Innovation Act of 2009).
Approval pathway: demonstrate similarity	• At the time of biosimilar approval, a biosimilar must have shown high similarity to the reference (i.e., innovator) product in quality attributes and pharmacodynamic and pharmacokinetic parameters.
	• Efficacy and safety of the biosimilar product must be comparable (i.e., no meaningful difference in safety and efficacy) to the reference product.
Standardization with reference product	• The NCCN Work Group agrees with current regulations that elements of a biosimilar drug product should follow the reference product (for the purpose of consistency of practice avoiding medication errors). For example, the dosing for a biosimilar agent should be the same as for the reference product. Additionally, Risk Evaluation and Mitigation Strategies (REMS) and the associated provider workflow process should be standardized between biosimilar and reference products.
Tracking product use	• The ability to track a patient's receipt of a biosimilar product during routine clinical use down to the level of a specific manufacturer and batch was seen as a critical element of assessing and ensuring the safety of these medications.
Need for education: patients and health care providers	• Patients and health care providers require education to increase their understanding of biosimilars. Patients should also know all the medicines they receive.
	• In the context of multisourced biologics being available, this may help avoid medication errors if patients know the exact drug product they receive.

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Table 3 NCCN Biosimilars Work Group Recommendations

Category	Recommendation
Approval pathway: use appropriate end points	• Clinical end points that are most sensitive to show a difference (if any difference does exist) between the reference and biosimilar products should be studied.
	• Data regarding end points such as overall response, overall survival, and/or progression-free survival may be helpful for health care providers.
Approval pathway: consistency and transparency	• A consistent approach and transparency in the FDA process is recommended to assess biosimilarity as defined by the law: 1) highly similar quality attributes, and 2) no meaningful differences in efficacy and safety.
	• The required scientific data will be defined based on the known safety and efficacy profiles (i.e., risk/benefit ratio for the reference biologic).
Biosimilars and the NCCN Guidelines Panels	• The NCCN Guidelines Panels should evaluate biosimilars and discuss their role in the context of the disease when appropriate, and provide specific recommendations regarding the use of biosimilars.
	• The work group did not anticipate recommendations against biosimilars in NCCN Guidelines but felt that this information would be helpful to add clarity for clinicians, patients, and payors.
Pharmacy & Therapeutics (P&T) Committee	• As with other drugs and biologics, an institution's P&T Committee should review biosimilar products for use in their own specific patient population. This is a different approach from that used for generic small-molecule drugs.
	• For practitioners who do not routinely practice under the auspices of a P&T Committee (e.g., in community practice), consideration and review of individual biosimilar products (either informally or formally) should be instituted before routine use is implemented, as with other drugs and biologics.
Need for education: health care practitioners and policy makers	• Biologics and biosimilars are complex, and education on the topic is usually provided in the context of the treatment of a specific disease. Therefore, more education regarding the basic scientific principles about biologic manufacturing processes and pharmacovigilance efforts should be disseminated to health care practitioners, including physicians, pharmacists, nurses, and mid-level practitioners (e.g., physician assistants, nurse practitioners).
	• Additionally, this education should be disseminated to legislators and other policy-makers.
Biosimilar safety, product specific tracking, and naming	• The FDA must provide guidance regarding the naming of biosimilars and whether they will have unique nonproprietary names.

> condition or conditions of use prescribed, recommended, or suggested in the proposed labeling, but only to the extent the mechanism or mechanisms of action are known for the reference product;

and the proposed biosimilar product have the same route of administration, dosage form, and strength as the reference product.[1]

The objectives of the BPCI Act are conceptually similar to those of the Drug Price Competition and Patent Term Restoration Act of 1984 (commonly referred to as the Hatch-Waxman Act), which established an abbreviated pathway for the approval of generic drug products under the Federal Food, Drug, and Cosmetic Act (FD&C Act). The BPCI Act amends Section 351 the Public Health Service Act (PHSA) to add subsection (k), which establishes an abbreviated approval pathway for biosimilars. This creation of an abbreviated approval pathway under the PHSA largely aligns with the Hatch-Waxman concept of permitting reliance for approval, at least partly, on an appropriate previously approved drug as the reference product, with the potential of saving time and resources and avoiding unnecessary duplication of human or animal testing. The implementation of an abbreviated approval pathway for biological products may present challenges given the scientific and technical complexities that may be associated with the larger and often more complex structure of biological products, and the processes through which these products are manufactured.

The policy issues surrounding biosimilars have come to the forefront of discussion because of biosimilars' potential to reduce health care costs. However, there are scientific and manufacturing challenges to ensuring that a biosimilar is "highly similar" to the innovator product. As of the drafting of this manuscript, the FDA has not released any guidances for

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industry, raising questions about what will be necessary to gain FDA approval. Furthermore, because biosimilars will be new to the United States market, they present challenges to health care practitioners, who must be educated on the topic to make decisions about safe and appropriate use of biosimilars.

The development of biosimilars is anticipated to have a major impact on the management of cancer. The use of biologics is widespread and has become an essential component in cancer treatment and supportive care management. Given the current development of new biologics in cancer, the use of biologics will clearly increase. Patents for older cancer biologics will soon expire, removing one of the barriers to commercialization of biosimilars. The potential to provide wider access to more affordable cancer biologics may be realized through the BPCI Act; however, the regulatory process for the approval of biosimilars is under development by the FDA. As the FDA implements elements of the BPCI Act, stakeholders must actively engage in discussions to ensure that biosimilars are safe and effective for the treatment of patients with cancer.

Biosimilar Versus Interchangeable Drugs

A biosimilar may be shown to be highly similar to a reference product based on data derived from analytical, animal, and clinical studies. Minor differences are allowed in clinically inactive components as long as no clinically meaningful differences exist between the proposed biosimilar and the reference product with regard to safety, purity, and potency (presumably pharmacokinetics, pharmacodynamics, clinical safety, and efficacy). Requirements to meet the "no clinically meaningful differences" standard have not been defined in the law, and, depending on FDA's implementation of the biosimilar approval pathway, may be variable among products based on the known safety and efficacy profile of the reference products.

The BPCI Act also establishes that biosimilars may be further determined to be interchangeable products. To be deemed interchangeable with the reference product, the biosimilar is expected to produce the same clinical results in any given patient. The law also defines interchangeable to mean "that the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product." For biologics that are administered more than once to a patient, the risks in terms of safety and efficacy of alternating or switching between use of the reference product and biosimilar must be equal to the risk of using only the reference product. However, methods for adequate switching/alternating studies have not yet been defined.

Acceptance of Biosimilars

Ultimately, physicians, pharmacists, payors, and others will influence the uptake and diffusion of biosimilars into clinical practice. Oncologists will need to be confident in the data used to support FDA approval of biosimilars, both in terms of biosimilarity and the potential for interchangeability as assessed and communicated by the FDA.

Cancer is often catastrophic and complex to treat, and therefore, before prescribing a biosimilar, oncologists must have the utmost confidence in the data supporting biosimilar approval. Also, efficacy and safety, including immunogenicity profiles of the biosimilar and reference biologic, will need to be examined before most oncologists will prescribe a biosimilar. Because of the widespread accepted use of biologics off-label in oncology (such as use guided by the NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines] and other guidelines), oncologists will likely extrapolate data for FDA-approved indications to off-label uses.

Regulation Experience in the European Union

Biosimilars are already established in the European Union (EU). The EU established a legal pathway starting in 2004, before many biologics started coming off patent. To date, 4 companies have successfully developed and received approval for biosimilars to be marketed in the EU. EU regulators began using the term "biosimilars" ("similar biological medicinal products") to describe the biopharmaceuticals produced to closely replicate existing biologic drugs, and also developed a regulatory approval pathway for biosimilars beginning in 2005. The European Medicines Agency (EMA) oversees the authorization of biosimilars in the entire EU, much as the FDA does in the United States based on the BPCI Act.[2,3] The following section explores the EMA experience with

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biosimilars, including interchangeability and substitution; marketing authorization; extrapolation of data; and safety.

As noted by Mellstedt et al.,[4] the EMA approach to biosimilars is based on the idea that, "…biosimilars are not generic equivalents of the innovator products." The EMA provides the following description of biosimilar medicine:

> "…a medicine which is similar to a biological medicine that has already been authorized (the 'biological reference medicine'). The active substance of a biosimilar medicine is similar to the one of the biological reference medicine. Biosimilar and biological reference medicines are used in general at the same dose to treat the same disease. Since biosimilar and biological reference medicines are similar but not identical, the decision to treat a patient with a reference or a biosimilar medicine should be taken following the opinion of a qualified healthcare professional."[5]

As noted in the above description, health care professionals decide the interchangeability of a biologic reference medicine and the biosimilar; the individual member state control automatic substitution, not the EMA. Several EU member nations have passed measures prohibiting or restricting automatic substitution of biosimilars for innovator biologics at the hospital or pharmacy level.[2,3] In the United States, interchangeability of a biosimilar is determined by the FDA per the BPCI Act. Substitution practices with regard to drug products have been historically guided by state laws and State Pharmacy Boards.

Marketing authorization can be acquired in the EU once the EMA has approved a biosimilar for safety, efficacy, and quality.[5] These standards are governed by the EMA's Committee for Human Medicinal Products (CHMP), which defines the required purity of the biosimilar; requirements for clinical safety and efficacy, nonclinical studies, and clinical trials, which must demonstrate pharmacodynamic and pharmacokinetic properties; and drug class–specific guidelines for select biosimilars, with varying requirements for clinical trials. Seven biosimilar molecules have been approved under 14 different marketing applications in Europe, whereas 5 products were withdrawn or rejected by the EMA. Biosimilar erythropoiesis-stimulating agents (ESA), myeloid growth factors, and somatropins are currently available in the European market.[2,6] The EMA is expected to finalize its guideline on requirements for biosimilar products containing monoclonal antibodies in 2011.[7]

The EMA also allows for extrapolation of data, if properly justified, for use of biosimilars in indications that were not formally studied. Additionally, because of rare serious adverse effects, postapproval pharmacovigilance and monitoring of immunogenicity are required based on the known safety profile of the reference product.[4]

The aforementioned experience in the EU will be useful for developing policy on biosimilars in the United States. However, differences between the EU and United States health care systems will translate into some differences in how the United States will incorporate biosimilars into practice.

WHO Guidance on Biosimilars

The WHO, the public health arm of the United Nations, developed guidance for biosimilars through its Expert Committee on Biological Standardization (ECBS), which issued its finalized,"Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs)" in April 2010. The guidelines are meant

> …to provide globally acceptable principles for licensing biotherapeutic products that are claimed to be similar to biotherapeutic products of assured quality, safety, and efficacy that have been licensed based on a full licensing dossier.[3,8]

These guidelines are a relevant resource for nations that have not yet established a standard for integrating biosimilars into practice, and are similar to EMA guidance on establishing biosimilarity.[3] Furthermore, the WHO guidance may be useful in less strictly regulated markets (e.g., China and India) where copied biopharmaceuticals have already been in use for many years.[2]

It is important to distinguish biosimilars approved in highly regulated environments from biologic products in less-regulated environments. One author has referred to biologic products on the market in areas of the world with limited regulations as "biopharmaceuticals not subject to regulatory approval" (B-NSRA) products.[9]

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Biosimilars in the United States

Although the BPCI Act was passed in 2010, many details of the United States biosimilar approval process are not yet clear. In 2011, the FDA is expected to release guidance to further define the United States biosimilar approval process as established by the BPCI Act. The pending biosimilar guidance is expected to provide important perspective on current FDA thinking on biosimilars and improve the transparency of the process for biosimilar approval. However, the BPCI Act allows sponsors to submit applications without guidance, and therefore biosimilar sponsors could submit an application at any time.

Before the BPCI Act, United States law did not provide an abbreviated approval process for non-innovator biologics approved under the PHSA. The pathway for abbreviated approval of generic small-molecule drugs provided by the Hatch-Waxman Act did not apply to those biologics. The Hatch-Waxman Act amended the FD&C Act to provide for a generic pathway for only those drug products subject to approval under the FD&C Act. Most biologics are subject to the approval pathway under section 351 of the PHSA, and therefore the Hatch-Waxman generic approval pathway does not apply.[10] A few simple biologic drugs, such as human growth hormones and insulin, are exceptions to this rule, because they have been approved under the FD&C Act.[11]

Several developments have made the introduction of biosimilars imminent in the next several years in the United States. Although details of the abbreviated pathway for biosimilar approval are still emerging, legislation that develops the framework of the regulatory process has removed an important legal barrier to the introduction of biosimilars in the United States. Furthermore, patents will soon expire on many biologic products commonly used in the treatment of patients with cancer (Table 4). As the introduction of biosimilars for these patients nears, clinicians must be well informed to understand the appropriate application of all biologics (reference products and biosimilars) in their practice setting.

Work Group Description

To describe potential challenges for incorporating biosimilars into clinical practice and to offer recommendations and guidance to relevant stakeholders, NCCN convened a Work Group comprising thought leaders from NCCN Member Institutions and other organizations external to NCCN. These multidisciplinary thought leaders represented providers (physicians, pharmacists, and nurses), patients, manufacturers, payors, and government. The work group included representatives from both academic centers and the community practice setting. The NCCN Work Group meeting was held on March 12, 2011, during the 2011 NCCN 16th Annual Conference in Hollywood, Florida. In addition, NCCN conducted an Oncology Policy Summit: Biosimilars – Regulatory, Scientific, and Patient Safety Perspectives held on April 29, 2011, in Washington, DC. This summit included additional thought leaders representing the aforementioned groups and other relevant stakeholders.

The overall objective of the work group was to identify issues related to biosimilars that health care providers who care for patients with cancer will encounter. Because regulations are emerging, some discussion of the regulatory aspects of biosimilars occurred, but the focus remained on implications of biosimilars in the care of patients with cancer.

Additionally, the work group realized the need to collect data regarding provider knowledge, educational needs, and planned use of biosimilars. Therefore, the NCCN Work Group developed a survey that was administered through the NCCN Trends Surveys and Data program. These survey data were presented at the NCCN Oncology Policy Summit: Biosimilars – Regulatory, Scientific, and Patient Safety Perspectives.

This document encapsulates the discussion during the work group meeting and at the policy summit, including background on biologics, identified

Table 4 Sample of Important Biologics in Oncology and Their United States Approval Dates

Biologic	FDA Approval
Bevacizumab (Avastin)	February 6, 2004
Cetuximab (Erbitux)	February 12, 2004
Darbepoetin alfa (Aranesp)	September 17, 2001
Epoetin alfa (Epogen/Procrit)	June 1, 1989
Filgrastim (Neupogen)	February 20, 1991
Pegfilgrastim (Neulasta)	January 31, 2002
Rituximab (Rituxan)	November 26, 1997
Trastuzumab (Herceptin)	September 25, 1998

Data from U.S. Food and Drug Administration Web site. Available at: http://www.fda.gov/. Accessed August 5, 2011.

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challenges to incorporating biosimilars into oncology practice from a health care provider's perspective, and a descriptive analysis of the data obtained from the NCCN Trends Survey. Finally, this document outlines the consensus statements and recommendations offered by the NCCN Work Group.

Biologics and Biosimilars in Oncology

Although the use of biologics encompasses many specialties of medicine, biologics have made a major impact in the medical management of cancer. Biologics have improved clinical outcomes (including overall survival) and are integral for supportive care management of symptoms caused by cancer or chemotherapy. Biologics are essential in most NCCN Guidelines, including breast, colorectal, esophageal, gastric, head and neck, kidney, and non–small cell lung cancers, in addition to Hodgkin and non–Hodgkin's lymphoma (B-cell lymphoma, Burkitt lymphoma, chronic lymphocytic leukemia, diffuse large B-cell lymphoma, follicular lymphoma, gastric mucosa-associated lymphoid tissue [MALT], lymphoblastic lymphoma, mantel cell lymphoma, nongastric MALT, primary cutaneous B-cell lymphoma, and splenic marginal zone lymphoma). They are also vital in the treatment of cancer and chemotherapy-induced anemia and neutropenia according to the NCCN Supportive Care Guidelines. To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

A significant early example is rituximab, an anti-CD20 monoclonal antibody that was initially approved by the FDA in 1997 for the treatment of relapsed or refractory low-grade or follicular B-cell non–Hodgkin's lymphoma.[12] Since its approval, numerous studies have shown rituximab to be beneficial in numerous types of B-cell lymphomas, including diffuse large B-cell lymphoma, in which multiple independent studies have shown that its addition to standard chemotherapy prolongs survival.[13] Trastuzumab is another example of a successful biologic for the active treatment of cancer. Studies have shown favorable outcomes with trastuzumab in terms of improved overall survival in patients with HER2-positive breast cancer.[14] Myeloid growth factors (e.g., pegfilgrastim, filgrastim), also biologics, play an important role in the supportive care management of symptoms caused by cancer or chemotherapy. In particular, myeloid growth factors have benefited patients through managing chemotherapy-related neutropenia in a wide range of tumor types.[15]

Economics of Biosimilars

Of the 199 individual agents listed in the NCCN Drugs & Biologics Compendium (NCCN Compendium), only 15% are classified as biologics. Despite the relatively small number of biologics in the NCCN Compendium, biologics account for most of the total oncology-related drug expenditures in outpatient clinics.[16] Recent drug expenditure data provided by Doloresco et al.[16] show the top antineoplastic drugs (i.e., drugs for the active treatment of cancer) on which outpatient clinics spent the most money in 2010; 5 of the top 20 are biologics (Table 5), and biologics constituted the top 3 expenditures (bevacizumab, rituximab, and trastuzumab). Collectively, biologics accounted for more than half (55%) of the total expenditures of the list of top 20 drugs (Figure 1). These data underestimate the proportion of total expenditures for all biologics in oncology care, because drugs for the supportive care management of cancer- or chemotherapy-related symptoms (e.g., epoetin alfa, darbepoetin, filgrastim, pegfilgrastim) are not reported in this study.

According to the previously described definition of "biosimilar," patients who receive biosimilars would fare no better or worse clinically than if they had received the originator biologic, leading some to question the need for biosimilars. Given that biologics for patients with cancer can be expensive, biosimilars may present an opportunity to improve patient access through providing lower-cost options without compromising patient outcomes.

Previous experience with generics for small-molecule drugs offered price reductions up to 80% compared with their branded counterparts.[17] Furthermore, a report by the Generic Pharmaceutical Association indicates that the use of generics saved the United States health care system an estimated $824 billion during the previous decade.[18] However, biosimilars have a different economic paradigm. Because of higher development, facility, and manufacturing costs, biosimilar savings are expected to be more modest. A Congressional Budget Office estimate suggested a discount of up to 40%.[19] In the EU, ESA biosimilars confer an estimated 25% to 30% cost savings compared with their innovator products, which also led to a decrease in innovator

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Table 5 Top 20 Antineoplastic Drug Expenditures in Outpatient Clinics

Rank	Drug	Biologic or Nonbiologic	2010 Total Expenditure (in Millions of Dollars)	Top 20 Total (%)
1	**Bevacizumab**	**Biologic**	**1884**	**22.1%**
2	**Rituximab**	**Biologic**	**1466**	**17.2%**
3	**Trastuzumab**	**Biologic**	**931**	**10.9%**
4	Docetaxel	Nonbiologic	688	8.1%
5	Pemetrexed	Nonbiologic	579	6.8%
6	Oxaliplatin	Nonbiologic	508	6.0%
7	Gemcitabine	Nonbiologic	463	5.4%
8	**Cetuximab**	**Biologic**	**329**	**3.9%**
9	Bortezomib	Nonbiologic	327	3.8%
10	Leuprolide	Nonbiologic	220	2.6%
11	Paclitaxel–albumin	Nonbiologic	212	2.5%
12	Bendamustine	Nonbiologic	208	2.4%
13	Azacitidine	Nonbiologic	148	1.7%
14	Liposomal doxorubicin	Nonbiologic	130	1.5%
15	Decitabine	Nonbiologic	92	1.1%
16	Topotecan	Nonbiologic	86	1.0%
17	Fulvestrant	Nonbiologic	81	0.9%
18	**Panitumumab**	**Biologic**	**70**	**0.8%**
19	Ixabepilone	Nonbiologic	60	0.7%
20	Temsirolimus	Nonbiologic	48	0.6%
		Total of Top 20	8528	100.0%

Adapted from Doloresco F, Fominaya C, Schumock GT, et al. Projecting future drug expenditures—2011. Am J Health Syst Pharm 2011;68:929; with permission.

ESA prices.[2] Mellstedt et al.[4] note that although cost savings for biosimilars will not be as great as for small-molecule generics, this should continue to increase access to biologic drugs in the EU.

Pending FDA data requirements for the established biosimilar pathway will have an effect on the cost of biosimilars, contingent on the level of data needed to establish biosimilarity, which could in turn affect patient access to these drugs. If data requirements are substantial, fewer biosimilars may be able to come to market because of associated higher clinical trial costs, and may have a lesser impact on potential cost savings. Alternatively, fewer data requirements could allow more biosimilars to come to market and may subsequently cause a greater impact on potential cost savings, but also greater uncertainty regarding the comparability of the biosimilars' clinical safety and efficacy.

Because economics will play an important role in the introduction of biosimilars into practice in the United States, policies and regulations should be in place to ensure that 1) a biosimilar product is "highly similar" to the reference product, and 2) systems are established to identify and mitigate any unintended consequences. NCCN challenged the Biosimilars Work Group with identifying the challenges of incorporating biosimilars into oncology practice (from the perspective of health care practitioners when caring for patients) and to subsequently offer recommendations to address those challenges. During early discussions of the work group, participants noted that one of the root causes of the challenges identified by the work group revolved around the differences between biologics and traditional small-molecule chemical entities. Specifically, the scientific principles surrounding the development of "copies" of the reference product (i.e., "biosimilars" for biologics and "generics" for small-molecule drugs) for these distinct classes of drugs are substantially different, and thus require further discussion before describing the challenges identified by the work group.

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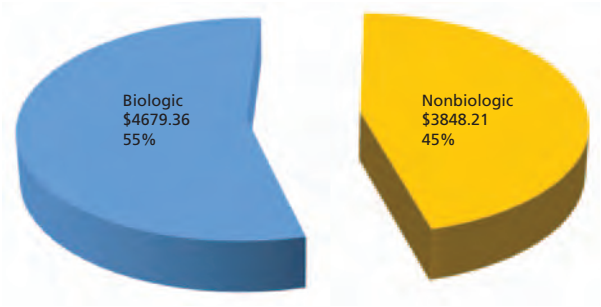

Figure 1 Biologics vs. nonbiologics distribution of drug expenditures of the top 20 antineoplastic drugs in outpatient clinics (in millions of dollars).
Data from Doloresco F, Fominaya C, Schumock GT, et al. Projecting future drug expenditures – 2011. Am J Health Syst Pharm 2011;68:921–932.

Biosimilars Versus Small-Molecule Generics

The differences between biosimilars and generics for small-molecule drugs relate to the chemical differences between their respective reference products (Table 6); biologics are far more complex than traditional small-molecule drugs. Biologics are "products of biotechnological origin that contain proteins derived from DNA technology and hybridoma techniques," and use living organisms (e.g., bacteria, yeasts, viruses, other animal cells) as part of the production process.[20] Figure 2 provides more detail on the production of biologics. However, small-molecule drugs are relatively simple in structure and are mainly synthesized through organic chemistry reactions.

The basic building blocks of biologics are glycoproteins (i.e., amino acids and sugar molecules), which transcends the basic atomic unit for small-molecule drugs. These amino acid building blocks are strung together in a specified sequence to form its primary structure (i.e., its amino acid sequence). Although this sequence is very important for the protein's function, one cannot discount the influence of the secondary, tertiary, and quaternary structures toward its therapeutic function. Therefore, even small changes in the folding of the protein can manifest into a clinically meaningful difference in efficacy or toxicity. Moreover, the glycosylation pattern of a biologic contributes to its clinical profile. Changes in the pattern of glycosylation can occur based on the cells in which the drug is produced and their intricate, multistep manufacturing process,[21–23] and these alterations in glycosylation patterns could also alter clinical outcomes.

Small-molecule generics, however, are structurally much simpler and generally not sensitive to process

Table 6 Summary of Key Differences Between How Biosimilars and Small-Molecule Generics Compare With Their Respective Reference Product

Area		Biosimilars	Small-Molecule Generics
Product	Chemical structure	The amino acid sequence is the same, but there is expected to be slight differences in terms of protein folding and glycosylation	The active drug is chemically identical to the reference product
	Analytical characterization	The final structure cannot be fully defined based on current analytical techniques; therefore, the degree of structural similarity to the reference product is unknown	Current techniques are available to ensure that the active drug in the generic product is identical to the reference product
Manufacturing	Complexity	Very complex; produced in living cells and involves several stages of purification, production, and validation of the final product	Relatively simple, uses organic medicinal chemistry reactions
	Impact of a change in manufacturing process	Small changes in process may alter the final structure and function of the protein	Likely to be negligible because the end product is identical
Regulation	Legislation approving an abbreviated pathway	The Biologics Price Competition and Innovation Act of 2009 establishes framework for an abbreviated approval pathway for biosimilars; guidance yet to be released by the FDA	Hatch-Waxman Act allows generics to be approved through an Abbreviated New Drug Application (ANDA)

Data from Nowicki M. Basic Facts about Biosimilars. Kidney Blood Press Res 2007;30:267–272; and Kuhlmann M, Covic A. The protein science of biosimilars. Nephrol Dial Transplant 2006;21(Suppl 5):v4–v8.

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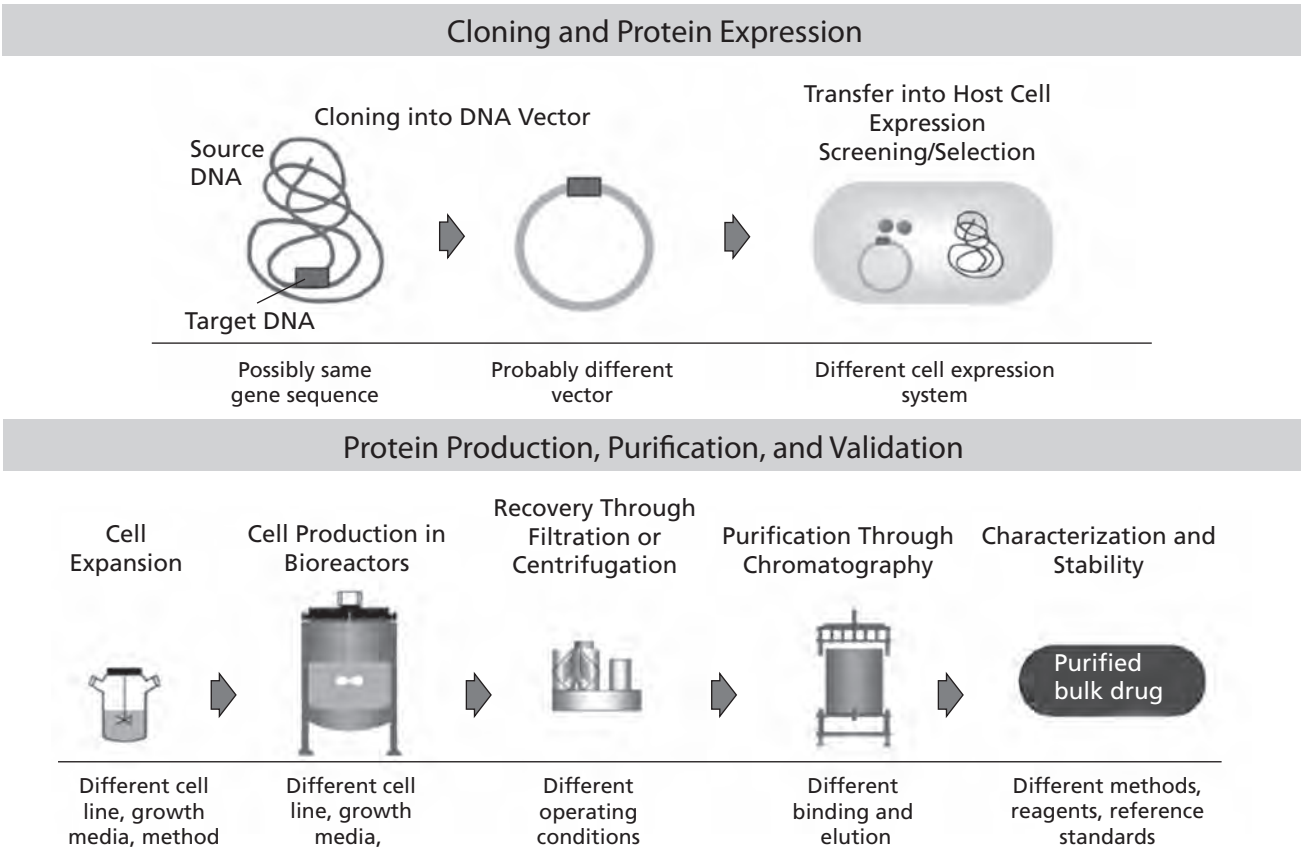

Figure 2 Biologics manufacturing process.
From Mellstedt H, Niederwieser D, Ludwig H. The challenge of biosimilars. Ann Oncol 2008;19:412–419; by permission of Oxford University Press.

changes. The basic atomic units (e.g., carbon, oxygen, hydrogen, nitrogen) that form the chemical structure of the completed molecule can be fully characterized using current technology to ensure that it is identical to the active drug in the reference product. Thus, if the active component of a generic drug can be shown to be completely identical to the reference product, the actual process for synthesizing it is of less concern.

Unlike generic small-molecule drugs, biosimilars will not be identical to the reference product because of differences in the cell lines of each manufacturer and in their different manufacturing processes; the complex process for manufacturing the reference biologic is often proprietary. Furthermore, the analytical technology currently available cannot fully characterize a protein's 3-dimensional structure.[21] Different lots of any biologic product manufactured by the same process are not 100% identical. Therefore, demonstrating analytically that a biosimilar is highly similar to its reference product and showing that any small differences in the molecule comparison do not have any clinically meaningful differences is a practical and appropriate policy, because it is applied to monitor various lots of any biologic product. Previous discussions have already established that this should be determined through assessments of quality, efficacy, and safety, using analytical, preclinical, clinical, and postmarketing surveillance studies to achieve this goal.[23]

These fundamental differences between biosimilars and generic small-molecule drugs warrant a paradigm shift in the thinking of all stakeholders (e.g., patients, health care practitioners, innovator and biosimilar manufacturers, payors, and government agencies) when dealing with these products; biosimilars must not be considered simply "generic biologics."

Additionally, stakeholders must come to a consensus to determine biosimilar policies that strike the right balance between the following competing benefits: innovation, access to medications, affordability, safety/efficacy, and availability of data. Com-

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peting interests exist among these core values; some values are supported by stricter policies and regulations, whereas other values are supported by more lenient ones (Table 7). A key example is the amount of data required for approval. If the amount of safety and efficacy data required for approval is too large, biosimilar development costs will be so high that few products will reach the market, and cost reductions will be limited. However, more limited data requirements for biosimilar approval will lead to potentially greater reductions in biosimilar costs, but uncertainty of clinical comparability for safety and efficacy will increase when fewer data are provided. Defining the appropriate balance in this debate may be challenging, and different stakeholders naturally will gravitate toward opposite ends of the spectrum.

Additionally, many of the challenges stakeholders face when dealing with biosimilars are not unique to these products. These challenges with all biologics (reference products and biosimilars) highlight some of the system complexities within the current United States health care system, further demonstrating that a better system would obviate the need for some of the recommendations stated in this document.

Incorporating Biosimilars Into Oncology Practice: Challenges in the United States

During the NCCN Biosimilars Work Group meeting and the NCCN Oncology Policy Summit, many challenges were identified for integrating biosimilars into oncology clinical practice, which can be divided into 6 broad categories: 1) use of biosimilars for off-label indications; 2) biosimilar economics and diffusion; 3) clinical trial enrollment; 4) biosimilar safety, product-specific tracking, and naming; 5) substitution practices; and 6) health care provider education. Table 1 further summarizes these challenges and offers additional detail. NCCN Work Group consensus statements and recommendations regarding these challenges are presented later.

Table 7 Competing Interests in Key Values for Biosimilars in Oncology

Supports Stricter Policies and Regulations		Supports More Lenient Policies and Regulations
Preservation of innovation to develop new treatments and cures	vs.	Broader access to medications
Data ensuring safety and efficacy	vs.	Affordability
Availability of data in a wide variety of indications	vs.	Extrapolate clinical utility from "key" efficacy data

Sound health care policy is a compromise between discovery of new medicines and broader or lower-cost access to existing ones without compromise in patient safety or efficacy.

Off-Label Indications

Oncology drugs are frequently prescribed for indications other than what is listed in the FDA label, and this approach is appropriate in many situations.[24] Therefore, substantial discussion at the Policy Summit centered on the use of biosimilars for off-label indications, including data requirements for extrapolation. Off-label use is generally driven by published clinical experience that is insufficient for regulatory approval. For example, a recent study using a claims database found an off-label prescribing rate of 25% for rituximab.[25] When biosimilars are introduced into the United States market, they are anticipated to carry labeled indications that are equal to (or perhaps more narrow than) the label of the reference product. However, the exact labeling will depend on the data package submitted to the FDA by the biosimilar manufacturers. Controversy exists about when it is clinically appropriate to extrapolate data obtained from the reference molecule to the biosimilar (i.e., when the biosimilar has never been tested in a particular clinical condition).

Overall, it seems that payors will prompt the use of biosimilars, but how the off-label prescribing of biosimilars will be interpreted by payors is uncertain. If the decision to use a biosimilar for an off-label indication is based on an extrapolation of data (and not on direct evidence), payors may decide that data are insufficient to justify payment for its use in that indication, and reimbursement will not occur. Conversely, an insurer may decide they will only reimburse for the biosimilar and not the originator biologic in that off-label setting, despite the lack of evidence proving safety and effectiveness, largely because of cost savings.

