Paul R. Eisenberg, M.D., M.P.H.
Senior Vice President
Global Regulatory Affairs and Safety

AMGEN

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
805.447.4632 – Telephone
805.375.7274 – Fax

March 01, 2014

Federal Trade Commission
Office of the Secretary
Room H-113 (Annex X)
600 Pennsylvania Ave NW
Washington, DC 20580

Subject: Workshop on Follow-On Biologics: Project No. P131208

Dear sir or madam:

Amgen is a global biotechnology and pharmaceuticals products company based in Thousand Oaks, CA. We are pleased to have the opportunity to offer comments on the Public Workshop on Follow-On Biologics: Impact of Recent Legislative and Regulatory Naming Proposals on Competition. We have included the following comments in an effort to support the FTC on this endeavor.

As a manufacturer with thirty years of experience and a producer of both innovative and biosimilar medicines, Amgen has a uniquely credible voice to provide insight on the questions posed by the FTC. Patients are always our top priority; we believe public health and safety can be strengthened while achieving a competitive marketplace. The science of biotechnology is complex and creates challenges that must be met by appropriate public policy solutions for product substitution and naming. To these ends, Amgen has collaborated with a broad range of stakeholders to identify solutions. We will continue to work to advance sound public policy and appreciate the robust dialogue around the questions posed by FTC.

For your convenience, we have provided some of the frequently cited materials. We would be happy to provide additional materials should you find that helpful.

Sincerely,

Paul R. Eisenberg, M.D., M.P.H.
Senior Vice President, Global Regulatory Affairs and Safety

ENCLOSURE: Amgen comments on: **Public Workshop: Follow-On Biologics: Impact of Recent Legislative and Regulatory Naming Proposals on Competition**

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

United States Federal Trade Commission Public Workshop: Follow-On Biologics: Impact of Recent Legislative and Regulatory Naming Proposals on Competition

EXECUTIVE SUMMARY

Amgen is a biotechnology pioneer and developer of one of the largest portfolios of biosimilar medicines designed to facilitate patient access. It is from this vantage point, with more than 30 years of experience in the challenges associated with biotechnology, that we provide comment on the questions of biosimilar policy posed by the Federal Trade Commission (the "FTC").

FTC is evaluating the competitive impact of product selection laws for biologic medicines and the options for assigning non-proprietary names. Amgen approaches these matters from a scientific perspective. Our first principle is that competition can and should be enabled in a manner that acknowledges the science behind complex biotechnology medicines and thereby protects patient safety and public health.

For Amgen, there is a simple test for every proposed policy provision: does it improve or degrade protections for patients? Degradation of either patient welfare or public health in the context of biological products is not acceptable - nor is it necessary as a means to increase access. We strive to provide both increased access and safety when it comes to biologic medicines. Working with other stakeholders, our collective goal must be to achieve a competitive marketplace while protecting patient safety.

The science of biologics is complex and therefore creates challenges that must be met by appropriate public policy solutions for substitution and naming. It is widely recognized that biologics are different from chemical drugs in ways that make longterm monitoring of individual biologics both more important and more challenging. Three characteristics of biotech medicines must inform consideration of both substitution policy and naming of these medicines: biologics' large molecular size and the attendant interaction with patient immune systems; biologics' molecular complexity and the inability of current science to fully associate structure with function; and biologics' sensitivity which can result in product changes following even mild alteration in manufacturing conditions.

In light of these inherent characteristics, all biologics (originators and biosimilars) must be carefully monitored throughout the lifecycle of the product, for any unexpected change in patient impact. Although our scientific knowledge continues to progress at a remarkable pace, the mysteries of living cells have not all been solved. Distinguishing among multiple manufacturers' versions of a particular biological product will enable all manufacturers to stand accountable and will help to ensure the optimal medical care of all patients that rely upon these important biological medicines.

Regarding biologic substitution rules under state laws, there is broad support for four principles that track the generic drug laws in most states. In addition to these four principles, there is also a distinct need for traceability of individual biologic products over time. Physicians – as the health care professionals most likely to report adverse event and product problems – must have ready access to a clear and complete record of the specific biologic medicines their patients have received. We know from physicians that they want this information and a response of "just contact the pharmacy" is neither practical nor sufficient. Without accurate knowledge of the patient's medication, problems are attributed to the wrong product and can go unidentified and/or unsolved. Through modest steps to

ensure transparency of the specific biologic medicine a patient receives, this very real risk can be mitigated.

State standards for biologic substitution that differ where appropriate from those of generic drugs should be expected in light of scientific differences between chemically synthesized medicines and biological medicines. These scientific differences are reflected in the federal laws governing their respective approval pathways and FDA's implementation of them. We welcome a robust dialogue and continue to seek consensus approaches on how best to ensure access to clear and complete patient medication histories.

Distinguishable biologic product names are equally essential in ensuring effective product monitoring over time. An indistinguishable nonproprietary name risks losing the specific identity of the product, by manufacturer, when it is most essential – when adverse events are reported and investigated. Quite simply, in situations where a brand name does not exist or is not used for prescribing, it is the non-proprietary name that will be captured in a patient's medication history. And regardless of how a particular product is prescribed, the non-proprietary name tends to be what is frequently used to report an adverse event report. Other product identifiers, such as national drug codes, are not widely used by, or even available, to those who most often report product problems and adverse events – the patients and the physicians. Distinguishable nonproprietary names have been implemented in Australia and Japan with biosimilar uptake commensurate with the experience in other markets, demonstrating that this can be implemented simply and without competitive impact. The evidence does not support that uptake has been affected by non-proprietary name. Amgen continues to engage other stakeholders to identify consensus and common ground on how best to achieve this important element of the biologic safety system.

Finally, Amgen believes that manufacturer accountability and product transparency – through access to accurate patient records and distinguishable product names – are fully consistent with FTC's ultimate goal as articulated by Chairwoman Ramirez. We, too, believe that "with necessary safeguards for patient health and safety competition from follow-on biologics can benefit patients through lower prices and expanded access to important biologic treatments."[1]

I. Questions regarding State FOB Legislative Proposals and Laws

I.1. How would new state substitution laws passed in 2013, or similar proposals pending in other states, affect competition expected to develop between biosimilar or interchangeable biologics and reference biologics? In the context of state substitution laws, what is the likely competitive impact of a biologic product being designated "interchangeable?"

Key points

- State biologic product selection laws create a clear pathway for substitution of interchangeable biologics where none currently exists and thereby expand market opportunities for interchangeable biosimilar medicines.

[1] Edith Ramirez, FTC Chairwoman, Opening Statement, FTC Follow-on Biologics Workshop (Feb. 4, 2014) ("We believe that with necessary safeguards for patient health and safety, competition from follow-on biologics can benefit patients through lower prices and expanded access to important biologic treatments.")

- The approach to biologic product selection that Amgen supports closely tracks existing generic substitution laws.
- Transparency through pharmacist/physician communication after dispensing, for all interchangeable products – both originator and biosimilar – will foster confidence in biosimilars and support competition.
- Payer cost-containment strategies drive product selection and thus market-based competition.

State biologic product selection laws create a clear pathway for substitution, which advances competition.

Amgen is both a pioneer in biotechnology and one of the leading developers of biosimilars.[2] We support principles for state biologic product selection laws (also referred to as biologic substitution laws) that advance competition by expanding the market opportunity for similar versions of previously approved biological products. Specifically, under these principles a pharmacist would have the discretion to select and dispense an interchangeable biologic (that is, choose between a prescribed biologic and any biosimilar deemed interchangeable for that biologic), as long as the prescriber did not affirmatively prohibit substitution as permitted to do under longstanding generic laws (by, for example, writing "dispense as written" on the prescription). A pharmacist would not be required to consult with the prescribing physician about a substitution. This expanded dispensing authority advances competition among biologics in a scientifically sound manner.

Amgen appreciates the FTC's question on competitive effects of the state laws governing biologic product selection as it appropriately differentiates biosimilars from biological products deemed "interchangeable" by FDA (also referred to as "interchangeable biologics" and "interchangeable biosimilars"). This differentiation is important when assessing the likely business models for each product category.

The Biologics Price Competition and Innovation Act of 2009 (BPCIA),[3] which authorized FDA to approve similar versions of biologic medicines under an abbreviated regulatory pathway, established two new categories of biologics: biosimilars and interchangeable biosimilars. The law thus set the stage for at least two different competitive dynamics: competition between originators (also referred to as "reference products") and biosimilars, and competition between originator products and interchangeable biosimilars.[4] Under the BPCIA, products approved as biosimilars are "highly similar" to the reference product with "no clinically meaningful differences" in terms of "safety, purity or potency."[5] Thus, biosimilars will have been deemed safe and effective but not necessarily evaluated as safe and appropriate for purposes of

[2] Bradway RA, Letter to Shareholders, Amgen Annual Report 2 (April 4, 2013) (noting that in early 2013 Amgen announced plans to develop and manufacture six biosimilar)..

[3] The BPCIA, enacted as part of the Affordable Care Act, authorizes the United States Food and Drug Administration to approve biologic drugs that are "biosimilar" to reference products already approved. Section 351(k) of the Public Health Service Act, *codified at* 42 U.S.C. § 262.

[4] The designation of biologic products as interchangeable is unique to the United States biosimilar framework.

[5] 42 USC 262(i)(2).

switching or alternating between or among products. This is consistent with the approach taken by regulators in other highly regulated markets.[6,7]

Separate from approval as a biosimilar, the BPCIA also permits FDA to designate a product as "interchangeable." To be designated as an interchangeable, the biological product must not only meet the standards for biosimilarity, but also demonstrate that two additional criteria are satisfied: (1) the product can be "expected to produce the same clinical result as the reference product in any given patient," and (2) for products administered more than once, alternating or switching between the biosimilar and the reference product presents no greater risk "in terms of safety or diminished efficacy" than the risk associated with using only the reference product.[8]

In light of the emergence of biosimilars and interchangeable biologics as new categories of approved medicines under the BPCIA, beginning in 2013, some states began enacting laws to explicitly address substitution of these biologic products. By way of historical background, state pharmacy substitution laws were designed to address the substitution of generic drugs. Most state pharmacy statutes reference the FDA publication "Approved Drug Products with Therapeutic Equivalence Evaluations" commonly known as the "Orange Book." Many of these states restrict substitution to those products listed in this publication as therapeutically equivalent. Publication in the "Orange Book" is currently limited to products licensed by FDA under the Food Drug and Cosmetic Act (FDCA). Those current state laws that do not follow the "Orange Book," *per se*, include other requirements that may not directly apply to biological products and thus would preclude their substitution. For example, some states require that the product to be substituted have the identical chemical active ingredient as the prescribed product. Accordingly, there has been little stakeholder disagreement that state pharmacy statutes must be updated and explicitly address substitution rules for biosimilars and interchangeable biologics.

As a result of the two categories of biosimilars established in the BPCIA, conditions for competition between originator products and biosimilars will likely be different than between originator products and interchangeable biosimilar products. Indeed, the FTC noted in its 2009 report[9] and analysts have long expressed an expectation[10] that competition between originators and biosimilar manufacturers is more likely to be akin to brand-to-brand competition than the longstanding brand-to-generic competition for chemically synthesized drugs. Manufacturers of biosimilar products that are not deemed interchangeable can be expected to have to market their products to healthcare providers, as do originator manufacturers and those in a therapeutic class with distinguishable characteristics. By contrast, interchangeable biologics will have the opportunity to compete more like generic drugs, where branding and associated

[6] Therapeutic Goods Administration, Australian Government , Evaluation of biosimilars: What is a biosimilar? (30 July 2013).

[7] Weiss, et al. aptly described biosimilars as, "therapeutic alternatives to their respective reference products.[7] Weise M, Bielsky MC, De Smet K et al., Biosimilars: What clinicians should know, Blood 120:5111–7 (2012) at 5114.

[8] 42 USC 262 (k)(4).

[9] FTC, Emerging Health Care Issues: Follow-on Biologic Drug Competition iii, 13-14, 19, 23(June 2009) (FTC Emerging Health Care Issues Report).

[10] Gilbert G et al., Bank of America Merrill Lynch Biosimilars Mini-Primer (Sept. 19, 2012) ("Significantly, it is important to note that variables such as discount to the brand, generic penetration, price erosion, and level of competition will likely be different from what is generally experienced by typical generics (especially if the biologic product is non-interchangeable)."). *See also* FTC Emerging Health Care Issues Report, *supra* note 11 at iii.

marketing may not be as critical, because usage relies instead, in large part, on utilization management tools employed by payers and/or substitution by the pharmacist.[11]

The approach to biologic product selection that Amgen supports closely tracks existing generic substitution laws, which support competition.

The consensus principles on state substitution supported by Amgen and other biosimilar and originator manufacturers as well as doctor and patient groups not represented at the workshop[12] largely track those for generic drug substitution and advance competition while protecting patient safety. The practice of pharmacy, including pharmacist drug product selection authority, is a matter of state law and thus, the specific content of some generic substitution laws varies from state to state.[13] However, all proposed state biologic product selection laws share four core elements common to the generic drug provisions in most states and the FTC model generic drug framework discussed in the 1979 FTC report on drug product selection.[14] Consistent with generic drug substitution laws,[15] the biologic product selection principles that Amgen and other stakeholders, including other companies developing and manufacturing biosimilars, do the following:

- limit substitution to that which is medically and scientifically appropriate,[16] for biologics, that is products deemed interchangeable by FDA. This element puts similarly situated competitors on a level playing field whereby those interchangeable biologics FDA has determined can be switched safely and are thus approved by FDA as interchangeable

[11] FTC Emerging Health Care Issues Report, *supra* note 11 at 13-14, 19, 22-23.

[12] Patient and physician organizations have written letters to members of the Washington state legislature in support of House Bill 2326/ Senate Bill 6091, which embodies the principles of the consensus position on substitution of biologics. In contrast to the *post-dispense* communication supported by Amgen and others, a number of physician organizations have expressed a preference for notification *prior to dispensing*. Physician Groups include: American Medical Association, Alliance of Specialty Medicine (membership includes: American Academy of Facial Plastic & Reconstructive Surgery, American Association of Neurological Surgeons, American College of Mohs Surgery, American Gastroenterological Association, American Society of Cataract and Refractive Surgery, American Society of Echocardiography, American Society of Plastic Surgeons, Coalition of State Rheumatology Organization, Congress of Neurological Surgeons, North American Spine Society, Society for Cardiovascular Angiography and Interventions, Society for Excellence in Eyecare), Council of State Rheumatology Organizations, American Academy of Dermatology.
Patient Groups include: American Autoimmune Related Diseases Association, National Kidney Foundation, National Psoriasis Foundation, Global Healthy Living Foundation, Alliance for Safe Biologic Medicines (the steering committee members are: American Academy of Dermatology, Association of Clinical Research Organizations, Global Colon Cancer Association, Health HIV, Kidney Cancer Association, Alliance for Patient Access, American Autoimmune Related Diseases Association, Colon Cancer Alliance, Global Healthy Living Foundation, International Cancer Advocacy Network, ZERO-The End of Prostate Cancer), One in Four Chronic Health (members include: Molly's Fund Fighting Lupus, Hepatitis Education Project, Caring Ambassadors Program, Arthritis Foundation Great West Region).
Manufacturers who agree with these principles, including communication regarding the product received by the patient, include Abbvie, Activis, Amgen, Boehringer Ingelheim, Genetech, Hospira, Novartis/Sandoz

[13] This variation is due to states taking some and leaving some provisions of the FTC Model Act for generic substitution.

[14] FTC, Drug Product Selection: Staff report to the Federal Trade Commission 273-288 (Jan. 1979).

[15] The specifics of generic substitution laws vary by state.

