



September 17, 2013

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061
Rockville, MD 20852

CITIZEN PETITION

The Generic Pharmaceutical Association (GPhA) submits this petition under 21 C.F.R. § 10.30 to request that the Commissioner of Food and Drugs take the action requested below.

A. Action Requested

GPhA respectfully requests:

- that FDA implement its INN naming policy equally to all biologics; and
- that because all biologics approved under the Section 351(k) pathway are “highly similar”; and thus, have no clinically meaningful differences from the reference protein product (RPP) that they *share the same INN name as the RPP*, just as comparable originator products produced by a change in a manufacturing process or facility (post-change product) share the same INN as the original RPP (pre-change product).

B. Statement of Grounds

Background and Overview of the Naming of Biosimilars

The World Health Organization (WHO) administers the international naming convention known as the International Non-proprietary Naming (INN) system. An INN names the active ingredient, such that products that share the same INN can be readily identified as sharing the same active ingredient¹. Conversely, different INNs denote products with different active ingredients. The INN has never been the name of the final, formulated product itself. In addition to the INN, a product (including biosimilars) will have other names and identifiers; for example, a brand name and in the US a national drug code number (NDC), that readily distinguish it from other products that share the same INN.

In the US, local non-proprietary names can be assigned by the United States Adopted Name (USAN) Council, which is co-sponsored by the American Medical Association (AMA), the United

States Pharmacopeial Convention (USP), and the American Pharmacists Association (APhA) and includes FDA representation. The USAN program aims to select simple and informative non-proprietary names² (also called generic names) for drugs and biologics by establishing logical nomenclature classifications based on pharmacological and/or chemical relationships. The USAN Council works in conjunction with the WHO INN Expert Committee and other national nomenclature groups to standardize drug nomenclature and establish rules governing the classification of new substances. Usually the USAN and the INN match each other.

The Biologics Price Competition and Innovation Act (BPCIA), enacted March 23rd, 2010, specifically authorized the approval of biosimilars and interchangeable biologics. The legal and regulatory approval standards allow FDA to approve a biosimilar upon a showing that it is highly similar to its RPP and the Agency conclusion that the biosimilar does not have clinically meaningful differences from its RPP.³ After approval by FDA, a biosimilar would share one, some, or all of the labeled indications of its RPP. An interchangeable biologic is a biosimilar that must be supported by additional data to FDA to allow a conclusion that it can be switched with its RPP during treatment, and they are by law substitutable at the pharmacy without the need to inform the original prescriber of the switch (that prescriber can, as with any other product, preclude such a switch by checking the do not substitute box on the prescription).

No provision of the BPCIA addresses the naming of biosimilars.⁴ The absence of such provisions in the law does not reflect an oversight by Congress. In fact, during drafting of the bill, legislators discussed in detail whether unique INNs should be required for biosimilars, and then chose not to include language that would have provided for separate INNs. Without new statutory authority, FDA lacks specific authority to require separate INNs for biosimilars, and existing conventions for biologics should be expected to prevail.

FDA outlined its naming position for biosimilars in a policy paper sent to the WHO in 2006, in support of the current WHO naming conventions.⁵ In this paper, FDA clearly supports the original purpose of the INN (to identify the active ingredient of a product), rejects the use of non-proprietary names to communicate interchangeability, and states that concerns about pharmacovigilance “transcend a naming convention,” explaining that “[i]t would be the FDA’s preference that INNs continue to be granted based only on molecular characteristics and pharmacological class of the active ingredient(s).”⁶ In this paper FDA agrees that there should be no change in global policy and rejects distinctive INN designations for biosimilars. The 2006 FDA policy is widely supported by multiple stakeholders. For example, Congresswoman Anna Eshoo, in her April 16, 2012 letter to the FDA biosimilar guidance docket stated that a unique proprietary name for biosimilars is needed, but a unique non-proprietary name is not.⁷ Multiple pharmacy groups have expressed their support in letters to Commissioner Hamburg.⁸ While BPCIA was enacted subsequent to this policy position being presented to WHO, nothing in the new statute is incompatible with the 2006 FDA position on biosimilar naming.

Given that FDA is a scientific, data-driven agency, the Agency is obligated to apply its standards equally to all applicants and products. Requiring unique INNs for biosimilars while allowing sharing of INNs for other biologics in comparable situations would run contrary to this tenet. FDA routinely allows originator biologic products in the same class approved under separate 351(a) or 505(b) applications and using different manufacturing methods implemented by different sponsors to share the same INN. For example, a number of Anti-hemophilic Factor (Recombinant) products, some of the most complex biologics licensed in the US, share the same INN. Attached, as Appendix A, is a list of products which share INNs, most of which have never been compared and several of which have known differences but still share the same

INN.¹ Further, FDA has for many years without question authorized originator manufacturers to modify biologics' manufacturing processes and develop biologics that have minor changes and differences that are not clinically meaningful without requiring a change in non-proprietary name. This authorization is contingent on a sponsor submitting data that the post-change product is "comparable" to the pre-change product. If the sponsor demonstrates such comparability FDA deems the (pre- and post-change) products interchangeable for all indications irrespective of the mechanism of action being understood. The standard for both comparability and biosimilarity is "highly similar" quality attributes.⁹

As FDA itself articulated in its 2006 Policy Paper:

"Considering the inherent difficulties in additional INN product distinctions (e.g. retroactive and lifecycle changes in naming, additional INN responsibility and liability), if the world community decides to proceed with a change in the policies regarding the assigning of INNs, it should be preceded by (a) appropriate exploration of alternatives (e.g. improvements in education and/or labeling), (b) assuring the such changes fall within the scope, competence, and expertise of the INN program, and (c) the performance and independent validation of a formal risk assessment and/or documentation of events with appropriate statistical treatment."¹⁰

GPhA concurs that any concerns with pharmacovigilance call for tailored solutions capable of fixing the actual problem without creating additional confusion. Unsupported pronouncements of inadequate tracking capabilities for biosimilars with the same INN as their RPPs represents, at best, a hypothetical problem given that no biosimilars have yet been approved in the US and Europe has been successful at tracking biosimilars which share INNs with their RPPs. Rather than using inadequacies with pharmacovigilance systems as a whole to assert that biosimilars alone will have tracking and tracing issues and suggesting unique INNs will remedy the stated but unspecified concerns, patients would be better served if we focused on practitioner education and system enhancements to address any problems in the pharmacovigilance system for all pharmaceutical products. Currently, a well-established process exists to track product quality problems that does not rely primarily on INNs, but instead uses a product's brand name, manufacturer, lot number and NDC to track quality and safety events. GPhA does not believe requiring unique INNs for biosimilars could remedy the poorly defined concerns and, instead would cause confusion and potential harm to patients by interfering with the present system. In contrast, we fully support vigorous enhancement of track and trace and education of physicians and pharmacists to include NDCs, manufacturer names and other relevant identifiers on all safety reports. This applies equally to all biologics, and must not be used as a wedge to create an anticompetitive barrier to biosimilar development and commercialization.

In summary, a major goal of the BPCIA is to create competition in the marketplace for biologics, thereby expanding access to, and increasing the affordability of, these critical medicines. Adoption of unique names for each biosimilar could frustrate this goal as well as jeopardize patient safety, inhibit market competition and innovation, and disrupt the current global naming system. GPhA proposes that the same scientific principles that underlie the 60-year-old policy of INNs, as applied throughout the world to drugs and biologics, also must apply to biosimilars. This means that as a fundamental element of its licensure, each biosimilar product should have the same INN as the single RPP to which it has been demonstrated to be highly similar and to have no clinically meaningful differences.¹¹ FDA will not approve any biosimilar product that does not achieve these standards. Moreover, it is beyond any reasonable reading of the BPCIA

that interchangeable biologics would not share the same INN as the RPP, because FDA would have concurred that they had been shown to be fully substitutable without the need for physician intervention. While sharing an INN, each biologic and biosimilar will have a unique manufacturer name, NDC, lot number and brand/trade name and therefore will be readily distinguishable in the same manner as originator products are today. Biosimilars have already been given the same INNs as their RPPs in other highly regulated regions throughout the world and have not been confused¹². As explained below, maintaining consistency in applying scientific principles to regulatory matters requires that if FDA were to require new INNs for biosimilars, all existing products that share INNs would need to be renamed, and new INNs would be needed in every instance of a manufacturing change to a currently licensed product. This would require a significant and immediate regulatory review and renaming effort by sponsors and FDA for virtually every licensed biologic on the market in the US today. We expect that FDA's existing policy on naming will continue to be consistently applied to all biologics, biosimilars included. FDA should implement a policy that promotes biologic safety by allowing biosimilar products to share INNs with their RPPs.¹³ It is also very important to consider the negative impact on utilization and uptake of the 351(k) pathway that different INNs would create, and therefore the barrier to meet the overall access and competition objectives of the BPCIA that would be being created by any such requirement.

Biosimilars, as Highly Similar to their RPPs, Should Share INNs with their RPPs just as Post-Manufacturing Change Biologics Share INNs with their Pre-Change Versions

FDA uses state-of-the-art science to review and approve biologics. The Agency has in-depth understanding of all the biologics that it has reviewed and licensed for the US market, and by definition these will comprise the entirety of the RPPs for biosimilars in the US¹⁴. GPhA's goal is to see FDA's experience and expertise with biologics consistently and fairly applied to all sponsors based on the Agency's current application of the same scientific principles for changes made to biologics submitted pursuant to Section 351(a) as for approving biologics submitted under Section 351(k). Specifically, regulatory authorities oversee manufacturing changes with comparability approaches by using many of the same "highly similar" analytical standards as have been written into the biosimilar legislation enacted by Congress. This has been coordinated among regulatory authorities across the highly regulated markets and gone through full notice and comment rulemaking in the US¹⁵. It is the highly similar standard with which FDA has extensive experience and enables full extrapolation of indications and interchangeability of the resulting biologics on the US market today.

The highly similar biosimilar standard is conceptually the same regulatory standard that FDA currently applies to originator products undergoing manufacturing changes – a showing of similarity between batches of active ingredient before and after the manufacturing change enables FDA to conclude that the batches have no clinically meaningful differences. With this evidence, a comparable post-change product is permitted to use the same established non-proprietary name, and is even viewed as interchangeable with the pre-change product. A comparable biologic product must have all of the pre-change product's indications and be interchangeable for every single one of them (even without an understanding of the product's mechanism of action). Such is the confidence in the "sameness" of the resulting products that neither health care providers nor their patients are informed about the change (nor are the data that form the basis of these supplemental applications made publically available. This standard is already being successfully used for biosimilar approval (as well as manufacturing changes to biosimilars) in other highly regulated markets¹⁶. In scenarios, manufacturing changes and biosimilar approval, the demonstration of highly similar analytical and functional characterization

is an essential component for the regulatory authorities', including FDA's, expectation that the clinical outcomes of the products will be the same. Further, in contrast to manufacturing changes which do not routinely require thorough characterization involving animal and clinical studies¹⁷, biosimilar approval will likely require a higher level of characterization using a stepwise development approach where *in vivo* studies for immunogenicity are routinely expected. This approach, along with FDA's authority to request any information that it deems essential for approval of a biosimilar product, assures there are no meaningful clinical differences between a biosimilar and its RPP.

We recognize the biologic variability inherent in manufacturing changes and that comparability analysis is critical to the supply and availability of these products to the patients that need them. Data published in peer-reviewed scientific literature demonstrates that while originator products do change over time, they are generally well-controlled between manufacturing changes, and, even after manufacturing changes, the clinical attributes of the products are acceptable¹⁸. GPhA does not believe that FDA should vary from their own current practice and assign unique INNs for those approved biologics that undergo post-approval changes that are deemed acceptable based on comparability testing. However, because the post-change product bears the same name and its label is unaltered after a manufacturing change, patients and their providers are not informed that a change has occurred even though the post-change product is only similar to (i.e., not the same as) the pre-change product. In the interests of transparency and further regulatory consistency, all use of comparability for U.S. biologics should be made public, just as it is for biologics in Europe and just as it will be for biosimilars. A recent paper from a European regulator shows the extent of the use of comparability – one instance being 37 manufacturing changes post-approval for Remicade® (infliximab)¹⁹. This information could also be indicated in labeling so that patients and their health care providers can readily access this information. Likewise, having the manufacturer name on the label alerts providers and patients to a biosimilar.

In sum, because of the robust science used for both biosimilars and comparability assessments, GPhA believes that all products that are found to be highly similar should be assigned the same INN. Should FDA believe that biosimilars require different INNs than their RPPs, there will be consequences for all biologics because regulatory parity and consistent scientific reasoning dictates that if biosimilars require unique INNs then:

- (1) all current products sharing INNs must be re-examined;
- (2) in the future FDA must require new INNs for any product, originator or biosimilar, which undergoes a manufacturing change using comparability.