Biosimilar Safety, Product-Specific Tracking, and Naming

Because of the complexity of biologic development and production and the slight differences that will exist between biologics and biosimilars, some concern

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exists that adverse events unique to biosimilars may appear. Potential safety concerns regarding biosimilars prompted discussion of the need to track and retrieve data on the use of biosimilars. To determine if different adverse event profiles exist, adequate mechanisms for tracing and determining if a patient received the reference biologic or the biosimilar are needed.

A widely discussed approach to biosimilar tracking is to assign biosimilars a related, but unique and distinguishable, nonproprietary name compared with the reference product. Proponents of this strategy maintain that this is the most straightforward way to collect postmarket safety and efficacy data, track adverse events, and correctly attribute these events to the specific biologic source. Additionally, different names would prevent unintentional substitution of one product over another. Some contend that the current international rules governing naming (i.e., the International Nonproprietary Name [INN] system), first developed in 1950 by the WHO, are more correctly suited for small-molecule chemical substances that have an identical molecular structure, although they have since been adapted to address biologics.[26,27] The INN program's mandate is to "develop, establish and promote international standards with respect to biological, pharmaceutical and similar products."[28]

In the United States, nonproprietary names for all pharmaceuticals are approved through the United States Adopted Names Council (USANC). The USANC is trisponsored by the American Medical Association (AMA), the United States Pharmacopeial Convention (USP), and the American Pharmacists Association (APhA), and the FDA cooperates with and is represented on the USANC. The United States Adopted Names (USAN) program states that its goal is to select "simple, informative, and unique nonproprietary names [also called *generic names*] for drugs by establishing logical nomenclature classifications based on pharmacologic and/or chemical relationships."[29] The USANC retains authority over drug names in the United States but also works to harmonize drug names across the world. The USANC's international efforts include working with the WHO INN Expert Committee and other national nomenclature groups to standardize drug nomenclature and establish rules governing the classification of new substances worldwide.

The process for obtaining an USAN starts with the manufacturer completing an application. Two important requirements for applying are that the substance has entered clinical trials and has an Investigational New Drug (IND) number from the FDA. The manufacturer may suggest a name or names based on current nomenclature practices. These practices involve the adoption of standardized syllables called *stems* that relate new chemical entities to existing drug families. Stems may be prefixes, suffixes, or infixes in the nonproprietary name. Each stem can emphasize a specific chemical structure type, a pharmacologic property, or a combination of these attributes. The recommended list of USAN stems is updated regularly to accommodate drugs with new chemical and pharmacologic properties. After initial review by USANC staff, the USANC recommends and the sponsor accepts a name after the balloting process is complete. When considering an acceptable name, the following criteria are constantly kept in mind by the USANC: usefulness to health care providers, patient safety, adherence to the nomenclature rules, absence of conflicts with existing names, suitability for use internationally, ease of pronunciation, and other factors.

At the completion of the USANC review and after a name is accepted, the USANC Secretariat submits it to the INN Expert Group for consideration, additional trademark clearance, and linguistic evaluation on behalf of the sponsor (depending on the type of submission). The INN Expert Group evaluates suggested names following procedures somewhat similar to those of the USAN Council; however, the deliberation and actual name selection occurs at each of their biannual meetings, not through a year-round balloting process. Many firms seeking a USAN are multinational companies with subsidiaries outside the United States. It is highly desirable to the drug firms, the various nomenclature committees, and the medical community that a global name be established for each new substance. To prevent confusion with the use of multiple nonproprietary names in different counties, the WHO-INN Program coordinates drug nomenclature internationally.[30]

Small-molecule generic manufacturers do not need to go through the USAN process because their products are identical to the innovator, and the generic drug will automatically have the same nonproprietary name as the innovator. Because biosimilars are not identical to the innovator biologic,

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USAN has stated that they cannot assume they will have the same nonproprietary name. Therefore, the FDA must provide a decision declaring whether biosimilars and innovator biologics will share nonproprietary names, which will allow biosimilar manufacturers to move forward with naming their products.

The WHO, which coordinates the INN Program, advises that biosimilars should have a unique brand name, but recommends against unique INNs to identify nonglycosylated biosimilars, noting that INNs should not be relied on alone to determine interchangeability of biosimilars with biologic reference products. The authority to decide interchangeability and substitution rests with National Regulatory Authorities (NRAs). Additionally, the WHO recommends the use of lot numbers to ensure traceability.[3] However, in the case of naming epoetins and other glycoproteins, both reference products and biosimilars, the WHO recommended that amino acid differences should be denoted with prefixes in the INN name, and that glycosylation differences should be indicated by unique Greek letters (e.g., epoetin α, epoetin β).[2] Although WHO recommendations regarding the naming of biosimilars have provided the basis for global naming practices, they have not been applied with consistency worldwide for epoetin products.

A major disadvantage of unique naming of biosimilars is the potential confusion regarding comparability of the biosimilar to the reference product; clinicians and patients may interpret different names to mean that the products do not have similar efficacy and safety, even if regulatory agencies have determined that they meet biosimilarity requirements. Confusion of drug names has been frequently cited as a cause of medication errors.[31,32] Regarding biosimilars, unique names could cause confusion among prescribers, which may lead to prescribing errors that would have a limited risk of adverse events. However, a similar or related name with the same root but a small difference in prefix or suffix could represent that it is a similar molecule and simply identify a unique manufacturer of the specific product. This is now the approved practice in Japan for biosimilar products.

Hennessy et al.[26] evaluated the options for tracking reference biologics and biosimilars to conduct postapproval surveillance and pharmacovigilance. Several potential options were proposed, including,

> 1) Assign different nonproprietary names to biosimilar and innovator compounds…2) Develop different HCPCS [Healthcare Common Procedure Coding System] codes for biosimilar products that share the same nonproprietary name…3) Shift billing for physician-administered products from HCPCS codes to NDCs [National Drug Codes]…4) Establish prospective registries linked to electronic health data…[and] 5) Ensure that particular providers exclusively use a particular version of a biological product.

The working group discussed that an alternative means of tracking biosimilars for safety purposes would be to use NDCs, and that the lot number could be used for pharmacovigilance purposes. A concern was raised that current technology systems (e.g., electronic health records) and institutions/practices are not uniform in the capability or ability to track this information on a point-of-care basis. However, this is the method used for tracking small-molecule generics, although those are generally dispensed in outpatient pharmacies. Importantly, NDC codes are not always reported back to the prescribing physician once the patient picks up the prescription from a retail pharmacy. The feedback loop would need to be closed to make the use of NDCs for tracking possible. Also, if more than one biosimilar is available, a physician would not know the manufacturer of the drug their patient received without receiving feedback from the pharmacy. Many patients may also be unaware that information such as NDCs is available on the packaging of their medications, and of the possible use of NDCs for reporting events.

Substitution Practices

Laws and regulations governing the practice of substituting biosimilars for reference biologics will need to be fully elucidated, and this area could become very complex for clinicians. Consistent with longstanding practice regarding drug products approved under the FD&C Act, the BPCI Act allows the FDA to make an interchangeability determination. The practice of automatic drug substitution, which is when the pharmacist substitutes a generic product for the brand product unless the prescriber specifies otherwise, is governed by state law and state boards of pharmacy. However, current state substitution laws were drafted and enacted long ago, and the concepts of a biosimi-

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lar and an interchangeable biosimilar are new. The possibility exists that individual states could develop laws or regulations that would influence the use and substitution of biosimilars, and these laws may or may not take into account the interchangeability determination made by the FDA. Although unclear based on the limited information available to date, the approach to biosimilar substitution could vary widely among states, which could further confuse clinicians.

Additionally, substitution laws and practices may not be relevant in hospitals and other settings with a P&T Committee. In these settings, therapeutic interchange practices can be established, which provides flexibility for each organization to establish their preferred agents. (*Therapeutic interchange* is defined as the dispensing of a drug that is therapeutically equivalent to but chemically different from the drug originally prescribed by a physician or other authorized prescriber).[33] How many biosimilars will seek and obtain an FDA interchangeability determination and whether states will establish specific biosimilar substitution laws is currently unclear. However, developments in this area clearly will have an important influence on the practical application of biosimilars, and clinicians should carefully monitor developments in this area.

Health Care Provider Education

Because the practitioners are the ones who will ultimately prescribe, dispense, and administer these agents, provider knowledge regarding the differences in science and regulation between biosimilars and generic small molecules is of utmost importance. Currently, provider knowledge about this topic is suboptimal, as supported by preliminary data obtained by an NCCN Trends Survey, which are subsequently described. Appropriate education should be provided as this area develops further. Additionally, once naming conventions for biosimilars have been established by the FDA, specific education on biosimilar names should be provided.

NCCN Trends Survey Results

To gather initial baseline data about clinicians' knowledge and perceptions about biosimilars in oncology, the NCCN Work Group developed a survey to collect this information. This survey is one of the first to document oncology practitioners' knowledge and opinions regarding biosimilars. The 4-question survey was made available to attendees at the NCCN 16th Annual Conference and was administered on March 10 and 11, 2011. The survey questions were on the topics of familiarity with biosimilars legislation, interest in using biosimilars in practice, and importance of various types of data surrounding biosimilar products. The survey also asked participants to anticipate their future approach to using biosimilars for specific biologics (e.g., ESAs, myeloid growth factors).

The survey results are presented in this report as descriptive statistics of the aggregate data. When appropriate, further analysis of the data in the form of splitting the data by provider type (e.g., physician, nurse, pharmacist) and familiarity with biosimilars legislation (i.e., survey question number 1) is described.

A convenience sample of 277 conference attendees responded to the survey. Respondent demographics are depicted in Table 8. Most respondents were physicians (n = 129), followed by nurses (n = 71) and pharmacists (n = 38). Other types of clinicians or nonpracticing clinicians also responded to the survey (n = 39).

Familiarity With Biosimilars Legislation

The first question in the survey asked respondents to rate their familiarity with recent biosimilar developments, including recent legislation providing an abbreviated approval pathway. As depicted in Figure 3, more than half of the respondents were either not at all familiar (36%) or slightly familiar (19%) with recent developments regarding biosimilars. A small percentage of respondents were extremely familiar with the recent developments (7%). When analyzing this question according to provider type, physician responses coincided with the overall results, whereas proportionally more nurses responded that they were not at all familiar with recent developments with biosimilars (44% of nurses). Only 18% of pharmacists responded that they were not at all familiar.

Table 8 Distribution of Survey Respondents by Profession

Respondent	n	%
Physician	129	46.6%
Nurse	71	25.6%
Pharmacist	38	13.7%
Other clinician	7	2.5%
Other nonclinician	32	11.6%
Total	277	

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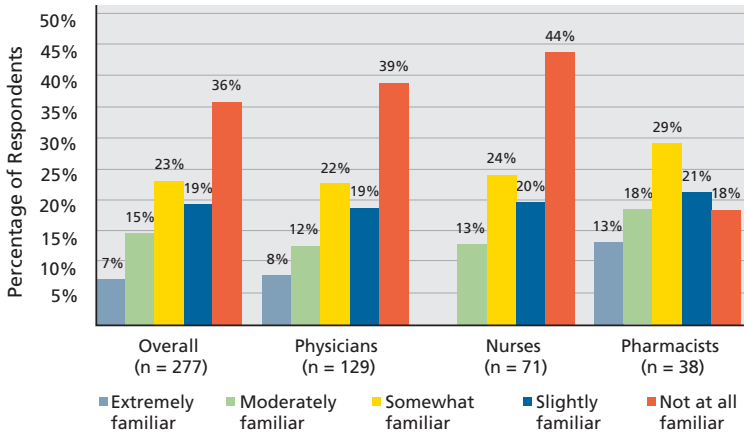

Figure 3 Please rate your overall familiarity with developments for biosimilars, including recent legislation that provides an approval pathway for noninnovator (e.g., "generic") manufacturers to introduce copies of biologics through an abbreviated review process.

Interest in Prescribing, Dispensing, and Administering Biosimilars

The overall interest in prescribing, dispensing, or administering biosimilars appeared to be high, with 27% and 35% responding high and moderate interest, respectively (Figure 4). However, approximately one-fourth of respondents indicated that they require more information to make a decision regarding their future interest in using biosimilars. Again, physician responses coincided with the overall results, whereas approximately one-third of nurses indicated that they need more information. Incidentally, 39% of pharmacists indicated high interest in using biosimilars.

Importance of Various Types of Information

To inform future educational efforts and to gauge what types of information clinicians will use when making clinical decisions surrounding biosimilars, the survey asked participants to rate the importance of various types of information. The types of information inquired by the survey and the responses are depicted in Figure 5. Although overall results indicate that studies directly comparing the clinical end points (i.e., safety, efficacy) between a biosimilar and the reference product garnered the most responses for being "very important," all of the types of information listed on the survey seem to be important, with at least 86% of respondents rating all types of information as somewhat or very important. Very few respondents listed any of these parameters as "not important."

Anticipated Use of Biosimilar Products

Lastly, the survey asked participants to consider a hypothetical situation in which biosimilars for specific

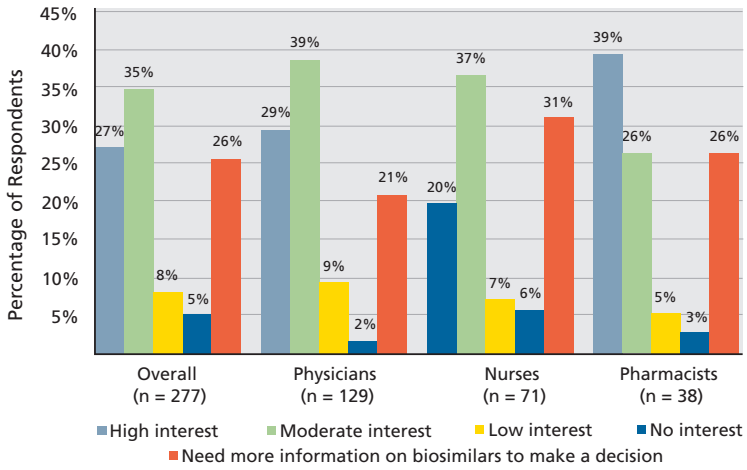

Figure 4 Once approved by the FDA, what is your interest in prescribing, dispensing, or administering biosimilars in your practice setting?

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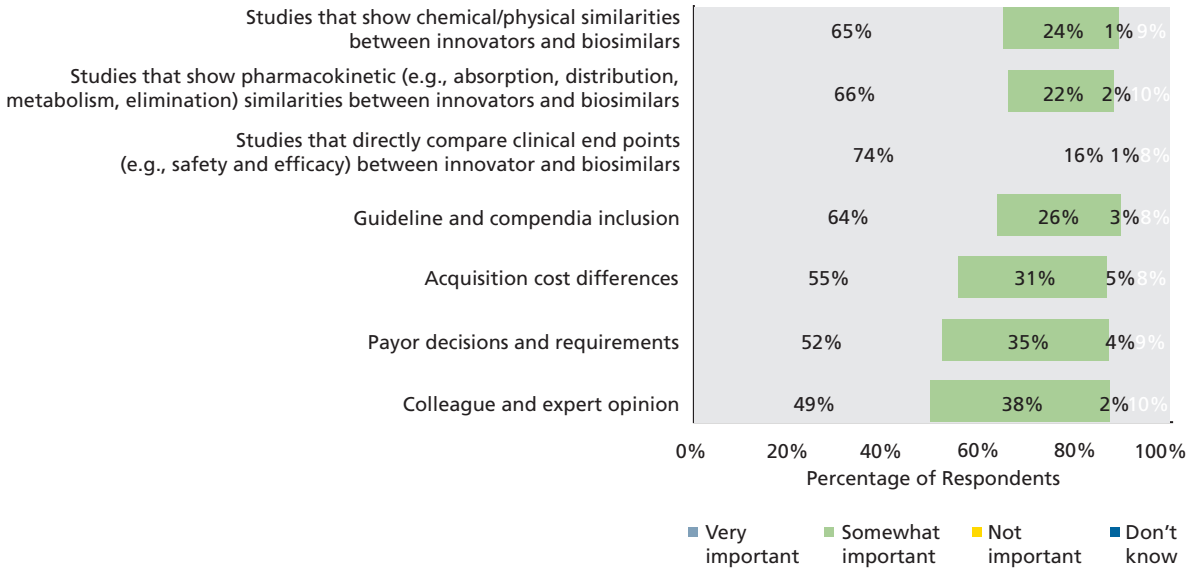

Figure 5 As more information on biosimilars becomes available, how important are the following types of information in helping you decide to use biosimilar products?

biologic products are FDA-approved and available. The question asked how the respondent would proceed in using these different agents, such as whether they would: 1) immediately use them, 2) review and discuss them before using, or 3) would not consider using them. The reason to distinguish between different types of products is to assess whether differences in use would occur based on what type of biologic is being copied. As Figure 6 shows, no overall major differences existed between the different biosimilar products. A few respondents would immediately use each biosimilar agent, and even fewer would not at all consider using them, whereas most respondents would require review and discussion before using the biosimilar.

This question was also cross-referenced with familiarity with biosimilar developments (i.e., the first survey question). Those who are more familiar with biosimilar developments tended to have a more defined opinion regarding the immediate use of (or refusal to use) the biosimilar (Figure 7). Percentage-wise, fewer respondents indicated that they would require review and discussion for the extremely/moderately familiar group compared with the somewhat/slightly familiar group.

Discussion and Survey Limitations

The data presented here represent a convenience sample of practicing clinicians, nonpracticing clinicians, and nonclinicians who attended the NCCN 16th Annual Conference. Therefore, the respondent pool may not represent the general population of oncology practitioners in the United States. Furthermore, most respondents were not at all familiar or only slightly familiar with biosimilars legislation, and therefore the applicability of some of the more complex questions (e.g., regarding interest in using biosimilars and anticipated approach to using specific products) is uncertain.

Data from this survey indicated that more education regarding the principles surrounding biosimilars is necessary. The knowledge of recent biosimilar developments was suboptimal among respondents, and contributed to several indicating that they require more information before they can speculate on their interest in prescribing, dispensing, and administering biosimilars. Despite the relative unfamiliarity, much interest in using biosimilars was still seen.

Interestingly, the type of biosimilar did not seem to correlate with how clinicians plan to use the drug. The NCCN Work Group had hypothesized that the biosimilar agents for supportive care indications may be more readily used without review/discussion than those for the active treatment of cancer. Based on the survey, this appears not to be the case. Certainly, the suboptimal knowledge of biosimilar developments tended to influence the data, resulting in more respondents indicating that a review/discussion is required before readily using the product. Regardless, few clinicians seem to have come to a conclusion regarding the use of individual biosimilars. This high-

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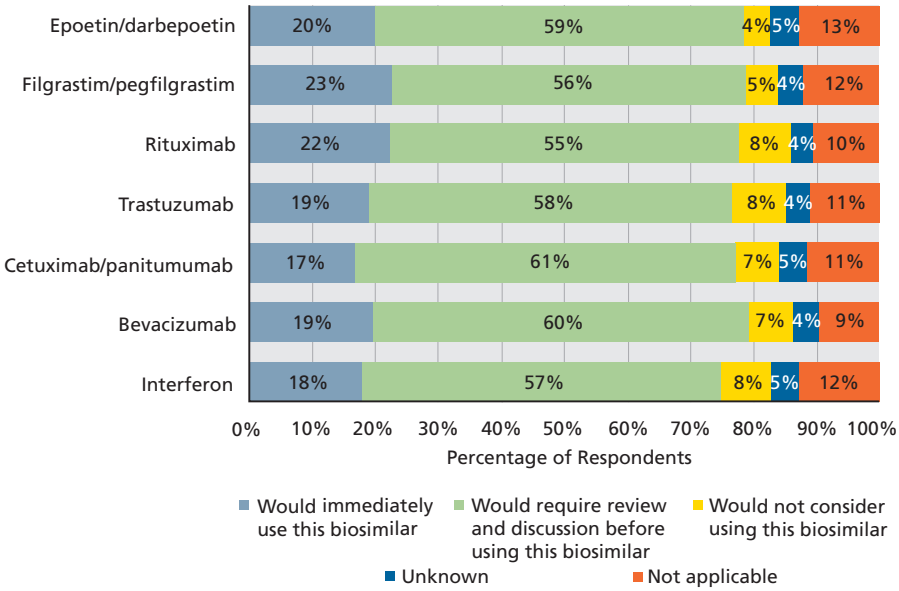

Figure 6 If a biosimilar was FDA-approved and available today for the following biologics, how would you proceed in routinely using the biosimilar instead of the innovator product tomorrow?

lights the need for access to emerging data showing comparability between the biosimilar and the reference product.

Despite the aforementioned limitations, the data provide insights as to some of the challenges regarding clinicians' knowledge about biosimilars. The need for additional education is probably because of the novelty of this concept in the United States. Currently no biosimilars are approved under the recent legislation establishing a biosimilar pathway, and the FDA has not yet issued any guidance document regarding its interpretation and implementation of the specific regulatory requirements or any other details of the pathway. Provider interest, and therefore the need for additional education, will likely increase when the first biosimilar is approved under this new abbreviated pathway. The work group discussed educational concepts and topics surrounding biosimilars that will help clinicians make the best decisions for their patients. Recommendations for education of clinicians and patients are provided.

NCCN Biosimilars Work Group Recommendations/Consensus Statements and Discussion

A list of the NCCN Work Group's consensus statements and recommendations for biosimilars in oncology practice are provided in Tables 2 and 3. The first 3 consensus statements in Table 2, referring to the importance of access and affordability, approval pathway, and standardization with reference product, are an affirmation by the work group of the importance of biosimilars in improving affordability and access to oncology medications. Furthermore, the work group supports the BPCI legislation and the approval pathway for biosimilars containing the elements mentioned in the table regarding the demonstration of similarity, the use of appropriate end points, and consistency/transparency of data, and of standardizing specific elements between the reference product and its biosimilar product.

Comments about legal and regulatory issues are limited because the goal of the work group was to concentrate on the patient care aspects of biosimilars in oncology. Patient care issues can be categorized into the following: tracking product use; addressing biosimilars in the NCCN Guidelines; using the P&T Committee; and the need for health care providers, policy makers, and patients to be educated about biosimilars.

Regarding the challenge of extrapolating the use of biosimilars to off-label indications, it was widely recognized that the appropriateness of extrapolation will depend on many variables. For example, a higher comfort level with extrapolating generally exists if factors such as the mechanism of action, use

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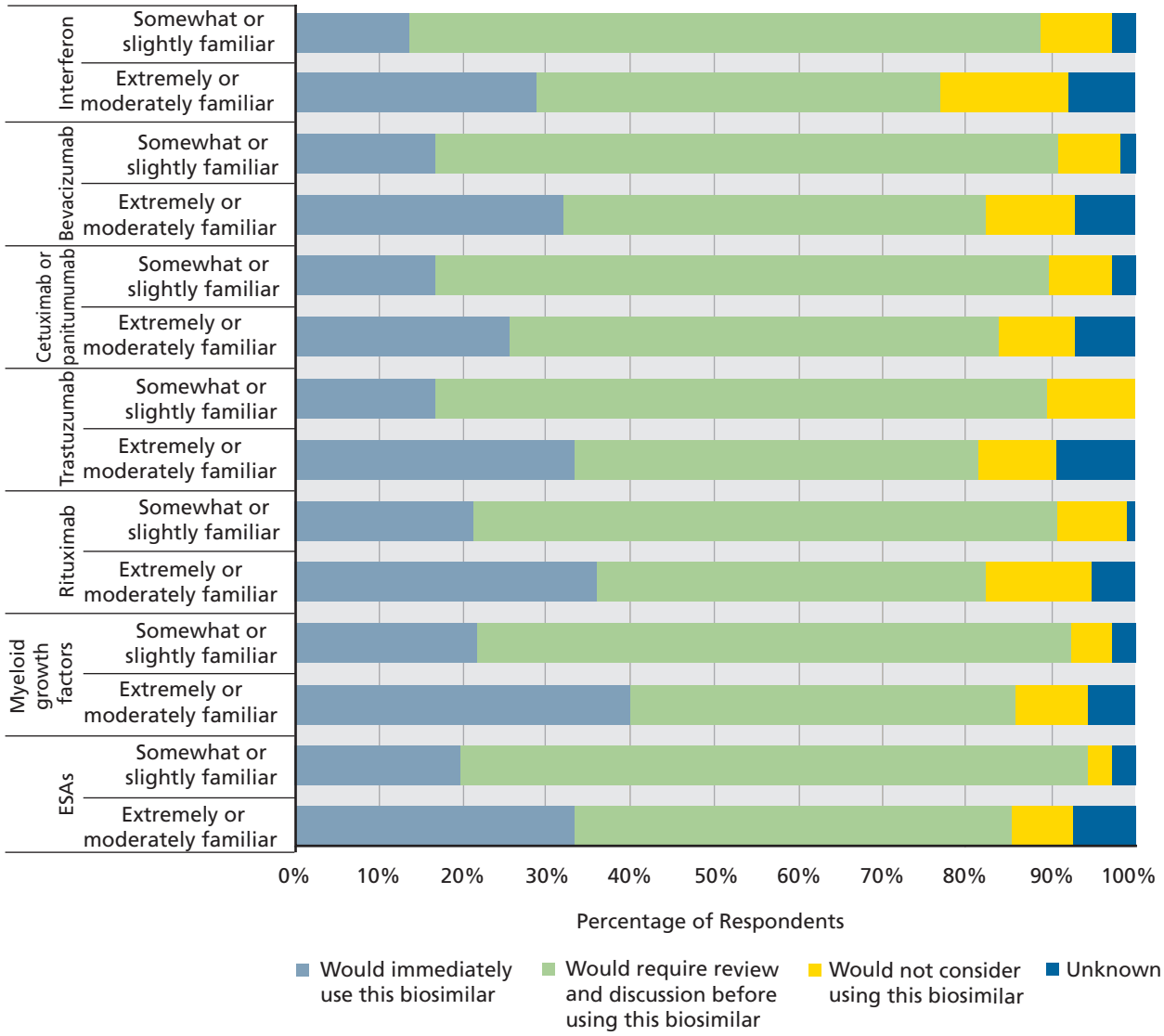

Figure 7 Anticipated use of biosimilar products according to familiarity of recent biosimilar developments. Abbreviation: ESAs, erythropoiesis-stimulating agents.

with chemotherapy, and tumor type remain constant in the indication to which use is being extrapolated from how it was studied compared with the reference product. Ultimately, a determination of use in unapproved indications should and will be made by practitioners and patients on a case-by-case basis, based on the existing data package and perceived risks versus benefits. On the policy level, the NCCN Work Group recognized that mechanisms are already in place to make determinations about the appropriateness of extrapolation. First, because the recommendations in the NCCN Guidelines are well recognized by clinicians and payors, the work group recommended that individual NCCN Guideline Panels should discuss the role of biosimilars in the context of their respective tumor type when appropriate. This should also include a recommendation for or against extrapolating to indications beyond the FDA-approved labeling.

Most biologics used in the active treatment of cancer are not routinely dispensed to the patient for self-administration; they are usually dispensed to health care providers for administration within an ambulatory clinic or inpatient setting. Thus, questions concerning substitution primarily lie with the biologics used for the supportive care management of cancer or chemotherapy symptoms that may be dispensed directly to patients for self-administration.

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Secondly, institutional P&T Committees should actively evaluate biosimilar products to determine appropriateness in their specific patient population, including cost and safety considerations. This is in great contrast to hospital practices for generic small-molecule drugs, where typically generics are used immediately without oversight from P&T Committees, and subsequently hospitals realize immediate cost savings.

Furthermore, local institutional P&T Committees should also address issues regarding substitution practices through the formulary system. In community settings without P&T Committee review, the appropriate use of biosimilars should also be reviewed carefully. Biosimilar agents are expected to be formally discussed during routine committee meetings for subsequent development of policies governing their use, including whether the medical staff will allow for therapeutic interchange (whereby a P&T Committee can decide which molecules can be substituted) of these agents. Thus, few instances exist in which the inappropriate substitution by dispensers is of concern, and these situations fall primarily within the setting of community or specialty pharmacies.

In these situations, considering the use of biosimilars, confusion about automatic substitution arises when 1) the nonproprietary names are identical, and therefore the pharmacist cannot determine the prescribing physician's intended source (i.e., manufacturer) of the biologic, and/or 2) the payor will pay for the biologic from a different source other than what has been specified by the physician. In these cases, pharmacists should be aware of the laws governing substitution and whether the physician will need to be contacted regarding a change in product, thus highlighting the emphasis for provider education about these issues.

The Patient Perspective on Biosimilars in Oncology

The NCCN Work Group included representation from the patient advocacy community, and issues about biosimilars from the patient perspective were discussed. The primary concern patients have about biosimilars is that they are safe, effective, and represent a quality treatment option compared with the innovator biologics. Patients do not want surprises and want regulatory issues to be clearly resolved to avoid potential safety risks. Patient and provider education about these products will help build trust in the science behind these drugs and a better understanding of how innovator biologics and biosimilars work and when substitution can occur.

The time required to conduct clinical studies that prove equivalent safety and efficacy of biosimilars or other drugs can often be lengthy, but these studies must be conducted in a manner that takes the minimum amount of time necessary to meet standards to ensure that patients with life-threatening diseases such as cancer have access to all available treatment options as quickly as possible. It is also important for patients to have access to cancer drugs, including biosimilars, where and when they are needed.

Patients also welcome the lower prices that are expected when biosimilars become available and provide more competition to existing biologics. The *Patient Data Analysis Report* recently released by the National Patient Advocate Foundation found that in 2009, 24% of the Patient Advocacy Foundation patients served reported "exceeded annual pharmacy benefit maximum" as the reason for needing assistance, and in 2010 this had increased to 27%. As many patients face challenges in paying for care, they have shown interest in understanding how payors will decide how and when to pay for biosimilars and how this will affect access to these drugs through pharmacy and potentially medical benefits.

Finally, it is important for patients to know that biosimilars are "highly similar" to their biologic reference products and "exhibit no clinically meaningful differences," as stated in the BPCI Act, in addition to their having access to the data available for the products. This can be accomplished through increased educational efforts for patients, caregivers, clinicians, and other relevant stakeholders and through product labeling.

Closing Statement

The NCCN Biosimilars Work Group is supportive of the recently passed legislation establishing a biosimilars approval pathway, and recognizes the important role that biosimilars can play in oncology care. The key goal of biosimilars is to increase the affordability and access to biologic medications for patients. The work group identified several challenges with integrating biosimilars into oncology practice, and discussions during the policy summit made it clear that clinicians, patients, and payors will look to NCCN for guidance about specific biosimilar products.

Moving forward, the oncology community awaits the release of the FDA's guidance to elucidate the existing biosimilars pathway, and this will likely answer

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some of the questions regarding expectations for regulatory approval of biosimilars. However, the guidance will not solve some of the challenges, such as how clinicians and payors will extrapolate the data to indications beyond the FDA-approved labeling. Although biosimilars may improve the access and affordability of expensive biologics in cancer care, it is not a panacea for the cost of care issues the country is currently facing, especially because the underlying cost savings and diffusion of biosimilars remains unknown.

As previously discussed, an NCCN Trends Survey suggests that provider knowledge of biosimilars is suboptimal. Fortunately, the widespread introduction of biosimilars into the United States market is expected to be a few years away, and therefore there is ample time for oncology providers, patients, and policy makers to become well informed about biosimilars and to keep abreast of any regulatory or legal policy changes or updates in this area.

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review

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The challenge of biosimilars

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Background: The purpose of this report was to review issues associated with the introduction of alternative versions of biosimilars used in the oncology setting.
Design: Data were obtained by searches of MEDLINE, PubMed, references from relevant English-language articles, and guidelines from the European Medicines Agency.
Results: When biosimilars are approved in EU, they will be considered 'comparable' to the reference product, but this does not ensure therapeutic equivalence. Inherent differences between biosimilars may produce dissimilarities in clinical efficacy, safety, and immunogenicity. Switching biosimilars should be considered a change in clinical management. Regulatory guidelines have been established for some biosimilar categories but, because of the limited clinical experience with biosimilars at approval, pharmacovigilance programs will be important to establish clinical databases. Guidelines also provide a mechanism for the extrapolation of clinical indications (approved indications for which the biosimilar has not been studied). This may be of concern where differences in biological activity can result in adverse outcomes or when safety is paramount (e.g. stem cell mobilization in healthy donors). These issues should be addressed in biosimilar labeling.
Conclusions: Biosimilars should provide cost savings and greater accessibility to biopharmaceuticals. A thorough knowledge surrounding biosimilars will ensure the appropriate use of biopharmaceuticals.
Key words: biosimilars, substitution, extrapolation, pharmacovigilance, labeling

introduction

Recombinant technology has provided a means of producing a variety of therapeutic proteins, allowing biopharmaceuticals to become important therapeutic options for a variety of indications [1]. The recent and pending patent expirations for a number of biopharmaceuticals (e.g. granulocyte colony-stimulating factors [G-CSFs], erythropoietin, interferons and human growth hormone) have prompted the study and development of alternative versions of biologic products, referred to as biosimilars or 'follow-on biologics.' Biosimilars are new biopharmaceutical agents that are 'similar' but not identical to a reference biopharmaceutical product. This is unlike the case with small-molecule generics, where the active substance of a generic is identical to the reference product. Characteristics of biopharmaceuticals are closely related to the manufacturing process, which cannot be duplicated. Thus, biosimilars are unique molecules and are not generic versions of the innovator biopharmaceuticals.