[16] *See* Vivian, J.C., Wayne State University "Generic-Substitution Laws" June 19, 2008, http://www.uspharmacist.com/content/s/44/c/9787/ (accessed Feb. 26, 2014).

may be able to leverage the generic drug model of competing without a large sales and marketing presence.[17] Biosimilar products not deemed interchangeable are expected to compete with the reference product and other non-interchangeable biological products using more of a brand-to-brand model, similar to the way new drugs approved based on full applications compete;[18]

- give the prescribing physician the authority to prohibit automatic substitution by the pharmacist by specifying "dispense as written" or "brand necessary," an authority physicians have in all fifty states for chemical drugs. The 90% market shift when some generics comes to market[19] as well as generic dispensing rates reaching 84% of all prescriptions dispensed demonstrate that this does not hinder competition;[20]

- seek to ensure that the patient or patient's representative is aware of the product actually received. This is also common practice with generic drug substitution[21] and helps to mitigate the risk of confusion for the patient and/or representative when the dispensed product or packaging looks different than what was received previously. It is arguable that such notification has served as a form of marketing in favor of generic competition as patients consistently have had positive experiences with less expensive medicines; and

- require the pharmacy to maintain a record of the product dispensed, as is the case with generic drugs.[22] The record keeping obligation remains uniform regardless of the actual product dispensed, thus having no net impact on the competitive dynamic.

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[17] See Gal, A. (Bernstein Research) slide 8, 2008 (accessed February 24 at http://www.ftc.gov/sites/default/files/documents/publicevents/emerging_health_care_competition_and_consumer_issues/rgal.pdf) (showing PBMs as the potential "kingmaker.")

[18] FTC Emerging Health Care Issues Report, *supra* note 11 at iii, 13-14, 19, 23.

[19] FTC Emerging Health Care Issues Report, *supra* note 11 at 13 (referencing Grabowski H et al., The Effect on Federal Spending of Legislation Creating a Regulatory Framework for Public Health Service Act Follow-on Biologics: Key Issues and Assumptions, White Paper (July 1, 2007) at 42 (unpublished paper on file with Analysis Group, Inc.), Available at http://public.econ.duke.edu/Papers//PDF/0907_H_Grabowski_I_Cockburn_G_Long_et_al_Effect_on_Federal_Spending_of_Follow_on_Biologics.pdf. (accessed Feb. 26, 2014)

[20] Christopher Cheney, "Drug Shortages Exacerbated by Supply Chain Woes", Health Leaders Media Feb. 18, 2014 (Referencing a statement released by Ralph Neas, President and CEO of the Generic Pharmaceutical Association in which he described 2013 as "a year of milestone achievements" for the generic drugs industry). *See also id.* ("Generic utilization hit an all-time high as 84 percent of prescriptions dispensed are now generic"). http://www.healthleadersmedia.com/page-4/QUA-301095/Drug-Shortages-Exacerbated-by-Supply-Chain-Woes (accessed Feb. 26, 2014)

[21] 38 states and U.S. territories have provisions "where consent is required and those that require the patient to be notified/informed of substitution." National Association of Boards of Pharmacy, Survey of Pharmacy Law 67 (2014).

[22] All states require pharmacy prescription records be maintained for a period of time, ranging from 2 to 7 years. National Association of Boards of Pharmacy, Survey of Pharmacy Law 72 (2014).

Pharmacist/physician communication after dispensing will foster confidence in biosimilars and support competition.

Amgen supports a fifth element for all biologic product selection laws: communication identifying the specific product dispensed to the patient, but only when there is an FDA-approved interchangeable biologic for the product prescribed. This is a modest and science-based addition to generic drug practices that will foster competition in the biotech marketplace. The proposal specifies:

- Communication regarding the product dispensed should occur no later than ten days after dispensing;
- Use of interoperable electronic health records (EHR) would satisfy the communication requirement and is the preferred means of communication; when EHR is unavailable or not in place, communication should be as practical as possible;
- Communication outside of EHR is not required where there is no FDA-designated interchangeable biologic product for the prescribed biologic or where a refill prescription is not changed from the product originally dispensed.

This communication provision for biologic product selection laws is supported by physician and patient groups as well as other biosimilar and originator manufacturers.[23] A discussion of the scientific rationale surrounding this element is provided in the answer to Question I.3, below.

Of greatest significance from a competition standpoint is that the biological product selection principles that Amgen and others support facilitate the generic competitive model for interchangeable biologics by amending current pharmacy laws to permit the automatic substitution of an interchangeable biological product.

Claims that the communication will somehow disparage biosimilars or interchangeable biologics are unfounded and disregard the facts. First, the post-dispense communication requirement applies to the dispensing of any biological product whenever there is an FDA-approved interchangeable available for the prescribed product, and entirely independent of whether there is a substitution for that prescribed product. In other words, it is a post-*dispense* pharmacist-prescriber communication, not a post-*substitution* pharmacist-prescriber communication. Second, if, in fact, a physician wanted the specific product prescribed to be that dispensed, he or she could simply exercise longstanding "Dispense As Written" (DAW) authority[24] at the time of writing the script. And the exercise of that DAW authority – regardless of whether for an originator, or specific biosimilar or interchangeable biosimilar – would not circumvent the pharmacist-physician communication requirement so long as there were an interchangeable product available for that prescribed product.

[23] See *Supra* 12. Manufacturers who agree with these principles, including communication regarding the product received by the patient, include Abbvie, Activis, Amgen, Boehringer Ingelheim, Genetech, Hospira, Novartis/Sandoz.

[24] This authority for physician choice is longstanding under generics law and is something that the FTC included in its Model Act for generics several decades ago.

Opponents of the communication provision acknowledge that the provision clearly states that the notice is "after" dispensing.[25] Nevertheless, those that oppose continue to try and confuse legislators, regulators, and others by claiming as analogous an unrelated and readily distinguishable Tennessee law requiring prior physician notification before a substitution of a specific class of medicines (anti-epileptic drugs) is made. Specifically, they argue that the pharmacists will treat the post dispensing communication as the need for prior physician consent to avoid a perceived risk of being "embarrassed" or otherwise being inconvenienced by having to restock a returned dispensed product once the "physician becomes aware of a substitution." This argument has no validity and was even received with a degree of skepticism by the pharmacist representing CVS Caremark when asked about it during the panel discussion at the FTC workshop.[5] The suggestion that a post-dispense communication would somehow be treated by pharmacists as a prior consent requirement for a substitution is also belied by the fact that the notification process associated with pharmacist administered vaccines does not appear to have become a prior notification practice.[6]

Post-dispense pharmacist-prescriber communication for biological products fosters competition by increasing physician familiarity and comfort with biosimilar products and poses no conflict with the BPCIA. The BPCIA defines the term "interchangeable" as meaning that the biological product "may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product."[26] After-the-fact communication does not in any way encroach upon the pharmacist's substitution discretion, does not intervene, come in between, hinder, or in any other way interfere with the pharmacist's complete discretion in biological product selection.

The transparency created by pharmacist communication about the product dispensed will facilitate manufacturer accountability and prescriber confidence in both biosimilar and interchangeable products – which will foster uptake of these important medicines and thus support a competitive biologics market. Physician confidence in a product helps drive broad adoption and uptake.[27] Physician confidence comes from clinical data and first-hand experience.[28] Physicians are more likely to accept substitution and prescribe biosimilars and

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[25] Amgen supports a communication period as 10 days after the product has been dispensed.

[5] FTC, "Follow-on Biologics Workshop: Impact of Recent Legislative and Regulatory Naming Proposals on Competition, Part 3, Transcript at 10-12, http://www.ftc.gov/news-events/audio-video/video/follow-biologics-workshop-impact-recent-legislative-regulatory-namin-1) .

[6] Surescripts' Physician Notification Letter for immunizations description says: "Notifications are sent out within two business days. Records are delivered to physician via best option available. Pharmacy is notified upon receipt by physician." Surescripts, Immunization notification registry reporting (2013), http://surescripts.com/docs/default-source/products-and-services/immunization_notification_surescripts.pdf?sfvrsn=6.

[26] 42 USC 261(i)(3) (emphasis added).

[27] Weise M, Bielsky MC, De Smet K et al., Biosimilars: What clinicians should know, Blood 120:5111–7 (2012) at 5111.

[28] European Commission, What You Need to Know about Biosimilar Medicinal Products: Process on Corporate responsibility in the Field of Pharmaceuticals Access to Medicines in Europe," Consensus Information Paper 2013 at 16-17 (2013) (discussing market factors influencing biosimilar uptake) (also referred to the "Tijani Initiative"), http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/biosimilars_report_en.pdf. *See also* FTC Emerging Health Care Issues Report, *supra* note 11 at 17, 19; Grabowski H. et al., The Effect on Federal Spending of Legislation Creating a Regulatory Framework for Public Health Service Act Follow-on Biologics: Key Issues and Assumptions, White Paper 42 (July 1, 2007) (unpublished paper on file with Analysis Group, Inc.), Available at

interchangeable biological products after they have seen their own patients do well on these medicines.[29]

Transparency both conveys and inspires confidence in biologics, including interchangeable biosimilars and the process of substitution, which supports a competitive marketplace. Complete medical records are important to the biologic market because, in addition to the product-class related safety hazards, there is a possibility that adverse events associated with biologics may be product specific.[30] Ensuring physicians can conveniently identify what product the patient received indicates that manufacturers are confident in the quality of their products and can be held accountable. It also means the physician doesn't have to prohibit substitution in order to know what the patient received, to carefully monitor the patient's progress or to accurately associate an adverse event with the correct product. Information fosters competition.

Payer cost-containment strategies drive product selection and thus market-based competition

While substitution laws play an important role in driving utilization of lower-cost generics, a primary driver in product selection is not only state law, but the economics of payer cost containment strategies. State substitution laws regulate the practice of pharmacy – and thus a pharmacist's authority to dispense a generic alternative for a prescribed product without consent from the prescriber – however, they generally do not address the all-important questions: (1) who is paying for the product; and (2) what are the costs and incentives involved.

Payer cost containment policies, whether by private payers, Medicare Part D entities, or state Medicaid programs, are key drivers for product choice through pharmacy benefit formulary design and utilization management tools, independent of the substitution laws. These payer-driven "switches," which may or may not involve a generic substitution, are ubiquitous in the U.S. health care system and include patient, pharmacy and physician focused incentives. For example, a payer may require or strongly favor (for example, through differential patient cost-sharing) utilization of a generic form of product X when product Y is prescribed. If product Y is patent-protected, and thus no generic is available, but product X is in the same therapeutic class and is subject to robust generic competition, many payers will provide significant incentives, in the form of lower patient cost-sharing, to utilize the generic form of product X. Because X and Y are completely different products (even though in the same class), state pharmacy laws would **not** typically allow for pharmacist substitution. Accordingly, the pharmacist would have to obtain consent from the physician before dispensing generic X in place of prescribed Y.

When generic alternatives are available for the prescribed product, substitution laws play the role of facilitating payer-driven switches. If a doctor prescribes X, and a generic version of X is available, payers utilize a variety of tools to encourage patients, pharmacies, and prescribers to select the generic version. Payers typically establish significantly lower cost-sharing for generics,

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http://public.econ.duke.edu/Papers//PDF/0907_H_Grabowski_I_Cockburn_G_Long_et_al_Effect_on_Federal_Spending_of_Follow_on_Biologics.pdf. (accessed Feb. 26, 2014).

[29] D'Ambrosio J, Ivashko A, Clarkston Consulting, Biosimilars are Coming. Are You Ready?, (noting that physicians who use biologics have a higher level of confidence in biosimilars), http://www.clarkstonconsulting.com/wp-content/uploads/2013/06/Insights_Biosimilars_US20133.pdf (accessed Feb. 23, 2014).

[30] *See* Comments of Amgen Inc. on GPhA and Novartis's Citizen Petitions Requesting Identical Non-proprietary Names for Biological Products and Their Respective Reference Products, Docket Nos. FDA-2013-P-1153 & FDA-2013-P-1398, Part II at 13 – 28, (emergent safety issues identified on 24-27) (Dec. 20, 2013).

driving patients to choose them over branded drugs. In addition, contracts between payers and network pharmacies often have "generic dispensing rate" targets or similar mechanisms that trigger additional compensation if satisfied.

Amgen anticipates that many of these payer-driven incentives will be applied to biosimilars and interchangeable biologicals. Under state legislation advocated by Amgen, if branded biologic A is prescribed, and a non-interchangeable, lower-cost A-biosimilar is available, it is likely that payers will incentivize switches to the A-biosimilar. Physician pre-approval for such a switch would be required. Contrast this to a scenario where an interchangeable version of branded biological A is available. In this instance, while payers will also likely attempt to drive utilization to interchangeable biological version of A, pharmacists would be permitted to make the substitution, as long as the change is communicated back to the prescriber, either through electronic health records or other prevailing means.

This interplay between payer-driven incentives and allowable substitution under state pharmacy laws has created a highly-competitive, market-based system where generics compete not just against their branded counterparts, but against brands and generics of different products in the same therapeutic classes. Amgen expects that legislation creating a clear pathway for substitution of interchangeable biologicals will similarly foster competition and promote more rapid uptake of biosimilars and interchangeable biologicals. Payers' preferences can be highly determinative of the product ultimately dispensed to the patient.

I.2. What are the compliance costs associated with new state law requirements? How are those costs likely to affect competition from biosimilar and interchangeable biologics?

Key points

- Compliance costs would be de minimis and must be calculated against benefits received for dispensing lower cost products.
- Any compliance costs would apply uniformly to all biological products: interchangeable, originator and biosimilar.
- States currently have a variety of communication requirements in effect now; thus no new process or infrastructure is necessary.
- Pharmacists have supported communication with physicians in other circumstances, and Express Scripts has noted that this is not an operational challenge.
- Limitations on when communication is needed further reduce the likelihood of compliance costs.

Compliance costs would be de minimis and must be calculated against benefits received for dispensing lower cost products.

We believe that compliance costs are likely to be de minimis. To the extent that there is any cost burden associated with the act of compliance, it must be calculated against the benefit received by the party incurring the cost. Pharmacists typically receive higher payment as a result of dispensing a lower priced drug.[31] Thus, the actual cost burden will depend upon the

[31] See "HealthPartners Pharmacy Partners in Excellence Program", 2014 at 3, https://www.healthpartners.com/ucm/groups/public/@hp/@public/documents/documents/cntrb_041092.pdf

parameters of the agreement with payers. It is likely that the pharmacist would benefit from dispensing the biosimilar or interchangeable product.

States currently have a variety of communication requirements in effect now; thus no new process or infrastructure is necessary.

The proposals Amgen supports leverage interoperable electronic health records when and where they are available between a pharmacist and a prescriber. Physician access to patient medication records is expected to be a feature of such systems and exist independently of state biologic product selection laws.

Until interoperable EHR is available, communication by any practical means (e.g., e-mail, telephone, mail, fax, etc.) would be accepted, and this non-EHR communication would present minimal compliance costs. The biologic product selection communication Amgen and others support is in line with current public policy governing prescription drug dispensing around the country; therefore a process for communication with physicians is already in place. Most states already have one or more requirements for pharmacists to proactively communicate with prescribing physicians. The most common category of mandated communication relates to the dispensing process, and the means of communication is generally not specified.[32] Costs for communication associated with biologic product selection, to the extent that there are any, would be consistent with what has historically been acceptable.[33] Furthermore, communication regarding products dispensed can be done in batches at a time that is convenient for the pharmacist because the pharmacist would have up to 10 days to communicate.

Pharmacists have supported communication with physicians in other circumstances, and Express Scripts made clear this is not an operational challenge.

Pharmacists and pharmacy benefit managers are on record supporting communication with prescribers in a variety of circumstances. For example, in California, pharmacists, retailers and drug stores supported a proposal to require pharmacist communication to the prescribing physician when dispensing an increased supply of certain drugs.[34] Express Scripts stated in testimony before the Indiana House of Representatives on February 19, 2014, that the mechanics of communicating with physicians would not present a challenge as they are in

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(accessed Feb. 26, 2014); See also "Strategies to Increase Generic Drug Utilization and Associated Savings", AARP Public Policy Institute, 2008 at 8-9, http://assets.aarp.org/rgcenter/health/i16_generics.pdf (accessed Feb. 26, 2014).

[32] The range of circumstances relating to dispensing include prescription drug substitution, potential drug interactions, expired prescriptions for patients with an emergency condition, and prescription details that are suspicious.

[33] *See* "Building Health Care Value Through Health Information Technology", Consumer-Purchaser Disclosure Project at 1, http://go.nationalpartnership.org/site/DocServer/Building_Health_Care_Value_Through_HIT.pdf?docID=5521 (accessed Feb. 26, 2014) (Each year pharmacists make 150 million calls to physicians on topics including non-formulary medications, potential drug interactions, illegible handwriting, and incorrect dosages on new handwritten prescriptions.).