Consequently, a significant and immediate regulatory review and renaming effort by sponsors and FDA would be triggered for virtually every licensed biologic on the market in the US today. This would then be the immediate priority for FDA as these are the products currently available on the US market today, whereas no biosimilar application has yet been filed with the FDA. There is simply no reasonable distinction between biosimilars (as highly similar to their RPPs) and post-manufacturing change biologics (as highly similar/comparable to their pre-change counterparts) that warrants a unique INN for biosimilars and not for post-manufacturing change biologics.

Pharmacovigilance

A. The Global Pharmacovigilance System Works, Products Sharing INNs in the US and European Biosimilars Sharing INNs with their RPPs Are Successfully Tracked and Tracked

In the current global system used for drugs and biologics, the INN is the name of the active ingredient, not the name of the product, nor the sole basis of prescribing²⁰. FDA has already endorsed this system for biosimilars as well (discussed above, and attached²¹). To keep with the intent of the INN, which is to allow immediate identification of a product's active ingredient, all biosimilar products should share an INN with their RPP because they must contain, as a fundamental requirement of their licensure, the same active ingredient. Some have asserted that biosimilars sharing an INN with their RPP can or will interfere with successful tracking of specific products leading to safety concerns. However, we are not aware of any evidence of a problem unique to products sharing INNs or even potentially unique to biosimilars alone. Nor do we believe that this will be the case given that (1) no biosimilars are currently marketed in the US, therefore any current problems in the US pharmacovigilance system cannot be attributed to biosimilars, (2) we know of no tracking issues with currently marketed originator products sharing INNs and (3) experience with marketed biosimilars in highly regulated markets outside the US has identified no safety issues resulting from biosimilars sharing INNs, and their use is now sufficiently extensive that even unusual events would be expected to be caught²². Thus, there is no safety reason to give a unique INN to a biosimilar in the US, especially since the biosimilar will have been found, by virtue of its FDA approval, to be highly similar and to not have any clinically meaningful differences from the RPP.

To elaborate, because biosimilars have not yet entered the US market, any problems with the current US pharmacovigilance system cannot be attributed uniquely to biosimilars and, therefore, a remedy specific to biosimilars alone is not appropriate if the goal is to optimize patient safety. Second, GPhA is unaware of pharmacovigilance issues that have arisen as a result of products sharing the same INN. For example, as expressed in our September 4, 2012 letter to FDA Commissioner Hamburg²³, FDA currently allows different recombinant and naturally-derived products from different manufacturers to share INNs. These examples include ones in which multiple products, *which have never been compared*, share the same INN. No demonstration of "sameness" was required by FDA for the approval of such products and indeed if they were to be compared, differences would be expected.²⁴ As further evidence that an INN is not meant to convey the "sameness" of the product itself, FDA routinely supports the same name for biologics even after comparability testing demonstrating that highly similar quality attributes have *not* been shown (see Myozyme[®] and Lumizyme[®] in the table attached as Appendix A). Similarly, with regard to comparability testing of pre- and post-manufacturing changes, FDA allows the same INN to remain with the product based on the pre- and post-change products having been shown to be "highly similar"/comparable (recognizing that they are not the same but only similar²⁵). And comparability has been used multiple times on the same originator products since their licenses were first issued – as mentioned above with 37 published in Europe for Remicade[®] (infliximab).²⁶ Importantly, these products are currently being marketed and made available to patients in the US today. If there are any concerns, at FDA or from other stakeholders, about possible confusion through shared nonproprietary names then these are the products that must be addressed first.

In fact, we believe that experience with manufacturing changes to originator products in the US demonstrates that track and trace mechanisms are more than adequate to assure patient safety among highly similar products (i.e., in this case post and pre-manufacturing changed originator

products) as well as standalone independently approved products (see Appendix A). Current regulations require the manufacturer's name on the product label, and GPhA member companies are committed to labeling biosimilar products with their corporate names and/or product proprietary (brand) names. Each container label will prominently display a brand name in addition to the INN (the same information as is required for an originator product), even on the smallest dispensed unit of a biosimilar (as a parenteral). Therefore, even if problems are specific to a particular product, the label information including the biosimilar proprietary name, manufacturer, lot number and NDC will allow for specificity in tracking and tracing of biosimilars. In practice, when an adverse event is reported to FDA that triggers a need to investigate, the Agency typically contacts the physician and then checks with the pharmacist to determine the product's manufacturer and precise batch information. This specific information, not the product's INN, enables FDA and the actual manufacturer to investigate possible causes of the adverse event. Unique INNs do not provide any additional information to enhance the current system of tracking and tracing products.

To better understand adverse event (ADE) reporting practices, GPhA commissioned an independent research group (Drug Safety Institute, a division of Brand Institute, Inc.) to evaluate health care practitioner preferences and recommendations related to ADE reporting.²⁷ This practitioner survey identified which reporting elements health professionals reported as most critical and thus which elements are most likely to be reported.²⁸ Health professionals typically report multiple elements whenever possible and include only the INN as the sole data point less than 30% of the time.²⁹ This data supports GPhA's view that the INN is only one of several identifiers of a product that is important to capture for purposes of pharmacovigilance, and further demonstrates that creating a unique or differentiated INN is not likely, in and of itself, to result in a substantive improvement in pharmacovigilance practices. Likewise, FDA's own Guidance for Industry "Contents of a Complete Submission for the Evaluation of Proprietary Names"³⁰ notes that:

"In the U.S. medication-use system, health care providers rely on the proprietary name as the critical identifier of the appropriate therapy in a market of thousands of products."

If a concern exists that the US track and trace system is inadequate for biosimilar products, then that same concern applies equally to post-manufacturing change products and arguably even more so to products that share the same non-proprietary name but have not been compared or have failed comparability. Moreover, if the problem perceived is precision reporting of pharmacovigilance information, then we should fix the actual problem for *all biologics and products*. Fortunately, emerging technology can contribute to improved reporting and record keeping using the current systems. For example, FDA in collaboration with Boston Children's Hospital and Harvard Medical School has developed a smartphone and computer APP, Medwatcher,³¹ which allows a physician, patient or pharmacist, with the click of a button, to submit a photograph of the label within an adverse event report from their mobile phone or personal computer. The photograph can clearly identify more than the INN name. For example, the following photograph could accompany the report and be sent in real time using the APP, leaving no doubt as to the manufacturer or the batch and lot number.

<p>24 mg Combination Package</p> <p>NDC 0002-8149-01 MS 8149</p>	<p>24 mg Combination Package</p>	<p>SH654FSAM00</p> <p>CARTON HAS BEEN OPENED</p>	<p>24 mg Combination Package</p>
 <p>Humatrope® somatropin (rDNA origin) for injection</p> <p>24 mg Cartridge Kit</p> <p>for use only with the Humatrope® (somatropin [rDNA origin] for injection) pen injection device</p>	 <p>Humatrope® somatropin (rDNA origin) for injection</p>	<p>For Parenteral Use Only</p> <p>Cartridge VL 7556 contains:</p> <ul style="list-style-type: none"> • Humatrope [somatropin [rDNA origin] for injection], 24 mg • Mannitol, 72 mg • Glycine, 24 mg • Dibasic Sodium Phosphate, 5.43 mg • Phosphoric Acid and/or Sodium Hydroxide may have been added to adjust pH • Nitrogen Overlay <p>Diluent Syringe VL 7617 contains:</p> <ul style="list-style-type: none"> • Water for Injection with 0.3% Metacresol as a preservative • 0.29% Glycerin <p>For Dosage and Administration, see accompanying package insert.</p>	 <p>Humatrope® somatropin (rDNA origin) for injection</p> <p>Humatrope: Product of United Kingdom Manufactured into cartridges by Lilly France, F-67640 Fegersheim, France for Eli Lilly and Company, Indianapolis, IN 46285, USA</p> <p>Diluent Syringe: Product of Belgium</p>
<p>Rx only</p> <p>Refrigerate Do Not Freeze Do Not Shake</p>		<p>Refrigerate • Do Not Freeze • Do Not Shake</p>	
<p>Kit contains:</p> <p>One Humatrope Cartridge 24 mg One Prefilled Diluent Syringe</p> <p>www.humatrope.com</p>		<p>Before Reconstitution: Store in a refrigerator 2° to 8°C (36° to 46°F).</p> <p>To Reconstitute: See accompanying package insert. Reconstitute only with diluent provided.</p> <p>After Reconstitution: Store reconstituted solution in a refrigerator 2° to 8°C (36° to 46°F) and use within 28 days.</p> <p>This container is not child resistant.</p>	
<p><i>Lilly</i></p>	<p><i>Lilly</i></p>	 <p>3 00028 14901 0</p>	<p><i>Lilly</i></p>

This is just one example of an APP that provides an opportunity to improve adverse event reporting by making it quicker and easier to be more complete. These technologies continue to emerge as valuable tools for physicians and pharmacists that ameliorate any additional burdens that might otherwise be being seen to be imposed.

Finally, in Europe, where biosimilars have been on the market since 2006, biosimilars and their corresponding RPPs share the same INN. In each case, the individual biosimilar product is identified by a brand name. A recent study of the identification of biosimilars in the European Union pharmacovigilance system found that the naming convention for biosimilars has a successful product identification rate of 96.2% across all three marketed biosimilar classes currently on the market (somatropin, filgrastim and epoetin).³² There is no reason to expect that the US pharmacovigilance system cannot achieve similar or even higher product identification rates given that, unlike the European Union, the US has the advantage of a singular nationwide NDC product identification system for tracking.

B. Requiring That Each Biosimilar Have a Unique INN Could Jeopardize Patient Safety

Not only would requiring unique INNs for biosimilars not fix any purported problems with the current pharmacovigilance system, but it would in and of itself compromise patient safety.³³ Shared INNs between a biosimilar and its RPP accurately reflect the regulatory determination that there are no meaningful clinical differences between these products and thus indicate that both produce the same clinical outcome. Conversely, requiring a biosimilar and its RPP to use different INNs would, instead, inaccurately suggest that these products have meaningful clinical differences for patients. This would compromise patient safety in that: (1) clinician confusion may lead to prescribing errors, (2) access could be compromised and patients go untreated, and/or (3) safety data for these molecules would be disaggregated from the current system that allows for pooling of data, ensuring rapid identification and communication of class effects and lower frequency safety signals.

Specifically, a patient's health could be jeopardized if, for example, a physician inadvertently double dosed a patient by prescribing two highly similar products because he thought, based on their different INNs, that they contained different active ingredients. To avoid this, physicians and pharmacists would need to know the INN of every biosimilar and the INN for each RPP, and how they relate to each other (as well as the brand names since prescribing in the US is still largely by brand). Physicians also would need to be aware of the relationship between not only the biosimilar and its RPP, but also of potentially multiple biosimilars to the same RPP (that, likewise, would not be identifiable through the same shared INN). This would occur irrespective of whether FDA had designated some biosimilars as interchangeable with their RPP, while other sponsors had not sought the interchangeability designation.

As FDA explained in its 2006 policy paper:

"The issue of interchangeability is not an issue of nomenclature but a scientific question that needs to be decided on its own merit. The question of nomenclature is more relevant to concerns about pharmacovigilance and the prevention of inappropriate substitution. However, the FDA believes that these issues transcend a naming convention. It would be the FDA's preference that INNs continue to be granted based only on molecular characteristics and pharmacological class of the active ingredient(s)."³⁴

Currently, appropriate product sharing of INNs functions to instantly alert the physician to these relationships. This function would be destroyed if biosimilars and their RPPs could not share INNs. It would be similarly disruptive to currently approved products, and products pre- and post-manufacturing changes, as those products would similarly need different INNs in order to maintain regulatory consistency.

Furthermore, assigning unique biosimilar INNs may cause the INN to replace brand names as the primary means of identification and prescribing, increasing the potential for medication errors, given that unlike brand names³⁵, INNs are not specifically reviewed by FDA for the potential of creating medication errors (a process whereby confusion with other products through similar sounding names is minimized).

Unique biosimilar non-proprietary naming may also imperil appropriate state pharmacy substitution of interchangeable biosimilars, as interchangeable biologics with different INNs could be incorrectly thought to have a different active ingredient. Each interchangeable biologic would then have to be detailed and marketed—an unnecessary cost that patients and payers

would bear. The BPCIA explicitly contemplates interchangeability of the RPP and biosimilar product and, as the products are deemed to be the same, they should share the same name. Interference with the substitutability of interchangeable products is legally questionable and would significantly reduce the savings from biosimilars that public and private payers as well as patients. This lack of competition will likely constrain access for patients and so limit the public health goals expected to be attained through the availability of biosimilars. This will undermine the intentions Congress had in enacting BPCIA.