Biological products have revolutionized the treatment of patients with cancer, and the pending introduction of biosimilar products in the oncology setting will have important consequences. Biosimilars should provide cost savings, which may broaden access to biopharmaceuticals and stimulate further research. However, there also are potential efficacy and safety implications, and it is important that the introduction of biosimilars in the oncology setting be conducted in an appropriate manner. Since data at approval will be limited to those from comparability exercises, post-marketing pharmacovigilance data will be critical to ensure patient safety with respect to duration of exposure, use in various patient populations, rare adverse events, immunogenicity and other treatment issues that might emerge post-approval. It is also vital that healthcare providers have access to all data regarding biosimilars, so that they can make informed clinical decisions.

There will be a number of issues facing clinicians once biosimilars come to market. Biosimilars are not generic biopharmaceuticals but rather new, non-innovative products that will be supported by limited clinical data sets at the time of approval. This article will discuss the introduction of biosimilars into clinical practice for managing cancers. The manufacturing process for biosimilars will be reviewed, as will steps for facilitating pharmacovigilance programs and approaches for the use of biosimilars for indications that are based on extrapolation of clinical data.

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characteristics of biosimilars

For small-molecule pharmaceuticals, the development and production of generic-equivalent products is relatively straightforward. All that is required is demonstration that the generic product contains the identical chemical composition of the innovator product and a bioavailability study demonstrating that the pharmacokinetic properties of the generic and reference products are similar [2].

In contrast, biosimilars are not generic equivalents of the innovator products [2]. This perspective was adopted by the European Medicines Agency (EMEA) and is the basis for its biosimilar approval guidelines [3]. This is because the active ingredients in a biosimilar are not identical to the innovator product. Since biopharmaceuticals are complex proteins that require multifaceted manufacturing processes, they are far more complex than small-molecule pharmaceuticals. Unlike conventional pharmaceuticals, there is a strong relationship between the manufacturing processes of biopharmaceuticals and the characteristics of the final product [4].

Indeed, the properties of biopharmaceuticals are dependent on the manufacturing processes [4]. Differences in manufacturing processes, protein source and extraction/purification processes result in heterogeneity of the resulting biopharmaceuticals (Figure 1) [2, 4–7]. For example, the unique cellular-expression systems used in protein manufacture inherently produce a variety of isoforms [2, 8]. In addition, small changes in manufacturing methods can produce alterations in the three-dimensional structure of the protein, the quantity of acid–base variants and the glycosylation profile [2, 3].

Biosimilar manufacturers will not have access to the manufacturing processes of innovator products because this is proprietary knowledge. Thus, it will be impossible for biosimilar manufacturers to precisely replicate any protein product [2]. In addition, since analytical techniques are not available for detecting or predicting all the biological and clinical properties of proteins, differences between biopharmaceutical products can easily remain undetected [2]. Regulatory guidelines must account for the differences between biosimilars and their reference products and must mandate rigorous pharmacovigilance.

The importance of the manufacturing process in the properties of biopharmaceuticals is highlighted by the variability in the composition and bioactivity of products produced outside of the United States and Europe. In a study comparing 11 epoetin products from four different countries (Korea, Argentina, China, India), the isoform distribution among these products was variable and there were substantial deviations from specifications for *in vivo* bioactivity. For example, *in vivo* bioactivity ranged from 71% to 226%, with five products failing to meet their own specifications [7]. However, it should be noted that these products are not regulated in European and US markets via the EMEA and FDA.

biosimilars of drugs that are used for the treatment of cancer

There are several biopharmaceutical products used in the treatment of patients with cancer for which biosimilar products are likely to be developed. Table 1 summarizes the

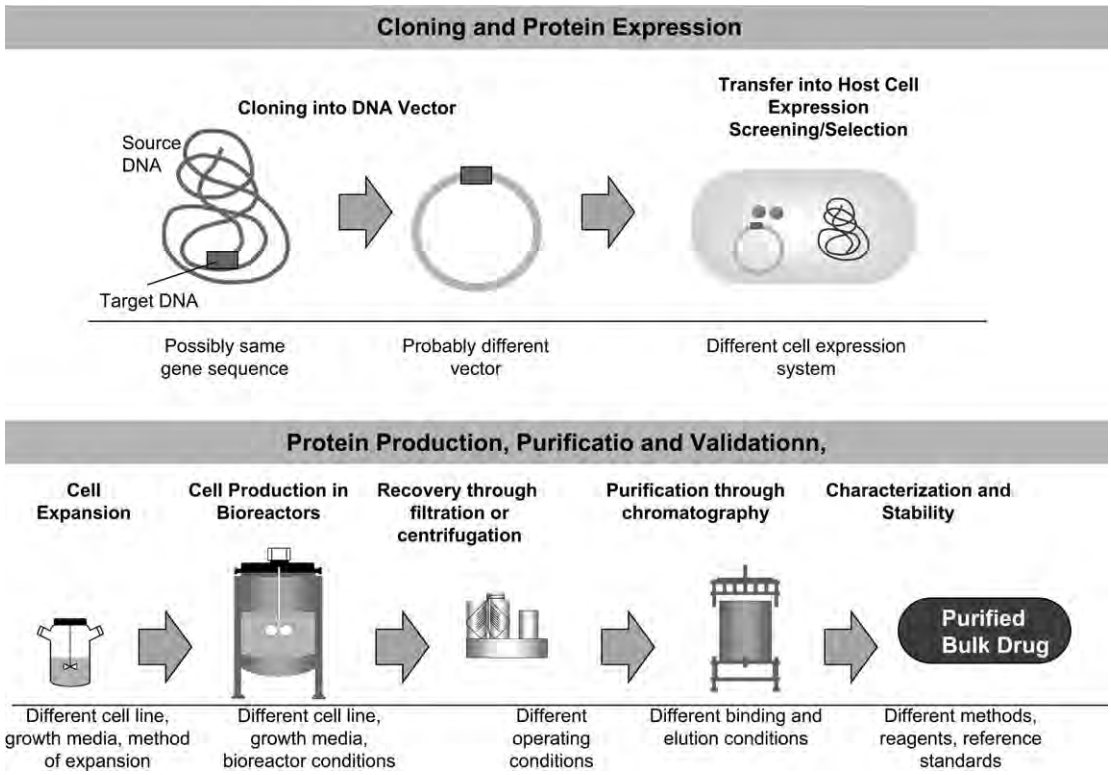

Figure 1. Recombinant protein production: sources of variation between manufacturers.

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Table 1. Summary of product characteristics for biopharmaceutical products that have already lost or will soon lose patent protection in Europe

Product	Description	Source	Indications
Colony-stimulating factors			
Filgrastim	Recombinant protein of 175 amino acids (extra methionine at N-terminus); nonglycosylated	*Escherichia coli*	Chemotherapy-induced neutropenia (except CML and MDS); chemotherapy for AML; receipt of BMT; mobilization of PBPC; severe congenital, cyclic, idiopathic neutropenia; HIV-related neutropenia
Lenograstim	Recombinant protein of 174 amino acids; 4% carbohydrate	CHO	Chemotherapy-induced neutropenia, receipt of BMT, mobilization of PBPC
Interferons			
IFN α2a	Recombinant protein of 165 amino acids (lysine at position 23); nonglycosylated	*E. coli*	Minimally pretreated patients with chronic-phase Philadelphia chromosome-positive chronic myelogenous leukemia, cutaneous T-cell lymphoma, AIDS-related Kaposi's sarcoma, chronic HCV (adults), chronic HBV (adults), follicular lymphoma, advanced renal cell carcinoma
IFN α2b	Recombinant protein of 165 amino acids (arginine at position 23); nonglycosylated	*E. coli*	Hairy cell leukemia, malignant melanoma, follicular lymphoma, condyloma acuminata, AIDS-related Kaposi's sarcoma, chronic HCV (adults), chronic HBV (≥1 year)
Epoetins			
Epoetin alfa	Recombinant protein of 165 amino acids; glycosylated	CHO	Anemia of CRF, chemotherapy-induced anemia, increasing yield during autologous blood transfusion, decreasing allogeneic blood transfusion during surgery
Epoetin beta	Recombinant protein of 165 amino acids; glycosylated	CHO	Anemia of CRF; symptomatic renal anemia; chemotherapy-induced anemia; anemia in patients with multiple myeloma, low-grade NHL or CLL; increasing yield for autologous blood donation

AML, acute myelogenous leukemia; BMT, bone marrow transplant; CHO, Chinese hamster ovary; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; CRF, chronic renal failure; HBV, hepatitis B virus; HCV, hepatitis C virus; MDS, myelodysplastic syndrome; NHL, non-Hodgkin's lymphoma; PBPC, peripheral blood progenitor cell.

characteristics of some of the innovator products used for the management of cancer that have lost patent protection in Europe or will lose it in the near future.

granulocyte colony-stimulating factors

Natural G-CSF is a single polypeptide protein with minimal glycosylation (i.e. one carbohydrate chain) that accounts for approximately 4% of overall mass and has no significant contribution to 3-dimensional structure [9]. G-CSF acts to support the proliferation, differentiation and activation of committed progenitor granulocytes. The two currently available G-CSF products in Europe (filgrastim and lenograstim) not only differ from the natural protein, but they also differ significantly from one another with respect to biological characteristics and approved indications [10–13]. Comparative studies have demonstrated differences between these products with regard to pharmacological properties and clinical outcomes [11].

Because of the differences between products, currently available G-CSFs are not considered interchangeable. For some indications (e.g. febrile neutropenia), even a slight difference in efficacy between products could result in substantial clinical risk. In particular, the risk of product-related differences is likely to be greatest in indications in which neutropenia is most prolonged and the risk of infection is greatest. Studies indicate that there are differences between filgrastim and lenograstim with respect to stem cell mobilization. A study in healthy volunteers found that lenograstim was associated with a 28% higher concentration of stem cell production compared with filgrastim [14]. In another study, Kim and colleagues demonstrated significant differences between lenograstim and filgrastim in hematologic recovery following autologous peripheral blood progenitor cell transplant (PBPCT) with high-dose chemotherapy [11]. Patients receiving filgrastim had faster neutrophil, white blood cell and platelet recovery; required fewer days of G-CSF administration and spent less time in the hospital compared with those receiving lenograstim [11].

interferons

Interferon alfa products indicated for the treatment of patients with cancer include interferon alfa-2a (Roferon-A®) and interferon alfa-2b (Intron A®) [15, 16]. Although these products are produced in similar expression systems, have similar molecular weights, and only differ by one amino acid, there are clinically meaningful differences between them, and they are not considered interchangeable. In particular, studies suggest a difference between products in the incidence of neutralizing antibodies [17–19]. Although the exact relationship between the development of neutralizing anti-interferon antibodies and treatment efficacy is unclear, a review of cancer trials observed an increased risk of relapse in patients who developed neutralizing antibodies [17].

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epoetins

Currently in Europe, epoetins are indicated for treating anemia in patients with chronic kidney disease or patients with cancer receiving chemotherapy [20–23]. All epoetin products in clinical use have a similar amino acid sequence to endogenous erythropoietin, but there are differences in source (Chinese hamster ovary cells versus human cells), manufacturing processes, glycosylation patterns, erythropoietin content, potency, dosage regimens, routes of administration and indications [5, 7, 24]. While all epoetins have the same molecular mechanism of action, there are differences in pharmacologic and clinical properties that have the potential to elicit a differential clinical response. These products are not considered interchangeable.

The differences in glycosylation patterns between epoetins are particularly important because glycosylation influences the pharmacokinetics of the product and may influence efficacy and safety, and especially, immunogenicity [24, 25]. For example, antibodies are often specific for the carbohydrate units of a particular glycosylation pattern. Depending on the structure of the antigenic site, glycosylation may also be required to allow reactivity with the antibody or may result in inactivation of the peptidic epitope [25].

The efficacy and safety of epoetins are related to the biopharmaceutical properties. Even small differences can have clinical consequences. Underscoring this is the recent observation of an increased incidence in antibody-mediated PRCA that was observed in patients with anemia of chronic kidney disease who were receiving a specific epoetin product. The increased incidence of PRCA corresponded to a change in the product formulation [26]. The removal of human serum albumin from the European formulation of Eprex®, as well as other manufacturing changes, coincided with a dramatic increase in the development of PRCA due to the development of neutralizing antibodies. The effect appears to be limited to this formulation of Epoetin; however, the exact causes of the immunogenicity of this formulation are still under debate [27].

Another issue with epoetins is that direct dosage conversions between epoetin products are not available. Further, dosing requirements in the oncology setting are 3- to 5-fold higher than for patients with anemia of chronic kidney disease. Different dose–response characteristics between agents are important because an exaggerated pharmacodynamic response may result in the development of hypertension and thrombotic complications [24, 28–30].

regulatory recommendations

The European Union has developed a general legal pathway, and the EMEA has developed regulatory guidelines, for the approval of biosimilars (Figure 2) [3, 8, 31]. Because of the substantial differences between biopharmaceutical products, the approval process will vary according to the product. In particular, the amount of clinical data available may depend on the inherent variability of efficacy endpoints and the availability of validated surrogate markers. In general, the approval of biosimilars will be based on the demonstration of comparable efficacy and safety to an innovator reference product in a relevant patient population (i.e. 'comparability'). EMEA guidelines will permit, with proper justification, the extrapolation of data from one therapeutic indication to another, allowing for the use of a biosimilar in indications for which it has not been formally studied. Because biopharmaceuticals are sometimes, although infrequently, associated with serious adverse events, EMEA guidelines also require immunogenicity testing and pharmacovigilance programs to monitor the efficacy and safety of biosimilar products post-approval. The importance of immunogenicity testing and pharmacovigilance is illustrated by the recent approval of the biosimilar growth hormone Omnitrope. During

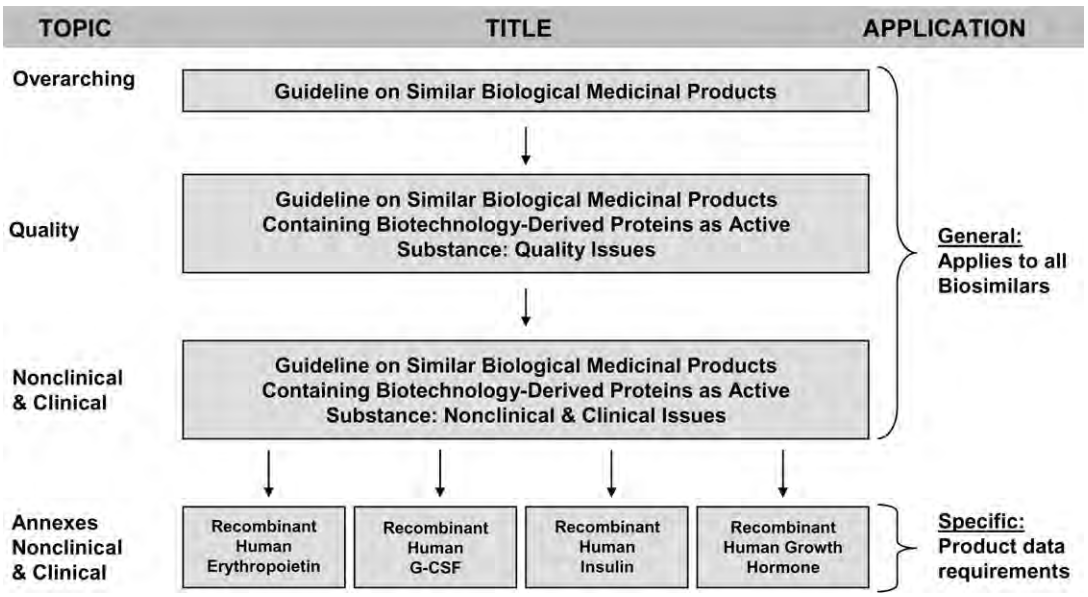

Figure 2. Overview of EMEA guidelines for biosimilars.

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development, production of this product was transferred from one facility to another. While qualitative testing demonstrated no notable differences between the end products of these facilities, a difference was observed with respect to immunogenicity, which was subsequently resolved by the manufacturer prior to approval [32]. There is currently no legal pathway in the United States for the approval of biosimilars and, accordingly, the US Food and Drug Administration has not yet developed guidelines regarding these types of products.

It is important that healthcare professionals be aware of the differences between the concepts of therapeutic equivalence (i.e. substitutability) and 'comparability'. Therapeutic equivalence is a term used with reference to generic equivalents, in which the generic and reference products have identical chemical composition and are bioequivalent (have similar pharmacokinetic profiles). In the context of biosimilars, comparability is used to convey the concept that the biosimilar and reference products are not identical but have comparable efficacy and safety. Studies establishing therapeutic comparability do not guarantee therapeutic equivalence.

product-specific regulatory guidelines

Although no biosimilar G-CSFs have yet been approved, current EMEA guidelines state that the clinical model for the demonstration of comparability of biosimilars to the reference product in this case is the prophylaxis of severe cytotoxic chemotherapy-induced neutropenia (Table 2) [10]. A two-arm comparability study is recommended for chemotherapy regimens with known frequency and duration of severe neutropenia, and a three-arm study (including placebo arm) is required for other chemotherapy regimens. The guidelines also allow for extrapolation of the results to the other indications of the reference product if the mechanism of action is the same, although no specific criteria are recommended [10]. Alternative models, such as pharmacodynamic studies in healthy volunteers, may also be allowed in the demonstration of comparability if justified.

The EMEA recognizes that erythropoietin is one of the most difficult products for the development of biosimilar agents (Table 2). The EMEA guidelines for erythropoietin state that comparability studies should be performed in patients with anemia due to chronic renal disease and that at least two randomized clinical trials are required [24]. In addition, clinical comparability should be shown for both intravenous and subcutaneous routes of administration. Current EMEA guidelines also allow for the extrapolation of safety and efficacy data from patients with renal anemia to other indications if the extrapolation can be appropriately justified [24].

issues to be considered with clinical use of biosimilars

pharmacovigilance

Because there is a limited clinical database at approval of a biosimilar, it is important to collect post-approval safety data for these drugs. This is because differences between biosimilars, with respect to efficacy and/or safety, may not become apparent in the pre-approval period, during which only limited numbers of patients receive the product over a specified time-span [3]. An important component of post-approval data collection is the ability to distinguish readily between different biosimilar products and the reference products, so that it is clear which specific product a patient has received.

The importance of post-marketing pharmacovigilance is highlighted by experience with epoetins, where the development of antibody-mediated pure red cell aplasia (PRCA) in patients with chronic kidney disease was associated with a formulation change for one product [26]. As noted

Table 2. Summary of EMEA requirements for approval of biosimilar G-CSFs and epoetins

	G-CSF	Epoetin
Preclinical studies	• Comparative non-clinical studies • 28-day toxicology	• Comparative non-clinical studies • 28-day toxicology
Human PK & PD studies	• Single-dose s.c. and i.v. in healthy volunteers • ANC and $CD34^+$ in healthy volunteers	• Single-dose s.c.and i.v. in healthy volunteers • Include PD evaluation (reticulocytes) in PK studies
Efficacy studies	• Two-arm (vs reference product)OR • Three-arm (vs reference product + placebo) equivalence trial in CIN OR • PD study in healthy volunteers (if justified)	• Two randomized, double-blind studies in nephrology • Both routes of administration (s.c. andi.v.) • Dose and Hb levels to be collected
Extrapolation	Yes— equivalence in CIN will allow extrapolation to other indications if mechanism of action is the same	Yes—equivalence in renal anaemia may allow extension to other indications if justified by applicant
Safety	• Evaluate AE's and immunogenicity in CIN study • Six-month follow-up	• Safety from efficacy studies is adequate for approval • Twelve-month, comparative immunogenicity data
Post-approval commitments	Specific monitoring for lack of efficacy in extrapolated indications	PRCA to be addressed Safety in cohort of patients from all indications (i.e. including extrapolated indications)

ANC, absolute neutrophil count; CIN, chemotherapy-induced neutropenia; Hb, hemoglobin; i.v., intravenous; PD, pharmacodynamics; PK, pharmacokinetics; PRCA, pure red cell aplasia; s.c., subcutaneous

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previously, differential immunogenic responses have also been observed between similar biopharmaceutical products (e.g. IFNs, epoetins).

Because of the potential risks associated with biopharmaceuticals, particularly immunogenicity, and the potential for clinically meaningful differences between products, there is a need for rigorous pharmacovigilance programs to monitor all biopharmaceuticals (including innovator products and biosimilars) for safety and efficacy issues during the post-approval period. Such post-marketing programs will need to be tailored to each biopharmaceutical category to address product-specific issues.

The EMEA in Europe and the Food and Drug Administration (FDA) in the United States have well-established pharmacovigilance programs for the monitoring of adverse events to medicinal products [33, 34]. EudraVigilance is the EMEA network for reporting and evaluating suspected adverse reactions during development and following marketing authorization. One component of pharmacovigilance is spontaneous reports by healthcare professionals. Ideally, these reports should contain as much information as possible, including the type of adverse event and information on the drug (e.g. proprietary name, INN, dosage given and lot number). However, adverse events are frequently not reported or the reports are incomplete. In addition, the rules for reporting vary from country to country [35, 36].

Pharmacovigilance plans developed and implemented by manufacturers are frequently part of the post-approval commitments to regulatory agencies to provide follow-up safety assessments [33, 34]. These programs provide a means of quantifying the frequency of adverse events and a way of expediting the reporting of serious or previously unknown adverse events. These programs may include patient registries and retrospective or prospective observational and pharmacoepidemiologic studies.

Pharmacovigilance programs for biosimilars are required by the EMEA to provide a continuous method for the monitoring and evaluation of safety issues so that responses are rapid and accurate [31]. Pharmacovigilance programs may be useful for the early detection of emerging safety issues. Pharmacovigilance programs are also important for assessing the safety of products in specific patient populations. This is particularly important for the safe use of biosimilars in therapeutic indications for which the product may not have been formally evaluated (i.e. for an extrapolated indication).

substitution

Automatic substitution allows for the dispensing of generic drugs in place of prescribed innovator products by pharmacists without the knowledge or consent of the treating physician. For the majority of small-molecule generics, automatic substitution is appropriate and can produce cost savings. However, there are situations where automatic substitution is not advisable and may compromise safety and pharmacovigilance programs. Automatic substitution may be inappropriate for drugs with a narrow therapeutic index, such as modified-release theophylline and calcium channel blockers [37]. For these drugs, the differences between drug concentrations required to produce therapeutic effect and concentrations associated with toxicity are too small to assume that the generic will have the same risk/benefit profile as the innovator.

In some European countries and US states the automatic substitution of such drugs is prevented by placing them on 'do not substitute' lists [38], while other European countries rely on the training and expertise of physicians and pharmacists to prevent inappropriate substitution. Regardless, inappropriate substitution with such drugs can occur when physicians and/or pharmacists do not understand the potential risks involved and the distribution systems allow or encourage automatic substitution. As a risk prevention measure, French legislators in early February 2007 approved a law that clearly distinguishes biosimilars from generics and prohibits automatic substitution with biosimilars [39].

For a variety of reasons, automatic substitution is not appropriate for biopharmaceutical products. As noted, biosimilars are not generic versions of innovator products, and there will be limited clinical experience with biosimilars at approval. Small differences between biosimilars and innovator products may affect clinical outcomes. Further, if automatic substitution is allowed, patients could receive multiple biopharmaceutical products over the course of therapy. Such practices would confound the collection of pharmacovigilance data. If an adverse event were to emerge after switching from one biopharmaceutical to another without documentation of the product change, the event would not be able to be linked to a specific product during the pharmacovigilance assessment, or it could be ascribed to the wrong product. For reasons of safety monitoring, it is essential that clinicians be aware of the exact biopharmaceutical product their patients are receiving.

naming and labeling biosimilars

For accurate pharmacovigilance, it is essential that physicians, pharmacists and patients are able to distinguish easily between biopharmaceutical products. It may not be possible to properly link adverse events to a specific product, if multiple products share one International Nonproprietary Name (INN) and pharmacovigilance reports do not contain additional identifying data for the specific product. The importance of this concept is supported by the EMEA. The position statement from the EMEA emphasizes that 'In order to support pharmacovigilance monitoring, the specific medicinal product given to the patient should be clearly identified' [3].

The EMEA does not oversee the allocation of INNs; this activity is conducted by a committee of the World Health Organization on the advice of an international expert advisory panel. It would appear prudent for this committee to assign unique INNs to biopharmaceuticals. This would help to facilitate accurate prescribing and dispensing of biopharmaceuticals. The EMEA should consider requiring comprehensive labeling of biosimilars so that physicians and pharmacists can make informed decisions. Because biosimilars are not equivalent to reference products and because unique efficacy and safety data will be available, labeling should include these data. Furthermore, labeling should note those indications that are based on extrapolation of data.

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extrapolation of clinical data

Extrapolation involves the approval of a drug for indications for which it has not been evaluated in clinical trials. Extrapolation has played a role in drug development and has a rational basis, but it is only applicable in limited circumstances, such as line extensions, new formulations, or new indications in closely related diseases [40]. The EMEA has generally endorsed the concept of data extrapolation for biosimilars with the appropriate justification. The rationale is that if the biosimilar shows adequate comparability to the innovator product for one indication, it may be reasonable to extend the approval of the biosimilar to all the indications of the innovator product. The biosimilar manufacturer would have to provide an adequate scientific explanation, although 'adequate' is not always well defined. If the mechanism of action differs between indications, the biosimilar manufacturer may have to provide additional clinical data.

The recent approval of two biosimilar growth hormones included extrapolation of clinical data for some indications. The approval process for Omnitrope included a number of comparability studies to the reference product, Genotropin, including quality studies, pharmacokinetic and pharmacodynamic studies, clinical efficacy and safety studies, and immunogenicity studies [32]. While the efficacy and safety comparability studies between Omnitrope and the reference product (Genotropin) were conducted only in children with growth disturbances, the product labeling for Omnitrope is virtually identical to that of the reference product, including the indication for use in adults. Reasons for the extrapolation of data between the innovator and biosimilar growth hormone products appear to include: (1) the long clinical history of safe use of growth hormone; (2) the wide therapeutic window of the drug; (3) the rarity of reports of neutralizing antibodies; (4) the ability to characterize the structure and biological activity of growth hormones by physicochemical and biological methods; and (5) the variety of assays available to characterize the active and product-related substances [41, 42].

While these criteria may be appropriate for the use of well-characterized proteins, such as growth hormones, in average-risk populations, they may not be applicable to more complex biopharmaceutical products or those used in critically ill patients. A potential concern with the concept of data extrapolation is that the risks for using a biopharmaceutical may differ in various patient populations (e.g. between patients with cancer and those with other diseases). This concern has a precedent in cytotoxic chemotherapy, in which the differences in biology between adult and pediatric tumors and in physiology between adults and children usually preclude extrapolation of clinical activity data from adults to children [43]. There may also be differences in immune responses between patients who are receiving recombinant G-CSF for chronic neutropenia versus chemotherapy-induced neutropenia. Since patients with chronic neutropenia are not immune suppressed, they may be more likely to develop antibodies to biopharmaceutical agents, although no antibody-related treatment issue has emerged to date with current G-CSF products.

Although data extrapolation has a rational basis as long as appropriate criteria are met, the process by which indications for a product were approved should be clear to healthcare professionals and patients. Physicians, pharmacists and patients should be aware of the clinical data directly supporting an indication and of the instances in which indications are based on extrapolation of data. Because the Summary of Product Characteristics (SmPC) of the biosimilar Omnitrope is virtually identical to that of the innovator product Genotropin, physicians and pharmacists reading the SmPC of Omnitrope will be unaware that the drug was approved based on clinical data that differ from those in the label, and that its indication in adult patients with growth hormone deficiency was based on data extrapolation [32, 44]. A more comprehensive and accurate approach would be for the SmPC to specify which data are based on extrapolation. With any biopharmaceutical, clinicians need to know the basis of approval for an indication so that they can make informed decisions.

economic and societal consequences

Biopharmaceuticals are more expensive than small-molecule drugs, and their use is increasing. An important benefit of biosimilars is that they are likely to be associated with cost savings. However, it is unclear how cost pressures from biosimilars will affect the prices of innovative products, as manufacturers may alter pricing strategies prior to patent expiration to help them recoup investment costs. Furthermore, the cost savings for biosimilars will likely not be as significant as those seen with small-molecule generics because of the substantial manufacturing costs for biosimilars and the costs of bringing the products to market. It also must be noted that drugs represent only a small fraction of the total cost of treatment for cancer patients [45]. Nevertheless, cost savings with biosimilars will likely increase access to therapeutic proteins and stimulate innovative research.

stem cell mobilization in healthy donors

The increasing use of CSFs for stem cell mobilization and collection from healthy donors for use in allografting [46–49] presents an ethical dilemma for biosimilar use. A 2003 survey by the European Group for Blood and Marrow Transplantation (EBMT) found that 65% of the 7091 allogeneic first transplants in Europe were performed using peripheral blood stem cells from related and unrelated healthy donors [50]. While the procedure appears to be relatively safe for donors, adverse events are common and include transient bone pain, headache, nausea and fever [51–53]. Serious and long-term adverse events appear to be rare, but the high incidence of CSF-induced splenomegaly has raised concern about the risk of splenic rupture [54]. Since healthy donors receive no therapeutic benefit from the receipt of CSFs for stem cell mobilization, ethical concerns dictate that drug safety be of paramount concern for these individuals. Considering the detrimental effect that unexpected toxicity might have in normal individuals donating their peripheral stem cells, sufficient experience with the biosimilar product and adequate follow up should be required. Needed safety data can only be obtained by performing an adequate number of stem cell mobilization procedures (successful mobilization procedures in 500 individuals might be sufficient) and conducting long-term

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follow up (3 years' follow-up) in patients undergoing autologous stem cell transplantation. Such experience has to be collected within a clinical study and analyzed by experts in the field and by regulatory authorities before healthy donors are routinely treated with growth factors. In general, a good history of clinical safety (low incidences of adverse events and immunogenicity) may be a more appropriate consideration for choosing a G-CSF product in these patients than any cost savings achieved with the use of a biosimilar.

conclusions

Since a number of biosimilar products are either already approved (somatropins, glucagons, hyaluronidase, calcitonin) or are under development (e.g. epoetins, G-CSFs), these agents will undoubtedly play an increasing role in disease management. While biosimilars provide a number of opportunities, it is important that they be introduced in an appropriate manner.

There are potential concerns regarding the use of biosimilars in patients with cancer that warrant consideration when making a biopharmaceutical product choice. Clinicians require a thorough understanding of the issues associated with biosimilars so that they can make informed decisions. Of primary importance, clinicians need to be aware that biosimilars are not generic versions of innovator products. Biosimilars will be approved as safe and efficacious agents by the EMEA, but they will be inherently different from innovator products. Therefore, switching or substitution between innovator products and biosimilars should be viewed as a change in clinical management. Because of the limited clinical experience with biosimilars at the time of their approval, these potential clinical differences may not become apparent until after approval. Thus, rigorous pharmacovigilance programs are needed to capture this data and to build a database establishing the clinical use of each product. To ensure that such pharmacovigilance programs establish an accurate database, automatic substitution should be prohibited, because physicians need to effectively monitor patients receiving a biopharmaceutical and such authorizations would confound accurate pharmacovigilance. This is particularly relevant in the community setting but also in the clinical trial setting when biopharmaceuticals are used as non-study drugs.

Extrapolation of clinical data from one therapeutic indication to another for biosimilars also warrants concern. Ultimately, data extrapolation entails a risk/benefit assessment. The assumption that a biosimilar will be effective for indications beyond those for which it has been formally tested is balanced against the implications for the patient if the efficacy or safety profile differs from that of the innovator product. Because the inherent differences between biopharmaceutical products may involve a greater risk-to-benefit ratio for certain patient populations (e.g. stem cell donors) than for others, extrapolation should be implemented on a case-by-case basis. If extrapolation of data is allowed, the package labeling should explicitly state this along with the clinical data used to support extrapolation.

In summary, information is the key to mitigating the potential concerns regarding the use of biosimilars. In particular, physicians and pharmacists must be fully aware of the differences between biosimilars and innovator biopharmaceuticals. For complex biopharmaceutical agents, any change from one product to another (innovator to biosimilar or vice versa) should be considered a change in clinical management.

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PUBLIC SUMMARY DOCUMENT
Product: EPOETIN LAMBDA, injection, 1,000 units in 0.5 mL, 2,000 units in 1.0 mL, 3,000 units in 0.3 mL, 4,000 units in 0.4 mL, 5,000 units in 0.5 mL, 6,000 units in 0.6 mL, 8,000 units in 0.8 mL and 10,000 units in 1.0 mL, pre-filled syringe, Novicrit®
Sponsor: Novartis Pharmaceuticals Australia Pty Ltd
Date of PBAC Consideration: July 2010

1. Purpose of Application

The submission sought a Section 100 (Highly Specialised Drugs Program) listing for treatment of anaemia requiring transfusion, defined as a haemoglobin level of less than 100 g per L, where intrinsic renal disease, as assessed by a nephrologist, is the primary cause of the anaemia.

Highly Specialised Drugs are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate specialist facilities.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Epoetin lambda (Novicrit®) was TGA registered on 27 January 2010 for:

- treatment of patients with symptomatic or transfusion requiring anaemia associated with chronic renal failure to improve their quality of life by improving energy levels, exercise performance, fatigue and sleep patterns and by reducing the need for blood transfusions.
- treatment of anaemia in patients with non-myeloid malignancies where anaemia develops as a result of concomitantly administered chemotherapy, and where blood transfusion is not considered appropriate.
- adult patients with mild to moderate anaemia (haemoglobin > 100 to less than or equal to 130g/L) scheduled for elective surgery with an expected moderate blood loss (two to four units or 900 to 1,800mL) to reduce exposure to allogeneic blood transfusion and to facilitate erythropoietic recovery.
- augment autologous blood collection and to limit the decline in haemoglobin in anaemic adult patients who are scheduled for major elective surgery and who are not expected to pre-deposit their complete perioperative blood needs.