[34] *See* California SB 1301, enrolled 8/21/2012, http://www.leginfo.ca.gov/pub/11-12/bill/sen/sb_1301-1350/sb_1301_bill_20120822_enrolled.html); *see also* Assembly Committee on Health, California State Assembly, SB 1301 Analysis 3-4 (June 26, 2012).

frequent communication with physician offices.[35] In the retail setting of so called "brick and mortar" pharmacies, pharmacists are unlikely to experience a significant uptick in calls or whatever their preferred means of non-EHR communication with physicians may be because retail pharmacies currently dispense an average of less than two biologic prescriptions a week.[36]

Limitations on when communication is needed further reduce the likelihood of compliance costs.

Any compliance burden on pharmacies is further limited by the narrow scope of the communication proposal that Amgen supports. Communication outside of EHR should be necessary only if there is an FDA-designated interchangeable biological product available for the prescribed biological product. Not all biosimilars are expected to be interchangeable, so the number of products to which the communication requirement would apply is likely to be more limited than if viewed solely from the context of a therapeutically equivalent generic. In addition, communication is needed where a refill prescription remains the same as the product originally dispensed.

In light of the negligible cost of communication about the product dispensed, Amgen expects those costs – if there are any – to have no impact on competition. In Question I.1 we discussed the ways in which communication is likely to benefit biosimilar uptake and biologic competition overall.

I.3. What are the rationales behind new state proposals and laws for regulating FOB substitution? Which provisions are most important? Are some provisions redundant or otherwise unnecessary?

Key points

- The biologic substitution proposals are designed to facilitate safe automatic substitution of interchangeable biologic medicines and enable manufacturer accountability when products are made by more than one manufacturer.
- The consensus proposals Amgen supports follow the generic drug framework with an additional provision to facilitate access to complete medical records after a product is dispensed.

[35] *See* Express Scripts testimony on SB 262 by, Allyson Blandford, Indiana House Public Health Committee, Feb. 19, 2014.

[36] Amgen analysis based on data from IMS National Prescription Audit and SK&A Information Services. Briefly, we took the total number of biologics prescriptions dispensed in the retail setting in a given state in 2012 (*e.g.,* 309,639 in CA), and this number was divided by 52 (for 52 weeks in a year) and then by the number of retail pharmacies in the state (Source: SK&A Information Services; *e.g.*, 4,933 in CA) to yield an average number of biologics prescriptions dispensed per week per retail pharmacy (*e.g.*, 1.2 for CA). In no state were there more than 2.0 biologics prescriptions dispensed per week per retail pharmacy; the national average was 1.2 biologics prescriptions dispensed per week per retail pharmacy. For this analysis, "biologics" are defined as those products that Amgen has assessed as covered by the terms of BPCIA and thus would be subject to the notification provision of proposed state biologics substitution law; this count does not includes several very low-volume biologics in the following categories: immunoglobulins, anticoagulants, coagulants, products with no sales in 2012, as well as several treatments for blood cancers, the conditions that result from chemotherapy, a hormone used as a diagnostic, and a treatment for digitalis poisoning.

- Physician access to complete and correct medical records is necessary for accurate adverse event reporting – an essential element of keeping all biologic medicines safe due to their sensitivity.
- Existing mechanisms for record keeping have gaps that leave medical records incomplete, ambiguous or inaccurate in a manner that disproportionally impacts biologics.

The biologic substitution proposals are designed to facilitate safe automatic substitution of interchangeable biologic medicines and enable manufacturer accountability when products are made by more than one manufacturer.

The biologic substitution proposals supported by Amgen are designed to achieve three objectives: (1) facilitate appropriate and safe automatic substitution of biologic medicines consistent with the BPCIA, (2) enable manufacturer accountability in the new environment of multiple manufacturers' versions of the same originator product, and (3) increase transparency about the product dispensed to improve record keeping and therefore patient care. Biologics differ from chemical drugs in several important ways that have implications for how these medicines are regulated.[37] These scientific differences also make it important to enable manufacturers to be accountable for product quality when there is more than one source of biological product. Amgen supports five key principles for state biologic product selection laws, as discussed in Question I.1, because they will achieve the objectives identified above. These principles are based on the science of biotechnology.

The particular need for state biologic substitution laws to facilitate access to complete medical records after a biologic is dispensed results from three important differences between biologic and chemical drugs – complexity, size, and sensitivity.[38] These three unique features of biologics are common to all biologic medicines (originator, biosimilar and interchangeable).[39]

Complexity: Biologics are vastly more structurally complex than chemical drugs.[40] Current science can ensure that the active ingredient in a generic chemical drug product is structurally identical to that of its brand name product equivalent, and such proven identity underlies the substitution framework for chemical drugs.[41] But because of the greater complexity of biologics, current science does not permit a determination that two biologics products have structurally identical molecules. While many such structural differences are of no clinical consequence, science today cannot fully explain the relationship between structure and

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[37] *See* European Commission, What You Need to Know about Biosimilar Medicinal Products: Process on Corporate responsibility in the Field of Pharmaceuticals Access to Medicines in Europe, Consensus Information Paper 2013, at 8-9 (2013) (also referred to the "Tijani Initiative"), http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/biosimilars_report_en.pdf); Weise M, Bielsky MC, De Smet K et al., Biosimilars: What clinicians should know, Blood 120:5111–7 (2012) at 5111.

[38] Weise M, Bielsky MC, De Smet K et al., Biosimilars: What clinicians should know, Blood 120:5111–7 (2012) at 5111.

[39] Roger SD, Mikhail A, Biosimilars: Opportunity or cause for concern?, J Pharm Pharm Sci 10:405–10 (2007) at 405.

[40] Health Canada, Fact Sheet: Subsequent entry biologics in Canada, http://www.hc-sc.gc.ca/dhp-mps/brgtherap/activit/fs-fi/fs-fi_seb-pbu_07-2006-eng.php (accessed Feb. 25, 2014).

[41] Mellstedt H, Niederwieser D, Ludwig H, The challenge of biosimilars. Ann Oncol 2008;19:411–9 ("[S]ince analytical techniques are not available for detecting or predicting all the biological and clinical properties of proteins, differences between biopharmaceutical products can easily remain undetected.").

function. This inability to confirm the molecular identity of biologics, combined with our incomplete understanding of the consequences of such non-identity, makes it prudent that any substitution framework for biologics promptly and reliably connect any patient adverse event to a specific biologic product, and not just to a group of interchangeable products. [42]

Size: Not only are biologics more complex than chemical drug active ingredients, they are hundreds to thousands of times larger. [43] This difference in size creates a known risk of immunogenicity – common to all biologic products – that requires physicians to have at hand an accurate record of which specific biologic products were administered to their patients not only recently, but for many prior months. [44,45,46,47] Specifically, because biologics are so large, they are always capable of being recognized by the patient's immune system. If the immune system identifies the molecules as foreign, the patient's body will mount an unwanted immune response referred to as immunogenicity, and this response could range from negligible to very serious. [48,49] This concern is not hypothetical, but instead is known to have occurred with a number of biologics. Importantly, the clinical manifestations of immunogenicity can first occur months after the patient receives the biologic. Just as importantly, immunogenicity adverse events have been known to be product-specific, in addition to known risks that apply to the entire class of molecules. For example, at a time when other original biologics from the epoetin product class experienced little or no immunogenicity, a cluster of hundreds of severe immune-related events occurred with patients treated with a particular member of the class. This observed risk of product-specific immunogenicity, in combination with the potential latency of resulting adverse events, requires that those who identify and report adverse events – usually doctors or patients – have ready access to complete and accurate medical records indicating the specific biologic product given to the patient.

Sensitivity: Because all biologics – by definition - are made in living cells, the products will reflect the cell line and processes used to make them. [50,51,52] Unlike the smaller and generally more molecularly stable chemical drug product active ingredients, biologics are very large molecules with relatively weak molecular interactions. One consequence of this difference is that biologics are susceptible to degradation by relatively mild changes in manufacturing conditions (such as heat, agitation, or light) that are less likely to seriously affect most chemical drugs. This sensitivity to manufacturing conditions is in part why biologics are more likely to be associated with product-specific adverse events (as opposed to adverse events impacting some

[42] Weise M, Bielsky MC, De Smet et al., Biosimilars: What clinicians should know, Blood 120:5111–7 (2012) at 5112, 5115.
[43] Roger SD, Mikhail A, Biosimilars: Opportunity or cause for concern?, J Pharm Sci 10:405–10 (2007) at 405-406.
[44] Weise M, Bielsky MC, De Smet K et al., Biosimilars: What clinicians should know, Blood 120:5111–7 (2012).
[45] Roger SD, Mikhail A, Biosimilars: Opportunity or cause for concern?, J Pharm Sci 10:405–10 (2007).
[46] Mellstedt H, Niederwieser D, Ludwig H, The challenge of biosimilars, Ann Oncol 19:411–9 (2008).
[47] Chirino AJ, Ary ML, Marshall SA, Minimizing the immunogenicity of protein therapeutics, Drug Discov Today 9:82–90 (2004) at 82.
[48] Weise M, Bielsky MC, De Smet K et al., Biosimilars: What clinicians should know, Blood 120:5111–7 (2012) at 5113.
[49] Roger SD, Mikhail A, Biosimilars: Opportunity or cause for concern?, J Pharm Pharm Sci10:405–10 (2007) at 405-406.
[50] Health Canada, Fact Sheet: Subsequent entry biologics in Canada, http://www.hc-sc.gc.ca/dhp-mps/brgtherap/activit/fs-fi/fs-fi_seb-pbu_07-2006-eng.php (accessed Feb. 25, 2014).
[51] Mellstedt H, Niederwieser D, Ludwig H, The challenge of biosimilars, Ann Oncol 19:411–9 (2008).
[52] Roger SD, Mikhail A, Biosimilars: Opportunity or cause for concern? J Pharm Pharm Sci 10:405–10 (2007) at 5-7.

broader class of products) than are chemical drugs.[53] As Health Canada notes in its fact sheet on biosimilars, "Changes to source materials, manufacturing processes, equipment or facilities may result in significant unexpected changes to the intermediate and/or final product."[54,55]

Consequently, all biologic medicines have the propensity to structurally "shift or drift" throughout their lifecycle requiring product-specific monitoring for all biologics, irrespectively of whether or not the product(s) were determined to be interchangeable at a point in time. Manufacturers carefully monitor and test throughout the manufacturing the process,[56] but examples in recent history show that the current limits of scientific knowledge make the possibility of product problems very real.[57] [58] This sensitivity and risk make accurate attribution of adverse events and manufacturer accountability absolutely essential to keeping products safe for patients.[59] Even the most vigilant and responsible manufacturer cannot solve a manufacturing or product problem if the records incorrectly associate the problem with another manufacturer's product.

The consensus proposals Amgen supports follow the generic drug framework with an additional provision to facilitate access to complete medical records after a product is dispensed.

The generic drug framework for substitution is the basis for all the pending biologic substitution proposals but an additional provision to facilitate access to complete medical records after a product is dispensed is essential due to the scientific features discussed above that distinguish biologics from chemical drugs. Four elements of the generic drug substitution framework have widespread support in the state biologic substitution proposals and can be found in the FTC model product selection legislation reflected in the 1979 FTC report.[60]

First, substitution is limited to products deemed interchangeable by FDA. These are the only products for which switching or alternating between products will have been evaluated as safe

[53] Weise M, Bielsky MC, De Smet K et al., Biosimilars: What clinicians should know, Blood 120:5111–7 (2012)at 5112.

[54] Health Canada, Fact Sheet: Subsequent entry biologics in Canada, http://www.hc-sc.gc.ca/dhp-mps/brgtherap/activit/fs-fi/fs-fi_seb-pbu_07-2006-eng.php(accessed 25 Feb. 2014) (Health Canada refers to biosimilars as "subsequent entry biologics" or "SEBs").

[55] Therapeutic Goods Administration, Australian Government, Evaluation of biosimilars: Naming conventions for biosimilars, Australian Biological Names (ABN) (July 30, 2013) ("A biosimilar is not identical to its reference product and must be assumed to be different to any other biosimilar as no direct comparability study has been conducted. As small differences between biosimilars can give rise to differences in clinical behaviour, in particular in immunogenic effects, certain additional nomenclature provisions are necessary to ensure that it is possible to distinguish between biosimilars and clearly identify the reference product.").

[56] Health Canada, Fact Sheet: Subsequent entry biologics in Canada, http://www.hc-sc.gc.ca/dhp-mps/brgtherap/activit/fs-fi/fs-fi_seb-pbu_07-2006-eng.php(accessed Feb. 25,2014).

[57] Weise M, Bielsky MC, De Smet et al., Biosimilars: What clinicians should know, Blood 120:5111–7 (2012) at 5113 (discussing excessive immunogenicity for a biosimilar somatropin and neutralizing anti-epoetin antibodies associated with the subcutaneous use of a biosimilar epoetin alfa in a clinical trial).

[58] Casadevall N, Edwards IR, Felix T et al., Pharmacovigilance and biosimilars: Considerations, needs and challenges, Expert Opin Biol Ther 13:1039–47 (2013)at 1040-41 ("It is currently not possible to predict how these subtle product differences may affect the efficacy or safety profile of a particular biosimilar.").

[59] Weise M, Bielsky MC, De Smet K et al., Biosimilars: What clinicians should know, Blood 120:5111–7 (2012)at 5112.

[60] FTC, Drug Product Selection: Staff report to the Federal Trade Commission 273-288 (Jan. 1979).

by FDA.[61] Experience in Europe related to product changes as a result of tendering decisions are not a scientifically valid evaluation of the safety of switching.[62] In 1979 the FTC model limited substitution to products deemed therapeutically equivalent.[63]

Second, the prescribing physician retains the authority to specify "dispense as written" (DAW). No two patients are the same or respond to disease or treatment in the same way. DAW authority ensures that the prescribing physician can tailor treatment to the needs of the patient. Physicians have DAW authority in all fifty states for chemical drugs, indicating that this is an important element of quality care. It was also an element of the FTC 1979 Model Act.[64]

Third, the patient or patient's representative must be informed of the product actually received. This is a practice with generic drug substitution as well. Patients and guardians are a vital and increasingly active part of patient medical care, including the reporting of adverse events.[65] An informed patient can provide meaningful input to the physician and the lack of information can create unnecessary risk and work for health care providers.[66] Alerting the patient or guardian to what was received can limit confusion if the medicine looks different from what was previously received for that prescription. The FTC's 1979 Model Act recommended that the party receiving the drug be notified of the lower cost option and the right to refuse the product selected.[67]

Fourth, the pharmacy is required to maintain a record of the product dispensed. This is consistent with requirements in existing pharmacy acts for chemical drugs dispensed. Adverse reactions to biologic medicines can occur months after the patient first received the medicine, long after all the product packaging has been disposed of.[68] The pharmacy records may play an important role in determining what product may have been responsible for an adverse event.[69]

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[61] Casadevall N, Edwards IR, Felix T et al., Pharmacovigilance and biosimilars: Considerations, needs and challenges, Expert Opin Biol Ther 13:1039–47 (2013) at 1041; *see also* FTC, Drug Product Selection: Staff report to the Federal Trade Commission at 274, 281 (Jan. 1979) (only products deemed therapeutically equivalent may be substituted).

[62] The European Medicines Agency does not have the authority to evaluate products for safety in switching. Decisions regarding automatic substitution are decided by the member countries. At least a dozen have adopted laws and policies prohibiting substitution. The economic model of tendering by which the yearly contract for supplying a medicine goes to a single manufacturer can result in patients changing medicines. However, this cannot be considered scientific evidence related to the safety of product substitution or switching due to the lack of any form of control or follow up. Furthermore, the EU has recently modified its pharmacovigilance practices following a recognition that existing practices were failing to effective track products and accurately attribute adverse events.

[63] FTC, Drug Product Selection: Staff report to the Federal Trade Commission, at 274, 281 (Jan. 1979).

[64] FTC, Drug Product Selection: Staff report to the Federal Trade Commission, at 275-6 (Jan. 1979).

[65] Vermeer NS et al., Traceability of Biopharmaceuticals in Spontaneous Reporting Systems: A Cross-Sectional Study in the FDA Adverse Event Reporting System (FAERS) and EudraVigilance Databases, Drug Saf. (2013) at section 3 and 4 (Published online 15 June 2013).