In addition, the use of unique biosimilar non-proprietary names would disrupt the current pharmacy systems (where the US established name³⁶ would not be the same as its INN, and may not even match its USAN³⁷), and this poses its own safety risks by interfering with the existing safety alert functions used today to protect patients. GPhA believes there is a real danger to forcing a separation of pharmacovigilance data into separate silos specific to each biosimilar product(s) and the RPP - this may represent a greater safety risks than the theoretical risks of sharing the same INN³⁸. Segregating relevant RPP and biosimilar pharmacovigilance data for their common active ingredient into two separate sets would obstruct appropriate pooling of data critical to patient safety³⁹. Importantly, it also would dissociate the US biosimilar from "itself" in markets outside of the US where its INN already matches that of its RPP. In a world of global pharmacovigilance, this would have a significant negative impact on patient safety by preventing timely data associations and making identifying and communicating safety signals difficult, if not impossible. Many post-marketing adverse events are quite rare and if each product is analyzed separately, the risk that a product's safety signals would remain undetected would increase. As such, when an adverse event is first observed in the RPP or the RPP's biosimilar product, unique INNs will limit the investigation to a single manufacturer when all the biosimilar products need to be considered. This is precisely how class effects are captured today for RPPs which may be manufactured at different manufacturing facilities, as well as for products made by different companies which share the same active ingredient as represented by the INN.

In sum, the INN is not currently used to communicate information regarding comparability or interchangeability to physicians and pharmacists, nor is it the basis for prescribing in the US. GPhA endorses the more comprehensive and currently- established strategy of a biosimilar identification system relying on NDC number, manufacturer name, lot number and a trade name, just as is applied to currently marketed US biologics today. Additionally, this would go a step further in the prevention of medication errors as FDA reviews all trade names for the specific purpose of minimizing errors⁴⁰.

C. NDCs Are One of the Most Effective Methods for Tracking Products and Educational Efforts to Promote Reporting of NDCs Will be Far More Productive than Implementing Unique INNs

GPhA agrees that for pharmacovigilance purposes all drug products and biologics must be tracked; however, a tracking system does not require, and would not be helped by, assigning unique INNs to biosimilars. Brand names, manufacturer names, lot numbers and NDC numbers are currently used widely and successfully for tracking purposes, and facilitate the collection of more information than INNs. NDCs in fact may be the most precise method of tracking products.

The NDC contains considerably more information about the product than does the INN.⁴¹ An NDC identifies the manufacturer and provides information on the drug strength, dosage form and formulation, as well as the package sizes. All pharmacy systems use NDCs to track drug products and biologics.⁴² GPhA supports and would actively collaborate with FDA and other stakeholders in educational efforts to promote reporting of NDCs whenever possible.

Figure: Placeholder for figure that makes clear how much more information the NDC# contains



NDCs are Assigned to Uniquely Identify Drugs

- Each drug product listed under Section 510 of the Federal Food, Drug and Cosmetic Act is assigned a unique 3-segment number
- **Labeler code:** Assigned to uniquely identify the entity that manufactures, repacks or distributes the drug
- **Product code:** Assigned by the manufacturer to represent the drug, strength, dosage form and formulation
- **Package code:** Assigned by the manufacturer to represent package sizes

44087-0022-03

Serono Inc	Rebif® (interferon beta 1-a), 22 mcg in 0.5ml syringe	0.5 ml, 12s
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21 Jan 14, 2012 | Confidential GPhA Presentation to FDA on INN

The FDA Sentinel System (Sentinel System), along with pharmacy and payer systems, uses NDCs to identify specific products. Some have raised the concern that the Sentinel System does not always draw from databases that capture NDCs. We note, however, that the Sentinel System has little utility (Positive Predictive Values of less than 50%) in identifying even the most clinically pronounced outcomes of an immunogenic reaction, anaphylaxis and other hypersensitivity reactions.⁴³ Thus, we believe it premature to point to the Sentinel System as a reason to change the current naming system, as development continues and the system can already accommodate NDCs.

Complete records with NDCs recorded at each transaction will be the most expeditious route to tracking and tracing each and every product in the most effective way possible. No system, however perfectly designed, can ever compensate for the failure to record the necessary data, and any new system requires significant investment and time for users to get up to speed. GPhA suggests that addressing any failure to include NDCs be addressed as the most immediate priority for those concerned with patient safety. GPhA also believes that approaches such as the current proposed federal legislation enhancing the track and trace system for all medicines will be better suited to assuring the quality of pharmacovigilance data than the introduction of different non-proprietary names for RPPs and biosimilars.

In sum, if problems exist with the current tracking system, assigning a unique INN to each biosimilar will not solve these problems, and indeed will distract from the real solution needed. Nonetheless, as stated by the FDA in their biosimilars naming statement to WHO in 2006:⁴⁴

“Considering the inherent difficulties in additional INN product distinctions (e.g. retroactive and lifecycle changes in naming, additional INN responsibility and liability), if the world community decides to proceed with a change in the policies regarding the assigning of INNs, it should be preceded by (a) appropriate exploration of alternatives (e.g. improvements in education and/or labeling), (b) assuring the such changes fall

within the scope, competence, and expertise of the INN program, and (c) the performance and independent validation of a formal risk assessment and/or documentation of events with appropriate statistical treatment.”

Conclusion

A major goal of the BPCIA is to create competition in the marketplace for biologics, thereby expanding access to, and increasing the affordability of, these critical medicines. As its title suggests, the BPCIA also is intended to stimulate innovation and investment in the next generation of originator biologics and it is mutually beneficial if this happens alongside the availability of biosimilars. Patient access to affordable biologics should be of significant interest to FDA given the Agency’s mission to protect and promote the public health. Biosimilar development provides a new opportunity to improve access to health care for many Americans to those products with which the FDA is already the most familiar. Adoption of unique non-proprietary names for each biosimilar could jeopardize patient safety, inhibit market competition and disrupt the current global naming system. Unsubstantiated concerns regarding biosimilar nomenclature must not be used as an anti-competitive barrier to biosimilar development and commercialization.

GPhA encourages the Agency and other stakeholders to begin a dialogue to explore how we can support our current pharmacovigilance system, and optimize complete and accurate data collection and analysis, rather than unilaterally assigning unique non-proprietary names to a specific subset of biologic products without any rationale or even preliminary data to suggest why this will improve outcomes for patients. We fully support vigorous enhancement of tracking systems and education of physicians, pharmacists and other healthcare practitioners to include the brand name, the INN, the NDC and the manufacturer name, as a minimum, on all safety reports whenever possible. These enhancements are of equal importance to all biologics, and most immediately to those already on the market in the US and available to patients today.

GPhA hopes that FDA will be consistent in applying the same scientific principles of nomenclature to biosimilars that it has applied successfully to all other products for 60 years. We look forward to a continued effort of working together with FDA to improve the lives of consumers by providing timely access to affordable pharmaceuticals.

C. Environmental Impact

The actions requested herein are subject to categorical exclusion under 21 C.F.R § 25.30.

D. Economic Impact

Pursuant to 21 C.F.R. § 10.30(b), an economic impact statement will be submitted only at the request of the Commissioner.

E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which is unfavorable to the petition.

Respectfully submitted,

Ralph G. Neas
President and CEO

Attachment

Table: Examples of FDA Approved/Licensed biologic products that share INNs

Brand/Trade Name	Common Name (established, generic, INN, USAN)	Sponsor	Original Approval Date	FDA Application Number
Myozyme®	Alglucosidase Alfa	Genzyme	April 28, 2006	BLA 125141
Lumizyme®		Genzyme	May 24, 2010	BLA 125291
Kogenate FS®	Antihemophilic Factor (Recombinant)	Bayer Corp	June 26, 2000	BL 103332
ReFacto®		Genetics Institute	March 6, 2000	BL 980137
Recombinate®		Baxter Healthcare Corporation	January 21, 2010	BL 103375
Advate®	Antihemophilic Factor (Recombinant) - Plasma/Albumin Free	Baxter Healthcare Corp	July 25, 2003	BL 125063
Xyntha®		Wyeth Pharmaceuticals, Inc.	February 21, 2008	BL 125264
Miacalcin®	Calcitonin Salmon	Novartis	August 17, 1995	NDA 020313
Calcimar®		Sanofi Aventis US	April 17, 1978	NDA 017760
Tripedia®	Diphtheria & Tetanus Toxoids & Acellular Pertussis Vaccine Adsorbed	Sanofi Pasteur, Inc	July 31, 1996	BL 103922
Infanrix®		GlaxoSmithKline Biologicals	January 29, 1997	BL 103647
Daptacel®		Sanofi Pasteur, Inc	May 14, 2002	BL 103666
VAQTA®	Hepatitis A Vaccine, Inactivated	Merck & Co, Inc	August 11, 2005	BL 103606
Havrix®		GlaxoSmithKline Biologicals	October 17, 2005	BL 103475
Engerix-B®	Hepatitis B Vaccine (Recombinant)	GlaxoSmithKline Biologicals	July 7, 1998	BL 103239
Recombivax HB®		Merck & Co, Inc	August 27, 1999	BL 101066

Wydase®	Hyaluronidase	Baxter	March 22, 1950	NDA 006343	
Vitrase®		Ista Pharms	May 5, 2004	NDA 021640	
Amphadase®		Amphastar Pharm	October 26, 2004	NDA 021665	
Hydase®		Akorn Inc	October 25, 2005	NDA 021716	
Fluzone®, Fluzone High- Dose and Fluzone Intradermal®	Influenza Virus Vaccine	Sanofi Pasteur, Inc	September 4, 2002	BL 103914	
Fluarix®		GlaxoSmithKline Biologicals	August 31, 2005	BL 125127	
Fluvirin®		Novartis Vaccines and Diagnostics Ltd	September 14, 2005	BL 103837	
Flucelvax®		Novartis Vaccines and Diagnostics Ltd	November 20, 2012	BL 125408	
FluLaval®		ID Biomedical Corp of Quebec	October 5, 2006	BL 125163	
Afluria®		CSL Limited	September 28, 2007	BL 125254	
Agriflu®		Novartis Vaccines and Diagnostics S.r.l.	November 27, 2009	BL 125297	
Iletin® I		Insulin Pork	Eli Lilly	June 17, 1966	NDA 017931
Insulin and Regular Insulin			Novo Nordisk	Unknown	NDA 017926
Iletin® II and Regular Iletin® II	Insulin Purified Pork	Eli Lilly	December 5, 1979	NDA 018344	
Regular Purified Pork Insulin		Novo Nordisk	March 17, 1980	NDA 018381	
Velosulin®		Novo Nordisk	Unknown	NDA 018193	

Exubera®	Insulin Recombinant Human	Pfizer	January 27, 2006	NDA 021868
Humulin® BR		Eli Lilly	April 28, 1986	NDA 019529
Humulin® R and Humulin® R Pen		Eli Lilly	October 28, 1982	NDA 018780
Novolin® R		Novo Nordisk	June 25, 1991	NDA 019938
Velosulin® BR		Novo Nordisk	July 19, 1999	NDA 021028
Humulin® 70/30 and Humulin® 70/30 Pen	Insulin Recombinant Human; Insulin Suspension	Eli Lilly	April 25, 1989	NDA 019717
Novolin® 70/30		Novo Nordisk	June 25, 1991	NDA 019991
Mixtard® Human 70/30	Insulin Recombinant Human; Insulin Suspension	Bayer Pharms	March 11, 1988	NDA 019585
Novolin® 70/30		Novo Nordisk	Unknown	NDA 019441
Novolin® R	Insulin Recombinant Purified Human	Novo Nordisk	Unknown	NDA 018778
Velosulin® BR Human		Novo Nordisk	Unknown	NDA 019450
Insulin Insulatard NPH Nordisk	Insulin Suspension Isophane Purified Pork	Novo Nordisk	Unknown	NDA 018194
NPH Lietin® II (Pork)		Eli Lilly	December 5, 1979	NDA 018345
NPH Purified Pork Isophane Insulin		Novo Nordisk	July 30, 1981	NDA 018623
Humulin® N	Insulin Suspension Isophane Recombinant Human	Eli Lilly	October 28, 1982	NDA 018781
Novolin® N		Novo Nordisk	July 1, 1991	NDA 019959
Insulatard® NPH Human	Insulin Suspension Isophane Semisynthetic Purified Human	Novo Nordisk	Unknown	NDA 019449
Novolin® N		Novo Nordisk	Unknown	NDA 019065