4. Listing Requested and PBAC's View

Section 100 (Highly Specialised Drugs Program)
<u>Private hospital authority required</u>
Treatment of anaemia requiring transfusion, defined as a haemoglobin level of less than 100 g per L, where intrinsic renal disease, assessed by a nephrologist, is the primary cause of the anaemia.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Chronic kidney disease (CKD) is marked by long-term and usually irreversible loss of kidney function and may further deteriorate into end-stage kidney disease, and renal replacement

therapy in the form of dialysis or transplantation is required for survival. Anaemia is a complication of chronic kidney disease.

Epoetin lambda would provide an alternative treatment for anaemia associated with CKD.

6. Comparator

The submission nominated epoetin alfa as the comparator. The PBAC considered this appropriate.

7. Clinical Trials

The submission presented the results of Study INJ-9 as the basis of the evidence in support of listing. Details of the published trial presented in the submission are in the table below.

Trial ID / First Author	Protocol title / Publication title	Publication citation
Study INJ-9 Haag-Weber M, et al	Therapeutic equivalence, long-term efficacy and safety of HX575 in the treatment of anaemia in chronic renal failure patients receiving hemodialysis.	Clin Nephrol 2009; 72(5):380-90

8. Results of Trials

Study INJ-9 evaluated the therapeutic equivalence of epoetin lambda with epoetin alfa in the long-term intravenous treatment of anaemia in chronic renal failure patients on haemodialysis only.

The primary efficacy outcome was mean absolute change in Hb level between the screening/baseline period and the evaluation period. Major secondary efficacy outcomes were:

- Percentage of patients with Hb within the target range of 10.0 – 13.0 g/dL;
- Frequency of patients with Hb values > 10.0 g/dL;
- Frequency of patients with changes in the epoetin dosage (adaptation of more than 25% at any visit);
- Development of the weekly epoetin dose (in IU and per kg);
- Frequency of responders (PP)% (95% CI); and
- Red blood cell transfusions.

For the primary endpoint, the difference between treatment groups of 0.084 g/dL (95% CI [-0.170; 0.338]) was within the pre-defined boundaries of -0.5 and 0.5 g/dL, therefore meeting the criteria to confirm, with statistical significance, therapeutic non-inferiority of epoetin lambda and epoetin alfa.

Regarding safety, the submission stated that no relevant differences between treatment groups, with regard to adverse events, serious adverse events and death were observed.

The submission claimed that Study INJ-9 showed epoetin lambda to be therapeutically non-inferior to epoetin alfa with respect to mean absolute change in Hb levels, and to have a comparable safety profile in the IV treatment of anaemia in patients with chronic kidney disease.

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The submission claimed that epoetin lambda is non-inferior in terms of efficacy and safety to epoetin alfa.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost-minimisation analysis. The equi-effective doses were 1000 IU epoetin lambda and 1000 IU epoetin alfa. The sponsor adopted a modified cost-minimisation approach where epoetin lambda was provided at a 10% lower price (ex-manufacturer) than the calculated equivalent price of the calculated equivalent dose of epoetin alfa.

11. Estimated PBS Usage and Financial Implications

The submission used a market share approach to estimate the financial impact of the requested listing for epoetin lambda. Anticipated utilisation of epoetin lambda was calculated based on substitution from the ESAs listed at the time of the submission (epoetin alfa, epoetin beta and darbepoetin alfa) and assumed that 50% of total current ESA usage is by intravenous administration.

The likely number of packs dispensed per year was estimated to be between 10,000 and 50,000 in Year 5.

The submission estimated net savings to the PBS of less than $10 million in Year 5 of listing.

12. Recommendation and Reasons

The PBAC recommended the listing of epoetin lambda on the Pharmaceutical Benefits Scheme as a Section 100 Highly Specialised Drug for the treatment of anaemia requiring transfusion defined as a haemoglobin level of less than 100 g per L, where intrinsic renal disease, assessed by a nephrologist, is the primary cause of the anaemia. Listing was recommended on a cost-minimisation basis with epoetin alfa at the prices proposed in the submission, which the PBAC noted are 10% lower than the current PBS price for the corresponding strengths of epoetin alfa.

In making this recommendation, the PBAC noted that epoetin lambda had been approved by TGA under the Similar Biological Medicinal Product guidelines. When approving this product, the TGA had concluded although the amino acid sequence of epoetin lambda was the same as that of epoetin alfa, there were significant differences in the glycosylation pattern of this product and epoetin alfa which made it appropriate for the former to have the different Australian Biologic Name, epoetin lambda.

The PBAC was satisfied that the results of Study INJ-9 demonstrate that epoetin lambda is non-inferior to epoetin alfa in terms of efficacy and safety when used at the same doses for the long-term intravenous treatment of anaemia in chronic renal failure.

The PBAC agreed to advise the Minister and the Pricing Authority that it is appropriate to apply the same price reduction offered in this submission to the other PBS-listed erythropoiesis stimulating agents; epoetin-alfa, epoetin beta, darbepoetin and

methoxypolyethylene glycol-epoetin beta, all of which were recommended for listing on a cost-minimisation basis with epoetin alfa.

In accordance with Subsection 101 (3BA) of the *National Health Act 1953* the PBAC advised that on the basis of the material available to it at this time, the Committee is of the opinion that epoetin lambda should not be considered as interchangeable on an individual patient basis with another drug or medicinal preparation. This is because, according to the TGA approved Product Information, epoetin lambda can only be administered intravenously, whereas the other PBS-subsidised erythropoiesis stimulating agents can be administered intravenously and subcutaneously, and the subcutaneous route of administration accounts for a significant proportion of use of the PBS-subsidised erythropoiesis stimulating agents. This means that these drugs are not sufficiently similar in their clinical use.

Recommendation

EPOETIN LAMBDA, injection, 1,000 units in 0.5 mL, 2,000 units in 1.0 mL, 3,000 units in 0.3 mL, 4,000 units in 0.4 mL, 5,000 units in 0.5 mL, 6,000 units in 0.6 mL, 8,000 units in 0.8 mL and 10,000 units in 1.0 mL, pre-filled syringe, Novicrit®

Restriction:	Section 100 (Highly Specialised Drugs Program) Authority Required (STREAMLINED) Private hospital authority required Treatment of anaemia requiring transfusion, defined as a haemoglobin level of less than 100 g per L, where intrinsic renal disease, as assessed by a nephrologist, is the primary cause of the anaemia. NOTE: Epoetin lambda should only be administered by the intravenous route.
Maximum quantity:	12
Repeats:	5

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Novartis Pharmaceuticals Australia welcomes the PBAC's recommendation to make Novicrit® available to patients with anaemia requiring transfusion.

Table 1. Products Approved in FY 2009: New Drugs

Category	Approval Date		Brand Name (Applicant Company)	Approval/ Partial Change	Active Ingredient(s) (underlined: new active ingredient)	Notes
1	Apr. 22, 2009	1	Niflec (Ajinomoto Co., Inc.)	Change	N/A for this combination drug	A drug with a new additional indication and a new dosage for cleansing of gastrointestinal tract for pretreatment of barium enema X-ray examination.
			Gasmotin Tablets 2.5 mg Gasmotin Tablets 5 mg Gasmotin Powder (Dainippon Sumitomo Pharma Co., Ltd.)	Change Change Change	Mosapride citrate hydrate	Drugs with a new additional indication and a new dosage for adjunctive treatment to pretreatment with orally gastrointestinal lavage solution for barium enema X-ray examination.
1	Jul. 7, 2009	2	Prograf Capsules 0.5 mg Prograf Capsules 1 mg Prograf Capsules 5 mg (Astellas Pharma Inc.)	Change Change Change	Tacrolimus hydrate	Drugs with a new additional indication and a new dosage for the treatment of refractory (steroid-resistant/steroid-dependent) active ulcerative colitis (limited to moderate-to-severe cases).
1	Oct. 16, 2009	3	Emend Capsules 80 mg Emend Capsules 125 mg Emend Capsules Set (Ono Pharmaceutical Co., Ltd.)	Approval Approval Approval	Aprepitant	Drugs with a new active ingredient indicated for the treatment of digestive symptoms (nausea and vomiting, including delayed phase) resulting from the administration of antineoplastic agents (cisplatin, etc.).
1	Oct. 16, 2009	4	Feron for Injection 6 MIU Feron for Injection 3 MIU Feron for Injection 1 MIU (Toray Industries, Inc.)	Change	Interferon beta	Drugs with a new additional indication and a new dosage for the improvement of viraemia in chronic hepatitis C on concomitant administration with ribavirin.
			Rebetol Capsule 200 mg (Schering-Plough K.K.)	Change	Ribavirin	A drug with a new additional indication and a new dosage for the improvement of viraemia in chronic hepatitis C on concomitant administration with interferon beta.
1	Oct. 16, 2009	5	Asacol Tablets 400 mg (Zeria Pharmaceutical Co., Ltd.)	Approval	Mesalazine	A drug in a new dosage form and with a new dosage indicated for the treatment of ulcerative colitis (excluding severe case).
1	Jan. 20, 2010	6	Aloxi I.V. Injection 0.75 mg (Taiho Pharmaceutical Co., Ltd.)	Approval	Palonosetron hydrochloride	A drug with a new active ingredient indicated for the treatment of digestive symptoms (nausea and vomiting, including delayed phase) resulting from the administration of antineoplastic agents (cisplatin, etc.).
1	Jan. 20, 2010	7	Epoetin Alfa BS Injection 750 syringe [JCR] Epoetin Alfa BS Injection 1500 syringe [JCR] Epoetin Alfa BS Injection 3000 syringe [JCR] Epoetin Alfa BS Injection 750 [JCR] Epoetin Alfa BS Injection 1500 [JCR] Epoetin Alfa BS Injection 3000 [JCR] (JCR Pharmaceuticals Co., Ltd.)	Approval Approval Approval Approval Approval Approval	Epoetin kappa (genetical recombination) [epoetin alfa biosimilar 1]	Follow-on biologics indicated for the treatment of renal anemia in patients on dialysis and anemia of prematurity.
1	Mar. 12, 2010	8	Protecadin Tablet 5 Protecadin Tablet 10 (Taiho Pharmaceutical Co., Ltd.)	Change Change	Lafutidine	Drugs with a new additional indication for the treatment of reflux esophagitis.
2	Apr. 22, 2009	9	Micombi Combination Tablets AP (Nippon Boehringer Ingelheim Co., Ltd.)	Approval	Telmisartan/ hydrochlorothiazide	New combination drugs indicated for the treatment of hypertension.
		10	Micombi Combination Tablets BP (Nippon Boehringer Ingelheim Co., Ltd.)	Approval		
2	Jul. 7, 2009	11	Caduet Combination Tablets 1ban Caduet Combination Tablets 2ban Caduet Combination Tablets 3ban Caduet Combination Tablets 4ban (Pfizer Japan Inc.)	Approval Approval Approval Approval	Amlodipine besilate/atorvastatin calcium hydrate	New combination drugs indicated for the treatment of comorbidity of hypertension or angina pectoris and hypercholesterolemia or familial hypercholesterolemia.
2	Jul. 7, 2009	12	Rasilez Tablets 150 mg (Novartis Pharma K.K.)	Approval	Aliskiren fumarate	A drug with a new active ingredient indicated for the treatment of hypertension.
2	Oct. 16, 2009	13	Adcirca Tablets 20 mg (Eli Lilly Japan K.K.)	Approval	Tadalafil	A drug with a new indication and a new dosage for the treatment of pulmonary arterial hypertension.
2	Jan. 20, 2010	14	Exforge Combination Tablets (Novartis Pharma K.K.)	Approval	Valsartan/amlodipine besylate	A new combination drug indicated for the treatment of hypertension.
2	Jan. 20, 2010	15	Rezaltas Combination Tablets LD Rezaltas Combination Tablets HD (Daiichi Sankyo Co., Ltd.)	Approval Approval	Olmesartan medoxomil/ azelnidipine	New combination drugs indicated for the treatment of hypertension.

Category	Approval Date		Brand Name (Applicant Company)	Approval/ Partial Change	Active Ingredient(s) (underlined: new active ingredient)	Notes
3-1	Apr. 22, 2009	16	Risperdal Consta Intramuscular Injection 25 mg Risperdal Consta Intramuscular Injection 37.5 mg Risperdal Consta Intramuscular Injection 50 mg (Janssen Pharmaceutical K.K.)	Approval Approval Approval	Risperidone	Drugs with a new route of administration indicated for the treatment of schizophrenia.
3-1	Apr. 22, 2009	17	Strattera Capsules 5 mg Strattera Capsules 10 mg Strattera Capsules 25 mg (Eli Lilly Japan K.K.)	Approval Approval Approval	Atomoxetine hydrochloride	Drugs with a new active ingredient indicated for the treatment of attention-deficit/hyperactivity disorder (AD/HD) in children. [Expedited review]
3-1	Apr. 22, 2009	18	Clozaril Tablets 25 mg Clozaril Tablets 100 mg (Novartis Pharma K.K.)	Approval Approval	Clozapine	Drugs with a new active ingredient indicated for the treatment of treatment-resistant schizophrenia.
3-1	Jul. 7, 2009	19	Remeron Tablets 15 mg (Schering-Plough K.K.) Reflex Tablets 15 mg (Meiji Seika Kaisha, Ltd.)	Approval Approval	Mirtazapine	Drugs with a new active ingredient indicated for the treatment of depression.
3-1	Oct. 16, 2009	20	Paxil Tablets 10 mg Paxil Tablets 20 mg (GlaxoSmithKline K.K.)	Change Change	Paroxetine hydrochloride hydrate	Drugs with a new additional indication and a new dosage for the treatment of social anxiety disorder.
3-1	Oct. 16, 2009	21	Prograf Capsules 0.5 mg Prograf Capsules 1 mg Prograf Granules 0.2 mg Prograf Granules 1 mg (Astellas Pharma Inc.)	Change Change Change Change	Tacrolimus hydrate	Drugs with a revised indication for the treatment of myasthenia gravis (limitation of patients to be treated was abolished.) [Orphan drug]
3-1	Jan. 20, 2010	22	Bi•Sifrol Tablets 0.125 mg Bi•Sifrol Tablets 0.5 mg (Nippon Boehringer Ingelheim Co., Ltd.)	Change Change	Pramipexole hydrochloride hydrate	Drugs with a new additional indication and a new dosage for the treatment of moderate to severe idiopathic restless legs syndrome.
3-1	Jan. 20, 2010	23	Cymbalta Capsules 20 mg Cymbalta Capsules 30 mg (Shionogi & Co., Ltd.)	Approval Approval	Duloxetine hydrochloride	Drugs with a new active ingredient indicated for the treatment of depression.
3-1	Jan. 20, 2010	24	Kenketsu Venilon-I for Intravenous Injection 500 mg (Kaketsuken [The Chemo-Sero-Therapeutic Research Institute])	Change	Freeze-dried sulfonated human normal immunoglobulin	A drug with a new additional indication and a new dosage for the improvement of neurological disorder in patients with Churg-Strauss syndrome or allergic granulomatous angiitis (for use only when steroids are not sufficiently effective). [Orphan drug]
3-2	Jul. 7, 2009	25	Lumigan Ophthalmic Solution 0.03% (Senju Pharmaceutical Co., Ltd.)	Approval	Bimatoprost	A drug with a new active ingredient indicated for the treatment of glaucoma and ocular hypertension.
3-2	Aug. 20, 2009	26	DisCoVisc 1.0 Ophthalmic Viscoelastic Substance (Alcon Japan Ltd.)	Approval	Sodium hyaluronate, chondroitin sulfate sodium	A drug in a new dosage form indicated for adjunctive treatment for crystalline lens reconstruction.
3-2	Jan. 20, 2010	27	Bridion Intravenous 200 mg Bridion Intravenous 500 mg (Schering-Plough K.K.)	Approval Approval	Sugammadex sodium	Drugs with a new active ingredient indicated for the recovery from neuromuscular blockade induced by rocuronium bromide or vecuronium bromide.
3-2	Jan. 20, 2010	28	Xalacom Combination Eye Drops (Pfizer Japan Inc.)	Approval	Latanoprost/timolol maleate	A new combination drug indicated for the treatment of glaucoma and ocular hypertension.
3-2	Jan. 20, 2010	29	Durotep MT Patch 2.1 mg Durotep MT Patch 4.2 mg Durotep MT Patch 8.4 mg Durotep MT Patch 12.6 mg Durotep MT Patch 16.8 mg (Janssen Pharmaceutical K.K.)	Change Change Change Change Change	Fentanyl	Drugs with a new indication for analgesia of moderate to severe chronic pain which cannot be managed by treatments with non-opioid analgesics and weak opioid analgesics (for use only in patients who switch from an opioid analgesic).
3-2	Mar. 12, 2010	30	Dormicum Injection 10 mg (Astellas Pharma Inc.)	Change	Midazolam	A drug with a new additional pediatric dosage indicated for anesthetic premedication and for sedation during artificial respiration in patients under intensive care.
4	Apr. 22, 2009	31	Orapenem Fine Granules 10% for Pediatric (Meiji Seika Kaisha, Ltd.)	Approval	Tebipenem pivoxil	A drug with a new active ingredient indicated for the treatment of pneumonia, otitis media, and sinusitis.
4	Apr. 22, 2009	32	Cravit Tablets 250 mg Cravit Tablets 500 mg (Daiichi Sankyo Co., Ltd.)	Approval Approval	Levofloxacin hydrate	Drugs in an additional dosage form and with a revised dosage of once-daily administration for conventional indications.
		33	Cravit Fine Granules 10% (Daiichi Sankyo Co., Ltd.)	Approval		

Category	Approval Date		Brand Name (Applicant Company)	Approval/ Partial Change	Active Ingredient(s) (underlined: new active ingredient)	Notes
4	May 20, 2009	34	Valixa Tablets 450 mg (Mitsubishi Tanabe Pharma Corporation)	Change	Valganciclovir hydrochloride	A drug with a new additional indication for the treatment of cytomegalovirus infection in organ transplantation (including hematogenic stem cell transplantation), malignant tumor, etc.
4	Jun. 17, 2009	35	AmBisome 50 mg for Intravenous Drip Infusion (Dainippon Sumitomo Pharma Co., Ltd.)	Change	Amphotericin B	A drug with new additional indications and a new dosage for the treatment of fungal infections caused by Mucor species, Absidia species, Rhizopus species, Rhizomucor species, Cladosporium species, Cladophialophora species, Fonsecaea species, Phialophora species, Exophiala species, Coccidioides species, Histoplasma species, and Blastomyces species and visceral leishmaniasis.
4	Oct. 16, 2009	36	Vancomycin Ophthalmic Ointment 1% (Toa Pharmaceutical Co., Ltd.)	Approval	Vancomycin hydrochloride	A drug with a new route of administration indicated for the treatment of conjunctivitis, blepharitis, meibomianitis, and dacryocystitis caused by vancomycin-sensitive methicillin-resistant Staphylococcus aureus (MRSA) and methicillin-resistant Staphylococcus epidermidis (MRSE). [Orphan drug]
4	Oct. 16, 2009	37	Ozex Fine Granules 15% for Pediatric (Toyama Chemical Co., Ltd.)	Approval	Tosufloxacin tosilate hydrate	A drug with new additional indications and a new dosage and in a new dosage form for the treatment of pneumonia, cholera, otitis media, and anthrax in children.
4	Dec. 18, 2009	38	Tamiflu Dry Syrup 3% Tamiflu Capsule 75 (Chugai Pharmaceutical Co., Ltd.)	Change Change	Oseltamivir phosphate	Drugs with a new additional indication and a new dosage for prophylaxis of influenza A or B virus infections.
4	Jan. 13, 2010	39	Rapiacta 300 mg Bag for Intravenous Drip Infusion Rapiacta 150 mg Vial for Intravenous Drip Infusion (Shionogi & Co., Ltd.)	Approval Approval	<u>Peramivir hydrate</u>	Drugs with a new active ingredient indicated for the treatment of influenza A or B virus infections.
4	Jan. 20, 2010	40	Meropen for Intravenous Drip Infusion Vial 0.25 g Meropen for Intravenous Drip Infusion Vial 0.5 g Meropen for Intravenous Drip Infusion Kit 0.5 g (Dainippon Sumitomo Pharma Co., Ltd.)	Change Change Change	Meropenem hydrate	Drugs with a new additional indication and a new dosage for the treatment of febrile neutropenia.
5	Jul. 7, 2009	41	Avolve Capsules 0.5 mg (GlaxoSmithKline K.K.)	Approval	<u>Dutasteride</u>	A drug with a new active ingredient indicated for the treatment of benign prostatic hyperplasia.
5	Jul. 7, 2009	42	Gonalef 75 Gonalef Pen 300 Gonalef Pen 450 Gonalef Pen 900 (Merck Serono Co., Ltd.)	Change Change Change Change	Follitropin alfa (genetical recombination)	Drugs with a new additional indication and a new dosage for induction of ovulation in patients with anovulation and infrequent ovulation associated with hypothalamic-pituitary dysfunction or polycystic ovarian syndrome.
5	Nov. 6, 2009	43	Rinderon Injection 2 mg (0.4%) Rinderon Injection 4 mg (0.4%) (Shionogi & Co., Ltd.)	Change Change	Betamethasone sodium phosphate	Drugs with a new additional indication and a new dosage for prevention of neonatal respiratory distress syndrome by way of enhancing fetal lung maturation by maternal administration for use in cases where premature birth is expected.
5	Dec. 18, 2009	44	Uritos Tablets 0.1 mg (Kyorin Pharmaceutical Co., Ltd.) Staybla Tablets 0.1 mg (Ono Pharmaceutical Co., Ltd.)	Change Change	Imidafenacin	Drugs with a new dosage indicated for the treatment of urgency of urination, pollakiuria, and urge urinary incontinence associated with overactive bladder.
5	Dec. 18, 2009	45	Bup-4 Tablet 10 Bup-4 Tablet 20 Bup-4 Fine Granule 2% (Taiho Pharmaceutical Co., Ltd.)	Change Change Change	Propiverine hydrochloride	Drugs with a new additional indication for the treatment of urgency of urination, pollakiuria, and urge urinary incontinence associated with overactive bladder.
6-1	Apr. 22, 2009	46	Allermist 27.5 μg 56 metered Nasal Spray (GlaxoSmithKline K.K.)	Approval	<u>Fluticasone furoate</u>	A drug with a new active ingredient indicated for the treatment of allergic rhinitis.
6-1	Apr. 22, 2009	47	Zyrtec Dry Syrup 1.25% Zyrtec Tablet 5 (UCB Japan Co., Ltd.)	Change Change	Cetirizine hydrochloride	Drugs with a new additional pediatric dosage indicated for the treatment of allergic rhinitis, urticaria, and itching associated with skin disease (eczema/dermatitis and pruritus cutaneous).
6-1	Jun. 17, 2009	48	Celecox Tablets 100 mg Celecox Tablets 200 mg (Astellas Pharma Inc.)	Change Change	Celecoxib	Drugs with new additional indications for the treatment of lumbago, scapulohumeral periarthritis, cervico-omo-brachial syndrome, and tendinitis/tenosynovitis.

Category	Approval Date		Brand Name (Applicant Company)	Approval/ Partial Change	Active Ingredient(s) (underlined: new active ingredient)	Notes
6-1	Jul. 7, 2009	49	Enbrel 25 mg for S.C. Injection (Wyeth K.K.)	Change	Etanercept (genetical recombination)	A drug with a new indication and a new dosage for the treatment of polyarticular-course juvenile idiopathic arthritis (for use only in patients who have not sufficiently responded to conventional treatments).
6-1	Jul. 7, 2009	50	Asmanex Twisthaler 100 µg 60 doses Asmanex Twisthaler 200 µg 60 doses (Schering-Plough K.K.)	Approval Approval	Mometasone furoate	Drugs with a new route of administration indicated for the treatment of bronchial asthma.
6-1	Jul. 7, 2009	51	Remicade for I.V. Infusion 100 (Mitsubishi Tanabe Pharma Corporation)	Change	Infliximab (genetical recombination)	A drug with a new indication and a new dosage for the treatment of rheumatoid arthritis (including prevention of structural joint damage) in patients who have not sufficiently responded to conventional treatments. [Expedited review]
6-1	Oct. 16, 2009	52	Erizas Capsule for Nasal Spray 400 µg (Nippon Shinyaku Co., Ltd.)	Approval	Dexamethasone cipecilate	A drug with a new active ingredient indicated for the treatment of allergic rhinitis.
6-1	Oct. 16, 2009	53	Symbicort Turbuhaler 30 doses Symbicort Turbuhaler 60 doses (AstraZeneca K.K.)	Approval Approval	Budesonide/formoterol fumarate hydrate	New combination drugs indicated for the treatment of bronchial asthma (when a combination treatment of an inhaled steroid and a long-acting beta-$_2$ agonist is needed).
6-1	Nov. 6, 2009	54	Mohrus Tape 20 mg Mohrus Tape L 40 mg (Hisamitsu Pharmaceutical Co., Inc.)	Change Change	Ketoprofen	Drugs with a new additional indication for relief of local pain associated with rheumatoid arthritis.
6-1	Jan. 20, 2010	55	Spiriva 2.5 µg Respimat 60 puffs (Nippon Boehringer Ingelheim Co., Ltd.)	Approval	Tiotropium bromide hydrate	A drug in a new dosage form and with a new dosage as a kit product consisting of Respimat inhaler and a cartridge (solution).
6-1	Jan. 20, 2010	56	Remicade for I.V. Infusion 100 (Mitsubishi Tanabe Pharma Corporation)	Change	Infliximab (genetical recombination)	A drug with new additional indications and a new dosage for the treatment of plaque psoriasis, psoriatic arthritis, pustular psoriasis, and erythrodermic psoriasis in patients who have not responded sufficiently to conventional treatments.
6-1	Jan. 20, 2010	57	Humira 40 mg for S.C. Injection Syringe 0.8 mL (Abbott Japan Co., Ltd.)	Change	Adalimumab (genetical recombination)	A drug with new additional indications and a new dosage for the treatment of plaque psoriasis and psoriatic arthritis in patients who have not responded sufficiently to conventional treatments.
6-1	Feb. 5, 2010	58	Enbrel 10 mg for S.C. Injection Enbrel 25 mg Syringe 0.5 mL for S.C. Injection (Wyeth K.K.)	Change Change	Etanercept (genetical recombination)	Drugs with a new dosage indicated for the treatment of rheumatoid arthritis (for use only in patients who have not sufficiently responded to conventional treatments).
		59	Enbrel 25 mg for S.C. Injection Enbrel 50 mg Syringe 1.0 mL for S.C. Injection (Wyeth K.K.)	Change Approval		
6-2	Apr. 22, 2009	60	Norditropin S Injection 5 mg Norditropin S Injection 10 mg Norditropin NordiFlex Injection 5 mg Norditropin NordiFlex Injection 10 mg Norditropin NordiFlex Injection 15 mg (Novo Nordisk Pharma Ltd.)	Change Change Change Change Change	Somatropin (genetical recombination)	Drugs with a new additional indication and a new dosage for the treatment of adult growth hormone deficiency (for use only in severe cases).
6-2	Apr. 22, 2009	61	Apidra Inj. Cart Apidra Inj. OptiClik Apidra Inj. SoloStar Apidra Inj. 100 U/mL （Sanofi-Aventis K.K.）	Approval Approval Approval Approval	Insulin glulisine (genetical recombination)	Drugs with a new active ingredient indicated for the treatment of diabetes mellitus where insulin therapy is indicated.
6-2	May 20, 2009	62	Melbin Tablets 250 mg (Dainippon Sumitomo Pharma Co., Ltd.) Glycoran Tablets 250 mg (Nippon Shinyaku Co., Ltd.)	Change Change	Metformin hydrochloride	Drugs with a new indication and a new dosage for the treatment of type 2 diabetes mellitus in patients who have not responded sufficiently to either (1) diet and exercise therapies alone or (2) sulfonylurea along with diet and exercise therapies.
6-2	Jun. 17, 2009	63	Norditropin S Injection 5 mg Norditropin S Injection 10 mg Norditropin NordiFlex Injection 5 mg Norditropin NordiFlex Injection 10 mg Norditropin NordiFlex Injection 15 mg (Novo Nordisk Pharma Ltd.)	Change Change Change Change Change	Somatropin (genetical recombination)	Drugs with a new additional indication and a new dosage for the treatment of dwarfism with no epiphyseal closure in patients born small for gestational age (SGA).
6-2	Jul. 7, 2009	64	Growject for Injection 1.33 mg Growject for Injection 8 mg Growject BC for Injection 8 mg (JCR Pharmaceuticals Co., Ltd.)	Change Change Change	Somatropin (genetical recombination)	Drugs with a new additional indication and a new dosage for the treatment of adult growth hormone deficiency (for use only in severe cases).