[66] Agency for Healthcare Research and Quality, The Role of the Patient in Safety, http://psnet.ahrq.gov/primer.aspx?primerID=17) (accessed Feb. 24, 2014) ("Both of these types of error [action and mental errors] are influenced by other definable safety hazards; for example, low health literacy and poor provider–patient communication are clearly linked to medication errors.").

[67] FTC, Drug Product Selection: Staff report to the Federal Trade Commission, at 279-80 (Jan. 1979).

[68] *See* Comments of Amgen Inc. on GPhA and Novartis's Citizen Petitions Requesting Identical Non-proprietary Names for Biological Products and Their Respective Reference Products, Docket Nos. FDA-2013-P-1153 & FDA-2013-P-1398, Part II at 13 – 28 (emergent safety issues identified on 24-27) (Dec. 20, 2013).

[69] For example one report can show which products were not administered, small group may highlight product(s) in common.

The importance of maintaining pharmacy records was demonstrated when contamination at a compounding pharmacy put many patients at risk of a deadly infection months after they received the injection.[70] The FTC 1979 Model Act included a recommendation to keep a record of the product dispensed and noted that it applied to all products, not just those selected by the pharmacist.[71]

In addition to the above principles that track generic drug laws and the FTC 1979 Model Act, Amgen supports a fifth element in state biologic substitution proposals: pharmacist-physician communication regarding the product actually dispensed to the patient when there is the potential for ambiguity.[72] Amgen believes it is important that pharmacists communicate the specific product dispensed within ten days after dispensing, regardless of whether the product selected was a biosimilar or originator. The communication requirement would be satisfied if the pharmacy enters the appropriate drug information in an interoperable electronic health records[73] system shared with the prescriber within the ten days. In the case that such an EHR system is not in place, the communication can occur by any practical means and need only apply if: (1) FDA had approved an interchangeable product for the prescribed biological product, and (2) a refill prescription is changed from the biological product originally dispensed. This communication is an essential step in completing the patient record accessible by the physician.

Physician access to complete and correct medical records is necessary for accurate adverse event reporting – an essential element of keeping all biologic medicines safe due to their sensitivity to manufacturing, handling, etc.

The communication element is an essential aspect of any biologic product selection law for effective pharmacovigilance for biologic medicines and thus product safety and manufacturer accountability.[74] As explained above, all biologic medicines – originator, biosimilar and interchangeable – are sensitive and therefore at risk of shifting or changing throughout the life of the product. The need for accurate product identification changes when there is more than one manufacturer of a particular product – referred to as a "multi-source" environment. Today if there is a problem with a biologic medicine, the problem can be clearly attributed to the sole manufacturer. When there is more than one source of the product and that product is highly sensitive to change that can have clinical implication for patients, it essential that we are able to

[70] ISPI, Special Report: The Current Crisis in Pharmacy Compounding and Its Implications, International Pharmaceutical Quality 3(10):14 (2012) (discussing meningitis outbreak resulting from contamination of product distributed by a compounding pharmacy).

[71] FTC, Drug Product Selection: Staff report to the Federal Trade Commission, at 281 (Jan. 1979).

[72] See *Supra* note 12. This approach is supported by many patient and physician organizations as well as other biosimilar and originator manufacturers, including Abbvie, Activis, Amgen, Boeringher Englheim, Genetech, and Novartis/Sandoz.

[73] Physicians using electronic health records are more likely to report adverse events. Doctors with an HER are more likely to report adverse events, Healthcare IT News (Dec. 9, 2009), http://www.healthcareitnews.com/news/doctors-ehr-are-more-likely-report-adverse-events (accessed Feb. 22, 2014).

[74] Weise M, Bielsky MC, De Smet K et al., Biosimilars: What clinicians should know, Blood 120:5111–7 (2012) [PubMed].

identify what specific product – by which manufacturer – a patient received in the event the patient experiences an adverse reaction.[75,]

Patient safety does not, and cannot end at product approval.[76] FDA has been clear on the matter, stating that tracking adverse events associated with biologic medicines will be difficult if the specific product or manufacturer cannot be readily identified.[77] For biologic medicines, sound policy means that pharmacists, physicians and patients all have ready access to the information about which medicine – by which manufacturer – is in the patient's body. Even the most vigilant and responsible manufacturer cannot solve a manufacturing or product problem if the records incorrectly associate the problem with another manufacturer's product.

The need for additional provisions regarding traceability of the dispensed product reflects the scientific differences between generic drugs and biologic medicines.[78] As discussed above, biologics are more sensitive to the manufacturing process, present a greater risk of unwanted immune response, and have potential for delayed adverse events as compared to chemical drugs. With biologics, it is more likely that adverse events will be product-specific but difficult to attribute to a specific product. Indeed, in Europe information for physicians regarding prescribing epoetins speaks to the need for traceability of these products that are especially at risk for causing immunogenicity.[79] Physician access to accurate medical records – through interoperable EHR or direct communication from the pharmacist – will facilitate accurate attribution of adverse events and ultimately advance competition.

Prompt and easy physician access to full and accurate medical records will have implications for patient safety and product quality.[80] Physicians and patients are the most likely reporters of adverse events.[81] They rely on their knowledge of the patient's treatment history, including the record at hand, as well as the patient's insight to determine whether a downturn in a patient's condition is an adverse event that needs to be explored or it is the course of disease, a new condition, or something else. Inaccurate or incomplete patient records make identifying an adverse event more difficult and attributing it to the wrong product more likely.

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[75] Casadevall N, Edwards IR, Felix T et al., Pharmacovigilance and biosimilars: Considerations, needs and challenges, Expert Opin Biol Ther 13:1039–47 (2013) [PubMed].

[76] Vermeer NS et al., Traceability of Biopharmaceuticals in Spontaneous Reporting Systems: A Cross-Sectional Study in the FDA Adverse Event Reporting System (FAERS) and EudraVigilance Databases, Drug Saf. (2013) at section 1 (noting that a distinctive property of biopharmaceuticals is that the safety profile may change over time as a result of manufacturing changes made for public health purposes) (Published online June 15, 2013).

[77] *See* Kozlowski S, Woodcock J, Midthun K, Sherman R, Developing the Nation's Biosimilars Program, New England J. Medicine 365:385 (2011).

[78] Weise M, Bielsky MC, De Smet K et al., Biosimilars: What clinicians should know, Blood 120:5111–7 (2012) at 5114 (noting "The importance of reliable traceability of biologicals has been acknowledged ….").

[79] Weise M, Bielsky MC, De Smet K et al., Biosimilars: What clinicians should know, Blood 120:5111–7 (2012) at 5114.

[80] Vermeer NS et al., Traceability of Biopharmaceuticals in Spontaneous Reporting Systems: A Cross-Sectional Study in the FDA Adverse Event Reporting System (FAERS) and EudraVigilance Databases, Drug Saf. at section 1 (2013) (Published online 15 June 2013).

[81] Vermeer NS et al., Traceability of Biopharmaceuticals in Spontaneous Reporting Systems: A Cross-Sectional Study in the FDA Adverse Event Reporting System (FAERS) and EudraVigilance Databases, Drug Saf. (2013) at section 3, Table 2 (Published online 15 June 2013).

Existing mechanisms for record keeping have gaps that leave medical records incomplete, ambiguous or inaccurate in a manner impactful to biologics disproportionately.

Existing mechanisms for record keeping have substantial gaps that put meaningful pharmacovigilance for biologics in doubt when there are multiple manufacturers producing a biologic medicine.

Today four categories of repositories for patient records are relevant in the context of automatic substitution. These are: (1) physician office records, (2) interoperable electronic health records, (3) electronic prescribing systems, and (4) pharmacy records. Each of these holds important information but falls short of providing a solution to ensuring physician access to a complete medication record. Physician office records have historically been paper based but are increasingly moving to an electronic format. At its most basic, this is a self-contained, computer-based record that is accessible by that physician or practice group. In more sophisticated arrangements, it may be connected to a network of providers, as seen with health systems such as Kaiser and Cleveland Clinic. The physician will record what is prescribed but when automatic substitution by the pharmacist is an option – that is, when an interchangeable product is available -- – the doctor's records will be ambiguous at best and may be incomplete or inaccurate.

Interoperable electronic health records are optimal in terms of accuracy and access to a patient's complete medication and treatment history. Ultimately, EHR is expected to be a means of data sharing between stakeholders that allows full transparency among providers. This could take a variety of formats and provide a range of information access, but to be useful for purposes of biologic product selection, it must at least allow the prescribing physician to see what was dispensed to the patient. It is widely acknowledged that uniform application of such EHR systems are years in the future for all but the self-contained health entities, such as those mentioned above (Kaiser, and Cleveland Clinic), that have both prescribers and pharmacies in their system. It is not at all clear that the self-contained systems would capture patient prescriptions filled outside the network, for example when on travel or in an emergency setting.

A step toward utilizing EHRs can be seen in electronic prescribing systems, also referred to as "e-prescribing", which may allow access to patient medication history. E-prescribing is the computer-to-computer transfer of prescription data between pharmacies, prescribers, and payers.[82] E-prescribing systems primarily route a biologic prescription to a patient's retail or mail order pharmacy and, in their most common application, do not include provide pharmacy transaction details back to the prescriber. Use of e-prescribing is growing in the U.S., with 69 percent of office-based physicians using the service in 2012.[83] While physician and patient access to patient medication history may be possible via growing e-prescribing systems or national pharmacy databases, additional services, like patient medication history, are advanced features that not all e-prescribing systems include. Adoption is not consistent across the

[82] NCPDP e-Prescribing Fact Sheet, http://www.ncpdp.org/NCPDP/media/pdf/Eprescribing_fact_sheet.pdf (accessed February262014).

[83] Surescripts, National Progress Report On e-Prescribing and Safe-Rx Rankings, Year 2012, http://www.google.com/url?sa=t&rct=j&q=&esrc=s&frm=1&source=web&cd=6&cad=rja&ved=0CEwQFjAF&url=http%3A%2F%2Fsurescripts.com%2Fdocs%2Fdefault-source%2Fnational-progress-reports%2Fnational-progress-report-on-e-prescribing-year-2012.pdf%3Fsfvrsn%3D2&ei=bDINU9zNOaiw0QHCiYDACw&usg=AFQjCNEaE6rIgyGCHCmUA9TIczcSQ8A6vg&sig2=1zBRrGYdM8k2kUxOWTSVzA (accessed Feb. 25, 2014).

country and also varies by state.[84] Although more than three hundred EHR/e-prescribing vendors are certified by Surescripts for e-prescribing, many have not been certified as capable of accessing patient medication history.[85]

The adoption of these systems is far from universal at this time, and additional measures are required to ensure ready access to complete and accurate medical records for all patients receiving biologic medicines.

In the debates over state laws for substitution of biologics, pharmacies have been very vocal about the completeness of the records they maintain as an answer to the question of what product a patient received. Unfortunately, the existence of an accurate record at the pharmacy does not resolve the problem because the physician is unlikely to call the pharmacy to confirm the accuracy of the physician's medical record.[86] First, the doctor may not know the information in the patient's record on hand is ambiguous or no longer accurate. Physicians are likely to be unaware which manufacturer's product a pharmacy stocks or which was dispensed. Second, it may not be clear that the patient's worsening condition is the result of a drug reaction, simply the course of the disease, or something else. Biologic medicines generally treat patients with serious illness who cannot be sufficiently treated with conventional medication; patients on biologic medicines often have complicated conditions that can cause them to respond in unexpected ways to even common health challenges such as the flu. Third, physicians contact pharmacies to prescribe medications for their patients, they are not likely to call again later to find out if the pharmacy changed the prescription or to find out which manufacturer's product they dispensed for each patient. Fourth, even if the doctor wants to contact the pharmacy, knowing which pharmacy to call requires its own research and may be impossible to determine for medicines dispensed many months in the past. The prescriber may know which pharmacy for prescriptions that are transmitted directly electronically, but will not know for all those that are handed to the patients to bring to a pharmacy. Achieving the goal of ensuring that "necessary safeguards for patient health and safety"[87] are incorporated into biosimilar policy choices requires a strong pharmacist-prescriber communication loop.

[84] Surescripts, E-Prescribing State Progress Reports http://surescripts.com/docs/default-source/communication-promotion/national_progress_report_on_e-prescribing_2012_surescripts.pdf?sfvrsn=4; see also http://surescripts.com/company-initiatives/saferx (accessed Feb. 26, 2014)

[85] Surescripts, Find E-Prescribing Software Vendors, http://surescripts.com/network-connections/mns/prescriber-software

[86] Lietzan E, Sim L, Alexander E, Biosimilar Naming: How Do Adverse Event Reporting Data Support the Need for Distinct Nonproprietary Names for Biosimilars?, FDLI's Food and Drug Policy Forum 3(6): 1 (March 2013). (Finding the rate of attribution of adverse events relative to prescriptions increased significant for the originator brands after loss of exclusivity and loss of market share while the corresponding generics received a disproportionately low percentage of reports but holding a big market share). *See infra* p. 40 for further discussion.

[87] Edith Ramirez, FTC Chairwoman, Opening Statement, FTC Follow-on Biologics Workshop (Feb. 4, 2014) ("We believe that with necessary safeguards for patient health and safety, competition from follow-on biologics can benefit patients through lower prices and expanded access to important biologic treatments.").

I.4. Could an FDA publication concerning biologics and FOBs, comparable to the Orange Book, provide an authoritative listing of FOBs that are biosimilar to or interchangeable with reference biologics? Would such a publication facilitate substitution? Would such a publication need to be limited to interchangeable FOBs, or should it include both biosimilar and interchangeable FOBs?

Key points

- Clear communication from FDA regarding whether products are approved as biosimilar or designated interchangeable is important for safe use and prescribing.
- A simple list, electronic or otherwise, may serve this purpose.

Clear communication from FDA regarding whether products are approved as biosimilar or designated interchangeable is essential for their safe use and prescribing. Amgen has learned from speaking with physicians about biologic medicines that many physicians are unfamiliar with the distinction between multiple manufacturers' versions of the same originator biological medicine and may be unaware that there are two different types of products, biosimilars and interchangeable biosimilars, which have different approval standards and patient safety consequences from substitution. Clear and easily accessible information from FDA regarding the approval status of biologics, facilitating their safe use, will be an essential tool for physicians and pharmacies when biosimilars enter the U.S. market. A simple list, electronic or otherwise, may serve this purpose.

I.5. Does the potential for many different state laws regulating FOBs affect the prospects for the development of FOBs? Does the answer differ between biosimilar versus interchangeable biologic products?

Key points

- Variation in state laws is not expected to have any implication for the development of biosimilar or interchangeable biologics.
- States govern the practice of pharmacy and already vary widely in how they structure the laws and policies.
- The success of the generic drug industry indicates that such variation is not relevant to the development of such products.

Generally speaking, predictability and consistency create a more favorable environment for investment. This is particularly true when the investment is very substantial in terms of time and money. However, variation in state substitution policies and practices are not likely to have a meaningful impact on the investment considerations of a manufacturer for several reasons. As a biosimilar manufacturer, potential variation in state laws has played no role in our decisions about whether and how to move forward in developing biosimilar or innovative products. The range of policies that states are likely to consider is narrow.

Ultimately, it isn't the variation among states but a policy of poor manufacturer accountability that could have consequences for the biosimilar and interchangeable market and thus investment decisions.

Biologic substitution provisions that seek to closely follow current state generic drug substitution provisions will necessarily lead to variance state to state due to differences in the current laws. However, if key principles are in place, as with generic laws, biologic substitution policy can provide a general consistency in approach that fosters investment, without concern for specific uniqueness from state to state.

I.6. Would it be helpful to develop a model state substitution biosimilar law? If so, what provisions should the law include? Should state laws coordinate their guidance with provisions in the BPCIA and guidance from FDA?

Key points

- Cogent and balanced principles for state regulation of biologic substitution have already been put forth and have been endorsed by patients and physicians.
- States are using the framework of the BPCIA to develop policies and proposals for biologic product selection state laws.
- FDA is not required to issue guidance prior to approving products as biosimilar or designating products as interchangeable.