Protamine Zinc and Iletin® II	Insulin Suspension Protamine Zinc Purified Beef	Eli Lilly	June 12, 1980	NDA 018476
Protamine Zinc Insulin		Bristol Myers Squibb	Unknown	NDA 017928
Lente®	Insulin Zinc Suspension Purified Pork	Novo Nordisk	March 17, 1980	NDA 018383
Lente Iletin® II		Eli Lilly	December 5, 1979	NDA 018347
Humulin® L	Insulin Zinc Suspension Recombinant Human	Eli Lilly	September 30, 1985	NDA 019377
Novolin® L		Novo Nordisk	June 25, 1991	NDA 019965
Avonex®	Interferon Beta-1A	Biogen	May 17, 1996	BLA 103628
Rebif®		Serono Inc	March 7, 2002	BLA 103780
Betaseron®	Interferon Beta-1B	Bayer Healthcare Pharms	July 23, 1993	BLA 103471
Extavia®		Novartis	August 14, 2009	BLA 125290
Asellacrin® 10, Asellarcrin® 2	Somatropin	EMD Serono	July 30, 1976	NDA 017726
Crescormon®		Genentech	April 6, 1979	NDA 017992

Accretropin®	Somatropin Recombinant	Cangene	January 23, 2008	NDA 021538
Bio-Tropin®		Ferring	May 25, 1995	NDA 019774
Genotropin® and Genotropin® Preservative Free		Pharmacia and Upjohn	August 24, 1995	NDA 020280
Humatrope®		Eli Lilly	March 8, 1987	NDA 019640
Norditropin® Flexpro and Norditropin® Nordiflex		Novo Nordisk	June 20, 2000	NDA 021148
Nutropin® and Nutropin® AQ		Genentech	Nov. 17, 1993 and Dec. 29, 1995	NDA 020168 and NDA 020522
Omnitrope®		Sandoz	May 30, 2006	NDA 021426
Saizen®		EMD Serono	October 8, 1996	NDA 019764
Serostim®		EMD Serono	August 23, 1996	NDA 020604
Tev-Tropin®		Ferring	May 25, 1995	NDA 019774
Valtropin®		LG Life	April 19, 2007	NDA 021905
Zorbtive®		EMD Serono	December 1, 2003	NDA 021597
Brand Name®	The blue background means the product has been withdrawn but not for safety or efficacy reasons, and so the product is still available as a reference product			

- ¹ WHO INN Home Page, available at: <http://www.who.int/medicines/services/inn/en/> (accessed August 23, 2013).
- ² For example, both Recombinate (Antihemophilic Factor (Recombinant)) and Kogenate (Antihemophilic Factor (Recombinant)) are full-length factor VIII products made by different manufacturing processes but from the same genetic information. Refacto (Antihemophilic Factor (Recombinant)) is a substantially modified b-domain deleted factor VIII product and also shares the same INN.
- ³ We recognize that some regions of the world do not use standards of highly similar/no clinically meaningful differences for marketed biosimilars and they may consider unique INNs due to lack of scientific support for comparability. However, for highly regulated regions that

adhere to scientifically sound approaches for assessing biosimilars, there is no justification for departing from FDA's long-held naming policy. In fact, with the expansion of highly sophisticated analytical technologies there is even more support for continuing to assign the same INN to products deemed highly similar/no clinically relevant differences throughout the world.

- ⁴ A search on the word “name” in the entirety of the BPCIA shows that the word is never used. The text of the BPCIA is available at:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf> (last accessed August 23, 2013).
- ⁵ FDA, “US FDA Considerations: Discussion by National Regulatory Authorities with World Health Organization (WHO) On Possible International Non-proprietary Name (INN) Policies for Biosimilars” (submitted to WHO in Sept. 2006), attached to this submission.
- ⁶ FDA, “US FDA Considerations: Discussion by National Regulatory Authorities with World Health Organization (WHO) On Possible International Non-proprietary Name (INN) Policies for Biosimilars” (submitted to WHO in Sept. 2006), attached to this submission.
- ⁷ Letter from Rep. Anna Eshoo to FDA Commissioner Hamburg (Apr. 16, 2012), available at: <http://www.regulations.gov#!documentDetail;D=FDA-2011-D-0611-0043> (accessed August 23, 2013).
- ⁸ The American Pharmacists Association (APhA), the National Association of Chain Drug Stores (NACDS) and the National Community Pharmacists Association (NCPA) letter to FDA, may 25, 2012, http://www.ncpanet.org/pdf/leg/may12/joint_biosimilar_letter.pdf
- ⁹ ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process. EU: Adopted by CPMP, Dec. 1, 2004, CPMP/ICH/5721/03, date for coming into operation: June 2005; MHLW: Adopted April 26, 2005, PFSB/ELD Notification No. 0426001; FDA: Published in the Federal Register, Vol. 70, No. 125, June 30, 2005, p. 37861-37862, available at:
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf (accessed August 23, 2013).
- ¹⁰ FDA, “US FDA Considerations: Discussion by National Regulatory Authorities with World Health Organization (WHO) On Possible International Non-proprietary Name (INN) Policies for Biosimilars” (submitted to WHO in Sept. 2006), attached to this submission.
- ¹¹ Section 7002 of the BPCIA defines the term reference product as “the single biologic product licensed under subsection (a) against which a biological product is evaluated in an application submitted under subsection (k)”, and with this relationship essential to the approval of a biosimilar, that relationship must be readily apparent to all stakeholders, especially patients and their health care providers.
- ¹² Niels Vermeer (UU/MEB) presentation to the EMA “Traceability of biopharmaceuticals in spontaneous reporting systems” (May 25, 2012), available at:

http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2012/05/WC500127934 (accessed August 23, 2013).

- ¹³ For a description of the debate, see e.g., Senior, Melanie, The Name Game: Will Innovators' Latest Battlefield Kill Biosimilars?, The RPM Report, September 2013, posted July 8, 2013, Available at: <http://www.elsevierbi.com/publications/rpm-report/9/8/the-name-game-will-innovators-latest-battlefront-kill-biosimilars> (accessed August 23, 2013).
- ¹⁴ Section 7002 of the BPCIA notes that the statute requires a single 351(a) reference product for each biosimilar and this section also provides a 12-year exclusivity provision, both of which is evidence of the experience that FDA has with that reference product.
- ¹⁵ ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process. EU: Adopted by CPM, Dec. 1, 2004, CPMP/ICH/5721/03, date for coming into operation: June 2005; MHLW: Adopted April 26, 2005, PFSB/ELD Notification No. 0426001; FDA: Published in the Federal Register, Vol. 70, No. 125, June 30, 2005, p. 37861-37862, available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf (accessed August 23, 2013).
- ¹⁶ Weise et al. Biosimilars: what clinicians should know. *Blood* (October 26, 2012 online pre-publication) 10.1182/blood-2012-04-425744.
- ¹⁷ Janet Woodcock, Deputy Commissioner, Chief Medical Officer, FDA, testimony before the House Committee on Oversight and Government Reform, March 26, 2007, available at <http://www.fda.gov/NewsEvents/Testimony/ucm154070.htm> (accessed August 23, 2013).
- ¹⁸ Schiestl, M et al. "Acceptable Changes in Quality Attributes of Glycosylated Biopharmaceuticals", *Nature Biotechnology*, (Apr. 2011); **29**, 4, 310-312.
- ¹⁹ Christian Schneider, "Biosimilars in rheumatology: the wind of change", *Ann Rheum March* 2013 Volume 72, No 3. Available at <http://ard.bmj.com/content/72/3/315.full.pdf+html?sid=1198ecf7-6e8f-4cda-8a8c-f343d0e7917b> (accessed August 23, 2013).
- ²⁰ WHO, Guidance on INN, available at <http://www.who.int/medicines/services/inn/innquidance/en/index.html> (accessed August 23, 2013).
- ²¹ FDA, "US FDA Considerations: Discussion by National Regulatory Authorities with World Health Organization (WHO) On Possible International Non-proprietary Name (INN) Policies for Biosimilars" (submitted to WHO in Sept. 2006), attached to this submission.
- ²² Presentation by Mark McCamish at FDA/DIA Biosimilars Conference Washington DC (Sept. 12, 2012): "Sandoz biosimilars are **sold in over 50 countries** and have accumulated **more**

than 50 million patient days drug exposure”, and this is just one sponsor of biosimilars in highly regulated markets.

²³ Complete Reference with hyperlink to GPhA website

²⁴ Mark McCamish, Agnieszka Moskal Gallagher, John Orloff, “Biosimilar By Name and Biosimilar By Nature”, July 2013 Feature Article RPM Report: June 28 2013. Available at: <http://www.elsevierbi.com/publications/rpm-report/9/7/biosimilar-by-name-and-biosimilar-by-nature> (accessed August 23, 2013).

²⁵ In their letter to Dr. Hamburg, dated June 25, 2012, PhRMA and BIO state: “Because a biosimilar or interchangeable biological product is highly similar to, but not the same as, its respective reference product, it would be inappropriate, from a patient safety perspective, to permit use of the same name for biological products that are not the same. Unique names will be necessary to ensure appropriate pharmacovigilance. Thus, it is essential that each biological product have a unique non-proprietary name.” Since the same name is maintained after a manufacturing change using the highly similar standard, GPhA reaches a different conclusion, but the one used by FDA and individual product sponsors, namely, that the same non-proprietary name is appropriate when the highly similar standard has been achieved. Nonetheless, we would agree with PhRMA and BIO that consistency is important and that the same rules should apply to all biologics.

²⁶ Christian Schneider, “Biosimilars in rheumatology: the wind of change”, Ann Rheum March 2013 Volume 72, No 3. Available at <http://ard.bmj.com/content/72/3/315.full.pdf+html?sid=1198ecf7-6e8f-4cda-8a8c-f343d0e7917b> (accessed August 23, 2013).

²⁷ Brand Institute/Drug Safety Institute Survey conducted among 270 healthcare professionals on behalf of GPhA, February 28, 2103.

²⁸ Ibid.

²⁹ Ibid.

³⁰ Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names U.S. Department of Health and Human Services, FDA February 2010. Available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> (accessed August 23, 2013).

³¹ About MedWatcher, available at <https://www.medwatcher.org/about.php> (accessed August 23, 2013).

“MedWatcher is a project out of [Boston Children's Hospital](#) and Harvard Medical School. It was created in collaboration with the Food and Drug Administration (FDA) Center for Devices and Radiologic Health. The system is run by [Epidemico](#), a Boston Children's spin-out company. Questions? Contact us at info@medwatcher.org.”

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- ³² Presentation by Niels Vermeer “Traceability of biopharmaceuticals in spontaneous reporting systems,” (May 25 2012), at the Fifth stakeholder forum on the implementation of the new pharmacovigilance legislation, available at:
http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2012/05/WC500127934.pdf (accessed August 23, 2013), and also presentations available at:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2012/05/event_detail_000582.jsp&mid=WC0b01ac058004d5c3 (accessed August 23, 2013).
- ³³ In its 2006 position, FDA demanded this be considered before any changes are made: “Considering the inherent difficulties in additional INN product distinctions (e.g. retroactive and lifecycle changes in naming, additional INN responsibility and liability), if the world community decides to proceed with a change in the policies regarding the assigning of INNs, it should be preceded by (a) appropriate exploration of alternatives (e.g. improvements in education and/or labeling), (b) assuring the such changes fall within the scope, competence, and expertise of the INN program, and (c) the performance and independent validation of a formal risk assessment and/or documentation of events with appropriate statistical treatment.” FDA, “US FDA Considerations: Discussion by National Regulatory Authorities with World Health Organization (WHO) On Possible International Non-proprietary Name (INN) Policies for Biosimilars” (submitted to WHO in Sept. 2006), attached to this submission.
- ³⁴ FDA, “US FDA Considerations: Discussion by National Regulatory Authorities with World Health Organization (WHO) On Possible International Non-proprietary Name (INN) Policies for Biosimilars” (submitted to WHO in Sept. 2006), attached to this submission.
- ³⁵ Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names U.S. Department of Health and Human Services, FDA February 2010. Available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> (accessed August 23, 2013).
- ³⁶ “Established name” is the historical term given to a FDA issued non-proprietary name. This becomes the United States Adopted Name when endorsed by the USAN Committee. Generally, the USAN committee tries to make the USAN match the INN, but this may not be possible for a biosimilar when an INN already exists that matches that of the reference product, if FDA decides to adopt a different approach.
- ³⁷ Comments of USP on “Draft Guidances Relating to the Development of Biosimilar Products; Public Hearing” (May 24, 2012), available at <http://www.regulations.gov/#!documentDetail;D=FDA-2011-D-0618-0053> (accessed August 23, 2013).
- ³⁸ FDA, “US FDA Considerations: Discussion by National Regulatory Authorities with World Health Organization (WHO) On Possible International Non-proprietary Name (INN) Policies for Biosimilars” (submitted to WHO in Sept. 2006), attached to this submission.