Category	Approval Date		Brand Name (Applicant Company)	Approval/ Partial Change	Active Ingredient(s) (underlined: new active ingredient)	Notes
6-2	Aug. 20, 2009	65	NovoRapid 70 Mix Penfill NovoRapid 70 Mix FlexPen (Novo Nordisk Pharma Ltd.)	Approval Approval	Insulin aspart (genetical recombination)	Drugs with a new dosage indicated for the treatment of diabetes mellitus where insulin therapy is indicated.
6-2	Aug. 20, 2009	66	Humalog Mix 50 Cart Humalog Mix 50 Kit Humalog Mix 50 MirioPen (Eli Lilly Japan K.K.)	Change Change Change	Insulin lispro (genetical recombination)	Drugs with a new dosage indicated for the treatment of diabetes mellitus where insulin therapy is indicated.
6-2	Sep. 18, 2009	67	NovoRapid 50 Mix Penfill NovoRapid 50 Mix FlexPen (Novo Nordisk Pharma Ltd.)	Approval Approval	Insulin aspart (genetical recombination)	Drugs with a new dosage and in an additional dosage form indicated for the treatment of diabetes mellitus where insulin therapy is indicated.
6-2	Oct. 16, 2009	68	Januvia Tablets 25 mg Januvia Tablets 50 mg Januvia Tablets 100 mg (Banyu Pharmaceutical Co., Ltd.) Glactiv Tablets 25 mg Glactiv Tablets 50 mg Glactiv Tablets 100 mg (Ono Pharmaceutical Co., Ltd.)	Approval Approval Approval Approval Approval Approval	<u>Sitagliptin phosphate hydrate</u>	Drugs with a new active ingredient indicated for the treatment of type 2 diabetes mellitus (for use only in patients who do not sufficiently respond to any one of the following treatments): 1. Dietary therapy and/or exercise therapy only 2. Use of sulfonylureas in addition to dietary therapy and/or exercise therapy 3. Use of thiazolidinediones in addition to dietary therapy and/or exercise therapy 4. Use of biguanides in addition to dietary therapy and/or exercise therapy
6-2	Oct. 16, 2009	69	Basen Tablets 0.2 Basen OD Tablets 0.2 (Takeda Pharmaceutical Company Limited)	Change Change	Voglibose	Drugs with a new additional indication and a new dosage for prevention of type 2 diabetes mellitus in patients with impaired glucose tolerance (only for whom glycemic control is not sufficient by diet and/or exercise).
6-2	Nov. 6, 2009	70	Seibule Tablets 25 mg Seibule Tablets 50 mg Seibule Tablets 75 mg (Sanwa Kagaku Kenkyusho Co., Ltd.)	Change Change Change	Miglitol	Drugs with a new additional indication for improvement of postprandial hyperglycemia in patients with diabetes mellitus (for use only in patients who have not responded sufficiently to treatment with biguanides in conjunction with dietary and exercise regimens).
6-2	Jan. 20, 2010	71	Equa Tablets 50 mg (Novartis Pharma K.K.)	Approval	<u>Vildagliptin</u>	A drug with a new active ingredient indicated for the treatment of type 2 diabetes mellitus (for use only in patients who have not responded sufficiently to either [1] diet and exercise therapies alone or [2] sulfonylurea along with diet and exercise therapies).
6-2	Jan. 20, 2010	72	Metgluco Tablets 250 mg (Dainippon Sumitomo Pharma Co., Ltd.)	Approval	Metformin hydrochloride	A drug with a new dosage exceeding the maximum dosage (750 mg/day) of the conventional formulation indicated for the treatment of type 2 diabetes mellitus (for use only in patients who have not responded sufficiently to either [1] diet and exercise therapies alone or [2] sulfonylurea along with diet and exercise therapies).
6-2	Jan. 20, 2010	73	Victoza Subcutaneous Injection 18 mg (Novo Nordisk Pharma Ltd.)	Approval	<u>Liraglutide (genetical recombination)</u>	A drug with a new active ingredient indicated for the treatment of type 2 diabetes mellitus (for use only in patients who have not responded sufficiently to either [1] diet and exercise therapies alone or [2] sulfonylurea along with diet and exercise therapies).
AIDS drugs	Aug. 20, 2009	74	Prezistanaive Tablets 400 mg (Janssen Pharmaceutical K.K.)	Approval	Darunavir ethanolate	A drug with a new dosage indicated for the treatment of HIV infection. [Orphan drug]
Blood products	Oct. 16, 2009	75	BeneFIX Intravenous 250 BeneFIX Intravenous 500 BeneFIX Intravenous 1000 BeneFIX Intravenous 2000 (Wyeth K.K.)	Approval Approval Approval Approval	<u>Nonacog alfa (genetical recombination)</u>	Drugs with a new active ingredient indicated for inhibition of bleeding tendency in patients with hemophilia B (congenital blood coagulation factor IX deficiency). [Orphan drug]
Blood products	Mar. 12, 2010	76	NovoSeven for Injection 1.2 mg NovoSeven for Injection 4.8 mg (Novo Nordisk Pharma Ltd.)	Change Change	Eptacog alfa (activated) (genetical recombination)	Drugs with a new additional indication and a new dosage for inhibition of bleeding tendency in patients with congenital factor VII deficiency.
		77	NovoSeven HI for Intravenous Injection 1 mg NovoSeven HI for Intravenous Injection 2 mg NovoSeven HI for Intravenous Injection 5 mg (Novo Nordisk Pharma Ltd.)	Change Change Change		
Oncology drugs	Apr. 22, 2009	78	Doxil Injection 20 mg (Janssen Pharmaceutical K.K.)	Change	Doxorubicin hydrochloride	A drug with a new indication and a new dosage for the treatment of ovarian cancer which has progressed after cancer chemotherapy. [Expedited review]

Category	Approval Date		Brand Name (Applicant Company)	Approval/ Partial Change	Active Ingredient(s) (underlined: new active ingredient)	Notes
Oncology drugs	Apr. 22, 2009	79	Tykerb Tablets 250 mg (GlaxoSmithKline K.K.)	Approval	Lapatinib tosilate hydrate	A drug with a new active ingredient indicated for the treatment of inoperable or recurrent breast cancer with HER2 overexpression. [Priority review]
Oncology drugs	May 20, 2009	80	Nexavar Tablets 200 mg (Bayer Yakuhin, Ltd.)	Change	Sorafenib tosilate	A drug with a new additional indication for the treatment of unresectable hepatocellular carcinoma. [Priority review]
Oncology drugs	May 20, 2009	81	Alimta Injection 100 mg Alimta Injection 500 mg (Eli Lilly Japan K.K.)	Approval Change	Pemetrexed sodium hydrate	Drugs with a new additional indication and a new dosage in an additional dosage form (Alimta Injection 100 mg) indicated for the treatment of unresectable advanced or recurrent non-small cell lung cancer.
Oncology drugs	Aug. 20, 2009	82	Elplat I.V. Infusion Solution 50 mg Elplat I.V. Infusion Solution 100 mg Elplat for Injection 50 mg Elplat for Injection 100 mg (Yakult Honsha Co., Ltd.)	Approval Approval Change Change	Oxaliplatin	Drugs with a new additional indication and a new dosage in an additional dosage form (Elplat I.V. Infusion Solution 50 mg and Elplat I.V. Infusion Solution 100 mg) for post-operative adjuvant chemotherapy for colon cancer. [Priority review]
Oncology drugs	Aug. 20, 2009	83	Miripla Suspension Vehicle 4 mL (Dainippon Sumitomo Pharma Co., Ltd.)	Approval	Iodine addition products of the ethyl esters of the fatty acids obtained from poppyseed oil	A drug with a new indication for suspending Miripla for intra-arterial injection 70 mg.
Oncology drugs	Sep. 18, 2009	84	Xeloda Tablet 300 (Chugai Pharmaceutical Co., Ltd.)	Change	Capecitabine	A drug with a new additional indication and a new additional dosage and administration for combination therapy with other anticancer drugs (XELOX + BV regimen) for advanced or recurrent colorectal cancer not suited for curative resection.
Oncology drugs	Sep. 18, 2009	85	Avastin 100 mg/4 mL Intravenous Infusion Avastin 400 mg/16 mL Intravenous Infusion (Chugai Pharmaceutical Co., Ltd.)	Change Change	Bevacizumab (genetical recombination)	Drugs with a new additional indication and a new additional dosage and administration for combination therapy with other anticancer drugs (XELOX + BV regimen) for advanced or recurrent colorectal cancer not suited for curative resection.
Oncology drugs	Sep. 18, 2009	86	Elplat for Injection 100 mg Elplat I.V. Infusion Solution 50 mg Elplat I.V. Infusion Solution 100 mg (Yakult Honsha Co., Ltd.)	Change Change Change	Oxaliplatin	Drugs with a new additional indication and a new additional dosage and administration for combination therapy with other anticancer drugs (XELOX + BV regimen) for advanced or recurrent colorectal cancer not suited for curative resection.
		87	Elplat for Injection 50 mg (Yakult Honsha Co., Ltd.)	Change		
Oncology drugs	Oct. 16, 2009	88	Miripla for Intra-arterial Injection 70 mg (Dainippon Sumitomo Pharma Co., Ltd.)	Approval	Miriplatin hydrate	A drug with a new active ingredient indicated for lipiodolization in hepatocellular carcinoma.
Oncology drugs	Oct. 16, 2009	89	Rasuritek 1.5 mg for I.V. Infusion Rasuritek 7.5 mg for I.V. Infusion (Sanofi-Aventis K.K.)	Approval Approval	Rasburicase (genetical recombination)	Drugs with a new active ingredient indicated for the treatment of hyperuricemia in patients receiving cancer chemotherapy.
Oncology drugs	Nov. 6, 2009	90	Fludara Tab. 10 mg (Bayer Yakuhin, Ltd.)	Change	Fludarabine phosphate	A drug with a new additional indication for the treatment of chronic lymphocytic leukemia with anemia or thrombocytopenia.
Oncology drugs	Nov. 6, 2009	91	Fludara for IV Inj. 50 mg (Bayer Yakuhin, Ltd.)	Change	Fludarabine phosphate	A drug with new additional indications and a new dosage for the treatment of recurrent or refractory low-grade B-cell non-Hodgkin's lymphoma and mantle cell lymphoma.
Oncology drugs	Nov. 6, 2009	92	Avastin 100 mg/4 mL Intravenous Infusion Avastin 400 mg/16 mL Intravenous Infusion (Chugai Pharmaceutical Co., Ltd.)	Change Change	Bevacizumab (genetical recombination)	Drugs with a new additional indication and a new dosage for the treatment of unresectable advanced or recurrent non-squamous non-small cell lung cancer. [Priority review]
Oncology drugs	Jan. 20, 2010	93	Temodal Injection 100 mg (Schering-Plough K.K.)	Approval	Temozolomide	A drug with a new route of administration indicated for the treatment of malignant glioma.
Oncology drugs	Jan. 20, 2010	94	Afinitor Tablets 5 mg (Novartis Pharma K.K.)	Approval	Everolimus	A drug with a new additional indication and a new dosage for the treatment of unresectable or metastatic renal cell carcinoma. [Priority review]
Oncology drugs	Feb. 5, 2010	95	Gemzar Injection 200 mg Gemzar Injection 1 g (Eli Lilly Japan K.K.)	Change Change	Gemcitabine hydrochloride	Drugs with a new additional indication and a new dosage for the treatment of inoperable or recurrent breast cancer.

Category	Approval Date		Brand Name (Applicant Company)	Approval/ Partial Change	Active Ingredient(s) (underlined: new active ingredient)	Notes
Biologicals	Oct. 16, 2009	96	Cervarix (GlaxoSmithKline K.K.)	Approval	HPV-16 L1 VLP and HPV-18 L1 VLP	A drug with a new active ingredient indicated for prevention of cervical cancer (squamous-cell carcinoma and adenocarcinoma) and its precursor lesions (cervical intraepithelial neoplasia [CIN] 2 and 3) associated with human papillomavirus (HPV) types 16 and 18 infection. [Priority review]
Biologicals	Oct. 16, 2009	97	Prevenar Suspension Liquid for S.C. Injection (Wyeth K.K.)	Approval	Pneumococcal polysaccharide (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F)-CRM_{197} conjugate	A drug with a new active ingredient indicated for prophylaxis of pneumococcal invasive infections (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F). [Priority review]
Biologicals	Jan. 20, 2010	98	Arepanrix (H1N1) Intramuscular Injection (GlaxoSmithKline K.K.)	Emergency approval	Inactivated split-virus influenza A (A/California/7/2009 [H1N1])	A drug with a new active ingredient indicated for prophylaxis of pandemic (H1N1) influenza. [Emergency approval]
Biologicals	Jan. 20, 2010	99	Cell-culture Derived Influenza A (H1N1) Emulsion HA Vaccine "Novartis" for Intramuscular Injection (Novartis Pharma K.K.)	Emergency approval	Pandemic influenza virus surface antigens of A/California/7/2009 (H1N1) like strain	A drug with a new active ingredient indicated for prophylaxis of pandemic (H1N1) influenza. [Emergency approval]
In vivo Diagnostics	Sep. 18, 2009	100	Indigocarmine Injection 20 mg "Daiichi Sankyo" (Daiichi Sankyo Co., Ltd.)	Change	Indigocarmine	A drug with a new route of administration, a new indication, and a new dosage for sentinel lymph node mapping in breast cancer and malignant melanoma. [Expedited review]
In vivo Diagnostics	Sep. 18, 2009	101	Diagnogreen for Injection 25 mg (Daiichi Sankyo Co., Ltd.)	Change	Indocyanine green	A drug with a new route of administration, a new indication, and a new dosage for sentinel lymph node mapping in breast cancer and malignant melanoma. [Expedited review]
In vivo Diagnostics	Mar. 12, 2010	102	FerriSeltz Powder 20% (Otsuka Pharmaceutical Co., Ltd.)	Change	Ferric ammonium citrate	A drug with a new additional indication and a new dosage for negative contrast of digestive tract in cholangiopancreatography.
Bio-CMC	Jun. 22, 2009	103	Somatropin BS S.C. Injection 5 mg [Sandoz] Somatropin BS S.C. Injection 10 mg [Sandoz] (Sandoz K.K.)	Approval Approval	Somatropin (genetical recombination)	Follow-on biologics indicated for the treatment of growth disturbance due to growth hormone deficiency before epiphyseal closure and growth disturbance associated with Turner syndrome or chronic renal insufficiency before epiphyseal closure.
Radio-pharmaceuticals	Sep. 18, 2009	104	Tin Colloid Tc-99m Kit (Nihon Medi-Physics Co., Ltd.)	Change	Technetium (^{99m}Tc) stannous colloid	A drug with a new route of administration and a new indication for sentinel lymph node mapping in breast cancer and malignant melanoma. [Expedited review]
Radio-pharmaceuticals	Sep. 18, 2009	105	Techne Phytate Kit (Fujifilm RI Pharma Co., Ltd.)	Change	Technetium (^{99m}Tc) phytate	A drug with a new route of administration and a new indication for sentinel lymph node mapping in breast cancer and malignant melanoma. [Expedited review]
Radio-pharmaceuticals	Nov. 6, 2009	106	MyoMIBG-I^{123} Injection (Fujifilm RI Pharma Co., Ltd.)	Change	3-iodobenzylguanidine (^{123}I) injection	A drug with a new additional indication and a new dosage for diagnosis of neuroblastoma in tumor scintigraphy.
Radio-pharmaceuticals	Feb. 5, 2010	107	Cardiolite Injection Daiichi Cardiolite Daiichi (Fujifilm RI Pharma Co., Ltd.)	Change Change	Technetium (^{99m}Tc) hexakis (2-methoxy-isobutyl isonitrile) Tetrakis (2-methoxy-isobutyl isonitrile) copper (I) tetrafluoroborate	Drugs with a new additional indication for diagnostic localization of hyperparathyroidism in parathyroid scintigraphy.

BRIEF REPORTS

What's in a Name? Use of Brand versus Generic Drug Names in United States Outpatient Practice

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BACKGROUND: The use of brand rather than generic names for medications can increase health care costs. However, little is known at a national level about how often physicians refer to drugs using their brand or generic names.

OBJECTIVE: To evaluate how often physicians refer to drugs using brand or generic terminology.

DESIGN AND PARTICIPANTS: We used data from the 2003 National Ambulatory Medical Care Survey (NAMCS), a nationally representative survey of 25,288 community-based outpatient visits in the United States. After each visit, patient medications were recorded on a survey encounter form by the treating physician or transcribed from office notes.

MEASUREMENTS: Our main outcome measure was the frequency with which medications were recorded on the encounter form using their brand or generic names.

RESULTS: For 20 commonly used drugs, the median frequency of brand name use was 98% (interquartile range, 81–100%). Among 12 medications with no generic competition at the time of the survey, the median frequency of brand name use was 100% (range 92–100%). Among 8 medications with generic competition at the time of the survey ("multisource" drugs), the median frequency of brand name use was 79% (range 0–98%; $P<.001$ for difference between drugs with and without generic competition).

CONCLUSIONS: Physicians refer to most medications by their brand names, including drugs with generic formulations. This may lead to higher health care costs by promoting the use of brand-name products when generic alternatives are available.

KEY WORDS: drug labeling; drug industry; prescriptions, drug; drugs, generic; names; prescription fees; ambulatory care.
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INTRODUCTION

Brand name drugs are often dispensed when bioequivalent generic alternatives are available, resulting in an estimated $8.8 billion in excess expenditures per year in the United States.[1] This potentially unnecessary use of brand name drugs may reflect physician and patient beliefs that brand name drugs are superior to their generic counterparts.[2] However, habitual use of brand name terminology may also play an important role in the dispensing of brand-name products, as the name recorded on a prescription can impact whether a drug is dispensed in brand or generic form even when the physician would accept the generic version, and the pharmacy is empowered to provide it.[3,4]

We used data from a large, nationally representative sample of outpatient visits to evaluate how frequently brand and generic name equivalents are used in clinical practice.

METHODS

We used data from the 2003 National Ambulatory Medical Care Survey (NAMCS), a nationally representative survey of 25,288 community-based office visits to 1,342 physicians in the United States.[5] After each sampled visit, forms were completed by the treating physician or by office staff and/or survey field representatives (who abstracted information verbatim from the medical record to the survey form). All medications (up to 8) prescribed or continued at the visit were recorded and subsequently entered into the NAMCS database using separate numeric codes corresponding to the name written on the form and to the drug's nonproprietary name. The route of administration is not specified in NAMCS; therefore, oral, topical, and other forms of the same compound were encoded using a single identifier.

We determined the 20 most frequently mentioned prescription medications in NAMCS, excluding vaccinations, combination products, and medications typically administered in the office setting. To avoid biasing this list toward specialties that prescribed and/or recorded many drugs, in this step we calculated drug frequencies based only on the first medication listed on the study form. Next, for each of the 20 drugs, we assessed the frequency of each name that the physician or assistant had recorded on the form (e.g., for atorvastatin, the frequency of mentions of "atorvastatin" and "Lipitor"). In this step we searched all 8 medication fields.

In all analyses, we adjusted for sampling probability and clustering effects to create nationally representative estimates for each drug present at the clinic visit.[6] Because numerous survey strata contained a single primary sampling unit, we performed our analyses without adjustment for stratification. This preserves the original point estimate while producing slightly wider confidence intervals around that estimate.

Finally, we searched the Food and Drug Administration (FDA) "Electronic Orange Book" (http://www.fda.gov/cder/ob/docs/queryai.htm) and supplemental sources to assess the presence of generic competition for each of the 20 drugs. We considered the date of FDA approval for the first generic formulation (in any dose or route of administration) to be the time at which generic alternatives became available. This research was exempted from review by the institutional review boards of the San Francisco VA Medical Center and the University of California, San Francisco.

RESULTS

At least one medication was recorded in 66% of visits. The majority (89%) of these visits occurred in private solo or group practice settings, with the most common specialties being general or family physicians (25%), primary care internists (16%), pediatricians (10%), and obstetrician–gynecologists (9%). Survey forms were completed by physicians in 16% of visits, by office staff in 34%, by census field representatives in 29%, by multiple personnel in 18%, and by other or unrecorded sources in 3%.

The 20 most commonly recorded medications are listed in Table 1. Overall, the median frequency of brand name use was 98% (interquartile range, 81–100%), and ranged from 0–100% of drug mentions. Among the 12 medications with no generic competition at the time of the survey, the median frequency of brand name use was 100% (range 92–100%). Among the 8 medications with generic competition at the time of the survey, the median frequency of brand name use was 79% (range 0–98%). This difference was statistically significant ($P<.001$).

Because office staff and census field workers completed the majority of forms, we performed additional analyses to evaluate if the proportion of brand versus generic names recorded by physicians differed from the proportion recorded by nonphysicians. For 18 of 20 medications, there were no significant differences between physicians and nonphysicians in the use of brand versus generic names ($P>=.10$ for each). The two exceptions were azithromycin (brand name used by 92% of physicians vs 98% of nonphysicians, $P=.09$) and prednisone (brand name used by 4% of physicians vs 0% of nonphysicians, $P=.002$).

DISCUSSION

In this nationally representative survey, physicians referred to medications by their brand names much more frequently than by their generic names. Brand names were used almost exclusively for drugs without generic competition at the time of the survey. Brand name use was also common for drugs with generic competition, although at lower rates and with greater variability between drugs. While to our knowledge no previous studies have evaluated the use of drug terminology on a national scale, our results are consistent with previous reports which have found that prescriptions are predominantly written using brand names.[3,4]

Table 1. Use of Brand Versus Generic Names for Commonly Prescribed Medications

Generic Name (Brand names*)	Mentions Per 1,000 Visits	Mentions by Brand Name (%)	Status in 2003†	Number of Years of Generic Competition Before 2003
Atorvastatin (Lipitor)	34.3	98%	Brand	–
Azithromycin (Z-pack, Zithromax)	17.0	98%	Brand	–
Rofecoxib (Vioxx)	15.6	100%	Brand	–
Amlodipine (Norvasc)	15.6	99%	Brand	–
Fluticasone (Flonase, Flovent, Cutivate)	14.5	100%	Brand	–
Cetirizine (Zyrtec)	13.8	100%	Brand	–
Celecoxib (Celebrex)	13.5	100%	Brand	–
Sertraline (Zoloft)	12.8	100%	Brand	–
Fexofenadine (Allegra)	12.2	100%	Brand	–
Escitalopram (Lexapro)	9.7	100%	Brand	–
Ciprofloxacin (Cipro, Cipro XR, Ciloxan)	7.7	92%	Brand	–
Clarithromycin (Biaxin, Biaxin XL)	6.9	100%	Brand	–
Metoprolol (Lopressor, Toprol XL)	20.0	78%	Brand + Generic‡	10‡
Amoxicillin (Amoxil, Sumox)	23.7	35%	Generic	>20
Levothyroxine (Unithroid, Levothyroid, Synthroid, Levoxyl, Levothyroid)	23.8	98%	Generic	>20§
Albuterol (Proventil, Ventolin, Volmax)	21.7	13%	Generic	14
Prednisone (Sterapred DS, Deltasone)	14.3	0%	Generic	>20
Triamcinolone (Azmacort, Aristocort Kenalog, Triam, Triamolone 40, Nasacort)	10.9	81%	Generic	>20
Fluoxetine (Prozac, Sarafem)	10.4	80%	Generic	2
Cephalexin (Keflex)	8.6	90%	Generic	16

*Brand names cited by surveyed office practices

†Generic competition available in 2003 versus only brand-name formulations available

‡Metoprolol tartate (Lopressor, a short-acting form) had generic competition before 2003, but metoprolol succinate (Toprol XL, a longer-acting form) remained under exclusivity protection at the time of the study. In comparative analyses, we classified metoprolol as a generically available drug. Alternative classifications produced similar results.

§Although formulations of levothyroxine received FDA approval starting in 2000, in practice many formulations have been on the market for decades.

Physicians may prefer brand names for a variety of reasons. Brand names are often more memorable or evocative than generic names and easier to pronounce (in our sample, brand names had on average 1.5 fewer syllables than their generic counterparts).[7] Many physicians may be familiar only with the brand name of certain drugs or unaware of the correspondence between generic and brand names.[8–10] In addition, in certain cases physicians may believe that generic formulations are not as effective as the brand name product.[11] Although the interchangeability of certain drugs remains a matter of debate,[12] many physicians may not be aware of the strict controls imposed by FDA to prove bioequivalence before a generic formulation can be approved.[13]

The use of brand names has substantial economic consequences.[14,15] Pharmacist substitution of generic equivalents is generally allowed and is encouraged by third party payers, and several programs have been developed to encourage generic substitution.[1,16] However, generic substitution is not mandated in most states, can be overridden by the prescribing physician and does not universally occur even when allowed by the physician.[3,4] Overall, 39% of drugs available as generics were filled with the brand formulation in a recent national study.[1] As brand name drugs usually retain a substantial price premium even after generic equivalents are introduced,[17] persistent use of brand name products has resulted in billions of dollars of excess spending.[1]

The use of brand names also has consequences for communication between physicians. Confusion over drug terminology can result in adverse drug events. For example, a patient may inadvertently be given a second formulation of a drug because the prescribing physician failed to recognize that the patient was already taking the medication under a different name.[18,19] In addition, use of brand names in communication between physicians can undermine efforts to minimize commercial influence on medical practice.

The use of brand names may reflect habitual use of a lexicon learned in training or shortly after introduction of new drugs.[11] Therefore, efforts to increase the use of nonproprietary names should focus on these periods of early exposure. Medical students and residents should be educated about these issues, and physician supervisors should be encouraged to promote use of generic terminology in their day-to-day interactions with trainees. Standards in continuing medical education programs could also be strengthened: while the Accreditation Council for Continuing Medical Education (ACCME) encourages the use of generic names in educational presentations, parts of their guideline place greater emphasis on balancing the use of brand names across different companies than on minimizing the use of proprietary terminology.[20] Electronic prescribing systems could also be engineered to convert brand to generic names. One place to start would be the official Medicare Prescription Drug Plan Finder website (http://plancompare.medicare.gov/drugselect.asp), which recognizes only brand names for drugs that are currently under patent and exclusivity protection.

Our study has several limitations. First, data were collected from research forms. We cannot determine whether physicians used the same terminology in their daily speech or when writing prescriptions. Similarly, we do not know to what extent use of brand name terminology reflected preference for specific brand formulations (e.g., for a specific brand of levothyroxine). Second, the majority of data forms were completed by office staff and survey field personnel. However, subsidiary analyses showed a similar distribution of brand and generic name use whether a physician or nonphysician completed the form. Third, our method for determining when generic competition first became available does not fully capture the complex approval histories for different formulations of the same drug. Finally, our list of drugs was dominated by agents that had no generic competition, limiting our ability to delineate terminology patterns among drugs with generic competition.

Physicians' preference for brand names may result in higher health care costs and use of branded products where bioequivalent alternatives are available. The use of nonproprietary terminology in medicine should be encouraged to save costs, limit commercial influence, and reduce the potential for prescribing errors.

Disclaimer: *The views expressed in this manuscript are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs.*

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Author's Contributions: *Study concept and design (MAS), acquisition of subjects and data (MAS), analysis and interpretation of data (all authors), preparation of the manuscript (MAS), and critical review of the manuscript (all authors). Dr. Steinman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.*

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ASPE ISSUE BRIEF
OFFICE OF THE ASSISTANT SECRETARY FOR PLANNING AND EVALUATION
OFFICE OF SCIENCE AND DATA POLICY - U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Expanding the Use of Generic Drugs

December 1, 2010

Introduction

Dramatic growth in the use of generic drugs has generated substantial savings for American consumers. To examine how the Department of Health and Human Services (HHS) can encourage the use of generic drugs, Secretary Sebelius asked the Assistant Secretary for Planning and Evaluation (ASPE) to examine barriers to, and opportunities for, expanding the use of generic drugs. In this Issue Brief we summarize the findings of ASPE's review of the existing literature on this topic. We begin by briefly reviewing trends in generic drug use, the legislative origin of generic drugs in the United States, and the pathways by which generic drugs can reduce healthcare costs. Next, we examine the literature on generic drug pricing and the associated healthcare savings. We group information on barriers to generic drug use in three broad areas: state laws on generic substitution; factors related to availability of generics; and consumer and prescriber perceptions and behavior. Overall, we found that current levels of generic drug use are fairly high. There is potential for increased savings from generic drug use both through increased availability of generic drugs and through increased substitution, particularly therapeutic substitution as discussed below.

Trends in Prescription Drug Spending and Generic Drug Use

The rate of generic prescribing for all prescriptions reached almost 75 percent in 2009, up from 57 percent in 2004. Generic drugs cost much less than their branded counterpart, so the high rate of generic prescribing resulted in billions of dollars of savings for the U.S. health care system. In 2010 to 2014, a number of blockbusters are projected to go off patent representing more than $209 billion in annual drug sales. This trend is projected to result in a decrease in branded sales of $113 billion[1]. Maintaining or improving the generic prescribing rate is an important tool in efforts to control health care costs.

Legislative Origin of Generic Drugs

Innovative branded drugs seeking Food and Drug Administration (FDA) approval are required to submit to FDA a new drug application that includes clinical trial data that establishes the safety and efficacy of the new drug. Manufacturers of innovative branded drugs expend considerable time and resources in research and development and the approval of new drugs. Some estimates indicate that bringing a new drug to market costs more than a billion dollars and takes 10-15 years[2]. Generic drugs are therapeutically equivalent to a branded drug. Generic drugs are required to have the same active ingredient and the same strength, dosage form, and route of administration as the brand name (or reference) product. Most generic drugs do not need to contain the same inactive ingredients as the brand product. In addition, a generic drug must be bioequivalent to the

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[1] Paul, SM, Mytelka, DS, Dunwiddie, CT, Persinger, CC, Munos, BH, Lindborg, SR, and Schacht, AL. How to improve R&D productivity: the pharmaceutical industry's grand challenge. *Nature Reviews Drug Discovery*. 2010;9:203-224.

[2] DiMasi. JA and Grabowski. HG. The cost of biopharmaceutical R&D: is biotech different? *Managerial and Decision Economics*. 2007:28:469-479.

brand drug, that is there must be no significant difference between the generic and brand product in the rate or the extent to which the active ingredient is delivered to the patient. There can be some variability between brand name and generic drugs, but FDA puts limits on how much variability is acceptable. Drugs approved by FDA as therapeutically equivalent can be substituted with the expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product.

The Drug Price Competition and Patent Term Restoration Act of 1984 (frequently referred to as the Hatch-Waxman Act) amended the Federal Food, Drug, and Cosmetic Act to create an abbreviated pathway for approval of new drugs that are therapeutically equivalent to a branded drug. In addition to the patents that protect new inventions, Hatch-Waxman granted periods of exclusivity to manufacturers that had new drugs approved by FDA. If the branded drug is still in the period of exclusivity or protected under patent, generic versions of the branded drug can not be brought to market. The generic manufacturer files an abbreviated new drug application (ANDA) with the FDA. Once the drug is approved by the FDA and the branded drug is no longer protected by patent or exclusivity, the generic can be brought to market. Because they can reverse-engineer an innovator drug, and need not repeat safety and effectiveness studies, generic manufacturers can bypass the time and costs to develop a new drug and bring a drug to market with a much smaller investment. The Hatch-Waxman Act also offered incentives for generic manufacturers to challenge the patents of innovator drugs by offering a 180-day period of exclusivity for the first generic applicant to challenge the validity of a patent. The Act also allows exemptions from patent infringement for pre-application activities by generic drug sponsors.

Most experts agree that the Hatch-Waxman Act greatly increased the availability of generic drugs in the U.S. market. Prior to the Act, 35 percent of top selling innovator drugs no longer under patent had generic equivalents. By the late 1990s, almost all had generic equivalents[3].

Pathways through which Generic Drugs Reduce Health Care Costs

Generic drugs can reduce healthcare costs through multiple pathways. These include generic substitution of drugs, substitution of drugs in the same therapeutic class, and reduction in the average branded prices paid by consumers due to generic substitution. The largest cost savings come from generic substitution of drugs by substituting the less expensive generic drug for the therapeutically equivalent branded drug. FDA publishes a list of drug products that are therapeutically equivalent in its publication *Approved Drug Products with Therapeutic Equivalence Evaluations*; however, generic substitution is not regulated by FDA. It can be done by the prescriber or the pharmacist, according to state laws and regulations. Because the generic drug is therapeutically equivalent to the branded drug, this substitution is straightforward. Generic substitution rates, the rate at which generic drugs are dispensed in the U.S., are almost 90 percent when there is a

[3] CBO. How Increased Generic Competition has Affected Drug Prices and Returns in the Pharmaceutical Industry. July 1998. Accessed at http://www.cbo.gov/ftpdocs/6xx/doc655/pharm.pdf on 9/30/3010.

generic equivalent available[4]. However, restrictions on the ability of pharmacists to carry out generic substitution vary by state.

Additional savings can result from therapeutic substitution. Therapeutic substitution is switching to a generic from a branded drug in the same therapeutic class. For example, a prescriber may switch a patient from the branded lipid-lowering statin, Lipitor (which as yet has no generic equivalent) to simvastatin, the generic equivalent of the branded lipid-lowering statin, Zocor. This substitution has to be done by the prescriber; a pharmacist can not substitute between drugs that are not therapeutically equivalent. Formularies[5], prior approval[6], prescriber incentives[7], and "step therapy"[8] create incentives for prescribers to substitute less expensive generics for branded drugs with the same indication. FDA does not regulate therapeutic substitution. Historically, there has been little evidence of significant savings from this type of substitution, but there is recent evidence that it is becoming a more important source of savings. For example, after introduction of generic simvastatin (therapeutically equivalent to Zocor), a study of Medicaid drug expenditures found that prescriptions of Lipitor declined from 43 percent of total statin use before the introduction of generic simvastatin to 31 percent a year after the introduction of generic simvastatin[9].

Another possible pathway for savings is a reduction in average branded prices paid by consumers resulting from generic substitution. A study by Rizzo and Zeckhauser found that a higher share of generic prescriptions result in lower average brand drug prices. The theory is that consumers are more likely to substitute generics for higher cost branded drugs and conversely less likely to substitute generics for lower cost branded drugs. This selective substitution would then effectively lower the average cost of branded drugs by leading brand name manufacturers to choose lower initial prices. This study found that a 10 percent increase in the generic substitution rate is associated with a 15.6 percent decline in the average price paid for branded drugs[10].

Generic Drug Pricing

Generic drug manufacturers face much lower costs to enter the market than manufacturers of branded drugs. While estimates of the cost to bring a new branded drug to market are in excess of a billion dollars, the research and development costs for a new

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[4] Shepard, Al. Generic Medicines: Essential contributors to the long-term health of society. IMS Health. 2010. Accessed at http://www.imshealth.com/imshealth/Global/Content/Document/Market_Measurement_TL/Generic_Medicines_GA.pdf.

[5] Formularies are a list of drugs that a payer will pay for.

[6] Requires the prescriber to obtain approval from the payer before prescribing certain drugs.

[7] Providing incentives, usually monetary, based on physicians prescribing behavior.

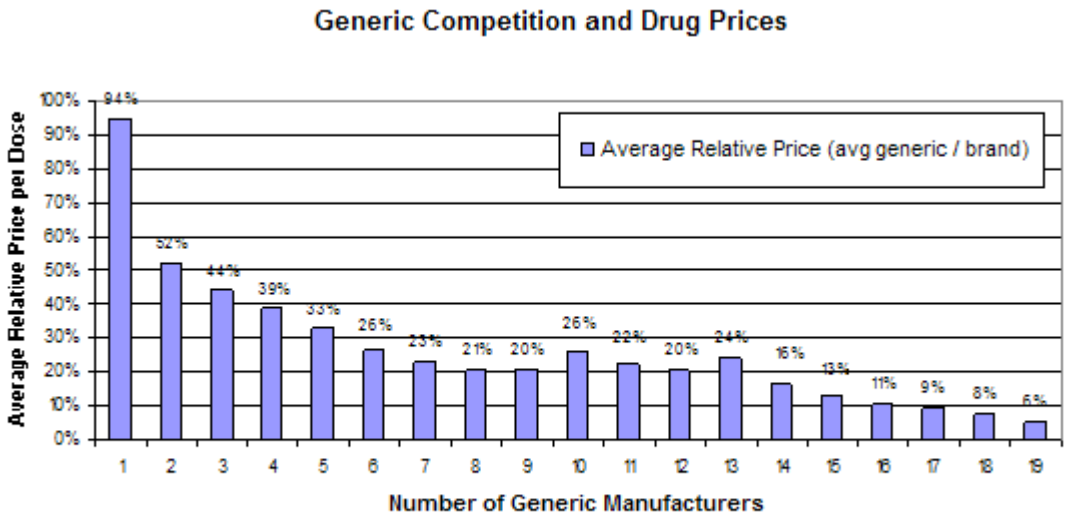
[8] Step therapy is when a less expensive drug is prescribed first and the patient is moved up to more expensive drugs if necessary.

[9] Shrank, WH, Choudhry, NK, Agnew-Blais, J, Federman, AD, Libermand, JN, Liu, J, Kesselheim, AS, Brookhart, MA, and Fischer, MA. State generic substitution laws can lower drug outlays under Medicaid. *Health Affairs*. 2010; 29(7): 1383-1390.

[10] Rizzo and Zeckhauser. Generic script share and the price of brand-name drugs: the role of consumer choice. *Int J Health Care Finance Econ*. (2009) 9:391-316.

generic drug are only 1 to 2 million dollars[11]. The relatively low costs to entry for generic drugs lead to increased competition, which drive prices for generic drugs down dramatically. Data from the National Association of Chain Drug Stores showed that the average retail prescription price for a generic drug in 2009 was $39.73, 76 percent less than $155.45, the average cost for a branded drug[12]. The number of generic entrants appears to affect the price difference between branded and generic drugs. FDA analyzed the effect of generic drug entry on average prices for generics as a percentage of the price of the branded drug. They found that the first entrant has a relatively small effect on price, but subsequent entrants dramatically reduce the average relative price. Figure 1 below shows the average relative price for generics relative to branded drugs by number of generic entrants in the market[13]. This analysis measures price as the price paid by the pharmacy, not the consumer. Pharmacies typically have higher markups for new generic drugs than branded drugs and older generic drugs[14]. Also, the FDA analysis does not account for the fact that the most profitable markets attract the most generic competitors. As a result, the FDA analysis may overestimate the size of the price decrease for early generic entrants.