Cogent and balanced principles for state regulation of biologic substitution have been endorsed by physicians and patient organizations. These principles address under what circumstances a pharmacist should have discretion to select the biological product dispensed to a patient as well as the communication mechanisms that should be in place to ensure that all reporters of adverse events – the patient, the prescriber and the pharmacist – all have access to an accurate medicine history for the patient. As discussed in section I.1, these principles support robust competition, protect patient safety and foster manufacturer accountability. States can and are tailoring these policies to meet the interests of their stakeholders.

States are using the definitions and structure of product approval provided in the BPCIA to develop laws and policies on biologic substitution. To date, the proposals for biologic substitution introduced across the country have specified which category of products approved by FDA is acceptable for substitution, thus deferring to FDA's authority on the science of product safety. FDA is not required to issue any guidance before approving products as biosimilar or designating products as interchangeable. Such guidance is unnecessary for states to adopt laws governing whether and under what circumstances a pharmacist may select the biologic product dispensed to a patient. States have the ability and the authority to make informed decisions about biologic substitution policy.

II. Questions related to the Naming of FOBs

II.1. What has been learned from the experience under Hatch-Waxman about the incentives necessary to encourage physicians and patients to switch between branded and lower cost, therapeutically substitutable products? Do naming and name changes affect switching? If so, how?

Key points

- The experience under Hatch-Waxman has shown that payers can drive uptake of therapeutically equivalent generic drugs to very high market share.
- Naming does not drive or deter market transition to generic; other incentives and pharmacy practices drive uptake.
- Non-proprietary name prescribing occurs at 21% to 39% in the U.S., and may contribute marginally to use of generics, but overall it is a minority covariant factor in driving generics to an average 89% market share.
- With very rare exceptions, the nonproprietary names of therapeutically equivalent generic products are identical to those of the reference product. Therefore, there is no meaningful evidence that distinguishable names might impact switching.
- Market uptake of biosimilars depends on all stakeholders having confidence in transparency and accountability for product safety.

Generic drug uptake under Hatch-Waxman has been driven largely by coverage and reimbursement policies and pharmacy incentives independent of prescription by generic name.

Public and private payers in the United States have been very successful in driving uptake of generic drugs in the past two decades under Hatch-Waxman. It is estimated that generics are used for greater than 80% of prescriptions for off-patent drugs.[88] This has been achieved through a variety of mechanisms which will be described in detail below. Prescribers use brand names for the majority of prescriptions, even when a generic is available,[89] so generic uptake is predominantly driven by factors other than shared non-proprietary names.

First, payers are able to drive utilization of lower cost drugs by placing them on formulary tiers with lower cost-sharing, employing other utilization management tools such as step edits and prior authorization, or, in some cases, not covering particular high cost drugs. Payers may determine that it is appropriate to prefer one drug over another in the absence of comparator data, which is generally not required as a condition of approval by the FDA. Patients and prescribers typically have an opportunity to overcome these barriers to access by demonstrating that a non-preferred drug is medically necessary.

[88] *See* IMS Health, Generic Medicines: Essential contributors to the long-term health of society, Figure 4, http://www.imshealth.com/imshealth/Global/Content/Document/Market_Measurement_TL/Generic_Medicines_GA.pdf (accessed Feb. 12, 2014) (showing 89% utilization of generics in unprotected markets in the US).

[89] A 2003 study showed that 21% of outpatient prescriptions for common drugs were written by the generic name when a generic was available. *See* Steinman MA, Chren MM, Landefeld CS, What's in a Name? Use of Brand versus Generic Drug Names in United States Outpatient Practice, J. Gen. Intern. Med. 22:645 (2007).

In institutional settings, decisions to prefer one product over another are made by Pharmacy and Therapeutics committees and are driven by cost and quality factors among others.[90] Such formulary decisions typically override any particular prescriber preferences. These policies generally apply to a class of drugs regardless of therapeutic equivalence status and therefore are independent of the existence of shared non-proprietary names.

Second, in the US, most states laws that permit generic substitution refer to the therapeutic equivalence (TE) of the product – either by reference to a state list or similar, or the federal list of products (known as the Orange Book). Substitution laws do not necessarily hinge on product name. Pharmacies can automatically substitute a therapeutically equivalent generic drug, and payers have developed incentive systems to encourage automatic substitution by pharmacists.[91]

While shared generic drug name need not be a criterion for substitution, many state pharmacy practice laws also list the specific elements of pharmaceutical equivalence (same active ingredient, strength, dosage form and route of administration) in addition to referencing the overarching TE status from an authoritative source.[92] These requirements for "same active ingredient" or "same generic name" are typically unnecessary to promote automatic substitution, and are potentially subject to misinterpretation. For example, some products that are not therapeutically equivalent share a nonproprietary name (and hence might be accidentally substituted by reference to their pharmaceutical equivalence).[93]

Third, payers have established mechanisms, unrelated to product name, by which to encourage prescribers to select less expensive alternatives (whether therapeutically equivalent generics or other). These mechanisms include call-back communications from the pharmacist to the prescriber requesting that the prescriber change to a generic drug prescription and computerized physician order entry system prompts that do the same.[94, 95]

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[90] *See* American Society of Health-System Pharmacists, ASHP guidelines on the pharmacy and therapeutics committee and the formulary system, Am J Health-Syst Pharm. 65:1272-83 (2008), http://www.ashp.org/DocLibrary/BestPractices/FormGdlPTCommFormSyst.aspx.

[91] *See* U.S. Department of Health and Human Services, Expanding the Use of Generic Drugs, ASPE Issue Brief (Dec. 2010), http://aspe.hhs.gov/sp/reports/2010/genericdrugs/ib.pdf ("Pharmacists have a financial incentive to prescribe generics, as the mark up received by pharmacies is largest for new generics.").

[92] For example, the Virginia Pharmacy Practice Act, as amended in 2013, retains the reference to pharmaceutical equivalence criteria in "§ 54.1-3401. Definitions." *See* http://www.dhp.virginia.gov/Pharmacy/pharmacy_laws_regs.htm (accessed Feb. 26, 2014) ("Therapeutically equivalent drug products" means drug products that contain the same active ingredients and are identical in strength or concentration, dosage form, and route of administration and that are classified as being therapeutically equivalent by the U.S. Food and Drug Administration.").

[94] For example, somatropins share the same established name but are not TE, and many chemically synthesized drugs licensed via a 505(b)(2) application, such the ENDO Pharma oxymorphone ER, are not TE with other products containing the same active ingredients. *See*, FDA, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, Active Ingredient Search, http://www.accessdata.fda.gov/scripts/cder/ob/docs/queryai.cfm (accessed Feb. 25, 2014).

[94] For example, Vanderbilt University Medical Center showed that generic substitution support, where the CPOE system defaulted to the lower cost generic, increased generic prescriptions from 32.1 to 54.2 percent over a two-year period. *See*, King D et al., Approaches Based on Behavioral Economics Could Help Nudge Patients and Providers Toward Lower Health Spending Growth, Health Affairs 32:661-668 (2013).

[95] E-prescribing systems can increase use of generics by making information about lower cost alternatives readily available to the prescriber. A study by California Blue Cross found a 5.9% increase in generic use through e-

Market research has shown that the net impact of these policies and incentives has been to drive uptake of therapeutically equivalent generics to greater than 80% relative to the originator brand.[96] The first TE generic that enters under the 180-day period of exclusivity captures roughly half the market, but it does so at only a small price discount to the brand.[97] Once multiple TE entries come on market, the price often drops and generics take an average of 78% market share within a year.[98]

Overall, due to the above-mentioned confounding of non-proprietary active ingredient naming and generic substitution in the United States, it is not possible to use historical data to conclude that distinguishable non-proprietary names would impact uptake of interchangeable biologics.

At the margins, there is indirect evidence that use of shared active ingredient names may have contributed to some portion of generic drug uptake. Some institutions and medical schools have encouraged prescribers to use the non-proprietary active ingredient name, rather than the trade name.[99] These practices are intended to reduce medication errors due to confounding of similar-sounding brand names for products with completely unrelated active ingredients[100] and to facilitate use of generics by giving pharmacists discretion to choose a product with the same active ingredient.[101,102] However, surveys have suggested that prescription by non-proprietary name occurs approximately 21 to 39% of the time,[103] so this is not the predominant mechanism

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prescribing. *See* U.S. Department of Health and Human Services, Expanding the Use of Generic Drugs, ASPE Issue Brief (Dec. 2010), http://aspe.hhs.gov/sp/reports/2010/genericdrugs/ib.pdf.

[96] *See* IMS Health, Generic Medicines: Essential contributors to the long-term health of society, Figure 4 (2010) (89% utilization of generics in unprotected markets in the US), http://www.imshealth.com/imshealth/Global/Content/Document/Market_Measurement_TL/Generic_Medicines_GA.pdf.

[97] *See* Reiffen D, Ward M, Branded Generics As A Strategy To Limit Cannibalization of Pharmaceutical Markets, Managerial and Decision Economics 28:251, 264 (2005).

[98] *See* Grabowski H et al., The Effect on Federal Spending of Legislation Creating a Regulatory Framework for Follow-on Biologics: Key Issues and Assumptions, White Paper at 42 (2007), http://public.econ.duke.edu/Papers/PDF/0907_H_Grabowski_I_Cockburn_G_Long_et_al_Effect_on_Federal_Spending_of_Follow_on_Biologics.pdf.

[99] *See* Brunton L et al., Goodman & Gilman's Manual of Pharmacology and Therapeutics 81 (2008) (instructing "[t]he nonproprietary or official name of a drug should be used whenever possible."). *See also* Eisenberg R, Faingold C, Knowledge Objectives in Medical Pharmacology 3 (2012) (noting that "[d]rugs may be prescribed by generic name, since often a less expensive drug product can be obtained in this way.").

[100] Dozens of examples of potentially confusing brand name pairs relating to functionally unrelated active ingredients are listed in Hoffman JM, Proulx SM, Medication Errors Caused by Confusion of Drug Names, Drug Safety 26:445 (2003). Examples of distinguishable names for related biologics were not among examples of name-related medication errors. Such distinguishable names (common root + distinguishing suffix/prefix) convey a common pharmacology and mechanism of action, and hence would not result in the types of medication errors described.

[101] Kwo EC, Kamat P, Steinman MA, Physician Use of Brand Versus Generic Drug Names in 1993-1994 and 2003-2004, Ann. Pharmacother. 43:459 (2009).

[102] Steinman MA, Chren MM, Landefeld CS, What's in a Name? Use of Brand versus Generic Drug Names in United States Outpatient Practice, J. General Internal Medicine 22:645 (2007).

[103] A 2003 study showed that 21% of outpatient prescriptions for common drugs were written by the generic name when a generic was available. Steinman MA, Chren MM, Landefeld CS., What's in a Name? Use of Brand versus Generic Drug Names in United States Outpatient Practice, J. General Internal Medicine 22:645 (2007). Another study found that brand name mention for 25 commonly prescribed drugs declined from 89% in 1993-1994 to 61%

for driving generic uptake to an average of 89% for unprotected markets in the United States. Thus, non-proprietary prescribing may contribute marginally to use of generics, but overall it is a minority covariant factor in generic uptake. Payer coverage and reimbursement policies and incentives to pharmacies to substitute generics are the predominant factor.

Prescribing by nonproprietary name could result in inadvertent switching of therapies between biologics that have not been shown to be interchangeable. Indeed, FDA established a differentiated non-proprietary name for a non-interchangeable version of filgrastim in order to mitigate the risks of non-proprietary name prescribing.[104] Similar concerns exist in Europe where, although some member states have policies to require or encourage use of nonproprietary name for prescriptions for chemical drugs, these countries have introduced specific policies for biologics and biosimilars to encourage use of brand or trade name prescriptions.[105]

Even where biological products are deemed interchangeable, it is important to know which specific product the patient receives. Accurate reporting of adverse events requires clear knowledge of the product to which the patient has been exposed. FDA cited this additional rationale for establishing a distinguishable non-proprietary name for a version of filgrastim in the United States.[106] Biologics are sensitive to the process of manufacturing, handling, the environment, etc., and even products deemed safe and effective at the time of approval can experience problems over their lifecycle.

Keeping patients safe requires prompt identification of the specific product that may be the source of a problem. When emergent safety signals from one product are buried in the aggregated data from multiple products in a class there may be a delay in detection of the problem (because the signal is diluted among the broader class), and there may be a further delay in isolating the problem to the responsible manufacturer. These avoidable delays are followed by the unavoidable lag while FDA and the manufacturer take appropriate measures to investigate and protect patients. In the meantime, patients would continue to be exposed to the suspected product leading to unnecessary harm to affected patients. Indeed, the impact of

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in 2003-2004. Kwo EC, Kamat P, Steinman MA, Physician Use of Brand Versus Generic Drug Names in 1993-1994 and 2003-2004, Ann. Pharmacother. 43:459 (Mar. 2009).

[104] *See* Center for Drug Evaluation and Research (CDER), FDA, Filgrastim Proprietary Name Review (August 2012) ("FDA has concluded that a nonproprietary name for Teva's product that is distinct from Amgen's product will help to minimize medication errors by (1) preventing a patient from receiving a product different than what was intended to be prescribed and (2) reducing confusion among healthcare providers who may consider use of the same nonproprietary name to mean that the biological products are indistinguishable from a clinical standpoint."), http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/125294Orig1s000NameR.pdf).

[105] For example, the United Kingdom's Medicines and Healthcare Products Regulatory Agency (MHRA) issued a Drug Safety Update in 2008 clarifying that biologics and biosimilars should be prescribed by brand name only. MHRA, Biosimilar Products, Drug Safety Update 1(7):8 (Feb. 2008) ("When prescribing biological products, it is good practice to use the brand name. This will ensure that automatic substitution of a biosimilar product does not occur when the medicine is dispensed by the pharmacist. Products (biosimilar and reference) that have the same international non-proprietary name (INN) are not to be presumed identical for the reasons given above."). *See* MHRA, Biosimilar Products, Drug Safety Update 1(7):8 (Feb. 2008), http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON084739.

[106] *See* CDER, FDA, Filgrastim Proprietary Name Review (August 2012). ("FDA also has concluded that unique nonproprietary names will facilitate postmarketing safety monitoring by providing a clear means of determining which "filgrastim" product is dispensed to patients.").

confounded data on FDA's ability to investigate a safety issue was cited by the Government Accountability Office as a significant concern with the heparin contamination investigation in the United States.[107]

There is no meaningful evidence that distinguishable names might impact switching of interchangeable products.

The history of generic drugs approved under Hatch Waxman cannot be used to draw conclusions regarding the impact of non-proprietary names on uptake, because all products approved under the generic pathway can use the nonproprietary name of the product copied. The generic drug law requires that the active ingredient in the copy be identical to the reference product, while there is no requirement of having an identical active ingredient in the biosimilars law.[108] To the contrary, certain differences between biosimilars and their reference products, and among biosimilars of the same reference product, are anticipated and acceptable.

A shared non-proprietary name is not a surrogate for therapeutic equivalence, but is often listed in U.S. state pharmacy practice acts as one of several criteria for permitting automatic substitution of generic drugs.[109] Pharmaceutical equivalence (a concept which does not apply to biologic medicines) comprises the same active ingredient or ingredients and the same dosage form, strength and route of administration. This is generally a necessary, but not sufficient condition for automatic substitution of non-biologic drugs. While many products that share a generic name are therapeutically equivalent, that is not always the case, and most U.S. states also require that a pharmacist refer to a therapeutic equivalence determination by FDA or by a state body.[110]

Notably, however, enacted state pharmacy practice acts for substitution of biologics do not reference the pharmaceutical equivalence language of Hatch-Waxman, but instead reference the BPCIA where interchangeability is a holistic determination.[111] These amended acts do not

[107] *See* U.S. Gov't Accountability Office, Response to Heparin Contamination Helped Protect Public Health; Controls That Were Needed for Working With External Entities Were Recently Added, GAO-11-95, at 34-37 (2010) under "FDA Analyzed Adverse Events Associated with Heparin and Heparin-Containing Medical Devices, but Was Unable to Link Them with Contaminated Heparin Due to Data Limitations and Confounding Factors Involving Patients."

[108] *See* FTC Emerging Health Care Issues Report, *supra* note 11 at note 55("Generally, the FDA approves the use of the same name for a generic small-molecule as the reference branded drug because both products share the same the active ingredient. In contrast, an FOB drug manufactured by a different process than the reference branded biologic drug may share the same mechanism of action, may share the same efficacy and side effects, and may even be considered or approved as interchangeable with the reference branded biologic drug but may still not be given the same name as the brand.").