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- ³⁹ Statement of Janet Woodcock, M.D., Deputy Commissioner, Chief Medical Officer, FDA before the House Committee on Oversight and Government Reform, "Follow-on Protein Products" (March 26, 2007), available at: <http://www.fda.gov/NewsEvents/Testimony/ucm154070.htm> (accessed August 23, 2013).
- ⁴⁰ Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names U.S. Department of Health and Human Services, FDA February 2010. Available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> (accessed August 23, 2013); MedERRS, available at <http://www.med-errs.com/> (accessed August 23, 2013).
- ⁴¹ Each drug product listed under Section 510 of the Federal Food, Drug and Cosmetic Act (21 USC. § 360) is assigned a unique 3-segment number called the NDC number – this comprises 5 digits that are known as the Labeler code, which are assigned to uniquely identify the entity that manufactures, repacks or distributes the drug; 4 digits which are known as the Product code, which are assigned by the manufacturer to represent the drug, strength, dosage form and formulation; and a final 2 digits, known as the Package code which are assigned by the manufacturer to represent package sizes.
- ⁴² Discussed in the GPhA submission to docket FDA-2011-D-0618 inviting comments on the FDA draft biosimilars guidances, proposed future guidance, and the FDA Part 15 Hearing of May 11, 2012, available at: <http://www.regulations.gov/#!documentDetail;D=FDA-2011-D-0618-0055> (accessed August 23, 2013).
- ⁴³ Platt, R et al. The US Food and Drug Administration's Mini-Sentinel Program: Status and Direction. *Pharmacoepidemiology and Drug Safety* 2012; 21(S1): 1–8.
- ⁴⁴ FDA, "US FDA Considerations: Discussion by National Regulatory Authorities with World Health Organization (WHO) On Possible International Non-proprietary Name (INN) Policies for Biosimilars" (submitted to WHO in Sept. 2006), attached to this submission.

October 28, 2013

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061
Rockville, MD 20852

CITIZEN PETITION

The Novartis Group of companies (Novartis) submits this petition under 21 C.F.R. § 10.30 to request that the Commissioner of the Food and Drug Administration (FDA) take the action requested below.

A. Action Requested

Novartis respectfully requests that, to encourage and protect the safe and rational use of all medicines, FDA require that a biosimilar, be identified by the same international nonproprietary name¹ (INN) as the reference product. A biosimilar, by definition of its approval, has successfully met FDA's demanding standard of high similarity to a reference product and, further, the Agency has concluded that the totality of the evidence demonstrates that there will be no clinically meaningful differences in terms of safety, purity and potency between it and the reference product.

B. Summary

The United States enacted the Biologics Price Competition and Innovation Act (BPCIA) in 2010 to establish a pathway for FDA to approve biologic products as biosimilar to already-approved biologics. Under the statute, a biosimilar must demonstrate to the satisfaction of FDA that it is highly similar to an originator reference product and, further, to demonstrate the safety, purity, and potency of the proposed biosimilar. The biosimilar will be considered interchangeable with its reference product if the applicant provides sufficient information to show that the biosimilar can be expected to produce the same clinical result as the reference product in any given patient.

The BPCIA is appropriately silent about the nomenclature FDA should apply to biosimilars, as such nomenclature should be self-evident from FDA's current practice. Nevertheless, the question of whether biosimilars should share an international non-proprietary name (INN) with their reference product has been the subject of much public debate.^{2, 3} Such debate has confused the concept and current utilization of INN by departing from the INN's intended purpose of facilitating the identification of pharmaceutical substances. Instead the current dialogue has implied that the INN is intended to facilitate the identification of a specific product. This implication is untrue and has resulted in confusing an otherwise straightforward issue. Many products, including biologics, currently marketed in the United States share INNs (see Table 1

below). But INNs are not, and cannot be, the only or even the primary tools used for tracking and tracing. Indeed, despite their shared INNs, these products have been successfully traced for pharmacovigilance purposes.

Moreover, assigning unique INNs to biosimilars that FDA concurs are highly similar to a reference product would imply that INNs are intended to communicate more than just molecular characteristics and a pharmacological class.⁴ It would imply that INNs are intended to communicate an aspect of the regulatory status itself, such as interchangeability or lack thereof. FDA has clearly argued against unique INNs for biosimilars when it stated: “INNs should not be used to imply pharmacologic interchangeability of products with the same active ingredient(s) when no credible scientific data exist that demonstrate such. Likewise, INNs should not be used to differentiate products with the same active ingredient(s) when credible scientific data demonstrate that no pharmacologically relevant differences exist.”⁵ Indeed, many biologic products on the market today share INNs even though they have never been compared directly to each other, and should a demonstration of “sameness” be required by FDA retrospectively today, many of these products would fail to meet it. Nevertheless, and most importantly, the fact that these products share INNs has not resulted in any safety issues being identified.

Assigning different INNs to products approved as biosimilars would introduce unnecessary confusion into the healthcare system and could unintentionally communicate increased caution, unfounded risk, or other regulatory reservations that are purely hypothetical. Significantly, it would put into question years of FDA’s practice of using the well-established analytical standard of high similarity⁶ to approve major manufacturing changes of originator biologic products without a parallel change in the originator INN, despite the fact that the manufacturing changes have altered, sometimes substantially, the originator biologics’ molecular structures.⁷ Using the high similarity standards, FDA has in these cases satisfied itself that the altered originator biologic would produce the same clinical result in terms of safety, purity and potency as its pre-manufacturing change version, and applied this reasoning multiple times for the same product with the same confidence.⁸ Similarly, FDA will use these same standards to satisfy itself that the biosimilar would produce the same clinical result as the reference product. Requiring separate INNs for biosimilars but not originator biologics would undermine FDA’s own approval decisions, which in both cases require FDA’s determination that the compared product (biosimilar or the post-manufacturing change originator biologic) produces the same clinical outcomes as its comparator (respectively, the reference product or the pre-manufacturing change biologic).^{9, 10}

Novartis submits that imposing unique INNs on biosimilars would not improve any aspects of patient safety, pharmacovigilance or tracking, and would instead undermine the safe use of all biologics by introducing unfounded confusion into the healthcare system. Novartis therefore respectfully requests that, rather than imposing unique INNs on biosimilars, FDA instead require them to be identified by the same international nonproprietary name as the reference product to encourage and protect the safe and rational use of all medicines.

C. Statement of Grounds

I. INNs are not, and cannot, be the primary tool relied on for tracking and tracing.

The World Health Organization (WHO) administers an international naming convention, known as the International Non-proprietary Naming system. INNs are intended to facilitate the identification of pharmaceutical substances or active pharmaceutical ingredients by health care

professionals worldwide.¹¹ They are granted based only on molecular characteristics and pharmacological class of active ingredients. In the United States, a sponsor may obtain a United States Adopted Name (USAN), and USANs have been generally consistent with the INN naming convention. INNs are by definition non-proprietary and therefore not designed to identify a specific product; indeed, once an INN is established, it identifies ALL products matching the respective molecular characteristics.

Novartis agrees that for pharmacovigilance purposes all drug products and biologics must be tracked. However, a tracking system does not require, nor would it be helped by, unique INNs for biosimilars. As INNs were designed to be shared among products, they were never intended to function as the basis – and certainly not the sole basis - for tracking and tracing specific products. It is the proprietary, or trade name of a product that is more useful in that regard. And even trade names comprise only a part of the track and trace tool portfolio as products are also traced by national drug codes (NDCs), manufacturer names, and batch and lot numbers.

Despite the suggestions to the contrary, there is no indication that this system will not work for biosimilars. Although no product has been approved as a biosimilar under the BPCIA to date, FDA has set the regulatory precedent by approving numerous biologics which appropriately share INNs even though they were approved under separate approval pathways and are manufactured by different manufacturers. (See Table 1 below). While a few of these products have been discontinued (but unless taken off the market due to safety or efficacy reasons can still be a reference product, hence they are included in the table¹²), the products that have not been discontinued are currently being marketed under separate brand names, and the fact that they share INNs has not resulted in any unique traceability issues.

If there are any weaknesses in the current system with regard to the traceability of a specific product to an adverse event, such weaknesses are not related to the INN and must be addressed for all currently approved products. Indeed, Novartis would support a vigorous enhancement of track and trace methods, and education of physicians and pharmacists.

Furthermore, there are compelling data from other highly regulated jurisdictions confirming that different INNs are not necessary as a mechanism for tracking and tracing. In Europe, where biosimilars have been on the market since 2006, they share the same INNs¹³ (see attached Table 2) with their corresponding reference products', and in each case the individual biosimilar product is identified by a brand name¹⁴. A recent study of the identification of biosimilars in the European Union pharmacovigilance system found that the naming convention for biosimilars has a successful product identification rate of 96.2% across all three marketed biosimilar classes (somatropin, filgrastim and epoetin).¹⁵ There is no reason to expect that the United States' pharmacovigilance system cannot achieve similar or even higher product identification rates given that, unlike the European Union, the United States has the advantage of a singular, nationwide NDC product identification system for tracking.

II. Assigning different INNs to products approved as biosimilars would unnecessarily put into question years of FDA's practice of approving manufacturing changes of originator biologic products without a resulting change in the originator INN.

FDA reviews and approves manufacturing changes in biological products using comparability approaches that use the same highly similar standard that has been written into the biosimilar legislation enacted by U.S. Congress. Both similarity exercises are based on the highly

similar concept as used in the BPCIA and described in FDA's draft guideline on the quality of biosimilars, as well as the International Conference on Harmonization Q5E guideline (ICH Q5E). ICH Q5E focuses on assessing quality of the altered molecule pre- and post-manufacturing change, and when the magnitude of the change so requires, on assessing preclinical and clinical data as well. This approach has been coordinated among regulatory authorities across the highly regulated markets,¹⁶ and also in the form of guidance by WHO for biosimilars in other, emerging markets where patient access is critically important.¹⁷

FDA has confirmed this approach. When discussing the biosimilar review process, FDA commented that "[its] 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."¹⁸ Indeed, data published in peer-reviewed scientific literature demonstrate that, while originator products do change over time, they are well controlled between manufacturing changes, and, even after manufacturing changes, the clinical attributes of the products are acceptable.¹⁹

Given the fact that the comparability assessment of biological products pre- and post-manufacturing changes not only mirrors, but is in fact the very basis for assessment of biosimilarity, requiring different INNs for biosimilars would unnecessarily put into question years of FDA practice in reviewing and approving such changes without requiring new INNs for post-manufacturing change biologics, whose molecular structure, variant composition or impurity profile has been altered, sometimes substantially, by the manufacturing change. If an identical, consistent naming system is not adopted, patients and physicians may - and should - ask why they were not notified of the change in the originator biologic, which continued to be identified by the same INN and brand name and whose label did not reflect the manufacturing change or the corresponding change in the product itself. The practice of maintaining the same INNs for post-manufacturing change originator biologics is well founded in law, health authority guidelines and science, and should apply equally to naming considerations for biosimilars.

There is no need to introduce confusion and doubt through an unequal application of naming conventions when FDA has such in-depth understanding of all the biologics that they have reviewed and licensed for the United States market, which by definition comprise the entirety of the reference products for biosimilars in the United States.²⁰ If FDA applies regulatory science consistently, such that the highly similar standard for manufacturing changes is the same as the highly similar standard for biosimilars, then patients can be confident that a biosimilar will generally be as similar to its reference as that reference is to itself over its lifetime, and more importantly, that in both cases any minor differences between them will be in clinically inactive components only.

III. Assigning different INNs to products which conform to an established compendial monograph in the US would be inconsistent with the current regulations governing USP names.

The United States Pharmacopeia (USP) General Notices specify how the compendial standards, including monographs for particular drug substances and drug products, are developed. The current USP and National Formulary (NF) standards are then publically listed and referenced

in the Federal Food, Drug, and Cosmetic Act (FDCA).²¹ FDA is therefore responsible for the enforcement of USP standards.

The FDCA states that drugs, including biologics,²² will be deemed adulterated²³ or misbranded²⁴ if they do not conform to recognized compendial standards relating to nonproprietary naming and identity, and strength, quality and purity. Therefore, if USP has a monograph for a biologic product, which would be applicable to a biosimilar, such biosimilar will be deemed misbranded unless its label bears the official title recognized in USP-NF.²⁵ Of course, FDA has the authority to change a USP name²⁶ in the interest of usefulness and simplicity, but first it must submit its act to public notice and comment and provide the opportunity for judicial review.²⁷

IV. Far from advancing it, unique INNs for biosimilars would be detrimental to patient safety.

Assigning unique INNs to biologics, which were proved to be highly similar to their reference products, would send a signal that INNs are intended to communicate more than the molecular characteristics and the pharmaceutical class of the active ingredient. It would send a signal that, instead of simply being used as a global cataloguing mechanism for products with a related active ingredient, INNs are somehow intended to communicate an aspect of the regulatory review and approval itself, such as pharmacologic interchangeability or lack thereof in products with the same active ingredient(s).