Figure 1: Average relative price of generic to brand by number of generic competitors



Source: FDA analysis of retail sales data from IMS Health, IMS National Sales Perspective (TM), 1999-2004, extracted February 2005

Estimates of Savings from Generic Drugs

[11] H. Grabowski, "Patents and New Product Development in the Pharmaceutical and Biotechnology Industries," *Georgetown Public Policy Review* 8, no. 2 (2003): 7–24.
[12] From National Association of Chain Drug Stores. Facts at a Glance. Accessed at http://www.nacds.org/wmspage.cfm?parm1=6536 on September 30, 2010.
[13] FDA. Generic Drug Prices. http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm129385.htm
[14] Kina and Wosinka. Pharmaceutical Pricing in Handbook of Pricing Research in Marketing. *Edward Alger Pub* May 2009.

In 2008, expenditures on prescription drugs reached $234 billion and were expected to grow 5.2 percent to $246.3 billion in 2009[15]. The Congressional Budget Office (CBO) estimated savings from generic drugs for Medicare Part D in 2007. Total spending by the Part D program and its enrollees was $60 billion for one billion prescriptions in that year. Although 65 percent of prescriptions were filled by generic drugs, those prescriptions accounted for only 25 percent of total drug costs. CBO estimated that the availability of generics resulted in $33 billion in savings in 2007[16]. A study by IMS Health, commissioned by the Generic Pharmaceutical Association, showed that savings from the use of generic drugs for the total healthcare system were estimated to be $139.6 billion in 2009[17].

A number of studies have estimated the potential savings from increasing the rate at which generics are dispensed. The CBO study found that increasing the generic substitution rate to 100 percent would result in an additional $900 million in savings[18] for the Part D program and enrollees. Haas et al analyzed data from the Medical Expenditure Panel Survey (MEPS) and estimated that if a generic had been substituted for the therapeutically equivalent branded drugs (increasing the generic substitution rate from 61 to 100 percent) that the total savings would have been $8.8 billion for the health care system in 2000. This estimate was likely an underestimate for 2000, as it did not include prescriptions for children and did not account for missing data in MEPS[19]. Another study from Fisher and Avorn estimated spending by Medicaid for drugs for 48 states and the District of Columbia. In 2000, the total amount reimbursed by Medicaid in the studied states was $20.9 billion for drugs, of which $4.3 billion were for drugs that were available in generic forms. Fisher and Avorn found that an additional $229 million could have been saved if the generic substitution rate had been 100 percent. They found considerable state-level variation in potential savings ranging from 3.3 to 10.3 percent of total spending on drugs with generics available. However, the authors did not explore reasons for the variability between states. Another study of Medicaid spending by Alex Brill found that Medicaid could have saved $271 million of the total Medicaid spending of $21.8 billion by achieving a 100 percent generic substitution rate for 20 studied drugs. Across the 20 reference drugs the substitution rate ranged from 44 percent to 99 percent with an average generic substitution rate of 87 percent. This study found that most of the potential savings were concentrated in newly available generic substitutes due to a time lag in prescriber and pharmacist adoption of substitution with the newly available generic[20].

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[15] Andrea M. Sisko, Christopher J. Truffer, Sean P. Keehan, John A. Poisal, M. Kent Clemens, and Andrew J. Madison. National health spending projections: the estimated impact of reform through 2019. *Health Affairs* Web First, September 9, 2010.
[16] CBO. Effects of using generic drugs on Medicare's prescription drug spending. September, 2010.
[17] GPhA. Savings achieved through the use of generic pharmaceuticals: 2000-2009.July, 2010.
[18] Ibid.
[19] Haas, JS, Phillips, K, Gerstenberger, SP, Seger, AC. Potential savings from substituting generic drugs for brand-name drugs: Medical Expenditure Panel Survey 1997-2000. *Annals of Internal Medicine*. 2005;142(11):891-897.
[20] Brill, A. Overspending on multi-source drugs in Medicaid. AEI Health Policy Working Paper _2010-01.

These studies consider the cost savings from achieving a 100 percent generic substitution rate. This is probably not a realistic or desirable goal. Generic drugs and their branded counterparts may differ in inactive ingredients, such as flavors, colors or binders and for some patients these differences can be important. For example, a patient with an allergy to a certain dye may be limited to using the branded drug or another generic that does not use that dye.

Studies of savings from Medicaid are uncertain due to rebates Medicaid receives from manufacturers. By law, Medicaid receives a larger rebate for branded than for generic drugs. These rebates are based on the average manufacturer price, which is proprietary, so researchers can not calculate the actual rebate. The difference in generic and branded drug price may be small in the first six months after introduction of the generic, when the first generic has exclusivity from other generic manufacturers. Therefore, in some cases generic drugs can be more expensive for Medicaid than branded drugs due to the larger rebate for branded drugs.

Further increases in savings are achievable from increasing therapeutic substitution. CBO examined seven therapeutic classes identified as having potential for therapeutic substitution and estimated that if all of the brand name drugs in those classes had been switched to a generic drug, prescription drug costs would have been reduced by $4 billion for the Part D program and its enrollees.

Barriers to Greater Savings from Generic Drug Use

Barriers to the use of generic drugs can occur at a number of points, including state laws on generic substitution; factors related to availability of generics; and consumer and prescriber perceptions and behavior.

State Generic Substitution Laws

State laws regulate the practice of pharmacy. As a result, there is variation in requirements for when pharmacists can or must dispense generics among states. Some states require a pharmacist to substitute a therapeutically equivalent generic for a brand name drug, unless the physician specifies that a generic must not be substituted. Other states take a more permissive approach and allow, but do not require, pharmacists to substitute a generic drug, as long as the prescriber does not specify brand only. Some states impose an additional limitation that the pharmacist must get consent from the patient before substituting a generic. All states also allow the physician to specify that the brand name must be prescribed, although with different levels of effort from the physician. Appendix A provides state laws governing generic substitution by pharmacies.

A recent study of the effect of state generic substitution laws on drug spending under Medicaid found that state generic substitution laws can have a significant impact on drug spending. The study looked at spending by state on Zocor, generic simvastatin, and Lipitor in the first six quarters after the introduction of generic simvastatin. The study found a significant impact of patient consent laws on generic substitution. States that

require patient consent had higher average prescription costs for Zocor and generic simvastatin combined than states that did not require patient consent. This difference was highest in the first quarter after patent expiration, $15.35, and declined to $2.68 by the fifth quarter after patent expiration. Similarly, six months after patent expiration, 98 percent of simvastatin prescriptions were written for generic simvastatin in states that did not require patient consent, while less than one third of prescriptions were filled by generic simvastatin in states that did require patient consent. The study did not find consistent differences in generic prescription rates between states that permitted pharmacists to prescribe generic alternative versus states that required pharmacists to prescribe a generic alternative[21]. Pharmacists have a financial incentive to prescribe generics, as the mark up received by pharmacies is largest for new generics.

The study also looked at the impact of state laws and Medicaid policies, like prior authorization, on prescriptions for Lipitor, another statin in the same therapeutic class, but not therapeutically equivalent to simvastatin. Lipitor use declined from 43 percent of statin use before the introduction of generic simvastatin to 36 percent six quarters after the introduction of generic simvastatin. In states that required prior authorization for the prescription of Lipitor, Lipitor use was 31 percent lower than in states that did not. Other state generic substitution laws did not affect the levels of Lipitor use.

These findings for statin use in Medicaid may not be generalizable. The analysis of state laws for the introduction of a single generic drug, simvastatin, may differ from results for other drugs. Evidence from other studies suggests that savings vary by drug[22]. More generics are likely to enter when the market for the branded drug is larger and more profitable. Also, drugs used by patients that are more responsive to price changes are also more likely to have generic competitors, such as drugs that are delivered in an inpatient setting or for chronic conditions[23].

There are also significant differences in the Medicaid and non-Medicaid populations. A survey on patients' perceptions of generic medications found that patients that are older, patients that are poorer and patients with self-reported poor health were more likely to believe that brand name drugs are safer than generic drugs[24]. Additionally, differences in co-pays between branded and generic drugs are much smaller in Medicaid than for most private insurance plans. Medicaid co-payments for retail drugs vary by state, but typically range from fifty cents to three dollars with lower amounts for generic and higher amounts for branded drugs[25]. In the private insurance market, the average co-pay for a

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[21] Shrank, WH, Choudhry NK, Agnew-Blais J, Federman AD, Libermand JN, Liu J, Kesselheim AS, Brookhart MA, and Fischer MA. State generic substitution laws can lower drug outlays under Medicaid. *Health Affairs*. 2010;29(7):1383-1390.

[22] Brill, A. Overspending on multi-source drugs in Medicaid. AEI Health Policy Working Paper _2010-01.

[23] Scott Morton, F. (1997), 'The strategic response by pharmaceutical firms to the Medicaid most-favored customer rules', *RAND Journal of Economics*, 1997: 28(2):269–90.

[24] Shrank, W, Cox, E, Fischer, MA, Mehta, J, Choudry, NK. Patients perceptions of generic medicines. *Health Affairs*, 2009;28(2):546-556.

[25] Kaiser Family Foundation. Medicaid Benefits: Online Database, 2008. http://medicaidbenefits.kff.org/service.jsp?yr=4&so=0&cat=5&sv=32&gr=off&x=87&y=18

generic drug is $10, while the average co-pay for a preferred branded drug is $25 and for a nonpreferred branded drug the average co-pay is $43[26].

A few states also limit generic substitution by the pharmacist for drugs with a Narrow Therapeutic Index (NTI). Drugs with a narrow therapeutic index require careful titration and patient monitoring because there are relatively small differences between the effective dose and a toxic dose. NTI drugs include some anti-epileptic drugs, warfarin, and digoxin. FDA's policy regarding NTI drugs is that the generics are therapeutically equivalent to the branded drugs. However, some states require that generic versions can not be substituted for NTI drugs without the prescriber's consent. No studies were identified that specifically address the impact of the state-level limitations on NTI drugs. Relatively few states impose this restriction and the impact of the state law would be difficult to disentangle from prescriber concerns about NTI substitution.

Availability of Generics

The most important factor for whether consumers purchase generic drugs is the availability of a generic. Innovator drugs are protected from generic rivals by patents and by exclusivity.

Patents are issued by the U.S. Patent Office and offer 20 years of protection from competition. However, sponsors typically apply for a patent early in the drug development process and so many of the years of patent protection will be expended before the drug reaches the market. The Hatch-Waxman Act offers restoration of some of the years of patent protection expended during clinical testing and FDA review. Up to five years of patent term may be restored, with the total patent time after FDA approval limited to 14 years. The patent owner has to apply to the U.S. Patent Office for the restoration of patent life.

The Hatch-Waxman Act also provides innovator manufacturers with different periods of marketing exclusivity, depending upon the novelty of the drug. Marketing exclusivity is independent of patent protection. Some of the exclusivity periods delay the submission of an ANDA to the FDA for review, while others delay approval of an ANDA.

Legal Settlement "Pay-for-Delay"

In some instances, a brand-name drug company may settle a patent challenge from a generic competitor by paying the generic company to delay entering the generic into the market. These settlements, called pay-for-delay or reverse payments, delay generic competition and the availability of generics. The FTC reports that there were 19 such agreements in fiscal year 2009, with each agreement on average delaying the availability of cost-saving generics by 17 months. The FTC also reported that, in January, 2010, such agreements were protecting at least $20 billion in sales of branded drugs from generic

[26] Pharmacy Benefit Management Institute. Prescription Drug Benefit Cost and Plan Design, Online Report, 2010-11, 2010. http://www.benefitdesignreport.com/CostSharingHighlights/RetailCopayments/tabid/84/Default.aspx.

competition. The FTC estimated that pay-for-delay agreements cost American consumers $3.5 billion per year – $35 billion over the next 10 years[27]. The FTC has attempted to prosecute pay-to-delay agreements; however, these efforts have not been uniformly upheld in federal courts[28]. The FTC has continued to litigate pay-for-delay cases in the courts and has recommended Congress pass legislation to prevent pay-for-delay agreements.

Speed of Generic Drug Application Approvals

As of June, 2010, FDA has 2,136 ANDAs pending, of these 850 are for generics not blocked by patents[29]. This has resulted in a median approval time of 27 months for new generic drugs which includes time awaiting responses to information requests to sponsors. Because the average ratio of generic to branded drug price continues to decrease as additional generic drugs enter the market, delays for additional market entrants even beyond the first generic equivalent may reduce cost savings. However, delays in generic drug approval may not necessarily result in lost cost savings. First generics are rarely delayed by FDA review; most first generics are available when the patent expires. Often generic drug manufacturers submit applications to the FDA in advance of patent expiration or in anticipation of resolution of a patent dispute. These generic drugs, even if approved, will not be able to enter the market until the patent expires or is found invalid. ANDAs in the FDA "backlog" may also not be delayed by FDA review, as ANDAs pending at FDA could include ANDAs that have been returned to the sponsor with an information request. It is difficult to assess the economic significance of the pending applications not blocked by patents without analysis of the markets for the drugs that have pending applications. To speed generic approvals, FDA has requested authority to collect user fees for the review of generic drugs in the FY2011 President's Budget.

Availability of Biosimilar Biologic Drugs

Another area of potential cost savings is the abbreviated pathway for approval of biosimilar biologic drugs under the Biologics Price Competition and Innovation Act of 2009 (BPCIA), within the Patient Protection and Affordable Care Act (PL 111-148). These biological drugs, regulated under the Public Health Service Act, are not eligible for the abbreviated approval pathway for generic drugs under the Hatch Waxman Act. The U.S. had $59 billion in sales in biologics in 2008[30] . A recent estimate in December 2008 by the CBO suggests that the federal government, primarily Medicare, will save between $9 billion and $12 billion over 10 years by creating an abbreviated approval pathway for

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[27] Jon Leibowitz, Chairman, Fed. Trade Commission, *"Pay-for-Delay" Settlements in the Pharmaceutical Industry: How Congress Can Stop Anticompetitive Conduct, Protect Consumers' Wallets, and Help Pay for Health Care Reform (The $35 Billion Solution)* at 8 (June 23, 2009), available at: http://www.ftc.gov/speeches/leibowitz/090623payfordelayspeech.pdf.

[28] "Pay-for-Delay: How Drug Company Pay-Offs Cost Consumers Billions," FTC Staff Study (Jan. 2010), http://www.ftc.gov/os/2010/01/100112payfordelayrpt.pdf.

[29] FDA. FDA-TRACK CDER Office of Generic Drugs Dashboard. Accessed at: http://www.fda.gov/AboutFDA/Transparency/track/ucm206235.htm

[30] IMS Biologics Webinar. 2009.

biosimilar biologic drugs[31]. The FDA is currently working to implement the provisions of the BPCIA.

Consumer Perceptions of Generics

Although physicians and pharmacists act as patients' agents in selecting appropriate drugs, patients have discretion in choosing whether to use generic drugs. Patients can communicate to their physicians or pharmacists their preference for branded drugs. Whether patients communicate a preference for branded drugs may depend on a number of factors, including drugs the patient is now using or has used in the past, knowledge about the specific generic or branded drugs, general knowledge about generics and branded drugs, and financial incentives to use generic drugs.

A recent survey of 2,500 commercially insured beneficiaries of a large, national pharmacy benefits manager found that although most consumers believe that generic drugs are a better value than branded drugs and are equally safe, this did not necessarily transfer into a preference for purchasing generic drugs. Fifty-six percent reported that Americans should use more generics, but only 36 percent of those surveyed preferred to take generics[32].

A study of the impact of alternative interventions on generic drug use examined claims level data from Blue Cross Blue Shield of Michigan[33]. The authors examined a number of interventions: communication to plan members about generic drugs, statewide advertising, physician incentives, generic sampling, and doubling the co-pay for branded drugs. The study found that only the change in co-pay had an effect on the generic dispensing rate. However, the lack of impact of the physician incentives may be due to the sample of physician groups chosen for the study. The program targeted physicians in well-managed practices, which may have had little room to improve in the generic dispensing rates.

Prescriber Behavior

Physician prescribing behavior is important to high generic prescription rates. Physicians may not prescribe generics due to habit or out of concerns about safety and efficacy of generic drugs. A study analyzing data from the National Ambulatory Medical Care Survey found that the majority of physicians referred to drugs by their brand name rather than generic name[34]. This means physicians when prescribing may prescribe the branded drug out of habit rather than intention. In these cases, permitting pharmacists to substitute generic drugs can be an important factor in maintaining high generic substitution rates.

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[31] CBO. Budget Options Volume 1: Health Care. 2008

[32] Shrank, W, Cox, E, Fischer, MA, Mehta, J, Choudry, NK. Patients perceptions of generic medicines. *Health Affairs*, March/April 2009;28(2):546-556.

[33] O'Malley, A, Frank, RG, Kaddis, A, Rothenberg, BM, and McNeil, BJ. Impact of Alternative Interventions on Changes in Generic Dispensing Rates. *Health Services Research*, 2006;41(5):1876-1894.

[34] Steinman, MA, Chren, MM, Lendefeld, CS. What's in a name? Use of brand-name versus generic drug names in United States outpatient practice. *J Gen Intern Med*. 2007;22(5):645-648.

Differences between branded and generics exist that may compel the physician to prescribe the branded drug. The generic drug can differ from the branded in inactive ingredients, as long as this does not interfere with therapeutic equivalence. Patient sensitivities or allergies to inactive ingredients may necessitate using the branded version. Physicians may also believe that there are safety or efficacy differences between the branded and the generic. For example, some health care providers are unwilling to substitute NTI drugs. The American Academy of Neurology's official position is that "The AAN opposes generic substitution of anticonvulsant drugs for the treatment of epilepsy without the attending physician's approval[35]. In these cases the physician chooses deliberately to prescribe the branded drug. Physician education may have some influence on physician behavior, but this is likely to be difficult to change.

Unlike substitution of therapeutically equivalent generics for branded drugs, substitution of a generic drug for a branded drug that is not therapeutically equivalent, but has the same indication for a branded drug, requires that the physician make a decision to prescribe a generic. Physician education, incentives, and use of e-prescribing may influence physicians to change their behavior. E-prescribing is theorized to increase generic drug use by making information about available generics, formularies and cost information available to physicians at the time of prescribing. One study found that in the Blue Shield of California system that e-prescribing increased generic drug use by 5.9 percent[36].

Conclusions

The rapid increase in generic prescribing makes estimates of savings and potential increases in savings from generic drug use a fast moving target. There is a clear consensus that generic savings are now a large and important source of health care savings. Increases in cost savings from greater substitution of generics for therapeutically equivalent drugs appear possible, though these increases are likely to be small relative to total spending on drugs. Limited evidence indicates that state prescribing laws that allow consumers more choice in whether to use generics reduce generic drug use.

Setting mechanisms to increase substitution of generic drugs for branded drugs that are not therapeutically equivalent, but have the same indication, has more potential for increasing cost savings. Increasing cost savings in this area relies most on educating physicians and setting mechanisms in place to encourage substitution. However, because in these cases the generics are not therapeutically equivalent, substitution must be done appropriately to ensure efficacy and patient safety.

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[35] Liow, K, Barkley, GL, Pollard, JR, Harden, CL, Bazil, CW. Position Statement on the coverage of anticonvulsant drugs for the treatment of epilepsy. *Neurology*. 2007;68:1249-1250.

[36] Chang, C, Nguyen, N, Smith, A, and Huynh, D. Impact of electronic prescribing on outpatient prescription drug use and adherence in a network-model health plan. Presented at: Academy of Managed Care Pharmacy 22nd Annual Meeting and Showcase: April 9-10; San Diego.

Increased availability of generic drugs by eliminating pay-for-delay agreements and speeding ANDA reviews by FDA also shows promise for increasing savings. The FTC estimates that American consumers could save $35 billion over the next ten years due to earlier access to generic drugs if pay-for-delay agreements were eliminated. Although FDA ensures that reviews of ANDAs for first generics are not delayed, speeding reviews of subsequent generic competitors may further decrease generic prices, as research shows that more generic competitors lead to lower prices. However, without analysis of the pending ANDAs, the economic significance of the review delays can not be assessed.

The greatest and most certain potential for increased savings in the near future lies in increased availability of generic drugs through patent expiration for current blockbuster drugs. The high level of acceptance of generic drugs and mechanisms set in place to encourage generic substitution should result in continuing increases in savings from this avenue.

Appendix A: List of state laws governing generic substitution by pharmacists.

State	**Allows for** Generic Substitution by Pharmacists if "Brand Only" Not Indicated by Physician	**Mandates** Generic Substitution by Pharmacists if "Brand Only" Not Indicated by Physician	**Allows for** Brand if Requested by Patient	**Mandates** Brand Only if Indicated by Physician	To Ensure Brand Name Only, Physician **Must Indicate** the Following on the Written Prescription **OR Communicate Orally**
Alabama	√		√	√	Sign the prescription signature line labeled "May not Substitute" or "Dispense as Written".
Alaska	√		√	√	In the physician's handwriting, the words "Brand Medically Necessary" must appear on the prescription.
Arizona	√		√	√	Clearly display on the prescription "DAW" or other wording indicative of Substitution not Permitted.
Arkansas	√		√	√	In the physician's handwriting, indicate that the product ordered should not be substituted.
California	√		√	√	In the physician's handwriting, the words "Do not substitute" must appear on the prescription.
Colorado	√		√	√	In the physician's handwriting, the words "Dispense as Written" must appear on the prescription.
Connecticut	√		√	√	In the physician's handwriting, indicate that the product ordered should not be substituted.
Delaware	√		√	√	Sign the prescription signature line labeled "May not Substitute" or "Dispense as Written".

Florida		√	√	√	In the physician's handwriting, the words "Medically Necessary" must appear on the prescription.
Georgia	√		√	√	In the physician's handwriting, the words "Brand Necessary" must appear on the prescription.
Hawaii		√	√	√	In the physician's handwriting, the words "Brand Medically Necessary" must appear on the prescription. **Mandates Brand Only for Anticonvulsant Medications.**
Idaho	√		√	√	Physician must indicate "Brand Only" by checking the "Brand Only" box on the prescription.
Illinois	√		√	√	Sign the prescription signature line labeled "May not Substitute" or "Dispense as Written".
Indiana	√		√	√	Sign the prescription signature line labeled "May not Substitute" or "Dispense as Written".
Iowa	√		√	√	Physician shall communicate to Pharmacist that product should not be substituted.
Kansas	√		√	√	In the physician's handwriting, the words "Dispense as Written" must appear on the prescription.
Kentucky		√	√	√	In the physician's handwriting, the words "Do not substitute" must appear on the prescription.
Louisiana	√		√	√	Physician must indicate "Brand Only" by checking the "Dispense as Written or DAW" box on the prescription.

Maine		√		√	In the physician's handwriting, the words "Dispense as Written", "DAW", "Brand", or "Brand Neccessary" must appear on the prescription.
Maryland	√		√	√	Physician shall communicate to Pharmacist that product should not be substituted.
Massachusetts		√		√	In the physician's handwriting, the words "No substitution" must appear on the prescription.
Michigan	√		√	√	In the physician's handwriting, the words "Dispense as Written" or "DAW" must appear on the prescription.
Minnesota		√	√	√	In the physician's handwriting, the words "Dispense as Written" or "DAW" must appear on the prescription.
Mississippi	√		√	√	Physician shall communicate to Pharmacist that product should not be substituted.
Missouri	√		√	√	Sign the prescription signature line labeled "May not Substitute" or "Dispense as Written".
Montana	√		√	√	In the physician's handwriting, the words "Brand Medically Necessary" must appear on the prescription.
Nebraska	√		√	√	In the physician's handwriting, the words "Dispense as Written", "DAW" or similar statements must appear on the prescription.
Nevada		√	√	√	In the physician's handwriting, the words "Dispense as Written" must appear on the prescription.

New Hampshire	√		√	√	Physician must specify that the Brand is Medically Necessary.
New Jersey		√	√	√	Physician must initial next to the option "Do not Substitute" on the prescription.
New Mexico	√		√	√	In the physician's handwriting, the words "No substitution" or "No sub" must appear on the prescription.
New York		√		√	In the physician's handwriting, "DAW" must appear on the prescription.
North Carolina	√		√	√	Sign the prescription signature line labeled "May not Substitute" or "Dispense as Written". **Narrow Therapeutic Range Drugs must be dispensed as originally prescribed.**
North Dakota	√		√	√	In the physician's handwriting, the words "Brand Necessary" must appear on the prescription.
Ohio	√		√	√	In the physician's handwriting, the words "Dispense as Written" or "DAW" must appear on the prescription.
Oklahoma	√		√	√	Physician shall communicate to Pharmacist that product should not be substituted.
Oregon	√		√	√	In the physician's handwriting, the words "No substitution" or "N.S" must appear on the prescription.
Pennsylvania	√		√	√	Physician shall communicate to Pharmacist that product should not be substituted.

Rhode Island		√	√	√	In the physician's handwriting, the words "Dispense as Brand Name Necessary" must appear on the prescription.
South Carolina	√		√	√	Sign the prescription signature line labeled "May not Substitute" or "Dispense as Written".
South Dakota	√		√	√	In the physician's handwriting, the words "Brand Necessary" must appear on the prescription.
Tennessee		√	√	√	In the physician's handwriting, the words "Dispense as Written", "DAW", or other language of intent must appear on the prescription.
Texas	√		√	√	In the physician's handwriting, the words "Brand Necessary" or "Brand Medically Necessary" must appear on the prescription.
Utah	√		√	√	Sign the prescription signature line labeled "May not Substitute" or "Dispense as Written" OR in the physician's handwriting, the words "Dispense as Written" must appear on the prescription.
Vermont		√	√	√	In the physician's handwriting, the words "Brand Necessary" or "No substitution" must appear on the prescription.
Virginia	√		√	√	In the physician's handwriting, the words "Brand Necessary" must appear on the prescription.
Washington		√	√	√	Sign the prescription signature line labeled "May not Substitute" or "Dispense as Written".

West Virginia		√	√	√	In the physician's handwriting, the words "Brand Medically Necessary" must appear on the prescription.
Wisconsin	√		√	√	In the physician's handwriting, the words "No substitutions" or "N.S" must appear on the prescription.
Wyoming	√		√	√	In the physician's handwriting, the words "Brand Medically Necessary" must appear on the prescription.

From Epilepsy.com/Professionals. State Laws or Statutes Governing Generic Substitution by Pharmacists. 4/25/2007. http://professionals.epilepsy.com/page/statutes_by_pharmacists.html.

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ORIGINAL RESEARCH ARTICLE

Traceability of Biopharmaceuticals in Spontaneous Reporting Systems: A Cross-Sectional Study in the FDA Adverse Event Reporting System (FAERS) and EudraVigilance Databases

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Abstract

Background Adverse drug reactions (ADRs) of biopharmaceuticals can be batch or product specific, resulting from small differences in the manufacturing process. Detailed exposure information should be readily available in systems for postmarketing safety surveillance of biopharmaceuticals, including spontaneous reporting systems (SRSs), in which reports of ADRs are collected.

Objective The aim of this study was to explore the current status of traceability of biopharmaceuticals in the US and the EU up to patient level in SRSs.

Design and Setting A cross-sectional study was conducted over the period 2004–2010, including ADR reports from two major SRSs: the FDA Adverse Event Reporting System (FAERS) in the US and EudraVigilance (EV) in the EU.

Main Outcome Measures The availability of batch numbers was determined for biopharmaceuticals, and compared with small molecule drugs. For biopharmaceuticals for which a biosimilar has been approved for marketing in the EU, the identifiability of the product (i.e. the possibility of distinguishing the biosimilar from the reference biopharmaceutical) was determined.

Results A total of 2,028,600 unique ADR reports were identified in the FAERS, reporting a total of 591,380 biopharmaceuticals (of which 487,065 were suspected). In EV there were 2,108,742 unique ADR reports, reporting a total of 439,971 biopharmaceuticals (356,293 suspected). Overall, for 24.0 % of the suspected biopharmaceuticals in the FAERS and 7.4 % of the suspected small molecule drugs ($p < 0.001$) batch numbers were available. A similar pattern was seen in EV: for 21.1 % of the suspected biopharmaceuticals batch numbers were available, compared with only 3.6 % of the small molecule drugs ($p < 0.001$). In both SRSs, consumers were most likely to report a batch number for suspected biologicals (36.3 % in the FAERS and 40.7 % in EV). A total of 13,790 biopharmaceuticals (9,759 suspected) for which a biosimilar has been approved in the EU were identified in EV. For 90.4 % of these biopharmaceuticals and 96.2 % of the suspected biopharmaceuticals the product was clearly identifiable.

Conclusion This study underlines the need for improving traceability of biopharmaceuticals, in particular with respect to individual batches, allowing better identification and monitoring of postmarketing safety issues related to biopharmaceuticals.

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1 Background

Biopharmaceuticals provide innovative and effective therapies for often severe and life-threatening diseases. Because of their specific characteristics, biopharmaceuticals have been associated with specific safety concerns, and challenges in pharmacovigilance and risk management [1, 2]. One of the distinctive properties of biopharmaceuticals is that the safety profile may change over time, resulting from changes in the manufacturing or formulating process. The unexpected increased occurrence of pure red cell aplasia in patients treated with recombinant human erythropoietin outside the US is an example of a postmarketing safety issue associated with such a specific characteristic of biopharmaceuticals [3]. More than 200 cases of this rare and severe haematological disorder have been attributed to the altered immunogenicity of an epoetin alfa for which formulation changes had recently been issued [4].

Biopharmaceuticals are subject to frequent manufacturing changes once a marketing authorization has been granted. Although these changes are adopted to benefit public health, e.g. by improving product properties or product yield, alterations in the production process may adversely impact the product quality attributes [5, 6]. Consequently, the clinical efficacy and safety, in particular immunogenicity, may be affected. Several examples, apart from epoetin alfa, are known whereby immunogenicity with potentially serious clinical consequences was associated with manufacturing and/or formulation changes, including thrombocytopenia with thrombopoietin and neutralizing antibodies with human growth hormone [6]. To ensure patient safety, regulatory authorities in the US and EU have adopted extensive guidance for evaluating comparability of biopharmaceuticals pre- and postmanufacturing changes [7, 8]. This comparability exercise represents a challenging task for manufacturers and regulatory authorities as there is no set of analytical techniques that can fully describe the structural properties of the biopharmaceutical [9]. Moreover, when substantial alterations in the structure products are found, regulatory authorities have the difficult task of deciding whether the identified changes are acceptable [10], i.e. that the changes don't affect the clinical performance of the biopharmaceutical.

Determining therapeutic equivalence is an even more difficult task when the whole manufacturing process of a biopharmaceutical is redeveloped by a second manufacturer, which is the case for biosimilars [11]. Manufacturers of biosimilars do not have access to the manufacturing process of the reference product since this is proprietary knowledge [12]. Consequently, the independent development of a new manufacturing process is likely to result in structural differences between biosimilars and their reference products, possibly affecting the product's immunogenicity [13]. Recently, biosimilar development has been receiving increasing attention due to expiring patent protection of top-selling biopharmaceuticals [14] and the need for cutting healthcare spending in the Western world [15]. It is already estimated that in 2015 biosimilars will represent approximately 40 % of the total worldwide biopharmaceutical market [16].

Ensuring the traceability of biopharmaceuticals up to batch and product level is essential in view of the risk of batch- or product-specific adverse drug reactions (ADRs). Detailed exposure information should be readily available in systems for postmarketing safety surveillance of biopharmaceuticals, including spontaneous reporting systems (SRSs), in which reports of ADRs are collected. It is known that SRS have played a pivotal role in detecting postmarketing safety issues for small molecule drugs in the past. These systems could also play an essential role in detecting and monitoring any future batch- or product-specific safety issues of biopharmaceuticals, provided that this information is captured. The current study therefore aims to explore the current status of traceability of biopharmaceuticals in the US and the EU up to patient level in SRSs.

2 Methods

The traceability of biopharmaceuticals was studied in a cross-sectional study over the period 2004–2010, including spontaneous ADR reports from two major SRS: the FDA Adverse Event Reporting System (FAERS) in the US and EudraVigilance (EV) in the EU.

2.1 FDA Adverse Event Reporting System Data Content and Structure

The FAERS was established in 1969 to support the postmarketing safety surveillance of the US FDA. The FAERS database encompasses individual case safety reports (ICSRs) for the majority of FDA-approved medicinal products. An ICSR is defined as the information provided by a primary source to describe suspected ADRs related to the administration of one or more medicinal products to an individual patient at a particular point of time [17]. The FDA receives ICSRs directly from consumers or healthcare professionals, or indirectly through manufacturers, when the ADR is initially brought to their attention. Manufacturers have an obligation to periodically report both serious and non-serious ADRs that occurred in domestic (US) clinical practice, and serious unexpected ADRs occurring in the US or a third country [18, 19]. FAERS data is freely accessible under the Freedom of Information Act, and FAERS data from 2004 onwards are directly available from the website of the FDA (http://www.fda.gov/Drugs/InformationOnDrugs/ucm135151.htm).

The FDA may receive multiple ICSRs, e.g. follow-up reports from the previous or a second reporter, referring to the same occurrence of ADRs in the same patient on the same time. All initial and follow-up ICSRs appear in the FAERS. If correctly linked, follow-up reports on an initial ICSR are identifiable in the FAERS upon identical 'case numbers'.