[109] For example, the Virginia Pharmacy Practice Act, as amended in 2013, retains the reference to pharmaceutical equivalence criteria in "§ 54.1-3401. Definitions." *See* http://lis.virginia.gov/cgi-bin/legp604.exe?131+ful+CHAP0412+pdf (accessed Feb. 13, 2014) ("Therapeutically equivalent drug products" means drug products that contain the same active ingredients and are identical in strength or concentration, dosage form, and route of administration and that are classified as being therapeutically equivalent by the U.S. Food and Drug Administration….".).

[110] *Id.*

[111] For example, Virginia revised Pharmacy Practice Act (2013) defines an "Interchangeable Biologic" as follows in "§ 54.1-3401. Definitions": "'Interchangeable' means a biosimilar that meets safety standards for determining interchangeability pursuant to 42 U.S.C. § 262(k)(4)." It permits substitution without reference to active ingredient names as follows in "§ 54.1-3408.04. Dispensing of interchangeable biosimilars permitted": "A

refer to "same active ingredient," "same generic name," or other requirements that would necessarily be linked to the existence of identical or distinguishable non-proprietary names. Assuming that the types of incentives for pharmacies to substitute drugs will be effective for interchangeable biologics, there is no reason to believe that a pharmacist would be dissuaded from substitution by mere nomenclature in lieu of following the state law which includes no requirements for the substituted biologic to have the "same active ingredient" or "same generic name."

Market success of biosimilars could be impacted if health care providers lack confidence in the transparency and accountability for biological medicines administered to patients.

Experience with generic substitution, and the entirety of the European biosimilar experience, has shown that physician confidence in products is a precursor to uptake.[112] FDA has commented that the entire biosimilar industry will be set back if an incident undermines confidence in biosimilar medicines.[113] [114] Transparency, education and distinguishable non-proprietary names (common root plus distinguishing prefix or suffix) are the most effective tools to advance the biosimilar industry.

II.2. How does the European Medicines Agency ("EMA") and other regulatory authorities comparable to the FDA handle the names of FOBs?

Key points

- The WHO INN system, to which most regulatory agencies refer for nomenclature, has historically provided for distinguishable naming for certain classes of follow-on biologics.

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pharmacist may dispense a biosimilar that has been licensed by the U.S. Food and Drug Administration as interchangeable …," http://lis.virginia.gov/cgi-bin/legp604.exe?131+ful+CHAP0412+pdf (accessed Feb. 13, 2014).

[112] *See* European Commission, "What You Need to Know about Biosimilar Medicinal Products: Process on Corporate responsibility in the Field of Pharmaceuticals Access to Medicines in Europe," Consensus Information Paper 2013, at 17 (2013), http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/biosimilars_report_en.pdf) ("It is thus essential that physicians and patients share a thorough understanding of biological medicines, including biosimilar medicines, and express confidence in using either type of therapy. This can be achieved by maintaining a robust regulatory framework and effective risk management, transparency with regard to biological medicinal products, and continued education on biological medicines, including biosimilar medicines.").

[113] *See* Udin S, Biosimilar Battlefronts, BioCentury (September 30, 2013) (comments in interview with Rachel Sherman, CDER) ("'As a matter of public safety, all these products must be traceable,' Sherman said. 'Particularly with biologics, we need to know who gets what, from where, so if there is a problem we can address it by going after the product, lot, whatever. We absolutely need to be able to trace the product.' She added: 'If we can't do that, one can see all kinds of terrible consequences, including having to withdraw a full class.'"), http://www.biocentury.com/biotech-pharma-news/coverstory/2013-09-30/how-biosimilar-battles-are-brewing-over-state-laws-names-and-labels-a1.

[114] Comments from Dr. Rachel Sherman, Director of the Office of Medical Policy, FDA at the June 28, 2011 BIO International Convention in Washington, DC. Concerning the importance of assuring that biosimilar products can be traced back to the right manufacturer. "The first catastrophe will end this program. It just takes one. We have to be able to trace these products. Period. End of discussion." Summary of panel discussion available via Prevision Policy syndicated report at: http://www.previsionpolicy.com/research/regulatory-policy/2011/07/18/fda-and-biosimilars-mid-year-update-key-themes-to-watch/

- As noted in the FTC Federal Register Notice announcing its "follow-on biologics" exploratory workshop and opportunity to submit written comments[115], FDA has the authority to designate the non-proprietary name in the US.[116]
- Outside the US, authority to designate a nonproprietary name is less clear, as most regulators allow the applicant to adopt a nonproprietary name without formal review and acceptance of that name by the regulator.
- The EMA has not necessarily insisted on following the existing WHO non-proprietary naming system that would otherwise require distinguishable names for some classes of biosimilars.[117]
- The Australian and the Japanese health authorities have the authority to assign non-proprietary names and have established policies that add identifier features to the names of approved biosimilar products.

The INN system provides for distinguishable naming of certain classes of follow-on biologics.

The World Health Organization (WHO) administers the International Non-proprietary Naming system (INN) which is the basis for establishing non-proprietary names that are used in most jurisdictions. The INN program has established naming rules for various classes of chemical and biological compounds according to their structural and mechanistic properties. A few smaller and simpler biologic products lack post-translational modifications (e.g., insulins and growth hormone), and these products typically share INNs with other products in the same class provided they have the same amino acid sequence as the first product approved.

However, most biologics, including many of the commercially successful products currently the subject of biosimilar development programs, are glycosylated proteins, meaning that they are biochemically modified by their host cell systems to include complex carbohydrate structures. This includes monoclonal antibodies (e.g., epoetins, etanercept, rituximab, infliximab). Glycosylation patterns are variable and heterogeneous, and typically differ among each independently sourced biologic. Therefore, longstanding WHO INN policy has been to assign distinct Greek letter suffixes for glycosylated products having the same amino acid sequence but differing in some aspect of their glycosylation patterns,[118] and this policy was extended in 2008 to include monoclonal antibodies.[119] Application for such a suffix has been voluntary and is procedurally decoupled from a regulatory determination of similarity, which is not within the remit of the WHO.

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[115] 78 Fed. Reg. 68840 (Nov. 15, 2013)

[116] *See* 78 Fed. Reg. 68840 (Nov. 15, 2013) ("In the United States, the FDA has the authority to determine the nonproprietary name for a biological product.").

[117] *See* World Health Organization, 50th Consultation on International Nonproprietary Names for Pharmaceutical Substances, Geneva, 18-20 May 2010: Executive Summary 4 ()(March 2010), http://www.who.int/medicines/services/inn/50thExecutiveSummary.pdf.

[118] WHO, Guidelines on the Use of International Nonproprietary Names (INNs) for Pharmaceutical Substances Annex 4 (1997), http://apps.who.int/medicinedocs/pdf/h1806e/h1806e.pdf.

[119] WHO, International Nonproprietary Names (INN) Working Group Meeting on Nomenclature for Monoclonal Antibodies, Geneva. 6-7 October 2008 (2008), http://www.who.int/medicines/services/inn/ApprovedFinalWHOINNWGroupMeeting NMAreport.pdf.

These policies were established prior to the approval of the first biosimilar products in Europe, but WHO officials have reaffirmed this policy in the context of subsequent public consultation meetings where nomenclature for follow-on biologics including biosimilars has been discussed. In particular, at a 2008 Consultation meeting the WHO INN Chair reaffirmed the policy and also noted that the WHO relies on regulatory review groups to implement this policy:

> Post-translational modifications such as glycosylation should be identified somehow, e.g. by the use of a Greek letter suffix, as for all glycoproteins. It was further suggested that since the biological impact of posttranslational modifications such as fucosylation can be quite significant, that mAbs even with identical amino acid sequences should be considered different drug substances and therefore should have different INNs; however, it was acknowledged that this would only work if the policy is for those making new mAbs to apply for a distinct INN. The Chair noted that the INN system cannot demand that a manufacturer applies for an INN.[120]

Although FDA and the USAN Committee generally defer to the INN system, FDA has the authority to designate a non-proprietary name in the U.S.

FDA generally supports the INN system and, via its participation in the United States Adopted Names Council (USANC), reviews and approves USAN applications in conjunction with WHO review of INN applications. In this context, the WHO and the USANC have both approved differentiated nonproprietary names (INNs / USANs) for structurally related biologics including interferon alfas (e.g., interferon alfa 2A, interferon alfa 2B); interferon betas (interferon beta 1a) and follitropins (follitropin alfa and follitropin beta); among other examples. However, FDA also has statutory authority to establish names for biologic products that are independent of such national or global standards organizations,[121] and has used or referenced this authority when needed to protect public health.[122]

In 1999 FDA worked with the USANC to devise a distinguishable nomenclature system for conjugated estrogens. These products included both naturally sourced and synthetic sourced versions with various mixtures of subcomponents, and while the overall pharmacology and safety profiles of the products are similar, they were not considered to be "pharmaceutically equivalent" and hence merited distinguishable active ingredient names. Resulting nomenclature convention included prefixes indicating whether the products were "natural" or "conjugated" and suffixes "A," "B," etc. indicating that the products were not pharmaceutically equivalent.[123] In this case FDA did not invoke its statutory authority because it was able to work with the USANC to obtain endorsement of this approach.

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[120] WHO, 46th Consultation on International Nonproprietary Names for Pharmaceutical Substances, Geneva (1-3 Apr. 2008): Executive Summary 3 (June 2008), http://www.who.int/medicines/services/inn/46thINNConsultation_ExecSummary.pdf.

[121] FDCA section 508 states that FDA "may designate an official name" for any drug through notice and comment rulemaking if it determines that such action is "necessary or desirable in the interest of usefulness and simplicity." FDCA §§ 508(a), (c), 21 U.S.C. §§ 358(a), (c).

[122] *See* 78 Fed. Reg. 68840 (Nov. 15, 2013) ("In the United States, the FDA has the authority to determine the nonproprietary name for a biological product.").

[123] *See* CDER, FDA, Complex Drug Substances Coordinating Committee, Memorandum on Conjugated Estrogens Nomenclature (Jan. 6, 1999), http://www.fda.gov/ohrms/dockets/dockets/98p0311/Tab0022.pdf.

FDA has used its authority to require the use of prefixes to differentiate structurally related biological products from the previously approved products to which they were related.[124] For example, in 2012, FDA approved two biological products through the Section 351(a) pathway—Teva's Granix™ (tbo-filgrastim) and Sanofi's Zaltrap® (ziv-aflibercept)—only after requiring the use of prefixes to differentiate them from Neupogen® (filgrastim) and Eylea® (aflibercept), respectively.[125]

With respect to Granix™, FDA required the use of a prefix to differentiate it from Neupogen®. FDA explained that distinguishable names were necessary "to minimize medication errors by (1) preventing a patient from receiving a product different than what was intended to be prescribed and (2) reducing confusion among healthcare providers who may consider use of the same nonproprietary name to mean that the biological products are indistinguishable from a clinical standpoint."[126]

In addition, FDA concluded that "unique nonproprietary names will facilitate post-marketing safety monitoring by providing a clear means of determining which 'filgrastim' product is dispensed to patients," explaining that "the use of distinct proprietary names [was] insufficient to address these concerns" because "health care providers may use nonproprietary names instead of proprietary names when prescribing and ordering products" and "pharmacovigilance systems often do not require inclusion of proprietary names."[127] Moreover, while declining in the context of that application to establish an across-the-board policy with respect to the naming of biological products, FDA stated that it "does not anticipate that any decision on nomenclature for biosimilar and interchangeable products will conflict with [its] determination regarding the nonproprietary name for this product."[128]

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[124] In 2005 FDA approved a binary biologic product, IPLEX®, that had the same active primary biologic component (mecaserim recombinant) as another biologic product, Increlex®. While the USANC assigned a distinguishable name for IPLEX® based on the salt form (mecaserim rinfabate), FDA reviewers were concerned that this did not adequately reflect the pharmacologically important effects associated with binding with the second biological component in the IPLEX® drug product. FDA requested that the sponsor apply to USANC for a distinguishable (but not completely unique) active ingredient name to avoid potential medical errors. As IPLEX® was subsequently withdrawn from the market there is no public record that this request was acted upon. Nonetheless, it demonstrates a clear intent of FDA to intervene with established naming organizations to apply special nomenclature provisions to multisource products in order to protect public health.

Another example of FDA naming policy was seen in 2009, when FDA decided to use prefixes to differentiate the non-proprietary names of several botulinum toxin products in order "to 'help reduce the potential for dosing errors.'" In accordance with this decision, Botox® and Botox® Cosmetic were renamed "onabotulinum toxin A"; Dysport® was approved as "abobotulinum toxin A"; and Myobloc® was renamed "rimabotulinum toxin B."

[125] CDER, FDA, Filgrastim Proprietary Name Review; CDER, FDA, Aflibercept Proprietary Name Review (available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/).

[126] CDER, FDA, Filgrastim Proprietary Name Review (available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/.

[127] *Id*.

[128] *Id.* FDA made nearly identical statements in its decision regarding Zaltrap®. *See* CDER, FDA, Aflibercept Proprietary Name Review (available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/).

Australian and Japanese regulatory agencies have established policies for distinguishable nonproprietary names for biosimilars in their jurisdictions.

Among other regulated markets there are a variety of jurisdictional systems for non-proprietary naming. Some regions defer to the WHO INN naming system, while other jurisdictions have the ability to assign non-proprietary names.

EMA

The EMA does not have a naming authority analogous to the FDA, but is subject to EU law and European Commission (EC) guidance regarding appropriate use of the INN or other common name. EMA has established procedural advice for sponsors of biosimilars that aligns with WHO's INN policies:

> In addition, the Applicant should also note that the INN designation is within the responsibility of the WHO. The Applicant/MAH should consider the WHO policy on INNs to decide whether it is appropriate to apply the INN used for the reference medicinal product or whether to request a new INN from the WHO. If, during the assessment of the submitted data, the Agency considers that the proposed INN is not suitable, the Applicant/MAH should be prepared to justify their choice of INN. The Applicant/MAH may be recommended to contact the WHO to apply for a new INN.[129]

Notwithstanding this formal reference to INN policies in EMA's procedural guidance, there have been questions regarding EMA's interpretation of, and cooperation with, the WHO's INN rules for follow-on glycosylated products. Specifically, with one historical exception for epoetin zeta (similar to reference epoetin alfa), EMA has generally accepted the applicants' proposals that biosimilar products should have the same name as their reference products.[130] EMA appears opposed to a new WHO naming system specific for biosimilars[131], but, of significance, EMA has not taken a position on use of a WHO distinguishable naming policy that would be applied

[129] EMA, EMA Procedural advice for users of the centralised procedure for similar biological medicinal products applications, EMA/940451/2011 (March 2013), http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/04/WC500125166.pdf.

[130] See the EC Pharmaceutical Committee Minutes, Document PHARM 630 from October 23, 2013. "Current EU thinking considers that biosimilar medicinal products should be closely aligned with their reference products and identification by INN together with a qualifier or code for each biosimilar medicinal product would be contrary to such alignment". Available at: http://ec.europa.eu/health/files/committee/71meeting/pharm630.pdf (Accessed February 19, 2014).

[131] See WHO, 57th Consultation on International Nonproprietary Names for Pharmaceutical Substances: Executive Summary 4-5 (22-24 October 2013) http://www.who.int/medicines/services/inn/57th_Executive_Summary.pdf (accessed Jan. 28, 2014). ("Many experts have voiced that the best way to distinguish between an SBP and its reference product, and between one SBP and another, is through nomenclature, with involvement of the INN Programme in developing a unique global biological qualifier (BQ) […] In contrast, the European Medicines Agency representative thought it unlikely that a biological qualifier would be used in the EU but could not state categorically that it would not be.")

equally to all biologics.[132] Indeed, some EMA officials have noted that such a biological qualifier policy would be considered once a WHO proposal is published.[133]

The WHO has publically raised objections to EMA's current practice, in particular with respect to the unfortunate situation where a biosimilar epoetin was permitted to use the originator INN in contradiction with WHO policies.[134] While this policy seemingly contrasts with WHO policy that follow-on glycoproteins with distinguishable glycosylation profiles should receive a new Greek letter suffix, the EU has policies emphasizing use of trade or brand names for all biologics,[135] product labeling warnings,[136] and legislative measures concerning prescribing and dispensing practices that seek to ensure that biologic products are tracked at the individual product level.[137] These measures might serve to address the gaps that are created by deviation from WHO's naming practices for glycosylated proteins. As the WHO INN system is voluntary, subject to enforcement only by regulatory agencies, WHO officials have publically expressed disappointment about the unwillingness of EMA/EC to follow the Greek letter suffix system in all circumstances.[138]

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[132] See also, BioPharma-Reporter.com, Feb. 19, 2014.