A determination of pharmacologic interchangeability of products with the same active ingredient(s) must be made by regulatory agencies based on credible scientific data.²⁸ For example, in the United States, FDA must make an affirmative determination that two products bearing the same INN are therapeutically equivalent, i.e., that in FDA's judgment they are expected to have equivalent clinical effect.²⁹ It is this determination by FDA and the subsequent listing of the products as therapeutically equivalent – **and not the products' INN** – that informs physicians, pharmacies, state agencies and other stakeholders that the products can be substituted with the full expectation that they will produce the same clinical effect and safety profile. Similarly, FDA will have to make a separate determination of interchangeability with respect to a biosimilar, and it will be that determination and its reflection on the biosimilar's label that will inform of the biosimilar's interchangeability with its reference product.

FDA previously expressed concern at the potential confusion that could be created by the implication that assigning the same INNs to products was tantamount to a determination of pharmacological interchangeability, as opposed to a high degree of similarity.³⁰ This concern was echoed in a number of stakeholder letters to the Agency.³¹ Representative of these comments are those from a letter authored by the American Pharmacists Association (APhA), the National Association of Chain Drug Stores (NACDS) and the National Community Pharmacists Association (NCPA) submitted to FDA's Draft Guidances Relating to the Development of Biosimilar Products docket:

“Unique INNs for common active ingredients may generally increase confusion, leading to increased safety concerns and possibly medication errors. Physicians are already pressed for time, and therefore it is imperative that there are no additional and unnecessary obstacles that hinder them from timely decision-making, especially in cases of urgent care. The use of different INNs would increase the burden of being able to distinguish which products are biosimilar and interchangeable with which reference drug and may pose

difficulties in recognizing the best alternative drug for therapeutic use in a timely manner. Such confusion may lead to medication errors such as therapeutic duplication.”³²

The determination of safety, efficacy, and in appropriate cases, interchangeability, is and should remain beyond the scope of any naming convention. If FDA were to assign different INNs to products with the same active substance for the purpose of preventing inappropriate substitution, it would necessarily create an equally inappropriate implication that all products with the same INNs are by definition interchangeable. This implication could have potentially negative effects on patient safety; especially if such an implication were to be applied to products which share INNs but which have never been compared with each other and which may even have been licensed by FDA for different indications. However, it must be remembered in this context that FDA already allows different recombinant and naturally-derived products from different manufacturers to share INNs, even though such products have been approved by FDA under separate Biologics License Applications (BLAs) and have never demonstrated comparability. The fact that they share INNs has not resulted in any safety issues, but an implication that the same INNs indicate that they are all interchangeable would indeed negatively impact the safe and rational use of these and other medicines which share INNs.

The corollary is also true. Requiring different INNs for biosimilars, and presumably other biologics produced by different sponsors that share active ingredients, would suggest that prescribing by INN could be as appropriate in the future as brand name prescribing is today – after all biologics would essentially have two unique names going forward. Anticipating that such an argument could be made, we tested a recent FDA decision to require that one of the biosimilars approved in Europe with the INN filgrastim to be licensed in the US with the interim established name³³ of TBO-filgrastim. See the MedERRs report summarized in Figure 1 below. Historically, in the context of Brand names, FDA has recommended against the use of pre-fixes and suffixes because of their ability to lead to confusion³⁴ and this policy is confirmed in the analysis conducted for TBO-filgrastim. Whether or not such confusion will result in practice has yet to be determined as the product in question has not yet been launched in the US.

Figure 1: Med-ERRS® Report for TBO-filgrastim found a “high vulnerability” for medication errors

Proposed name	Score	Vulnerability	Issues
tbo-filgrastim	2	high	Look-alike name(s) Sound-alike name(s) misinterpretation of prefix

Strong look-alike and strong sound-alike similarity was noted with filgrastim (NEUPOGEN, others: used in the treatment of chemotherapy-induced neutropenia), especially if the “tbo” prefix is separated from the rest of the name, missed or misinterpreted. Filgrastim is an injectable product that is used for the same indication as tbo-filgrastim. The dose, dosage strengths, clinical setting for use and patient population all are the same. Both drugs would be ordered by the same type of practitioner (eg., oncologist). Both filgrastim and tbo-filgrastim are stored in the refrigerator. If confusion occurred, the risk of harm generally is moderate due to the bone pain and fever associated with the use of filgrastim. However, due to the clinical similarities between the two drugs, the harm is likely to be negligible.

Slight sound-alike similarity was noted with pegfilgrastim (NEULASTA; used in the treatment of chemotherapy-induced neutropenia). Pegfilgrastim is an injectable product that is used for the same

indication as tbo-filgrastim. The clinical setting for use and patient population are the same. Both drugs would be ordered by the same type of practitioner (e.g., oncologist). Both pegfilgrastim and tbo-filgrastim are stored in the refrigerator. Pegfilgrastim is given at a different dose than tbo-filgrastim. If confusion occurred, the risk of harm generally is moderate due to the bone pain associated with the use of pegfilgrastim. However, due to the clinical similarities between the two drugs, the harm is likely to be negligible, unless pegfilgrastim is administered on a daily basis as if it were tbo-filgrastim, in which case the harm would be increased.

A number of misinterpretations were noted for the "tbo" prefix. These include "to be ordered," "TVO" for "telephone verbal order," "the," "Hb" for the abbreviation for hemoglobin, "TB" for the abbreviation for tuberculosis and "TKO" for the abbreviation "to keep [vein] open." If any of these misinterpretations occurred, the practitioner would likely dispense and/or administer a filgrastim product rather than a tbo-filgrastim product.

INNs are assigned based on the molecular structure and pharmacological class of products and have been utilized successfully as one component of pharmacovigilance monitoring. INNs are used in national and regional pharmacovigilance systems, along with other key identifiers such as brand name, to facilitate the detection of new safety information related to pharmaceutical substances on a global level. They allow the aggregation of safety data, detection of class effects, and appropriate and timely response to safety alerts. These significant safety benefits would be undermined if products with the same active ingredients were assigned different INNs, especially when such products have been shown to produce the same clinical result in terms of safety, purity and potency by credible scientific data. Different INNs (USANs) will necessarily decouple biosimilars approved in the United States from safety data of the same products elsewhere in the world, where consistent INNs are currently used, and vice versa. This could contribute to the breakdown of the current international system with ramifications for public health more broadly than just in the US.

V. Conclusion

The BPCIA was enacted to provide a pathway for approval of products that reference already-approved biological molecules. It is for FDA to determine whether an applicant under the BPCIA meets the demanding standards of high similarity to the reference biological molecule. If it does not demonstrate high similarity, it is for FDA to simply not approve it as a biosimilar. Approving it under a separate INN would run counter to the very purpose of the BPCIA, a major goal of which is to create competition in the marketplace for biologics and expand access to, and increase the affordability of, these critical medicines. This goal of providing patients and providers with access to high quality, lower cost alternative products and incentivizing innovation in the field of medicine should never compromise patient safety. It is the FDA review process, however, and not separate INNs, that will ensure patient safety is never compromised. Indeed, assigning separate INNs to biosimilars will undoubtedly undermine this objective by creating confusion in the healthcare system and unnecessarily casting doubt on FDA's robust and well-established practice of reviewing the relevance of differences in originator products after manufacturing changes. As unfortunate as such a result would be, it will only be compounded unnecessarily and equally tragically by thwarting the congressional intent of increasing patient access to affordable biologics. Therefore, Novartis submits that imposing unique INNs on biosimilars would not improve any aspect of patient safety, pharmacovigilance or tracking, and would instead undermine the safe use of all biologics by introducing unfounded confusion into the healthcare system. Novartis therefore respectfully requests that, rather than imposing unique INNs on biosimilars, FDA instead require

them to be identified by the same international nonproprietary name as the reference product to encourage and protect the safe and rational use of all medicines.

D. Environmental Impact

The actions requested herein are subject to categorical exclusion under 21 C.F.R § 25.30.

E. Economic Impact

Pursuant to 21 C.F.R. § 10.30(b), an economic impact statement will be submitted only at the request of the Commissioner.

F. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted on behalf of the Novartis Group of Companies

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Acronyms:

APhA = American Pharmacists Association
BLA = Biologics License Application
BPCIA = Biologics Price Competition and Innovation Act
FDA = Food and Drug Administration
FDCA = Federal Food Drug and Cosmetic Act
ICH = International Committee on Harmonization
INN = International Nonproprietary Name
NACDS = National Association of Chain Drug Stores
NCPA = National Community Pharmacists Association
NF= National Formulary
Novartis = Novartis Group of companies
USAN = United States Adopted Name
USP = United States Pharmacopeia
USP-NF= United States Pharmacopeia – National Formulary
WHO = World Health Organization

Table 1: Examples of FDA Approved/Licensed biologic products that share INNs (listed alphabetically by INN; products shaded in blue are currently discontinued, but not withdrawn for safety or efficacy reasons)

Brand/Trade Name	Common Name (established, generic, INN, USAN)	Sponsor	Original Approval Date	FDA Application Number
Myozyme®	Alglucosidase Alfa	Genzyme	April 28, 2006	BLA 125141
Lumizyme®		Genzyme	May 24, 2010	BLA 125291
Kogenate FS®	Antihemophilic Factor (Recombinant)	Bayer Corp	June 26, 2000	BL 103332
ReFacto®		Genetics Institute	March 6, 2000	BL 980137
Recombinate®		Baxter Healthcare Corporation	January 21, 2010	BL 103375
Advate®	Antihemophilic Factor (Recombinant) - Plasma/Albumin Free	Baxter Healthcare Corporation	July 25, 2003	BL 125063
Xyntha®		Wyeth Pharmaceuticals, Inc.	February 21, 2008	BL 125264
Miacalcin®	Calcitonin Salmon	Novartis	August 17, 1995	NDA 20313
Calcimar®		Sanofi Aventis US	April 17, 1978	NDA 17760
Calcitonin Salmon (Generic)		Apotex Inc	November 17, 2008	ANDA 076396
Calcitonin Salmon (Generic)		AstraZeneca	Unknown	ANDA 073690
Calcitonin Salmon (Generic)		Par Pharm	June 8, 2009	ANDA 076979
Tripedia®	Diphtheria & Tetanus Toxoids & Acellular Pertussis Vaccine Adsorbed	Sanofi Pasteur, Inc	July 31, 1996	BL 103922
Infanrix®		GlaxoSmithKline Biologicals	January 29, 1997	BL 103647
Daptacel®		Sanofi Pasteur, Inc	May 14, 2002	BL 103666
VAQTA®	Hepatitis A Vaccine, Inactivated	Merck & Co, Inc	August 11, 2005	BL 103606
Havrix®		GlaxoSmithKline Biologicals	October 17, 2005	BL 103475
Engerix-B®	Hepatitis B Vaccine (Recombinant)	GlaxoSmithKline Biologicals	July 7, 1998	BL 103239
Recombivax HB®		Merck & Co, Inc	August 27, 1999	BL 101066
Wydase®	Hyaluronidase	Baxter	March 22, 1950	NDA 006343
Vitrase®		Ista Pharms	May 5, 2004	NDA 021640
Amphadase®		Amphastar Pharm	October 26, 2004	NDA 021665
Hydase®		Akorn Inc	October 25, 2005	NDA 021716

Fluzone®, Fluzone High- Dose and Fluzone Intradermal®	Influenza Virus Vaccine	Sanofi Pasteur, Inc	September 4, 2002	BL 103914
Fluarix®		GlaxoSmithKline Biologicals	August 31, 2005	BL 125127
Fluvirin®		Novartis Vaccines and Diagnostics Ltd	September 14, 2005	BL 103837
Flucelvax®		Novartis Vaccines and Diagnostics Ltd	November 20, 2012	BL 125408
FluLaval®		ID Biomedical Corp of Quebec	October 5, 2006	BL 125163
Afluria®		CSL Limited	September 28, 2007	BL 125254
Agriflu®		Novartis Vaccines and Diagnostics S.r.l.	November 27, 2009	BL 125297
Iletin® I	Insulin Pork	Eli Lilly	June 17, 1966	NDA 017931
Insulin and Regular Insulin		Novo Nordisk	Unknown	NDA 017926
Iletin® II and Regular Iletin® II	Insulin Purified Pork	Eli Lilly	December 5, 1979	NDA 018344
Regular Purified Pork Insulin		Novo Nordisk	March 17, 1980	NDA 018381
Velosulin®		Novo Nordisk	Unknown	NDA 018193
Exubera®	Insulin Recombinant Human	Pfizer	January 27, 2006	NDA 021868
Humulin® BR		Eli Lilly	April 28, 1986	NDA 019529
Humulin® R and Humulin® R Pen		Eli Lilly	October 28, 1982	NDA 018780
Novolin® R		Novo Nordisk	June 25, 1991	NDA 019938
Velosulin® BR		Novo Nordisk	July 19, 1999	NDA 021028
Humulin® 70/30 and Humulin® 70/30 Pen	Insulin Recombinant Human; Insulin Suspension Isophane Recombinant Human	Eli Lilly	April 25, 1989	NDA 019717
Novolin® 70/30		Novo Nordisk	June 25, 1991	NDA 019991