2.2 EudraVigilance Data Content and Structure

EV was established in 2001 to collect ICSRs of (serious) ADRs to medicines licensed within the EU. ICSRs are received indirectly through EU national competent authorities and pharmaceutical companies. Pharmaceutical companies have a legal obligation to report all serious unexpected ADRs and any suspected transmission via a medicinal product of any infectious agents occurring outside the EU which are brought to their attention. National competent authorities are required to report any serious ADR occurring within the EU [20]. EV data was obtained through a request for access to data according to the EV Access Policy, as data from EV has only recently become accessible for research purposes. Recently, the European Medicines Agency (EMA) has begun publishing suspected ADR reports on their website to foster transparency (http://www.adrreports.eu).

An ICSR in EV reflects the most recent and comprehensive information on an event of an ADR. Follow-up ICSRs by the same reporter will automatically replace the previous ICSR. Duplicate ICSRs from multiple reporters are merged into 'master cases', containing the most comprehensive information from the individual ICSRs [17].

2.3 Data Extraction and Handling

All spontaneous ICSRs over the period 2004–2010 were selected from FAERS and EV. ICSRs originating from literature and clinical studies were not of interest as the current study aims to describe batch and product traceability in clinical practice. All literature and study ICSRs were therefore omitted from the FAERS ($n = 156{,}776$). Only spontaneous ICSRs were requested from EV.

All drug information from ICSRs in the FAERS referring to the same case number were merged into a single cumulative ICSR, similar to the EV approach mentioned above. One cumulative ICSR contains all unique drugs reported over time within these ICSRs. Duplicate drugs within the same ICSR were merged in EV. These steps were undertaken to avoid duplication of data in our final unit of analysis: one medicinal product, subject of a suspected ADR report, administered to an individual patient at a particular point of time. Figure 1 illustrates how EV and FAERS data were processed to our unit of analysis.

The following data was subsequently extracted from all cumulative ICSRs from EV and the FAERS: information on name of the drug and/or active substances, batch number, name of marketing authorization holder (EV only), role code of the drug (see Sect. 2.4), type of reporter and reporting date. In line with the International Conference on Harmonisation (ICH) E2B guideline, the following reporters are distinguished: physician, pharmacist, other health professional, lawyer and consumer. Since the reporter on a cumulative ICSR may be non-unique (due to duplicate reporting) a separate category was assigned for multiple reporters.

2.4 Classification of Medicinal Products

Biopharmaceuticals were defined as protein- or nucleic-based pharmaceutical products used for therapeutic or in vivo diagnostic purposes [21]. Medicinal products were classified into two groups: (i) biopharmaceuticals; and (ii) small molecule drugs using the WHO Anatomical Therapeutic Chemical (ATC) classification system (http://www.whocc.no/atc_ddd_index/; see Table S1 [Online Resource 1]). Two pharmacists confirmed the classification of the data. Medicinal products not classifiable to either group (e.g. verbatim data entered as 'unspecified drug' or 'radiation therapy') were excluded. Moreover, vaccines (ATC class J07) and whole blood or components of whole blood (ATC class B05A) were excluded as they are subject to different reporting requirements. The role code of the medicinal product was recoded into suspected (classified as 'primary suspect' or 'secondary suspect' in the FAERS or 'suspect' in EV) and non-suspected (classified as 'interacting' or 'concomitant' in both SRSs).

2.5 Classification of Traceability

Verbatim data entered in the designated field for batch number was recoded to a dichotomous variable describing the availability of the batch number. Any verbatim data entered into the designated field for batch number was considered to be a batch number. To validate whether the verbatim data did not contain any information referring to the unavailability of a batch number (e.g. 'unknown' or 'discarded package'), data were aggregated and carefully reviewed. A second reviewer reviewed the determination of the availability of batch numbers.

For biopharmaceuticals for which a biosimilar has been approved for marketing in the EU (see Table S2 [Online Resource 1]), the identifiability of the product in the cumulative ICSRs in EV was determined. For this analysis we included only ICSRs reported from the month following the approval of the first biosimilar within that product class: epoetin alfa, filgrastim and somatropin. Product

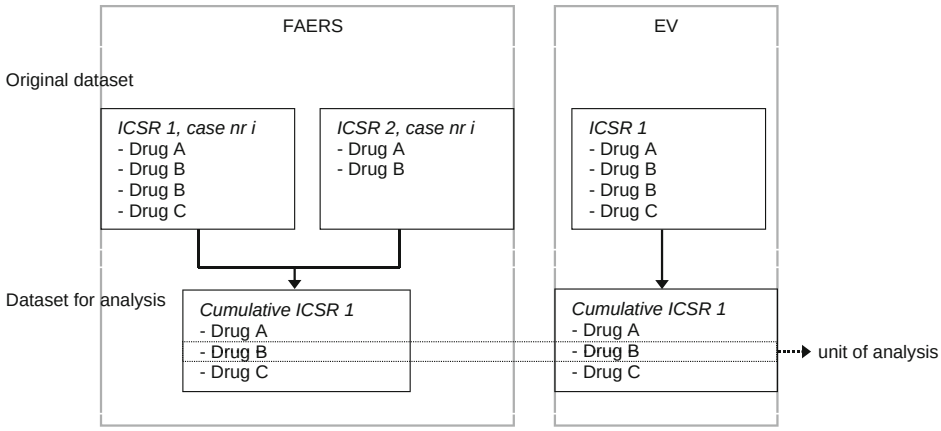

Fig. 1 Processing original FAERS and EV ICSRs to cumulative ICSRs. *EV* EudraVigilance, *FAERS* FDA Adverse Event Reporting System, *ICSR* Individual Case Safety Report

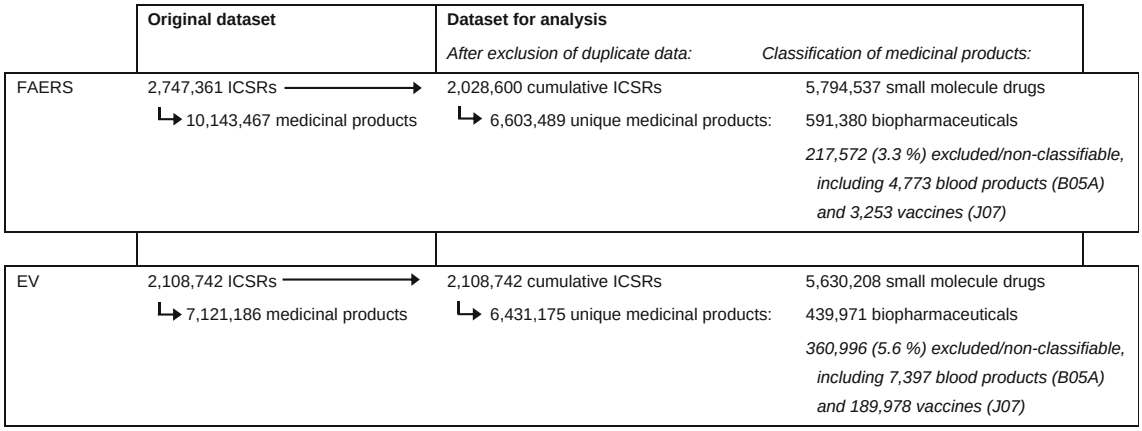

Fig. 2 Number of ICSRs and medicinal products in original dataset, and dataset for analysis. *EV* EudraVigilance, *FAERS* FDA Adverse Event Reporting System, *ICSR* Individual Case Safety Report

names were considered identifiable when the brand name or the international nonproprietary name (INN) plus the name of the marketing authorization holder were available. Products for which only the INN was available were considered non-identifiable, except for epoetin zeta, for which product the INN differs from the innovator (epoetin alfa).

2.6 Data Analysis

Descriptive statistics were calculated as proportions to describe the traceability of batch numbers for biopharmaceuticals and small molecule drugs in the FAERS and EV. Results were further stratified by the role code of drug and the type of reporter to identify whether proportions differed over the different variables. For the top eight most frequently reported ATC classes (see Table S1 [Online Resource 1]) the availability of batch numbers was calculated overall, and further stratified by type of reporter (medical doctor, pharmacist or consumer). The product identifiability, and subsequent batch traceability, for biopharmaceuticals for which a biosimilar has been approved in the EU were also calculated as proportions. Significance was tested using Chi-square statistics. All analyses were performed using SPSS statistical software version 18 (IBM Software, Chicago, IL, USA).

3 Results

A total of 2,028,600 and 2,108,742 cumulative ICSRs were reported in the FAERS and EV, respectively. Within these cumulative ICSRs, a respective total of 591,380 (from the 6,603,489) and 439,971 (from the 6,431,175) medicinal products concerned biopharmaceuticals (see Fig. 2).

Overall, for 24.0 % of the suspected biopharmaceuticals in the FAERS and 7.4 % of the suspected small molecule drugs ($p < 0.001$), batch numbers were available. A similar pattern was seen in EV: for 21.1 % of the suspected biopharmaceuticals, batch numbers were available, compared with only 3.6 % of the small

Table 1 Availability of batch numbers for reported biopharmaceuticals and small molecule drugs in the FAERS and EV, stratified by role code

Drug type, role code		FAERS		EV	
		Total number of drugs	Drugs with batch number available [*n* (%)]	Total number of drugs	Drugs with batch number available [*n* (%)]
Biopharmaceutical	All	591,380	117,523 (19.9)	439,971	75,713 (17.2)
	Suspected	487,065	116,812 (24.0)	356,293	75,272 (21.1)
Small molecule drug	All	5,794,537	164,755 (2.8)	5,630,208	79,610 (1.4)
	Suspected	2,221,229	163,670 (7.4)	2,169,721	77,724 (3.6)
Total	All	6,385,917	282,278 (4.4)	6,070,179	155,323 (2.6)
	Suspected	2,708,294	280,482 (10.4)	2,526,014	152,996 (6.1)

EV EudraVigilance, *FAERS* FDA Adverse Event Reporting System

Table 2 Availability of batch numbers for reported suspected biopharmaceuticals, stratified by type of reporter

Reporter type	FAERS ($n = 487{,}065$)		EV ($n = 356{,}293$)	
	Total number of drugs[a]	Drugs with batch number available [*n* (%)]	Total number of drugs	Drugs with batch number available [*n* (%)]
Physician	112,770	15,026 (13.3)	94,928	6,667 (7.0)
Pharmacist	12,971	2,984 (23.0)	9,999	1,896 (19.0)
Other healthcare professional	64,235	9,087 (14.1)	46,765	5,366 (11.5)
Consumer	198,282	72,006 (36.3)	117,411	47,800 (40.7)
Lawyer	1,489	10 (0.7)	1,242	5 (0.4)

[a] For a total of 97,318 biopharmaceuticals in the FAERS and 85,948 in EV, the reporter type was not unique or unavailable

EV EudraVigilance, *FAERS* FDA Adverse Event Reporting System

molecule drugs ($p < 0.001$). The traceability of individual batches for the overall group of drugs in the FAERS and EV, including concomitant and interacting drugs, was less well guaranteed (see Table 1).

For the 487,065 suspected biopharmaceuticals in the FAERS and 356,293 suspected biopharmaceuticals in EV, the availability of batch numbers was calculated for different reporter types. Biopharmaceuticals reported by consumers most frequently contained a batch number (36.3 % in the FAERS and 40.7 % in EV). Batch traceability of biopharmaceuticals reported by physicians in the FAERS (13.3 %) and EV (7.0 %) was substantially lower (both $p < 0.001$). Biopharmaceuticals reported by pharmacists or other healthcare professionals were also less likely to contain a batch number (see Table 2).

This pattern differed, however, between the eight most frequently reported pharmacological and therapeutic subgroups of biopharmaceuticals. Overall, batch numbers were most frequently available for parathyroid hormone (H05AA) in the FAERS (43.1 %) and immunoglobulins (J06) in EV (42.0 %). Most notably, the overall availability of batch numbers for parathyroid hormone in the FAERS was higher than in all three separate reporter categories (see Fig. 3), representing the high availability of batch numbers in reports of which the reporter was not known (62.5 %, not shown in Fig. 3). Respectively, 43.1 % and 44.2 % of the tumour necrosis factor (TNF)-α inhibitors, the most frequently reported ATC class, reported by consumers contained a batch number in the FAERS and EV. Batch traceability of TNF-α inhibitors reported by physicians and pharmacists was lower in the FAERS (16.2 % and 13.5 %, respectively), and particularly in EV (3.8 % and 10.5 %, respectively). Pharmacists did remarkably well in reporting batch numbers for immunoglobulins in the FAERS (59.4 %) and EV (55.2 %). The traceability of antineoplastic monoclonal antibodies (ATC class L01XC) was overall poorly maintained (see Fig. 3).

There was variability in the traceability of suspected biopharmaceuticals over time for EV and the FAERS (see Fig. 4). Batch traceability of biopharmaceuticals in EV showed a sharp increase between 2007 (10.7 % of reported biopharmaceuticals contained a batch number) and 2008 (22.8 % contained a batch number). Batch traceability of biopharmaceuticals in the FAERS showed a peak in 2007, with 35.8 % of the reported biopharmaceuticals containing a batch number, but declined thereafter.

A total of 13,790 biopharmaceuticals (of which 9,759 were suspected) for which a biosimilar has been approved in the EU were extracted from cumulative ICSRs in EV. For 90.4 % of these biopharmaceuticals, and 96.2 % of the suspected biopharmaceuticals, the product was clearly identifiable. The batch traceability of biosimilars was, interestingly, poorly maintained (see Table 3).

4 Discussion

The present study showed that for 24.0 % of the suspected biopharmaceuticals in the FAERS and 21.1 % of the

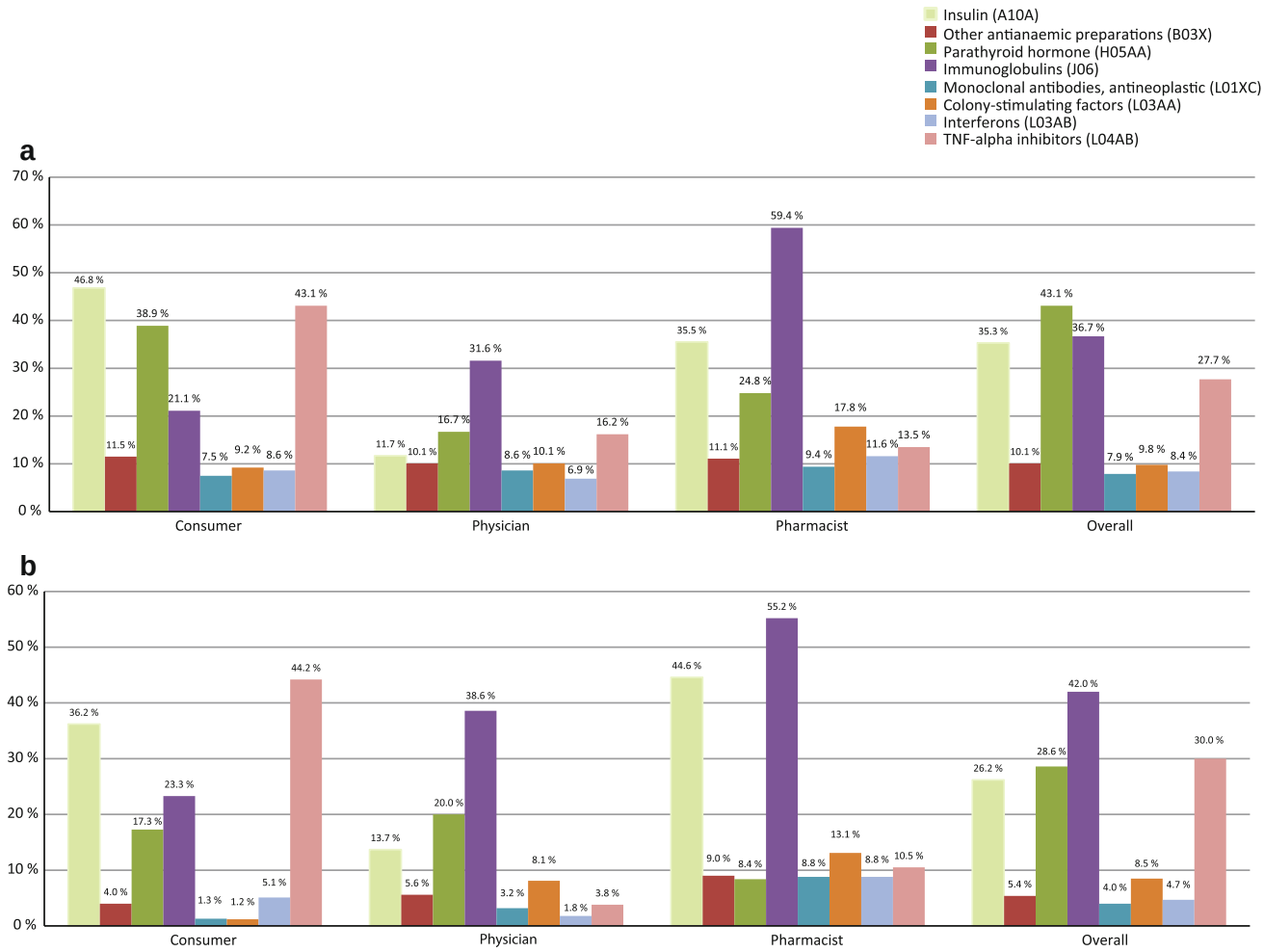

Fig. 3 Availability of batch numbers (%[1]) for eight groups of suspected biopharmaceuticals in FAERS (**a**) and EV (**b**), stratified by type of reporter. [1]Calculated as number of biopharmaceuticals containing batch number/number of biopharmaceuticals reported by reporter within group. *EV* EudraVigilance, *FAERS* FDA Adverse Event Reporting System

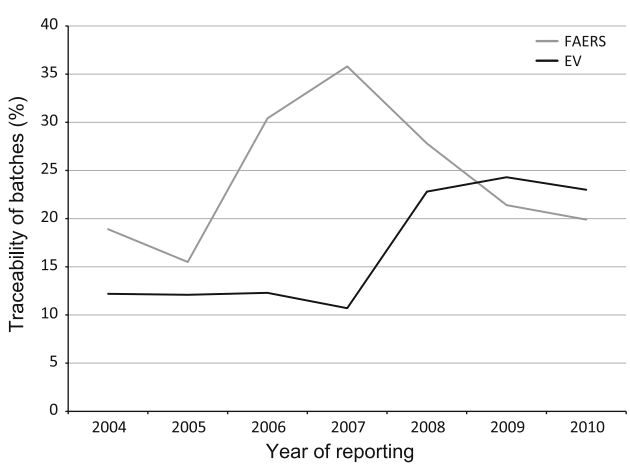

Fig. 4 Availability of batch number for suspected biopharmaceuticals from 2004 until 2010 in FAERS and EV. *EV* EudraVigilance, *FAERS* FDA Adverse Event Reporting System

Table 3 Identifiability of biosimilars[a] in EudraVigilance

Biopharmaceutical, role code		Total number of drugs	Drugs with identifiable product name [*n* (%)]	Drugs with identifiable product name and traceable batch number [*n* (%)]
Epoetin alfa	All	9,125	8,615 (94.4)	320 (3.5)
	Suspected	6,903	6,829 (98.9)	318 (4.6)
Filgrastim	All	2,227	1,702 (76.4)	73 (3.3)
	Suspected	706	600 (85.0)	72 (10.2)
Somatropin	All	2,438	2,148 (88.1)	128 (5.3)
	Suspected	2,150	1,963 (91.3)	128 (6.0)
Total	*All*	*13,790*	*12,465 (90.4)*	*521 (3.8)*
	Suspected	*9,759*	*9,392 (96.2)*	*518 (5.3)*

[a] Biopharmaceuticals for which a biosimilar has been approved in the EU

suspected biopharmaceuticals in EV a batch number was available. In addition, the current study showed that for 96.2 % of the suspected biopharmaceuticals for which a biosimilar was available in the EU the product name was clearly identifiable in EV. Accurate traceability of biopharmaceuticals up to batch and product level in these SRSs is essential for identifying and monitoring any batch- or product-specific safety issues, resulting from differences in the manufacturing process. Batch traceability may, in addition, help to distinguish between, and assess the safety profile over, different pharmaceutical forms and dosage strengths of biopharmaceuticals. Furthermore, accurate batch traceability is pivotal for relating any batch-related problems of biopharmaceuticals, e.g. pathogen-contaminated batches [22] or other host cell impurities [23], to reported ADRs. Biopharmaceuticals might be at increased risk of batch-related problems as the production process, which involves living expression systems, gives rise to a large number of host cell-, process- and product-related impurities.

The proportions of biopharmaceuticals containing a batch number in the FAERS and EV were much higher than we found for suspected small molecule drugs (7.4 % and 3.6 %, respectively), but lower than elsewhere reported for vaccines (54.4 %) [24]. The lack of information on batch numbers for approximately three in four biopharmaceuticals in the FAERS (approximately four in five in EV) could either be the result of incomplete recording of exposure information at dispensing or incomplete reporting of the available information to regulatory authorities and/or manufacturers. The reported differences in batch traceability between different pharmacological/therapeutic groups of biopharmaceuticals suggest, in particular, a role for incomplete recording of exposure information in clinical practice. Whereas consumers reported a batch number for 36.2–46.8 % of frequently home-administered insulins, they reported a batch number for only 1.3–7.5 % of antineoplastic monoclonal antibodies, which are primarily administered in hospitals. For consumers it is relatively easy to obtain batch numbers if the medicine is applied at home, as is the case for insulins. As in the case of antineoplastic agents, the preparation, administration and reporting might very well be by different persons, and the patient or physician confronted with the ADR might not have access to the batch information. This indicates that once the batch numbers are readily available consumers are likely to report this information.

Another finding from the current study was that batch traceability was, overall, well maintained for immunoglobulins, particularly when reported by pharmacists. Overall, batch numbers were available for 36.7–42.0 % of the reported immunoglobulins, and 55.2–59.4 % of the immunoglobulins reported by pharmacists. This might be explained by the fact that immunoglobulins were historically plasma-derived medicinal products, for which separate regulations are in place. The safety of blood-derived products has been under close scrutiny, especially in Europe, following the HIV-infected blood-products scandal that occurred in France in the 1990s [25], and concerns for transmission of Creutzfeldt-Jakob Disease via whole blood and plasma-derived products in Europe [26], although the latter has only been a theoretical risk until 2009 [27].

The current study showed that patients play an important role in ensuring traceability of biopharmaceuticals. In 36.3 % and 40.7 % of the consumer reports on biopharmaceuticals a batch number was available in the FAERS and EV, respectively. These results underpin the importance of patient reporting of adverse events. Patients have been able to report adverse events to the FAERS since its establishment in 1969. In most European countries, patient reporting schemes have only recently been established and in some countries patients are still not able to report adverse events directly to the competent authorities [28]. On the other hand, we showed that physicians played only a minor role in ensuring traceability of biopharmaceuticals. Despite being a major contributor in the absolute number of reports, only in 13.3 % and 7.0 % of the reports on biopharmaceuticals in the FAERS and EV, respectively, was a batch number available.

The present study showed that product identifiability of biopharmaceuticals for which a biosimilars has been approved in the EU is reasonably well ensured in Europe, especially for epoetin alfa. This is an important finding, taking into account that biosimilars are frequently given the same INN as the reference innovator. Of the six currently approved biosimilars in Europe (sold under 12 different trade names), five contain the same INN as the innovator (see Table S2 [Online Resource 1]). It has therefore been recognized that the INN system, although playing an important role in global pharmacovigilance, cannot be relied upon for product identification of biosimilars [29]. As the number of biosimilars on the market is expected to increase in a vast pace, and a road for biosimilar registration is currently been paved in the US [30], traceability of biosimilars will only become increasingly important.

The need to ensure traceability is not unique to biopharmaceuticals, but is also a well-known aspect in numerous other industries [31]. In particular, the traceability of medical devices is receiving increased scrutiny following recent concerns in Europe of a possible association between frequently used PIP (Poly Implant Prothèse) breast implants and cancer [32]. The European Commission has already announced plans to enhance traceability of medical devices [33]. Similarly, several initiatives are currently ongoing to further promote the traceability of biopharmaceuticals. These initiatives are not only fuelled

by increased interest in drug safety, but also by the need for improving supply chain efficacy and the need for taking measures against counterfeit medicines [31]. Two-dimensional barcodes that could include detailed product information such as batch numbers is one of the presented solutions for promoting traceability of biopharmaceuticals [34]. When such information is automatically recorded in clinical practice, it is essential that patients and healthcare professionals are aware that this accurate exposure information is necessary to link the adverse event properly to the specific product. Regulatory authorities in the product information of biopharmaceuticals may encourage patients and healthcare professionals to report such information. This may be one of the increased efforts taken by the EU and its Member States to ensure traceability of biopharmaceuticals, demanded by recently adopted new European pharmacovigilance legislation [35].

It should be noted that SRSs may not be the sole point in the community where detailed exposure information on biopharmaceuticals is captured. In the current study we did not assess whether population-based databases or disease registries contain the necessary exposure information to monitor and ascertain the safety of biopharmaceuticals over different batches or products. A second limitation that should be addressed is that the databases we have used might contain a large number of duplicate reports. In particular, extensive duplication of reports has been reported in the FAERS [36]. To limit any influence of duplicate information on our study results, efforts were undertaken to reduce data duplication. As we were, however, not interested in the frequency of certain adverse events but only in the reporting quality of the submitted reports, we feel any residual duplication might have little influence on our results.

5 Conclusion

The present study was, to our knowledge, the first study to explore the current status of traceability of biopharmaceuticals in major SRSs of ADRs in the US and the EU. We have reported that the current system insufficiently ensures the traceability of individual batches of biopharmaceuticals, although the identifiability of biosimilars is reasonably well ensured. Stakeholders in pharmacovigilance should undertake efforts to improve the traceability of biopharmaceuticals.

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Conflicts of interest Niels S. Vermeer, Sabine M.J.M. Straus, Aukje K. Mantel-Teeuwisse, Francois Domergue, Toine C.G. Egberts, Hubert G.M. Leufkens and Marie L. De Bruin have no conflicts of interest that are directly relevant to the content of this review.

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Biosimilars: what clinicians should know

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Biosimilars: what clinicians should know

Martina Weise,[1] Marie-Christine Bielsky,[2] Karen De Smet,[3] Falk Ehmann,[4] Niklas Ekman,[5] Thijs J. Giezen,[6] Iordanis Gravanis,[4] Hans-Karl Heim,[1] Esa Heinonen,[5] Kowid Ho,[7] Alexandre Moreau,[7] Gopalan Narayanan,[2] Nanna A. Kruse,[8] Gabriele Reichmann,[9] Robin Thorpe,[10] Leon van Aerts,[11] Camille Vleminckx,[4] Meenu Wadhwa,[10] and Christian K. Schneider[8,12]

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Biosimilar medicinal products (biosimilars) have become a reality in the European Union and will soon be available in the United States. Despite an established legal pathway for biosimilars in the European Union since 2005 and increasing and detailed regulatory guidance on data requirements for their development and licensing, many clinicians, particularly oncologists, are reluctant to consider biosimilars as a treatment option for their patients. Major concerns voiced about biosimilars relate to their pharmaceutical quality, safety (especially immunogenicity), efficacy (particularly in extrapolated indications), and interchangeability with the originator product. In this article, the members and experts of the Working Party on Similar Biologic Medicinal Products of the European Medicines Agency (EMA) address these issues. A clear understanding of the scientific principles of the biosimilar concept and access to unbiased information on licensed biosimilars are important for physicians to make informed and appropriate treatment choices for their patients. This will become even more important with the advent of biosimilar monoclonal antibodies. The issues also highlight the need for improved communication between physicians, learned societies, and regulators. (*Blood*. 2012;120(26):5111-5117)

Introduction

A similar biologic medicinal product, commonly referred to as biosimilar, is a copy version of an approved original biologic medicine whose data protection has expired. Since the implementation of a biosimilar approval pathway in 2005, several biosimilars, including somatropins, filgrastims, and epoetins, have been licensed and become available in the European Union (EU), and numerous other biosimilars, most importantly monoclonal antibodies, are being developed.[1] Recently, a biosimilar infliximab has been filed for regulatory review to the European Medicines Agency (EMA).[2] Product-class specific guidelines for these and other biologicals describing a targeted nonclinical and clinical development program are in place or currently under development.[3] In the United States, after the recent enactment of a specific approval pathway for biosimilars[4] and publication of the first draft guidelines on biosimilar product development by the United States FDA,[5] biosimilars are expected to be available soon. An EMA-FDA Biosimilar Cluster has been established for scientific discussion between the FDA and EMA and facilitation of global development of biosimilars. However, uptake of biosimilars in the European market has been slower than expected, which may, at least partly, be attributed to a lack of trust in the efficacy and safety of biosimilars as well as their interchangeability with the originator product by both patients and clinicians.[6]

This article addresses frequent concerns raised about biosimilars in the medical community and explains the scientific principles underlying the biosimilar concept established in the EU and put forward in the United States, allowing the licensing of biosimilars based on a reduced, or better scientifically tailored data package, which relies, as appropriate, on the extensive knowledge gained with the originator product.

What is special about biosimilars?

In principle, biosimilars are the biologic medicines' equivalent of chemical generics. However, biologicals are derived from living cells or organisms and consist of relatively large and often highly complex molecular entities that may be difficult to fully characterize. Because of inherent variability of the biologic system and the manufacturing process, any resulting biological will display a certain degree of variability (microheterogeneity), even between different batches of the same product. Because of unavoidable differences in the manufacturing processes, a biosimilar and the respective originator product, the reference product, will not be entirely identical. However, the amino acid sequence is expected to be the same, and only small differences in the microheterogeneity pattern of the molecule may be acceptable. A very thorough comparison of the structural and functional characteristics, and the product and process-related impurities of the biosimilar and the reference product will be necessary. Any differences found will need to be explained and justified with regard to the potential impact on the clinical performance of the biosimilar.[5,7]

Data requirements for the development and licensing of biosimilars are considerably greater than for small chemically synthesized

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and easily characterizable generic products. For a generic, physicochemical identification and demonstration of a similar pharmacokinetic profile (bioequivalence) to the originator product are usually sufficient to conclude on therapeutic equivalence. In contrast, a biosimilar needs to be developed based on a more extensive head-to-head comparison with the reference product, to ensure close resemblance in physicochemical and biologic characteristics, safety, and efficacy.[3,5] It should be emphasized that the scientific principles underlying the comparability exercise for biosimilars are the same as those for changes in the manufacturing process of a given biological, for which guidance and experience already exist.[8] However, because the biosimilar will be produced by a different manufacturer, the data requirements for demonstration of biosimilarity will usually be more extensive than for demonstration of comparability of a given biological before and after manufacturing changes by the same manufacturer.

As with generics, biosimilars are intended to be used at the same dose(s) and dosing regimen(s) to treat the same disease(s) as their reference products. Therefore, the focus of biosimilar development is not to establish patient benefit per se—this has already been done for the originator product—but to convincingly demonstrate high similarity to the reference product as basis for relying, in part, on its efficacy and safety experience. For these reasons, the study design, study population, and/or end points used in studies comparing the biosimilar with the reference product may be different from those previously used to establish therapeutic benefit of the reference product.

The type and extent of clinical data requirements for biosimilars vary and depend on the complexity of the active substance and how well it can be characterized, on the availability of an accepted surrogate end point to compare efficacy, on the type and seriousness of safety concerns that have been encountered with the reference product or the substance class, and on the possibility to extrapolate efficacy and safety data to other indications of the reference product, which have not been studied for the biosimilar. However, a repetition of the entire development program of the reference product is scientifically not necessary and could even be considered unethical.

Frequent concerns about biosimilars

Frequent concerns about biosimilars voiced by clinicians, mainly through learned societies, relate to their pharmaceutical quality, safety, and their interchangeability with the reference product. They also include doubts about clinical efficacy and safety in extrapolated indications for which no formal clinical studies have been performed with the biosimilar. Inconsistent terminology may also add to misperceptions about biosimilars.[9] It is thus necessary to discuss these concerns in view of the scientific principles established for biosimilars in the EU and shared in other highly regulated regions of the world:

1. The fear of low quality or substandard biosimilar products is not substantiated because the manufacturing process for a biosimilar must comply with quality requirements just as for any new biological and thus must demonstrate that the production process is capable of consistently producing a high-quality product. The manufacturing process needs to include state-of-the-art scientific knowledge and process understanding, which in some aspects may have evolved since the development of the originator product.[5,7] The extensive comparison of physicochemical and functional characteristics of the biosimilar with the reference product is an additional requirement and the foundation of biosimilar development. A recently published analysis supports the high pharmaceutical quality of biosimilars licensed in the EU.[10]

2. In our experience, the "similar but not identical" paradigm of biosimilars appears to fuel uncertainties about them. However, this principle is not new to biotechnology; even consecutive batches of originator products are never identical to each other—this is normal and is why adequate controls on batch to batch consistency have to be imposed. Indeed, biosimilars are usually specifically engineered and designed to closely resemble the originator molecule to the best extent possible using current technologies. Small differences (eg, in epitope or binding characteristics of a biosimilar monoclonal antibody) may have an impact on efficacy, but these would normally be picked up early on in product development from the extensive physicochemical and functional characterization required for biosimilars and biologicals in general. Sensitive state-of-the-art methods and methods orthogonally complementing these are very sensitive when used in combination. As mentioned in the section "What is special about biosimilars?", structural differences between a biosimilar and its reference product are only acceptable within the heterogeneity pattern of the molecule, and any differences found will need to be explained and justified with regard to the potential impact on the clinical performance of the biosimilar. One example of a difference, which has been accepted by EMA, is the increased level of phosphorylated high mannose-type structures in a biosimilar epoetin alfa compared with the reference product because the applicant could prove that these are common glycoforms of recombinant erythropoietins and cytokines and a large variety of nonlysosomal proteins from human plasma.[11]

3. Concerns have been expressed that the safety database of biosimilars could be insufficient at the time of approval, with immunogenicity being a particular concern.[12-19]

For a biosimilar, an extensive comparability exercise with the reference product is required, including human efficacy and safety data. Based on similarity being demonstrated with the reference product, the biosimilar can also refer to the safety experience gained with the reference product. Particularly for adverse drug reactions (ADRs) that are related to exaggerated pharmacologic effects, the demonstration of similar physicochemical characteristics, biologic activity, pharmacokinetics, and efficacy will already provide reasonable reassurance that such events can be expected at similar frequencies for the biosimilar and the reference product. The risk for detection of new (serious) adverse effects after licensing is considered much lower for a biosimilar than for a biological containing a new or modified active substance.