[133] See Minutes of the ABPI/ BIA meeting with MHRA to discuss biologics and biosimilars. November 25, 2013. Available via The Association of the British Pharmaceutical Industry, 7th floor, Southside, 105 Victoria Street, London, SW1E 6QT. ("MHRA support the view of EMA, that the INN should be the same for the originator and biosimilar, with traceability via the brand name. However, JB said MHRA would support a global approach. Patience Holland (PH) said the WHO have not yet released details of their proposed process but confirmed that MHRA would support the proposals if they do not impact EU practice. The WHO INN Expert group's next meeting is in April 2014 and a proposal will be released for consultation after that meeting so discussions now may be a little premature. In principle, PH did not see any harm in a codification system, noting that it was aligned to substances rather than products. She also confirmed that Japan and Australia said they were happy to drop their national provisions for a more harmonised international code. This will be published when the WHO publishes the minutes from the meeting. US FDA have been part of the process throughout and have not raised any objections to date.")

[134] *See* WHO, 50th Consultation on International Nonproprietary Names for Pharmaceutical Substances, Geneva, 18-20 May 2010, Executive Summary 4 (March 2010), http://www.who.int/medicines/services/inn/50thExecutiveSummary.pdf. ("It is the responsibility of a company to apply for an INN and unfortunately, the European regulators accepted Sandoz's own INN assignment of epoetin alfa without question. The WHO has expressed their concern about this situation to the EMA.").

[135] *See* Directive 2001/83/EC, art. 1(20), 2001 O.J. (L 311) 67 (defining the name of a medicinal product to be "either an invented name or a common or scientific name, together with a trade mark or the name of the manufacturer").

[136] *See* EMA, Aranesp: EPAR – Procedural steps taken and scientific information after authorisation 10 (Nov. 2013), http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000332/human_med_000651.jsp&mid=WC0b01ac058001d124 (Aranesp: Epar – Procedural Steps) ("In order to improve the traceability of erythropoiesis-stimulating agents (ESAs), the trade name of the administered ESA should be clearly recorded (or stated) in the patient file.").

[137] *See* E.C. Council Directive 2010/84/EC, art. 102(e), 2010 O.J. (L 348) 74, 84 (amending Council Directive 2001/84/EC) ("The Member States shall: (e) ensure […] that all appropriate measures are taken to identify clearly any biological medicinal product prescribed, dispensed, or sold in their territory . . . with due regard to the name of the medicinal product").

[138] *See* WHO, WHO 50th Consultation on International Nonproprietary Names for Pharmaceutical Substances, Geneva, 18-20 May 2010: Executive Summary (March 2010), http://www.who.int/medicines/services/inn/50thExecutiveSummary.pdf ("It is the responsibility of a company to

Australia

In Australia all medicines are required to use the Australian Approved Name (AAN). In the case of biologicals this name will generally be the Australian Biological Name (ABN). The ABN is typically derived from non-proprietary names originally assigned by other reference organizations (INN, USAN) but may include additional source descriptors. For example, ABNs for biotechnological products typically include the suffix "rbe."[139] In 2010 the Department of Health issued a discussion paper outlining government policy for biosimilar product nomenclature.[140] Briefly, this policy stipulated that when there were no detectable analytical differences the biosimilar product could share the same ABN with the reference product, but if there were detectable differences the biosimilar product may require a different ABN.

In the same timeframe as this policy was published, the Therapeutics Goods Administration approved Novicrit® (epoetin lambda), a biosimilar of Eprex® (epoetin alfa). The active ingredient of Novicrit®, HX-575, was shared with Binocrit® (epoetin alfa), a biosimilar authorized by the EU and permitted to share the same INN with its reference product notwithstanding analytical differences. The TGA took a different view of the situation and, consistent with its policy, assigned the distinguishable ABN, epoetin kappa, due to the existence of analytical differences.[141]

More recently, Australia has issued a revised policy that promotes distinguishable biosimilar ABNs independent of analytical findings. This revised policy would incorporate the reference product ABN with a suffix comprised of the mnemonic "sim" (indicating approval as a biosimilar) with a random three letter identifier (e.g., infliximab simfam).[142]

Japan

In Japan the non-proprietary name is the Japan accepted name (JAN) assigned by the Japanese health authorities. (A sponsor also may obtain an INN from the WHO, at its discretion.[143]) For innovative biologics, the JAN is derived from the INN, if an INN exists.[144] For a biosimilar, the JAN is determined by applying the following formula: JAN of the reference product + "[" + JAN

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apply for an INN and unfortunately, the European regulators accepted Sandoz's own INN assignment of epoetin alfa without question. The WHO has expressed their concern about this situation to the EMA.").

[139] Therapeutic Goods Administration, Australian Government, TGA Approved Terminology for Medicines, Section 2, Biological Substances (July 1999), http://www.tga.gov.au/pdf/medicines-approved-terminology-biological.pdf.

[140] *See* Department of Health, Australian Government, Discussion paper on Similar Biological Medicinal Products (SBMPs) (July 1, 2010), http://www.pbs.gov.au/info/publication/factsheets/shared/2010-07-01-Discussion_paper_on_SBMPs.

[141] *See* WHO, 50th Consultation on International Nonproprietary Names for Pharmaceutical Substances, Geneva May 18-20, 2010: Executive Summary (March 2010)), http://www.who.int/medicines/services/inn/50thExecutiveSummary.pdf; Pharmaceutical Benefits Advisory Committee, Department of Health, Australian Government, Public Summary Document July 2010 PBAC Meeting, 3 (July 2010), http://www.health.gov.au/internet/main/publishing.nsf/Content/22C8C4368FC0D8C1CA257BF0001D7BE7/$File/Epoetin%20lambda%20NOVICRIT%20Novartis2.pdf.

[142] *See* Therapeutic Goods Administration, Australian Government, Evaluation of Biosimilars 15-16 (July 2013), http://www.tga.gov.au/pdf/pm-argpm-biosimilars.pdf.

[143] Notification No. Yakushoku-shinsa hatsu 0331004 (Mar. 31, 2006).

[144] *Id. See also* http://jpdb.nihs.go.jp/jan/Default.aspx (an online database of JANs maintained by the National Institute of Health Sciences Japan).

of the reference product minus "rDNA," if any + "Biosimilar" + the order number of the biosimilar product + "]". Accordingly, the biosimilar approved most recently in Japan has the non-proprietary name "Filgrastim (rDNA) [Filgrastim Biosimilar 2]." A more complex example concerns a biosimilar of epoetin alfa which received the distinguishable INN epoetin kappa (according to WHO rules discussed in Section II.2.1)[145] and whose JAN is therefore "Epoetin kappa (genetical recombination) [Epoetin Alfa Biosimilar 1]".[146]

There is an exception for biosimilars whose "essence" is considered "identical" to that of a reference product, in which case the biosimilar is given the same non-proprietary name as the reference product.[147] For example, the non-proprietary name for both the biosimilar and the reference product Somatropin (rDNA) is "Somatropin (rDNA)."

Japan also has special rules for biosimilar trade names. While a manufacturer of an innovative biologic is typically free to propose a unique trade name, subject to review,[148] the biosimilar trade name is determined by applying the following formula: JAN of the reference product + "BS" + dosage form + strength + company name (the company name may be in brackets if it would otherwise be confusing). Accordingly, the proprietary name of the biosimilar approved most recently in Japan is "Filgrastim BS Injection 750μg Syringe [NK]."

Thus, Japan has taken measures to ensure that both non-proprietary names and trade names for biosimilars clearly indicate the reference active ingredient name while maintaining distinguishability of the biosimilar product names for the purposes of prescribing, dispensing, and tracking.

II.3. A prefix or suffix, such as "ado" or "TBO", has been attached to the nonproprietary names of several biological products licensed under a stand-alone biologic license application. How does the use of such prefixes or suffixes affect the inclusion of that product in third-party publications, compendia references, and health information systems, such as electronic health records and prescription processing systems?

Key points

- Scientific publications can easily bridge name distinctions and do so now.
- NCCN guidelines for breast cancer refer to both "ado-trastuzumab emtansine" and "trastuzumab" separately and clearly.
- The three-letter prefix with a hyphen and no spaces was specifically designed by FDA in conjunction with Roche/Genentech to work with electronic systems.

Scientific publications can easily bridge name distinctions for structurally and mechanistically related therapeutics and do so now. Therefore, the inclusion of a prefix or suffix in a nonproprietary name should have no effect on its use in a scientific publication. For example, a recent search in the NIH database PubMed produced 58 results for "ado-trastuzumab

[145] WHO consultation notes on epoetin kappa WHO INN List 59, http://whqlibdoc.who.int/druginfo/INN_2008_list59.pdf (accessed 2/26/2014)
[146] *See* PMDA approvals, http://www.pmda.go.jp/english/service/pdf/list/NewdrugsFY2009.pdf (accessed Nov. 4, 2013).
[147] Notification No. Yakushoku-shinsa hatsu 0214-1 (Feb. 14, 2013).
[148] *See* https://www.ruijimeisho.jp/ (accessed Feb. 25, 2014).

emtansine" versus 5695 for just "trastuzumab" (which includes both Herceptin® and Kadcyla®, as well as products in development) and 94 for "-trastuzumab emtansine" (which of course would include scientific publications published before FDA issued a name).

Hyphenated prefixes are a relatively new feature for biologic nomenclature, but the INN system has historically used suffixes to distinguish structurally related, but not identical, biologic products. In this context, the scientific and medical literature has long accommodated these classes of structurally related biologics by referring to the shared INN root name. Examples of review articles covering safety profiles for classes of biologics with distinguishable suffixes include interferon alfas,[149] interferon betas,[150] and epoetins.[151]

As with scientific publications, medical practice guidelines accommodate related families of therapeutics with distinguishable names. As a result of the 2012 introduction of the "ado" prefix to the nomenclature for drug-conjugated trastuzumab NCCN guidelines for breast cancer refer to both "ado-trastuzumab emtansine" and "trastuzumab" separately and clearly.[152] In fact, NCCN guidelines even specify that "ado-trastuzumab emtansine" is the preferred agent in certain settings.

Electronic health records and prescription processing systems can accommodate a variety of distinguishable naming conventions including prefixes and suffixes. These systems increasingly use the RxNorm nonproprietary "clinical drug" or "SCD" nomenclature standard (USAN + dosage form + strength) which has been designed by the National Library of Medicine to facilitate electronic systems interoperability and with the intent to cover all prescription medicines approved in the U.S.[153] Classes of structurally related biologics with distinguishable nomenclature features preceded the implementation of electronic systems, so nomenclature and search rules were designed to accommodate them. Thus, the health care provider can search for the shared USAN root name (e.g., "interferon alfa") and the system should return all options or records including additional suffixes or prefixes on the USAN. If the health care provider prefers to use a more selective search for a particular member of the class, the additional prefix or suffix information can be entered (e.g., "peginterferon alfa 2a").

One advantage of a USAN prefix in an e-prescribing interface would be that all dosage forms of a given biologic product would sort out as a group with the differentiating feature clearly visible to the prescriber (e.g, "tbo-filgrastim 5 mcg injection"). In contrast, a suffix would tend to be buried in the string of the RxNorm clinical drug name (e.g., "filgrastim tbo 5 mcg injection"), and this could result in inadvertent switching of the patient between biologics.

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[149] *See* review of safety profile of alfa interferons in Weiss K, Safety profile of interferon-alpha therapy, Semin Oncol 25(1 Supp. 1):9 (1998).

[150] *See* review of safety profile of beta interferons in Walter EU, Hohlfeld R, Multiple sclerosis: Side effects of interferon beta therapy and their management, Neurology 53:1622 (1997).

[151] *See* review of effects of epoetins on disease progression in cancer patients in Aapro M et al., Effects of erythropoietin receptors and erythropoiesis-stimulating agents on disease progression in cancer, British J. Cancer 106:1249 (2012).

[152] National Comprehensive Cancer Network, NCCN Clinical Practice Guidelines in Oncology, Breast Cancer, Version I.2014 (2014), http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site.

[153] Liu S et al., RxNorm: Prescription for Electronic Drug Information Exchange, IT Pro., at 17 (Sept–Oct. 2005) ; Nelson SJ et al., Normalized Names for Clinical Drugs: RxNorm at 6 years, J Am Med Inform Assoc 18: 441 (2008).

Another concern with suffixes is that some systems or human operators might erroneously truncate suffix information.[154] For this reason the three-letter prefix with a hyphen and no spaces was specifically designed by FDA in conjunction with Roche/Genentech to work with electronic systems.[155] The prefix allows a user to search by "tras" (or some variant thereof) and return results that include both Herceptin® and Kadcyla®. The hyphenated prefix prevents systems errors due to character-length truncation. However, concerns related to use of a prefix have been raised. For example, it has been suggested that clinicians may not recognize the INN name at first, leading to confusion and potentially patient safety issues.[156]

II.4. How does the use of certain identifiers, such as National Drug Codes, brand names, or nonproprietary names, work with existing adverse event reporting, track and trace, or other pharmacovigilance systems?

Key points

- Pharmacovigilance systems must be robust to the nature of prescribing and reporting in multiple applications and settings of use. This need requires redundant measures.
- National Drug Codes (NDCs) are not commonly used in AE reporting and there is no data field for NDCs in the FDA Adverse Event Reporting System (FAERS) database.
- Publications demonstrate that brand names are insufficient and inaccurate as a means of reporting and tracking adverse events in the United States.
- Other numerical identifiers that might confirm product identity are rarely used.

Product identifiers should be evaluated in the context of all relevant pharmacovigilance systems and settings of use for biologics.

The utility of any given product identifier for safety monitoring of biologics must be evaluated in the context of both the available mechanisms for safety data collection and the settings of use. Proposals to use certain identifiers (e.g., National Drug Codes (NDCs)) in pharmacovigilance systems and settings selectively reference possibilities and ignore practicalities, including shortfalls identified by FDA in its evaluation of identifiers.

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[154] According to testimony from the American Pharmacists Association (APhA), suffixes may not be included in a prescription; they may fall off an electronic drop down menu for product selection, and may not fit into the data field in a database. *See* Statement of the American Pharmacists Association to the Food and Drug Administration's Public Hearing: Draft Guidances Relating to the Development of Biosimilar Products, Docket No. FDA-2011-D-0618-0066, at 2 (May 11, 2012), http://www.regulations.gov/, Document No. FDA-2011-D-0618-0066. The APhA has since dropped its opposition to a suffix.

[155] *See* FDA, Memorandum from OND Therapeutic Biologics and Biosimilars Team regarding BLA 125427 – [xxx]-trastuzumab emtansine 2(Dec. 20, 2012), http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/125427Orig1s000NameR.pdf ("For example, while distinguishing labels and labeling can help to prevent mix-ups at the point of dispensing, the potential still exists for a healthcare provider to select the incorrect product (trastuzumab vs. 'trastuzumab emtansine') from a computerized drop-down menu during medication order entry.").

[156] *See* Hospira, Hospira Biosimilars Policy Positions, http://www.hospira.com/about_hospira/government_affairs/biosimilars_policy_positions/index (accessed Feb. 25, 2014).

Pharmacovigilance in the U.S. is performed primarily using two types of systems: (1) spontaneous reporting systems (SRS) via reports to the manufacturer and via the FDA's Medwatch program, and (2) active surveillance (AS) via analysis of medical billing records.[157] Both of these systems have limitations in signal detection for multisource products, but when used optimally, their attributes can be complementary. The SRS are most effective to detect new signals and generate hypotheses, whereas the AS is more useful for hypothesis testing for risk-benefit analysis. In the context of multisource product safety monitoring, both of these systems are subject to the provisos that the relevant adverse events must be reported or otherwise captured in billing system diagnosis codes and that the associated suspect products must be properly identified.