Mixtard® Human 70/30	Insulin Recombinant Human; Insulin Suspension Isophane Semisynthetic Purified Human	Bayer Pharms	March 11, 1988	NDA 019585
Novolin® 70/30		Novo Nordisk	Unknown	NDA 019441
Novolin® R	Insulin Recombinant Purified Human	Novo Nordisk	Unknown	NDA 018778
Velosulin® BR Human		Novo Nordisk	Unknown	NDA 019450
Insulin Insulatard NPH Nordisk	Insulin Suspension Isophane Purified Pork	Novo Nordisk	Unknown	NDA 018194
NPH Lietin® II (Pork)		Eli Lilly	December 5, 1979	NDA 018345
NPH Purified Pork Isophane Insulin		Novo Nordisk	July 30, 1981	NDA 018623
Humulin® N	Insulin Suspension Isophane Recombinant Human	Eli Lilly	October 28, 1982	NDA 018781
Novolin® N		Novo Nordisk	July 1, 1991	NDA 019959
Insulatard® NPH Human	Insulin Suspension Isophane Semisynthetic Purified Human	Novo Nordisk	Unknown	NDA 019449
Novolin® N		Novo Nordisk	Unknown	NDA 019065
Protamine Zinc and Iletin® II	Insulin Suspension Protamine Zinc Purified Beef	Eli Lilly	June 12, 1980	NDA 018476
Protamine Zinc Insulin		Bristol Myers Squibb	Unknown	NDA 017928
Lente®	Insulin Zinc Suspension Purified Pork	Novo Nordisk	March 17, 1980	NDA 018383
Lente Iletin® II		Eli Lilly	December 5, 1979	NDA 018347
Humulin® L	Insulin Zinc Suspension Recombinant Human	Eli Lilly	September 30, 1985	NDA 019377
Novolin® L		Novo Nordisk	June 25, 1991	NDA 019965
Avonex®	Interferon Beta-1A	Biogen	May 17, 1996	BLA 103628
Rebif®		Serono Inc	March 7, 2002	BLA 103780
Betaseron®	Interferon Beta-1B	Bayer Healthcare Pharms	July 23, 1993	BLA 103471
Extavia®		Novartis	August 14, 2009	BLA 125290

Asellacrin® 10, Asellarcrin® 2	Somatropin	EMD Serono	July 30, 1976	NDA 017726
Crescormon®		Genentech	April 6, 1979	NDA 017992
Accretropin®	Somatropin Recombinant	Cangene	January 23, 2008	NDA 021538
Bio-Tropin®		Ferring	May 25, 1995	NDA 019774
Genotropin® and Genotropin® Preservative Free		Pharmacia and Upjohn	August 24, 1995	NDA 020280
Humatrope®		Eli Lilly	March 8, 1987	NDA 019640
Norditropin® Flexpro and Norditropin® Nordiflex		Novo Nordisk	June 20, 2000	NDA 021148
Nutropin® and Nutropin® AQ		Genentech	Nov. 17, 1993 and Dec. 29, 1995	NDA 020168 & NDA 020522
Omnitrope®		Sandoz	May 30, 2006	NDA 021426
Saizen®		EMD Serono	October 8, 1996	NDA 019764
Serostim®		EMD Serono	August 23, 1996	NDA 020604
Tev-Tropin®		Ferring	May 25, 1995	NDA 019774
Valtropin®		LG Life	April 19, 2007	NDA 021905
Zorbtive®		EMD Serono	December 1, 2003	NDA 021597

Table 2: Examples of EU Approved biosimilars and their INNs (all are shared between the biosimilar and its reference, with the exception of Epoetin zeta and that was at the election of its sponsor)

Trade Name	Common Name (INN)	Biosimilar Sponsor	Reference Product	Decision	Biosimilar Approval Date
Omnitrope®	Somatropin	Sandoz	Genotropin®	Approved	April 12, 2006
Valtropin®		BioPartners	Humatrope®	Approved	April 24, 2006
Binocrit®	Epoetin alfa	Sandoz	Eprex®	Approved	August 28, 2007
Epoetin alfa Hexal®		Hexal	Eprex®	Approved	August 28, 2007
Abseamed®		Medice	Eprex®	Approved	August 28, 2007
Retacrit®	Epoetin zeta	Hospira	Eprex®	Approved	December 18, 2007
Silapo®		STADA	Eprex®	Approved	December 18, 2007
Biograstim®	Filgrastim	CT Arzneimittel GmbH	Neupogen®	Approved	September 16, 2008
Filgrastim Ratiopharm®		Ratiopharm GmbH	Neupogen®	Approved	September 16, 2008
Ratiograstim®		Ratiopharm GmbH	Neupogen®	Approved	September 16, 2008
Tevagrastim®		Teva Generics GmbH	Neupogen®	Approved	September 16, 2008
Zarzio®		Sandoz	Neupogen®	Approved	February 6, 2009
Filgrastim Hexal®		Hexal	Neupogen®	Approved	February 6, 2009
Nivestim®		Hospira	Neupogen®	Approved	June 6, 2010
Remisima®		Infliximab	Celltrion	Remicade®	Positive Opinion
Inflectra®	Hospira		Remicade®	Positive Opinion	June 28, 2013

Endnotes

- ¹ For the sake of simplicity, the term “international nonproprietary name” or “INN” is used throughout this paper, though of course in the United States the applicable term is “United States Adopted Name” or “USAN”.
- ² See e.g., FDA, Part 15 public hearing on approval pathway for biosimilar and interchangeable biological products November 3, 2010, transcript available at <http://www.fda.gov/downloads/Drugs/NewsEvents/UCM289124.pdf> (accessed Oct. 18, 2013); FDA, Center for Drug Evaluation and Research, Office of Medical Policy, Part 15 public hearing on draft guidances relating to the development of biosimilar products May 11, 2012, transcript available at <http://www.fda.gov/downloads/Drugs/NewsEvents/UCM310764.pdf> (accessed Oct. 18, 2013); Richard Dolinar, *It’s All About the Name: What Is the Imperative of Adopting Unique Names for Biologic and Biosimilar Therapeutics?*, FDLI’s Food and Drug Policy Forum, 2 (22) (Nov. 28, 2012); Steve Miller, *Is it Necessary to Depart from International Naming Conventions for Biosimilars in the US to Ensure the Safety of Biologic and Biosimilar Therapeutics?: A Response to ‘It’s All About the Name: What is the Imperative of Adopting Unique Names for Biologic and Biosimilar Therapeutics?’* FDLI’s Food and Drug Policy Forum, 3 (1) (Jan. 9, 2013).
- ³ McCamish, Gallaher, Orloff “Biosimilar by Name and Biosimilar by Nature”, RPM Report, June 28, 2013.
- ⁴ WHO, “International Nonproprietary Names,” available at: <http://www.who.int/medicines/services/inn/en/> (accessed Oct. 18, 2013).
- ⁵ FDA paper submitted to WHO, “U.S. FDA Considerations: Discussion by National Regulatory Authorities with World Health Organization (WHO) On Possible International Non-proprietary Name (INN) Policies for Biosimilars” (Sept. 2006) (attached below as an Appendix).
- ⁶ ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process. EU: Adopted by CPMP, December 1, 2004, CPMP/ICH/5721/03, date for coming into operation: June 2005; MHLW: Adopted 26 April 2005, PFSB/ELD Notification No. 0426001; FDA: Published in the Federal Register, Vol. 70, No. 125, June 30, 2005, p. 37861-37862, available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf (accessed Oct. 18, 2013). The guidance defines comparable as follows:
- A conclusion that products have highly similar quality attributes before and after manufacturing process changes and that no adverse impact on the safety or efficacy, including immunogenicity, of the drug product occurred. This conclusion can be based on an analysis of product quality attributes. In some cases, nonclinical or clinical data might contribute to the conclusion.
- ⁷ Schiestl, M et al., *Acceptable Changes in Quality Attributes of Glycosylated Biopharmaceuticals*, Nature Biotechnology, 29 (4): 310-312 (Apr. 2011).
- ⁸ Schneider C. “Biosimilars in Rheumatology The Wind of Change”, Am Rhem Dis March 2013, available at <http://ard.bmj.com/content/72/3/315.full.pdf> (accessed Oct. 18, 2013). While the data on the number of manufacturing changes is provided for Europe, similar changes will have been undertaken for the US, but the use of comparability is not made public in the US.

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- ⁹ BPCIA definition of biosimilar/biosimilarity is that “there are no clinically meaningful differences between the biological product and the biosimilar in terms of safety purity and potency of the product.” PHS Act § 351(i)(2).
- ¹⁰ ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process. EU: Adopted by CPM, December 1, 2004, CPMP/ICH/5721/03, date for coming into operation: June 2005; MHLW: Adopted 26 April 2005, PFSB/ELD Notification No. 0426001; FDA: Published in the Federal Register, Vol. 70, No. 125, June 30, 2005, p. 37861-37862. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf (accessed Oct. 18, 2013).
- ¹¹ WHO, “International Nonproprietary Names,” available at: <http://www.who.int/medicines/services/inn/en/> (accessed Oct. 18, 2013).
- ¹² Such was the case with the hyaluronidases where the reference product, Wydase[®], was no longer commercially available.
- ¹³ The one exception is Hospira’s epoetin zeta, a biosimilar to Eprex[®], but it must be pointed out that a separate INN was requested at the sponsor’s own initiative.
- ¹⁴ As Novartis has previously stated in the context of this discussion, it expects that biosimilars would have unique brand names in the United States. Indeed, Novartis would support a FDA requirement that all biosimilars must have unique brand names.
- ¹⁵ Presentation by Niels Vermeer “Traceability of biopharmaceuticals in spontaneous reporting systems,” (May 25, 2012), at the European Medicines Agency, Fifth stakeholder forum on the implementation of the new pharmacovigilance legislation, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2012/05/WC500127934.pdf (accessed Oct. 18, 2013), and also presentations available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2012/05/event_detail_000582.jsp&mid=WC0b01ac058004d5c3 (accessed Oct. 18, 2013).
- ¹⁶ ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process. EU: Adopted by CPM, Dec. 1, 2004, CPMP/ICH/5721/03, date for coming into operation: June 2005; MHLW: Adopted April 26, 2005, PFSB/ELD Notification No. 0426001; FDA: Published in the Federal Register, Vol. 70, No. 125, June 30, 2005, p. 37861-37862, available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf (accessed Oct. 18, 2013).
- ¹⁷ WHO, Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs) (2009), available at: http://www.who.int/entity/biologicals/areas/biological_therapeutics/BIO_THERAPEUTICS_FOR_WEB_2_2APRIL2010.pdf (accessed Oct. 18, 2013).
- ¹⁸ Kozlowski, S et al., *Developing the Nation’s Biosimilars Program*, N Engl J Med 365(5):385-388 (Aug. 4, 2011).
- ¹⁹ Schiestl, M et al., *Acceptable Changes in Quality Attributes of Glycosylated Biopharmaceuticals*, Nature Biotechnology, 29 (4): 310-312 (Apr. 2011); see also Dörner et al., *The role of biosimilars in the*

treatment of rheumatic diseases, Ann Rheum Dis, published online Dec. 19, 2012, doi:10.1136/annrheumdis-2012-202715; Christian K Schneider, *Biosimilars in rheumatology: the wind of change*, Ann Rheum Dis, 72 (3): 315- 318 (Mar. 2013)(looking at the number of manufacturing changes for certain European biologics, and finding these products have undergone up to 37 manufacturing changes since approval).