Immunogenicity, on the other hand, is an ongoing concern, especially for biologicals for which immune responses have been linked to serious safety issues, the most quoted example being pure red cell aplasia caused by cross-reacting neutralizing antibodies against erythropoietin. Immunogenicity may be influenced by patient-, disease-, or product-related factors. Patient- and disease-related factors are already known from the experience gained with the originator product and therefore do not need to be reinvestigated for the biosimilar. The focus of the evaluation is thus on potential product-related factors, such as structural alterations (eg, aggregation, which has been implicated in the immunogenicity of epoetins[20]) or impurities/contaminants, most of which are readily detected by state-of-the-art analytical methods. However, even seemingly small differences may have an impact on immunogenicity, and analytical or animal data cannot predict immune responses

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in humans. Therefore, human immunogenicity data are generally necessary before licensing to exclude a marked increase in immunogenicity of the biosimilar compared with the reference product.[3,5,21] If the incidence of the immune response is known to be rare and thus unlikely to be captured before licensing, an additional post-marketing study designed to detect more subtle differences in immunogenicity may be requested, which, as in the case of biosimilar epoetins, can be of substantial size.

The current prelicensing requirements are supported by the finding of excessive immunogenicity for a biosimilar somatropin because of the presence of increased amounts of host-cell-protein, which could be eliminated by introduction of an additional purification step[22] and, more recently, the observation of 2 cases of neutralizing anti-epoetin antibodies associated with the subcutaneous use of a biosimilar epoetin alfa in a clinical trial in patients with renal anaemia, resulting in premature study termination.[23] A thorough root-cause analysis of the latter cases identified tungsten-mediated unfolding and aggregation of the epoetin alfa as a potential cause for the increased immunogenicity.[20] Because the soluble tungsten found in some of the syringes used for the product is not present in the drug product per se but stems from the manufacture of the syringes, this problem, if confirmed, could also be relevant to other epoetin-containing products. It should be emphasized that immunogenicity is a potential concern for all biologicals, not just for biosimilars.

4. The need for strict postmarketing surveillance and potentially large, post-marketing studies for complete reassurance regarding the safety of biosimilars, particularly epoetins, has been highlighted.[6,18] For a biosimilar, as for any new drug, a comprehensive risk management plan, including a plan for post-authorization safety surveillance, has to be submitted to the authorities at the time of the marketing authorization application.[24] This must address identified and potential safety concerns for the biosimilar, the reference product and/or the substance class. The post-marketing program for a specific drug product is tailored taking into account these considerations and to best evaluate potential remaining risks. Thus, the safety of biosimilars is actively and comprehensively followed up on an ongoing basis.

5. The basis for considering the efficacy of a biosimilar to be comparable to that of the reference product has been questioned.[6] Specifically, the acceptance range for therapeutic equivalence for biosimilar epoetins was considered wide.

As stated in the section "What is special about biosimilars?" above, the intention of the biosimilar development is to show similarity with the reference product, not to independently demonstrate patient benefit. Therefore, the study population should be as homogeneous as possible, reasonably sensitive to the effects of the biological and the end points should ideally reflect its unconfounded pharmacologic action to create a sensitive test model. This should be able to detect potential drug-related differences in efficacy and safety and to minimize variability caused by disease- or patient-related factors. End points measuring activity of the drug are usually more sensitive for detecting product-related differences than hard end points evaluating patient benefit and may be acceptable if they are clearly related to the desired clinical effects. Examples of pharmacodynamic parameters that have been accepted as surrogate end points for the evaluation of efficacy of biosimilars in the EU include glucose infusion rate in clamp studies for insulins, absolute neutrophil count for G-CSF, and number of oocytes retrieved (in the context of in vitro fertilization) for follicle-stimulating hormones.[3] On the other hand, efficacy of a biosimilar somatropin still has to be assessed in a clinical trial of at least 6 months' duration in growth hormone-deficient children because insulin-like growth factor 1, although a good marker of pharmacologic activity of a somatropin, lacks clear relationship with growth response.

In a statistical and regulatory sense, therapeutic equivalence infers that the test drug does not have better or worse efficacy than the reference product, thus allowing the use of the same dosage for the same indication, as is intended for biosimilars. When defining comparability margins, clinical considerations need to be taken into account; the selected margins should represent the largest difference in efficacy that would not matter in clinical practice. Treatment differences within these margins would thus be acceptable because they have no clinical relevance. The principles of margin selection are not unique to biosimilar testing but are used in any clinical trial comparing treatment alternatives or prechange and postchange product in case a biological has undergone a change in its manufacturing process and clinical data are required for assessment of comparability. Comparability margins proposed for licensing studies for a given medicinal product, including biosimilars, will always need sound scientific justification to be acceptable for regulators.

The acceptance range of $\pm$ 0.5 g/dL in blood hemoglobin concentrations for demonstration of similar efficacy of a biosimilar and the originator epoetin as suggested in the respective EMA guideline is considered tight in the view of the rather high background variability in blood hemoglobin levels in patients with renal anemia, especially those on dialysis.[3] It should be noted that, not only the observed mean treatment difference (between biosimilar and reference product) but also the 95% confidence interval of this difference needs to be fully contained within the equivalence margins, thus providing sufficient statistical reassurance that efficacy is indeed similar. The assumption that patients switched from an originator product to the respective biosimilar may need to change dosage, dosage intervals, or route of administration is unsubstantiated.[25]

6. Concerns have been expressed about using biosimilars in indications or in patient populations that are approved for the reference product but have not been formally investigated during the clinical development of the biosimilar and, therefore, have been licensed on the basis of extrapolation of efficacy and safety data.[6,12,17,19,25-28] In this respect, particular concerns have been raised regarding the use of biosimilar G-CSF for the mobilization of stem cells in healthy donors and the use of biosimilar epoetins in patients with cancer.[25,29,30] In addition, there is growing concern in the rheumatology, gastroenterology, and dermatology communities regarding the future use of biosimilar anti-inflammatory monoclonal antibodies based on extrapolation of data.[31-33]

It must be clearly understood that a biosimilar, as opposed to a small chemical generic, cannot automatically claim all indications of the reference product and that any extrapolation of data requires sound scientific justification.[34] For extrapolation of data to be considered, several requirements need to be fulfilled:

A. Similarity with the reference product must be convincingly demonstrated, based on the totality of the evidence from a thorough comparability exercise. Clinicians need to be aware that clinical data are not the only cornerstone of a biosimilar development to be relied on. Extensive characterization and comparison of the physicochemical properties and biologic activity of the biosimilar and the originator product play a fundamental role in this, and close

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similarity in these aspects is a prerequisite for any reduction in the amount of nonclinical and clinical data requirements. Clinical data provide complementary information (eg, regarding the clinical relevance of any observed differences and on immunogenicity).

B. If clinical similarity can be shown in a key indication, extrapolation of efficacy and safety data to other indication(s) of the reference product may be possible (eg, if the relevant mechanism of action and/or the receptor(s) involved in the extrapolated indications are the same).[3] If the mechanism of action is different or unknown, additional convincing data [eg, on pharmacodynamic parameters and/or specific and sensitive functional assays reflecting the respective pharmacologic action(s)] are necessary to provide further reassurance that the biosimilar will behave as the originator product in these indications. In this sense, comparative pharmacodynamic studies in healthy subjects are required for biosimilar G-CSF, evaluating, in addition to absolute neutrophil count, the $CD34^+$ cell count to assess mobilization of stem cells from the bone marrow.[3] Such data should not be considered in isolation but as a further building block in the overall proof of biosimilarity. Based on such considerations, extrapolation of efficacy and safety data to other indications of the reference product has been approved for biosimilar somatropin, epoetin, and filgrastim-containing medicinal products.[1]

C. Another prerequisite for extrapolation is that the safety profile of the biosimilar must have been properly characterized and unacceptable immunogenicity excluded. Extrapolation of immunogenicity data is only possible from high-risk to low-risk patient populations and clinical settings. For example, pure red cell aplasia resulting from neutralizing anti-epoetin antibodies is a potential concern for subcutaneous use of epoetins in patients with renal anemia but less for intravenous administration or use in cancer patients receiving chemotherapy. Therefore, extrapolation of immunogenicity data is considered possible from subcutaneous use in renal anemia patients to intravenous use in the same population or to subcutaneous use in immunocompromised cancer patients but not vice versa. In this respect, the concern expressed in a recent review,[35] that immunogenicity data collected for intravenous use of epoetin could be extrapolated to subcutaneous use, is not substantiated because the respective guideline[3] clearly states that comparative immunogenicity data will always be required for subcutaneous use, if applied for.

In this context, it should be emphasized that the scientific principles of extrapolation of data are not new for biosimilars but also apply to the comparison of prechange and postchange product on a change in the manufacturing process of a biological, which is already licensed for use in several indications. To the knowledge of the authors, up to now, there has not been a case, even with extensive changes to the manufacturing process, where new clinical data have been generated or requested in every indication because the overall data from the comparability exercise already conclusively demonstrated that the manufacturing change has no adverse impact on efficacy and safety.

In conclusion, extrapolation of data to other indications of the reference product, and thus formal lack of a clinical trial in the respective clinical indication, does not imply less reassurance as regards efficacy and safety of the biosimilar if all the aforementioned considerations are taken into account, and represents a logical consequence of the scientific concept. Therefore, clinicians should have confidence in using biosimilars for all indications for which they have been licensed.

7. The question has been raised whether biosimilars could be considered interchangeable (in the sense of a therapeutic alternative initiated by, and under surveillance of the treating physician) with the respective reference product and, consequently, the concern that automatic substitution at the pharmacy level (without the knowledge of the physician) might follow.[6,18,28]

Undoubtedly, biosimilars developed in line with EU requirements can be considered therapeutic alternatives to their respective reference products. Interestingly, it has been stated that the originator products epoetin alfa and epoetin β are considered as interchangeable by healthcare professionals because of the long medical experience with both products.[36] Although both epoetins can undoubtedly be considered efficacious and safe, similarity has never been demonstrated in a head-to-head comparison and dosage recommendations are not fully identical as would be required for a biosimilar.

The main argument against automatic substitution is the concern regarding traceability, which is necessary for a root cause analysis in case an ADR occurs.[6,17,30,35] The importance of reliable traceability of biologicals has been acknowledged, particularly for epoetins, and a respective statement has been introduced into the prescribing information of all epoetins licensed in the EU.[37] In addition, the novel pharmaceutical pharmacovigilance legislation being implemented in 2012 should, among other things, ensure European-wide traceability of medicinal products.[38] Another, more theoretical concern regarding automatic substitution is the possibility that repeated switches between the biosimilar and the reference product may increase immunogenicity with potentially negative effects on the safety and/or efficacy of the products.[13,36] This would, however, also apply to switches between different originator biologicals of the same class. Automatic substitution may be difficult from a practical viewpoint, especially for patients self-administering the medicinal product, in case of differences in injection devices, preparation and handling of the biosimilar, which may increase the risk of medication errors or impair treatment compliance.

It has been suggested that a change from an established epoetin to a biosimilar agent should require informed consent from the patient.[39] Although the authors agree that patients should always be informed about the medicine they are prescribed or given, the necessity of an informed consent for the switch to a biosimilar is considered a disproportionate measure because biosimilars, as any new drugs, are scrutinized by the competent authorities during the marketing authorization procedure to ensure that only products with adequate quality, efficacy, and safety are approved.

It should be noted that substitution policies are decisions outside the remit of the EMA because the regulation of substitution of medicinal products is the responsibility of the individual EU member states. To our knowledge, up to now, automatic substitution has not been implemented for any biosimilar in the EU; and, according to the European Generics Association, more than a dozen countries across Europe have introduced rules to prevent automatic substitution of biologic medicines by biosimilars.[40]

Implications for patients and treating physicians

The expected benefits of biosimilars are reductions in acquisition expenses and consequently better access to biotherapeutics while

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containing health expenditure.[41] Because of the long development time and related high costs of biosimilars, partly because of considerable regulatory requirements to ensure their quality, safety, and efficacy, the reduction in their acquisition price is unlikely to be as profound as for chemical generics. Still, the absolute price difference between biosimilar and originator products can be substantial for expensive biopharmaceuticals and can be expected to increase as biosimilars gain market share. For instance, it has been estimated that a 20% price reduction of 5 off-patent biopharmaceuticals would save the EU > €1.6 billion per year and the US federal government $9 billion to $12 billion over the next 10 years.[41,42]

Of course, physicians should only prescribe medicines for which quality, safety, and efficacy have been demonstrated according to state-of-the-art science and technology, with the exception of drugs used in clinical trials or for compassionate purposes. Because biosimilars are licensed based on a reduced data package, physicians might misinterpret this as a nonreassuring basis to use biosimilar drugs for their patients. To alleviate unsubstantiated fears, physicians need to gain a clear understanding of the biosimilar philosophy, including the scientific principles as discussed in this article. The data package required for licensing of a biosimilar is not simply reduced. It is scientifically tailored and includes an extensive comparability exercise using sensitive analytical tools and sensitive test models to provide reassurance that the biosimilar and the respective reference product are indeed highly similar. Based on such extensive comparative data, there is no scientific reason to assume that the biosimilar would behave differently from the reference product when used in clinical practice.

The understanding of the biosimilar concept will become increasingly important when even more complex biologicals, such as monoclonal antibodies, are developed as biosimilars.[43] For example, the most sensitive clinical model for investigating potential product-related differences in efficacy of anticancer monoclonal antibodies might not necessarily use overall survival as the primary end point, which is usually considered as the gold standard to establish patient benefit. However, overall survival is usually confounded by many factors unrelated to the performance of the drug itself, which might, despite randomization, not be sufficiently balanced between treatment groups unless the study is extremely large. For a biosimilar, other primary clinical end points that are more sensitive (eg, objective response rate or change in tumor mass), focusing on the detection of potential differences in efficacy rather than the demonstration of efficacy per se, may be more appropriate.[44]

With regard to safety, physicians should understand that the nonidentical nature of a biosimilar and the more familiar reference product is inherent to all biologicals, and is also true for differences that might arise from a change in the manufacturing process of an established biologic product.[45] It is well known that the problem of epoetin antibody-induced pure red cell aplasia was first recognized after a major change in the manufacturing process used for an originator epoetin, and not with a biosimilar.[46] Because immunogenicity may be altered by such major but also by seemingly minor changes, human immunogenicity data are always required for the licensing of biologicals, including biosimilars.

Regulatory oversight and scrutiny are important to ensure the safe use of any biological. In particular, active postauthorization surveillance is a key factor. Therefore, physicians would be well advised to always document exactly which biological is used for an individual patient, as has been established for plasma-derived medicinal products. If an ADR occurs or is suspected, it is important to identify the specific product causing it. Thus, ADR reports should include, in addition to the International Nonproprietary Name, other indicators, such as brand name, manufacturer's name, lot number, and country of origin of the batch used.[47] This highlights the central role of well-informed and vigilant prescribing physicians and pharmacists in the overall concept of regulatory control of patients' health.

Finally, clear information about existing guidelines, access to unbiased information on biosimilars, and education of physicians regarding the clinical utility of biosimilars as well as improved communication between learned societies and regulators have been requested.[18,19,48]

Guidelines on the requirements for the development and licensing of biosimilars and responses to comments received during the external consultation phase are posted on the EMA homepage.[3] Information on the documentation submitted in support of a specific biosimilar application and the related scientific discussion and considerations of the Committee for Medicinal Products for Human Use are also publicly available as European Public Assessment Reports.[1] In addition, the prescribing information of a biosimilar product provides information about its biosimilar nature and directs the reader to the EMA homepage for further detailed information, which may assist physicians in making informed and appropriate treatment choices for their patients. The Working Party on Similar Biological (Biosimilar) Medicinal Products (BMWP) is open to discussions with all stakeholders and welcomes scientific input on their guidelines. Considering the previous absence of feedback from the European medical associations on the biosimilar guidelines, BMWP considers a more proactive approach to better involve the organized medical community in the public process of creating and updating the guidelines. To reassure practicing physicians, quality, safety, and efficacy of biosimilars are a key priority and of paramount importance to the BMWP in its efforts to act in the best interest of patients and particularly to ensure patient safety.[18]

Summary of key points

- The principles guiding biosimilar development are scientifically sound and shared in the European Union, the United States, and other highly regulated regions of the world.
- The scientific principles for establishing biosimilarity are the same as those for demonstrating comparability after a change in the manufacturing process of an already licensed biological.
- A biosimilar should be highly similar to the reference product in terms of physicochemical and functional characteristics, and clinical performance.
- The focus of biosimilar development is not to establish patient benefit per se but to convincingly demonstrate close similarity to the originator product as a basis for relying, in part, on efficacy and safety experience gained with this reference product.
- The biosimilar development program is scientifically tailored using up-to-date analytical tools and sensitive test models to best detect even small potential product-related differences between the biosimilar and the reference product. Clinical end points may thus be different from those used in the reference product's clinical trials if clinically meaningful and scientifically justified.
- Extensive structural and functional characterization and comparison of the biosimilar and the reference product are the foundation of biosimilar development.
- The primary amino acid sequence should be the same for the biosimilar and the reference product. Small differences in the

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micro-heterogeneity pattern of the molecule may be acceptable if appropriately justified with regard to its potential impact on safety and efficacy.

• The requirements for the pharmaceutical quality of biosimilars are the same as for any new biological.

• The type and magnitude of clinical data requirements depend on the complexity of the active substance and how well it can be characterized, on the availability of an accepted surrogate end point to assess efficacy, on the type and seriousness of safety concerns, and the possibility to extrapolate efficacy and safety data to other indications of the reference product.

• Human safety (including immunogenicity) data are always required for biosimilars before approval.

• Extrapolation of efficacy and safety data to other indications of the reference product that have not been investigated during the clinical development of the biosimilar always requires convincing scientific justification, which should address the mechanism of action, toxicities, and immunogenicity in each indication of use.

• Decision-making of the regulatory authority is based on the totality of the evidence provided by the applicant in support of biosimilarity.

• A risk management plan for post-licensing surveillance is routinely required for all new drugs, including biosimilars.

• Traceability is important for all biologicals, including biosimilars.

• Biosimilars can be considered therapeutic alternatives to the reference product.

• Information on licensed biosimilars is available from the European Public Assessment Reports and may further assist clinicians in making informed and appropriate treatment choices for their patients.

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Teaching Point
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Pure red cell aplasia after treatment of renal anaemia with epoetin theta

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Introduction

The treatment of renal anaemia in patients with chronic kidney disease (CKD) has always been a challenge. The introduction of erythropoiesis-stimulating agents (ESAs) appeared to be a milestone, enabling physicians to avoid red blood cell transfusions in this patient group. In the last decade, however, these assumed advances were tarnished by the occurrence of a new condition: ESA-induced, antibody-mediated, pure red cell aplasia (PRCA). PRCA is characterized by the combination of anaemia, low reticulocyte count, absence of erythroblasts in the bone marrow, resistance to therapy with ESAs and detection of neutralizing antibodies against erythropoietin.

The exposure-adjusted incidence of 0.02–0.03 per 10 000 patient years is considered rare. In the years 2002 and 2003, it peaked, however, at an incidence of 4.5 cases per 10 000 patient years, mainly caused by a preparation of epoetin alfa [1]. Hypothetic explanations concerning the PRCA-inducing potential of this specific preparation of epoetin alfa have been published [1]. Nevertheless, we have to accept the possibility that all ESAs can induce an immunological response in the form of neutralizing antibodies [2, 3]. Because of the complexities of manufacturing biopharmaceuticals, there are safety concerns regarding me-too biologicals and biosimilars and the automatic substitution of originator drugs for economic reasons [4, 5]. In the interest of patient safety, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines only recommend the use of biosimilars approved by an independent regulatory agency that are subject to pharmacovigilance plans [6].

We report on a patient treated with the originator drugs such as epoetin theta, epoetin beta and darbepoetin alfa, who developed ESA-induced PRCA. The repetitive switching of agents hampered our ability to attribute PRCA to the appropriate agent.

Case description

A male patient, born in 1943, first presented in our nephrology unit in 2006 with glomerulonephritis [nephritic urine, hypertension, creatinine 1.90 mg/dL (168 μmol/L), haemoglobin (Hb) 14.3 g/dL (143 g/L), Figure 1], refusing a morphological diagnosis (kidney biopsy). The patient returned in 2009, again presenting with nephritic urine, creatinine at 4.56 mg/dL (403 μmol/L) and Hb 12.2 g/dL (122 g/L). In 2010, there was a slow progression of renal insufficiency, with creatinine at 5.20 mg/dL (460 μmol/L) and Hb stable at >12.0 g/dL (120 g/L). In 2011, creatinine increased to 8.30 mg/dL (734 μmol/L), with decreasing Hb levels. In May 2011, Hb was at 10.3 g/dL (103 g/L). A normochromic, normocytic blood count was unsuspicious of iron deficiency. We started subcutaneous (s.c.) erythropoietin substitution using epoetin theta. Hb rapidly increased to 12.0 g/dL (120 g/L), where we stopped epoetin theta administration upon reaching the upper limit of the Hb target. In October 2011, Hb had again decreased severely to Hb 9.3 g/dL (93 g/L), triggering a new sequence of epoetin theta. Because of the beginning of uraemic symptoms, we started renal replacement therapy, choosing continuous ambulatory peritoneal dialysis (CAPD). After initiation of CAPD, we observed a continuous decrease of Hb to 7.9 g/dL (79 g/L), despite an increase of epoetin theta dose. A detailed workup was initiated to identify reasons for the Hb non-response, showing an iron status of total iron 66 μg/dL (11.81 μmol/L), transferrin level 168 μg/dL (19.09 μmol/L), transferrin saturation 27.9% and ferritin 358 μg/mL (755.38 pmol/L). Reticulocyte counts remained constantly low with levels of ≤1.2% (proportion of red blood cells of ≤0.012). A bone marrow sample showed a hyporegenerative state. We tested for anti-erythropoietin antibodies using radioimmunoprecipitation (RIP), with negative results (Laborinstitut Prof. Seelig, Karlsruhe, Germany).

Subsequently, the patient changed to a different dialysis centre, where he was switched to epoetin beta. Since the patient self-administered the product, he was further switched to the longer-acting, subcutaneously administrable darbepoetin alfa. Both epoetin beta and darbepoetin alfa were unable to improve the patient's Hb. In May 2012, we repeated the test for anti-erythropoietin antibodies in two different laboratories: (i) Laborinstitut Prof. Seelig, Karlsruhe, Germany (RIP), and (ii) IPM Biotech,

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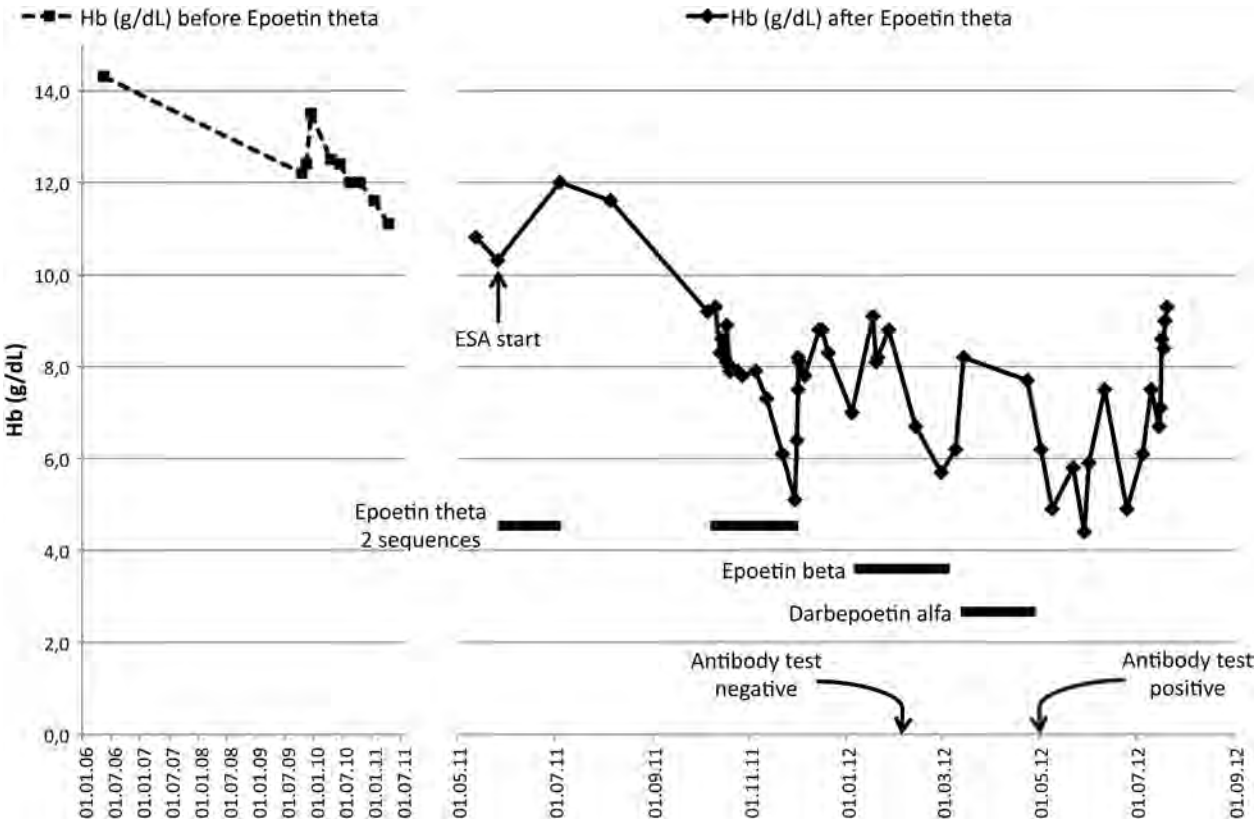

Fig. 1. Hb trajectory and treatment history. ESA, erythropoiesis-stimulating agent.

Hamburg, Germany (bioassay using the human erythroleukaemia cell line TF-1; see Supplementary Material for a description of the testing procedure). Both antibody tests were positive, with the bioassay revealing a highly positive antibody titre of 1:1600. We immediately stopped the administration of any ESA and switched the patient to red blood cell transfusions. We started immunosuppression with prednisolone 75 mg and cyclosporine A 200 mg (target cyclosporine A level: 100–150 ng/mL; 83.2–124.8 nmol/L), which resulted in a life-threatening peritonitis caused by *Prevotella melaninogenica* and *Bacteroides* sp. We stopped immunosuppressive treatment and evaluated the patient for renal transplantation after earlier refusal.

Discussion

PRCA is triggered by the development of neutralizing antibodies against endogenous erythropoietin that may cross-react with different ESAs [7]. It is assumed that all biopharmaceuticals, including protein-based ESAs, are immunogenic [5]. However, the mechanism of how the natural B-cell tolerance is broken remains to be elucidated. Two major causes have been identified: (i) changes to the three-dimensional (3D) structure of the protein (protein aggregation) and (ii) route of administration.

(i) Protein aggregates can activate autoreactive B-cells by resembling the repeated self-epitope structure of viral capsids. Protein aggregation is not fully understood, but there are three potential mechanisms. First, aggregation may be triggered by the presence of small amounts of a contaminant, such as a damaged form of the protein itself, host cell proteins or even non-protein materials (organic leachate of uncoated rubber stoppers of prefilled syringes, polysorbate 80, tungsten). A second mechanism is partial unfolding of the native protein during storage. Some partially or fully unfolded protein molecules are always present in protein solutions, but mostly refold to their native structure. Alternatively, these unfolded proteins may co-aggregate with other such molecules or may be incorporated into an existing aggregate to form larger aggregates. Elevated temperature, shaking (shear and airliquid interface stress), surface adsorption and other physical or chemical stress factors facilitate the aggregation of unfolded proteins. Since the patient self-administered the ESAs, it is thinkable that an interrupted cold chain had triggered this process. The interruption of the cold chain may be less problematic with long-acting ESAs, as they have a longer stability at room temperature compared with short-acting ESAs [8–11]. A third aggregation mechanism is self-association of the native protein to form oligomers. Oligomers vary with solvent conditions such as pH and ionic strength, are very difficult to detect and can become irreversible [12]. These product-related factors are of high interest, especially in consideration of the increasing number of ESAs and manufacturers entering the markets and the high economic pressure to produce and prescribe cheaper medical products. The specific demands on storage and handling of a sensitive product, such as erythropoietin, may also be too complex for—mostly elderly—patients.

(ii) The route of administration of ESAs was also related to PRCA. The s.c. route seems to evoke a stronger immune response than the intravenous (i.v.) route,

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possibly due to the high concentration of antigen-presenting cells in the skin and the longer local presence of the antigen. Epidemiological data support this theory. The incidence of PRCA is estimated at 0.67 per 100 000 patient years for i.v. and 20.66 per 100 000 patient years for s.c. administration [13]. However, the s.c. route of administration has organizational benefits, especially for both CAPD and CKD patients not on dialysis.

The detection of the neutralizing antibodies was a challenge in our case. In retrospect, the Hb trajectory, the reticulocyte count and the bone marrow sample clearly identify epoetin theta as the trigger of PRCA. Nevertheless, the first examination of the patient's serum using a RIP assay was negative. Only the control tests months later (RIP and TF-1 bioassay) were positive. By this time, however, two more ESAs (epoetin beta and darbepoetin alfa) had been administered. Therefore, the sensitivity and degree of reliance of the antibody tests are essential [14]. There are several types of binding antibody assays, including enzyme-linked immunosorbent assays (ELISA), RIP, the BIAcore biosensor assay and various other bioassays, as reviewed in detail by Thorpe and Swanson [15]. ELISA assays generally have a poor ability to detect lower-affinity anti-erythropoietin antibodies with limited utility as a screening assay. RIP assays are more apt for screening purposes. They measure binding antibodies and their production in amplitude or time to appearance and have been shown to correlate with the severity of symptoms of PRCA. In our case, however, the RIP assay did not detect antibodies, despite the apparent Hb drop and non-response to epoetin theta. Bioassays are used for measuring the neutralizing capability of anti-erythropoietin antibodies. They are also used for studying the binding stoichiometries of antibodies with their target proteins [15]. In our case, a bioassay using cultures of the human erythroleukaemia cell line TF-1 was used to confirm the results of the second RIP test.

An immunological response usually develops gradually over several months and can be present before the occurrence of clinical symptoms. Additionally, the life-cycle of erythrocytes is ~2 months, making an abrupt drop in Hb a rare event, thus dampening the chances to perform clarifying tests in time. For these reasons, it is assumed that full-blown antibody-mediated PRCA may be identified as late as 1 year after the first occurrence of an immunological response. As we have observed a continuous decline in Hb early in the course of ESA treatment and started a detailed workup to detect the underlying causes at the first signs of hyporesponsiveness to epoetin theta, it is unclear, why the RIP test did not detect the presence of antibodies in our patient. It has been observed that the RIP assay is used in various laboratory conditions and formats, leading to large differences in sensitivities and specificities of different assays [15]. In our case, however, the results of the second RIP test were confirmed by the bioassay, excluding quality issues as an explanation.

Due to the wide range of marketed ESAs, including me-too biologicals and biosimilars, there is a high economic pressure on ESA manufacturers and health care providers. The reimbursement authorities expect physicians to prescribe the cheapest products and to accept repetitive switching of agents. As the presented case impressively demonstrates, it seems—from a safety point of view—preferrable to avoid repetitive switching. After a series of different products has been administered, the PRCA-triggering product can only be identified if the accompanying severe anaemia and/or antibodies have been detected before the switch. Therefore, traceability of all ESAs given to a patient is essential. Ideally, a serum sample should be stored before any switch is made, but this seems to be very difficult in clinical practice [4, 16, 17].

Conclusion

The pathogenesis of ESA-induced PRCA remains unclear. Several, partly hypothetical, causes are discussed in the literature, such as patient- or product-related factors. Additionally, treatment duration, route of administration, inappropriate transport and storage, or the frequent change of ESAs may play a role. Until the true causes of PRCA have been identified, it is necessary to be alert to the dangers of frequent, cost-driven changes in ESAs, to reconsider the route of administration and to increase our efforts in pharmacovigilance.

Teaching points

(i) The main challenges with biopharmaceuticals—originators, me-toos and biosimilars—are variable potency and immunogenicity. These are hypothesized to be due to glycosylation, contamination and changes to 3D structure, which may occur between products and even between batches.
(ii) PRCA is a potentially life-threatening immune response caused by neutralizing antibodies against endogenous erythropoietin that may cross-react with different ESAs. It can theoretically be induced by any protein-based ESA.
(iii) Any product substitution should only be made with the specific approval of the prescribing physician. Procurement practices in the hospital sector should always provide for a sufficiently broad choice of products.
(iv) In the case of PRCA, product changes may prohibit the identification of the antibody-causing product, a practice, which has to be reconsidered in the interest of pharmacovigilance.

Supplementary data

Supplementary data are available online at http://ckj.oxfordjournals.org.

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