- ²⁰ Section 7002 of the BPCIA notes that the statute requires a single 351(a) reference product for each biosimilar and this section also provides a 12-year exclusivity provision, all of which is evidence of the experience that FDA has with that reference product.
- ²¹ FDCA § 501(j).
- ²² Public Health Service Act (PHS Act) 351(j), confirming that all biological products approved under PHS Act are subject to the FDCA.
- ²³ FDCA § 501(b).
- ²⁴ FDCA § 502(e).
- ²⁵ FDCA § 502(e)(3).
- ²⁶ It should be pointed out that such a change would necessitate a parallel change to the USP name of the originator.
- ²⁷ FDCA § 508.
- ²⁸ FDA paper submitted to WHO, "U.S. FDA Considerations: Discussion by National Regulatory Authorities with World Health Organization (WHO) On Possible International Non-proprietary Name (INN) Policies for Biosimilars" (Sept. 2006) (attached below as Appendix).
- ²⁹ As a statutory matter BPCIA defines biosimilar/biosimilarity as meaning that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product."
- ³⁰ FDA paper submitted to WHO, "U.S. FDA Considerations: Discussion by National Regulatory Authorities with World Health Organization (WHO) On Possible International Non-proprietary Name (INN) Policies for Biosimilars" (Sept. 2006)(attached below as Appendix).
- ³¹ See *e.g.*, comments to Docket No. FDA-2011-D-0618, letter dated May 25, 2012, from American Pharmacists Association (APhA), the National Association of Chain Drug Stores (NACDS) and the National Community Pharmacists Association (NCPA); letter to Commissioner Hamburg, dated April 17, 2013 from the National Association of Boards of Pharmacy ("The use of INNs as a naming convention is unfamiliar to health care providers and patients and could cause confusion, resulting in the incorrect drug being dispensed to patients or therapeutic duplication"); letter to Commissioner Hamburg, dated August 20, 2012 from the National Council for Prescription Drug Programs (NCPDP) ("[Unique individual nonproprietary names for biosimilars] could cause public health concerns due to therapeutic duplication and healthcare professional and patient confusion regarding appropriate use, safety and efficacy of biologic products. Over the years we have observed how small, seemingly

inconsequential, changes in product descriptions and data formatting or structure can have significant consequences within healthcare.”); letter to Commissioner Hamburg, dated June 4, 2012 from 22 stakeholders including AARP, Blue Cross Blue Shield Association, California Public Employees Retirement System, National Association of Chain Drug Stores.

³² Comments to Docket No. FDA-2011-D-0618, letter dated May 25, 2012, from American Pharmacists Association (APhA), the National Association of Chain Drug Stores (NACDS) and the National Community Pharmacists Association (NCPA).

³³ Reference to the terminology in the USP submission to the docket on the three biosimilar draft guidances published February 2012.

³⁴ FDA Guidance for Industry “Contents of a Complete Submission for the Evaluation of Proprietary Names”, February 2010, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> (accessed Oct. 18, 2013). See Page 10:

4. Intended Meaning of Proprietary Name Modifiers (e.g., prefix, suffix)

A modifier, such as a prefix or suffix, in the proprietary product name might suggest different meanings to health care professionals and consumers, which could potential lead to product confusions. When an applicant or sponsor submits a product name with a modifier (for example with the prefix Lo- or suffix XR), the submission should include the intended meaning of the modifier, the rationale for the modifier, and any studies that have been conducted to support the use of the modifier.

Appendix

U.S. FDA Considerations: Discussion by National Regulatory Authorities with World Health Organization (WHO) On Possible International Non-proprietary Name (INN) Policies for Biosimilars

September 1, 2006

Support of INN's Original Purpose

The United States Food and Drug Administration (U.S. FDA) continues to support the original purposes, premises, and uses of the INN and believes the system has provided many positive elements to the world's public health, especially in facilitating the exchange of scientific data and reports on various products with the same active ingredient(s).

The USA recognizes the INN system as a cataloging system whereby many products worldwide may share the same internationally recognized nonproprietary name based on drug substance. In this manner, the INN system provides a clear mechanism to health care professionals worldwide for identifying medicines and communicating unambiguously about them based on pharmacological class.

The U.S. FDA's concerns in today's discussion are (a) that the INN not be used in ways that could jeopardize the health of patients, and (b) that we not unnecessarily institute changes that could jeopardize the public health benefits of the present INN system.

Specifically, INNs should not be used to imply pharmacologic interchangeability of products with the same active ingredient(s) when no credible scientific data exist that demonstrate such. Likewise, INNs should not be used to differentiate products with the same active ingredient(s) when credible scientific data demonstrate that no pharmacologically relevant differences exist.

Pharmacologic Interchangeability

“Interchangeability” is a term used for purposes of this discussion to designate the situation where scientific data convincingly demonstrates that two products with very similar molecular compositions or active ingredient(s) can be safely substituted for one another and have the same biologic response and not create adverse health outcomes, e.g., generation of a pathologic immune response.

With small molecular products, there is a long history to support the use of various scientific approaches to establishing “bioequivalence” between products with the same active ingredient(s) produced by different manufacturers. We know now that these “bioequivalent” products can indeed be expected to behave in a pharmacologically interchangeable manner when used in patient care.

With protein products, as of today, the FDA has not determined how interchangeability can be established for complex proteins.

Different large protein products, with similar molecular composition may behave differently in people and substitution of one for another may result in serious health outcomes, e.g., generation of a pathologic immune response

When scientific data establishing pharmacologic interchangeability do not exist, especially with more complicated protein molecules with potential critical immunologic safety issues, it is important that patients and physicians be aware that protein products with similar molecular composition may indeed not be interchangeable.

U.S. FDA believes that the only way to establish pharmacologic interchangeability is through scientific data, and nomenclature should not be used as a way to imply such when there are not credible supporting data.

Situation in the United States of America

Product Dispensing

To date, the USA does not use non-proprietary names as a vehicle for communicating pharmacologic interchangeability. There are examples in both small molecule products and more complex proteins of products having the same non-proprietary name and there not being scientific data establishing the interchangeability of the products. For example, multiple innovator products containing interferon β -1a, insulin, or somatropin share the same non-proprietary name and there are not scientific data that support the pharmacologic interchangeability of these products.

In the USA there are recognized mechanisms in place other than non-proprietary names for assigning pharmacologic interchangeability: e.g., equivalence ratings in the Orange Book; specific labeling regarding pharmacologic interchangeability.

In addition, in the USA, there are drug dispensing systematic “checks” to help assure appropriate dispensing of products based on whether or not there are scientific data establishing interchangeability. However, this might not be true in other countries.

Because of the many alternative mechanisms in the U.S. for preventing inappropriate substitution, at this time the U.S. FDA does not consider the proposed change to the INN policy for naming biosimilars to be necessary to prevent inappropriate substitution in the United States. Appropriate prescribing and dispensing practices in the U.S. encompass more than just conveyance of a drug name from prescriber to pharmacist. Regulations concerning drug substitution by pharmacists vary from state to state in the United States. However, there is always a mechanism by which the prescriber can authorize that the brand or innovator product be dispensed. As an additional safeguard, many states utilize a state drug formulary that includes listings of drugs with the “same” active ingredient(s) considered to be pharmacologically interchangeable. Even if two biosimilars would have the same nonproprietary name, they would

only be included on a list of interchangeable products, if there were scientific data to justify such. Thus, a common INN in itself does not imply or warrant inclusion on a state's list of interchangeable drugs. The FDA recognizes that the authorized prescribing information represents the most important means of communicating information about an authorized product to prescribers and pharmacists. The authorized prescribing information should distinguish a product from others considered to be biosimilar if indeed there is not data to substantiate pharmacologic interchangeability. In addition, the role of continuing professional education about interchangeability risks with biosimilars should be further emphasized.

The issue of interchangeability is not an issue of nomenclature but a scientific question that needs to be decided on its own merit. The question of nomenclature is more relevant to concerns about pharmacovigilance and the prevention of inappropriate substitution. However the FDA believes that these issues transcend a naming convention. It would be the U.S. FDA's preference that INNs continue to be granted based only on molecular characteristics and pharmacological class of the active ingredient(s). Regarding similar protein products, this view is predicated on the situation in the U.S., where there are alternative mechanisms in place for preventing potentially dangerous substitutions and ensuring that potentially unsafe drug dispensing decisions are not made because of a misperception that the same INN implies pharmacologic interchangeability. These mechanisms might not exist in other countries. In the event that granting the same INN name to similar drugs that are nonetheless pharmacologically distinct may lead to inappropriate substitutions, then it may be determined at a later date that changes to the INN policy are needed to ensure safe prescribing and dispensing of drug products including similar protein products throughout the world. Concerns about inappropriate substitutions that can create safety issues may be beyond the scope of the INN program to address through nomenclature alone, and may be better addressed by specific steps taken by individual regulatory authorities to ensure appropriate prescribing."

Pharmacovigilance:

In the USA, the non-proprietary name may serve as a useful tool in pharmacovigilance as it may be one means of product identification, but it should not be relied upon as the sole means of product identification. Pharmacovigilance is the dual responsibility of the manufacturer and the U.S. FDA. In order to practice the most robust pharmacovigilance, all involved should employ all the various tools available for product identification, including lot numbers, NDC codes or other such national coding systems, etc.

As such, the USA does not see any reason to change present INN practices for pharmacovigilance purposes when there are other identification systems in place to allow product identification beyond the level of the non-proprietary name.

U.S. FDA Concerns Regarding INNs and Complex Proteins

If the outcome of assigning the same INN to two products with highly similar ingredient(s) created the implication that the two products were pharmacologically interchangeable AND there were NO scientific data to support that finding, then the U.S. FDA would have serious concerns

about such an outcome, especially with more complicated proteins. As of today, FDA has not determined how interchangeability can be established for complex proteins.

If the outcome of assigning different names or names with unique identifiers to two products with highly similar active ingredient(s) created the implication that two products were not interchangeable when indeed there were scientific data establishing such, the U.S. FDA would have serious concerns.

It is beyond the role of the INN Expert Committee to make product interchangeability determinations. This would place an unrealistic burden of responsibility with accompanying liability on the INN Expert Committee. The INN should not be used as a determinant of interchangeability. It would be bad public health policy to allow, just because they share the same INN, the substitution of products with a shared INN in patient care when there are no scientific data to demonstrate pharmacologic interchangeability.

Likewise, it would be bad public health policy to disallow, solely because they have different INNs, the substitution of products with different INNs which indeed have scientific data that demonstrate pharmacologic interchangeability.

Each national regulatory authority should oversee the evaluation of interchangeability based on bioequivalence and/or other validated scientific data and not link such decisions to INNs.

Conclusions

This discussion among national regulatory authorities and the WHO should be a first discussion on this issue to fact find and to determine how changes to the INN system would impact both positively and adversely, the regulatory systems and public health of WHO member states.

- The FDA is concerned that some countries may be using the INN as an indicator of interchangeability. Although this is not the case in the U.S., the U.S. FDA considers this apparent inappropriate use of the INN to be a public health concern.
- The U.S. FDA encourages the WHO to further investigate the worldwide prevalence of using the INN as a determinant of interchangeability (note: the BCG study sponsored by Amgen investigated 6 EU countries and use of the INN in prescribing was encouraged in most of these 6 countries, but not required).
- The U.S. FDA suggests that the WHO/INN Expert Committee clarify and re-iterate the intent of the INN with participating countries.

It would be the U.S. FDA's preference that INNs continue to be granted based only on molecular characteristics and pharmacological class of the active ingredient(s). Regarding similar protein products, this view is predicated on the situation in the U.S., where there are alternative mechanisms in place for preventing potentially dangerous substitutions and ensuring that potentially unsafe drug dispensing decisions are not made because of a misperception that the same INN implies pharmacologic interchangeability. These mechanisms might not exist in other countries. In the event that granting the same INN name to similar drugs that are nonetheless pharmacologically distinct may lead to inappropriate substitutions, then it may be determined at

a later date that changes to the INN policy are needed to ensure safe prescribing and dispensing of drug products including similar protein products throughout the world. Concerns about inappropriate substitutions that can create safety issues may be beyond the scope of the INN program to address through nomenclature alone, and may be better addressed by specific steps taken by individual regulatory authorities to ensure appropriate prescribing."

At this time, the U.S. FDA acknowledges that biosimilars have not been demonstrated to be interchangeable through any scientific process. The world community may ultimately decide that INN policy for this class of products should be treated differently than that for small molecule drugs. A different naming scheme for these products might involve utilizing a different level of granularity, which may be more detailed or less detailed depending upon the utility in the INN system. Considering the inherent difficulties in additional INN product distinctions (e.g. retroactive and lifecycle changes in naming, additional INN responsibility and liability), if the world community decides to proceed with a change in the policies regarding the assigning of INNs, it should be preceded by (a) appropriate exploration of alternatives (e.g. improvements in education and/or labeling), (b) assuring the such changes fall within the scope, competence, and expertise of the INN program, and (c) the performance and independent validation of a formal risk assessment and/or documentation of events with appropriate statistical treatment.

Date created: September 5, 2006

<http://www.fda.gov/cder/news/biosimilars.htm> (accessed 16Apr08, no longer available)