Another consideration is that product identifiers such as NDCs that are relevant to medicines dispensed by retail or mail-order pharmacies may not be widely used for medicines administered in institutional settings such as physician offices or hospitals.[158] Indeed, the majority of therapeutic biological products are administered in the physician's office or hospital outpatient settings.[159]

Finally, a clarification regarding the phrase "track and trace" is necessary to distinguish between the more common usage in reference to supply chain security measures and the less common usage concerning product safety monitoring. Some stakeholders have confused these usages in suggesting that under the Drug Quality and Security Act[160] of 2013 (DQSA), a "track and trace" system is to be created that might address the problem of product identification in pharmacovigilance.[161] It is important to clarify that the product labeling and serialization provisions of the DQSA are intended only to enhance supply chain security. Track and trace for DQSA stops when the drug is received by the pharmacy. These provisions do not cover pharmacy dispensing transactions or capture data into patient electronic health records.

NDCs have limitations in other systems and settings where most biologic use occurs.

For therapies administered in the hospital or physician office settings, the systems for tracking and billing drugs are not well suited to identifying specific products for AS. In-house pharmacies used by such providers do not typically use NDCs because hospitals bill based on the service

[157] FDA, FDA's Sentinel Initiative, http://www.fda.gov/Safety/FDAsSentinelinitiative/ucm2007250.htm (accessed Feb. 25, 2014) (providing a general description of the Sentinel Initiative).

[158] For example, hospital inpatient claims (reimbursed under Medicare Part A) typically use a Diagnostic Related Group (DRG) to assign a bundled payment according to ICD-9-CM diagnosis and procedure codes. With very rare exceptions procedure codes are not specific to a given biologic therapy or underlying event. Physician office and hospital outpatient claims (reimbursed under Medicare Part B) use HCPCS codes, but these may not always correlate to unique codes for each biologic. *See* DiMartino LD et al., Using Medicare Administrative Data to Conduct Post-Marketing Surveillance of Follow-on Biologics: Issues and Opportunities, Food Drug Law J 63:896 (2008).

[159] In 2012, approximately 64% of top-selling biologics in the U.S. (each representing 1% or more of total biologics sales, and cumulatively representing 83.7% of total biologics sales) were distributed through physician office (clinics) and hospitals. Approximately 31% of top-selling biologics were distributed through the mail-order or retail pharmacy channel. The remaining 5% were distributed through other institutional settings (e.g., veterans' facilities, prisons, HMOs). *See* Amgen Analysis of IMS Data (on file with author).

[160] *See* Drug Quality and Security Act, Pub. L. No. 113-54 (2013).

[161] GPhA, Citizen Petition, Docket No. FDA-2013-P-1153, at 11 (Sept. 17, 2013) (stating that federal legislation enhancing the track and trace system would assure the quality of pharmacovigilance data).

provided, rather than product dispensed.[162] Instead, other billing codes such as Healthcare Common Procedure Coding System (HCPCS) codes are commonly used in such settings.[163] [164]

Regardless of setting of use, NDCs are rarely available to patients and rarely used by physicians, and hence of limited utility as a reliable product identifier to support the SRS.[165] FDA officials have observed that, "while the [MedWatch] reporting system may include a field for NDC, I think it's very rare we get that level of information."[166] Indeed, while the MedWatch 3500 form includes an option to enter an NDC, there is no corresponding data field in the FDA Adverse Event Reporting System (FAERS) database, and a published analysis of FAERS data for 8 multisource drugs showed that NDCs are captured in less than 0.01% of records, primarily as part of the lot number field (perhaps indicating that numerical codes are often confusing to reporters).[167]

Brand names are insufficient and potentially inaccurate as a means of reporting and tracking adverse events.

Stakeholders to the naming debate have cited spontaneous reporting data from Europe and the U.S. that has mistakenly been used to conclude that safety reports for multisource biologics will have a high rate of accurate attribution by brand or trade name.[168] However, these analyses omit important caveats to the completion or accuracy of the underlying datasets. A more complete analysis demonstrates that, although a valid name may be in the field, a significant portion of adverse event reports may be attributed to the wrong manufacturer.

There is a bias towards attributing adverse events to the originator brand when a generic product is actually administered. Lietzan et al. analyzed data before and after generic entry for 8 chemical drugs to demonstrate that there is a strong decoupling of adverse event rates from prescription volume once a product moves from single-source (brand only) to multisource (with

[162] For example, Medicaid and Medicare/Medicaid dual eligible claims may require NDC codes.

[163] DiMartino et al., Using Medicare Administrative Data to Conduct Post-Marketing Surveillance of Follow-on Biologics: Issues and Opportunities, 63 Food & Drug L.J. 896 (2008).

[164] HCPCS Codes, Healthcare Common Procedure Coding System numbers, are the billing codes used by Medicare and monitored by CMS, the Centers for Medicare and Medicaid Services. This coding system was established in 1978 to provide a standardized coding system for describing the specific items and services provided in the delivery of health care. Such coding is necessary for Medicare, Medicaid, and other health insurance programs to ensure that insurance claims are processed in an orderly and consistent manner. Initially, use of the codes was voluntary, but with the implementation of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) use of the HCPCS for transactions involving health care information became mandatory. (Press Release, CMS, New CMS Coding Changes Will Help Beneficiaries (Oct. 6, 2004). http://www.cms.gov/Medicare/Coding/MedHCPCSGenInfo/downloads/HCPCSReform.pdf.

[165] Felix T et al., Biologic product identification and US pharmacovigilance in the biosimilars era 32 Nat Biotechnol 32:128 (2014).

[166] *See* Meeting Transcript, Docket. No. FDA-2010-N-0477, at 169 (Nov. 2, 2010) (statement of John Jenkins, MD, Director, Office of New Drugs, FDA); *see also* Zelentz A et al., NCCN Biosimilars White Paper: Regulatory, Scientific, and Patient Safety Perspectives, J. Nat. Comprehensive Cancer Network 9:S-1, S-14 (2011).

[167] *See* Lietzan E, Sim L, Alexander E, Biosimilar Naming: How Do Adverse Event Reporting Data Support the Need for Distinct Nonproprietary Names for Biosimilars?, FDLI's Food and Drug Policy Forum 3(6): 1 (March 2013), http://www.fdli.org/docs/default-document-library/lietzan-faers-bio-final-3-27-13.pdf?sfvrsn=0.

[168] Vermeer NS et al., Traceability of biopharmaceuticals in spontaneous reporting systems: A cross-sectional study in the FDA Adverse Event Reporting System (FAERS) and EudraVigilance databases, Drug Safety 36:617 (2013), abstract available at http://www.ncbi.nlm.nih.gov/pubmed/23771794.

generic competition).[169] Specifically, the rate of attribution of adverse events relative to prescriptions increased significantly for the originator brands after loss of exclusivity and loss of market share while the corresponding generics received a disproportionately low percentage of reports, but holding a high market share. This finding aligns with FDA's own assessment of generic drug safety reporting[170] and it illustrates the fallacy inherent in the frequently made claim by opponents of distinguishable names that adverse event reporters will consult the dispensing pharmacy to obtain product identifier information.[171] Clearly, if prescribers and other reporters were inclined to consult with the dispensing pharmacy prior to submitting an adverse event report, the statistics cited in the Lietzan et al. article would show a different pattern for off-patent drugs.

There is a systemic problem that leaves generic drug records erroneously absent of adverse event reports. When ambiguous reports are sent either to the originator company or to the FDA, there is no mechanism for them to be forwarded to a specific generic sponsor. Consequently, it is not surprising that a generic company's own safety data set would not reflect such reports. Amgen's procedures and bench marking surveys with industry peers enable us to conclude that some portion of ambiguous reports submitted directly to the originator companies are assigned to the originator product name as a default and without clear association before being forwarded to the FAERS database.[172] For those reports submitted directly to FDA, the ambiguous attribution is retained in FAERS and such reports would not generally be forwarded to a generic manufacturer for follow-up. To date, there has been no argument in support of shared non-proprietary names that accounts for this reality and the implications thereof.

Finally, many analyses do not address the fact that health care providers can use non-proprietary names for prescribing and reporting. We previously described that 21% to 39% of prescriptions are currently written by non-proprietary name and that this practice is a minority covariant in driving generic uptake.[173] Conversely, this statistic means that up to 39% of prescribing records for generics could be ambiguous as to the specific product used when the prescriber refers to the prescribing record for an adverse event report.

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[169] *See* Lietzan E, Sim L, Alexander E, Biosimilar Naming: How Do Adverse Event Reporting Data Support the Need for Distinct Nonproprietary Names for Biosimilars?, FDLI's Food and Drug Policy Forum 3(6): 1 (March 2013), http://www.fdli.org/docs/default-document-library/lietzan-faers-bio-final-3-27-13.pdf?sfvrsn=0 (accessed Nov. 19, 2013).

[170] CDER, Handling of adverse experience reports and other generic drug postmarketing reports, MaPP 5240.8 (Nov. 1, 2005) ("Generally, OGD receives few AERs or similar reports since the reports may not specify a generic manufacturer for the drug product.").

[171] See BioCentury TV, Segment 4, Craig Wheeler interview (Feb. 16, 2014), http://www.biocenturytv.com/player/3203440019001/3197851279001 ("You can actually look to the pharmacy and you are already tracking all of these products at the pharmacy level, not just on the manufacturer, but the actual lot that the product came from. So, we see that the current naming system with the brand names on the labels, which they already are, and then using the tracking numbers at the pharmacy to be able to actually understand exactly what product and what lot they came from, if there was a problem it's sufficient to ensure safety.").

[172] Amgen's practice for ambiguous reports is to contact the reporter to solicit additional identifier information, and if the Amgen brand cannot be ruled out, to process the report into MedWatch using Amgen's originator brand.

[173] *See* Question II.1 *supra.*

Statistics for use of product names in adverse event reports demonstrate the effect of reliance on non-proprietary names. For example, a survey recently sponsored by GPhA claims that a survey privately conducted on its behalf suggested that prescribers would use the brand name in more than 70% of case reports, leaving up to 30% of case reports without the brand name.[174]

Reports with ambiguous product names rarely include additional identifiers such as manufacturer, lot number or NDC.[175] As discussed in above, NDCs are not commonly used or tracked in the spontaneous reports. Published analysis of FAERS data show that batch numbers are rarely used as well. For example, a study performed by the Tufts Center for Drug Development examined MedWatch reports between 2005 and 2010 for several product classes, including biologics and chemical drugs, and determined that batch numbers were completed in only 9% of reports.[176] A similar study by Vermeer et al. covered FAERS from 2004 to 2010 and determined that batch numbers were available in 24.0% of reports for biotherapeutics, and 7.4% for chemical drugs.[177]

II.5. With respect to prescription drugs, does the use of nonproprietary names globally contribute to or detract from competition and consumer protection? Do any studies exist to show increased or decreased consumer benefits or harms, due to changes in names or naming conventions?

Key points

- The use of nonproprietary names globally has advanced patient protection by reducing double dosing of the same products known by different names. Proposed naming conventions for biosimilars would continue this benefit by retaining shared roots and including distinguishing prefix or suffixes rather than entirely unique names.
- Distinguishable names facilitate accurate attribution of adverse events. This is an important safety consideration for all biologics – not specifically biosimilars or reference products. Biologics are highly sensitive to the manufacturing process, handling, etc. Small changes can have meaningful implications for patients. Misattribution of adverse events through confusion with naming could result in increased and unnecessary exposure of patients when a product promptly identified could have prevented this.
- Experience in Europe with PRCA in 1999-2001 demonstrates that the concerns with product safety after marketing approval are very real. Even with distinct names, it still took 18 months to identify the problem.
- There is no compelling evidence that existing WHO naming conventions for glycosylated biologics, or the distinguishable naming policies for biosimilars adapted in certain regions, have impacted competition.

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[174] *See* GPhA Petition, Docket No. FDA-2013-P-1153-(Sept.17, 2013) at 7 n.27 (referencing a privately conducted Brand Institute Study on behalf of GPhA).

[175] Felix T et al., Biologic product identification and US pharmacovigilance in the biosimilars era, Nat. Biotechnol 32:128 (2014).

[176] Getz K et al., Evaluating the completeness and accuracy of Medwatch, Am. J. Therapeutics (Sept. 2012), (E-publishing before print), http://journals.lww.com/americantherapeutics/toc/publishahead (accessed Dec. 10, 2013).

[177] Vermeer NS et al., Traceability of biopharmaceuticals in spontaneous reporting systems: A cross-sectional study in the FDA Adverse Event Reporting System (FAERS) and EudraVigilance databases, Drug Safety 36:617 (2013), abstract available at http://www.ncbi.nlm.nih.gov/pubmed/23771794 (accessed Nov. 18, 2013).

- Pricing and uptake objectives can be and are achieved through a wide range of business strategies employed by insurers. These include tiered co-pays and restrictive formularies. Mechanisms to advance patient safety must not be dismissed in the pursuit of commercial objectives.

Distinguishable non-proprietary names for biologics can further enhance consumer protection.

Consumer protection in the context of medicines has multiple facets including increasing access, facilitating choice, minimizing errors, and supporting safety monitoring. The dual naming system for drugs (brand name and nonproprietary name) has been important for consumer protection.[178] Brand names may be more memorable to patients and practitioners, and can thereby facilitate communication. Non-proprietary names are important for communicating relationships between medications among potentially thousands of choices on a formulary. Distinguishable non-proprietary names for biologics, with a common root and distinguishing prefix or suffix, would fulfill the latter purpose. The common root would communicate the shared structure and pharmacology of the related biologics, while the distinguishing feature would facilitate disaggregation by biologic active ingredient source.

To the extent that prescribing and drug product selection practices are linked to non-proprietary names their use can improve access (by facilitating the selection of the lowest cost alternative and minimize errors by avoiding confusion between similar sounding brand names). These are worthy objectives that can be supported through either identical or distinguishable names.

Non-proprietary names also serve safety monitoring when they are used as the product-name identifier for adverse event reports. Brand names are preferred for adverse event reporting, but are not always available, especially for generic drugs, and hence the non-proprietary name may be the only correct product identifier available to the reporter (i.e., when the NDC code or manufacturer name are not retrievable).

In the case of multisource biologics there are additional considerations in facilitating choice, minimizing errors, and safety monitoring that merit distinguishable names. For the situation of non-interchangeable biologics, distinguishable names with common cores can communicate that the active ingredients are closely related, if not identical, and can be considered together as available alternatives within the class. In this context an informed choice can be made among the options to optimize patient care, cost sharing, and access. Distinguishable but closely related names can simultaneously help prevent dosing errors from double prescriptions while also preventing inadvertently substitution of non-interchangeable biologics by reference to "same generic name."

Distinguishable names can support product-specific safety monitoring for biologics, and this monitoring is also necessary for consumer protection. Because biologic products are sensitive to manufacturing conditions and hence susceptible to unexpected changes in quality, it is necessary to monitor their safety post-approval on a manufacture-specific level. Consumers must be protected from the rare, but serious, situations where a batch or batches of product are adversely impacted by unexpected manufacturing conditions or by unexpected handling in the supply chain. If such situations are not promptly traced to the correct manufacturer, there

[178] Lobo F, Feldman R, Generic drug names and social welfare, J Health Politics, Policy Law 38:574-597 (2013).

might not only be a delay in mitigating the issue (during which consumers would be unnecessarily harmed), but there may be a class-based safety alert which could reduce access of consumers to the otherwise unassociated members of the class.

These situations are not merely hypothetical. In the past 15 years there have occurred serious manufacturing related safety issues related to originator epoetin alfa in Europe,[179] heparin in the U.S.,[180] a blood product in Europe,[181] and a biosimilar epoetin alfa in Europe.[182] In the first three examples, consumers were harmed due to a delayed detection and mitigation of the issue. The fourth case with the biosimilar product occurred, fortunately, in a controlled clinical trial setting where the trial could be promptly paused. While some may take comfort in the fact that the fourth example occurred in a clinical study prior to product's approval for the indication being studied, it should be noted that the same product was already authorized and marketed for other indications.[183] Furthermore, the adverse event is normally extremely rare (occurring in less than 1 case per 10,000 patients for other members of the product class[184]) and therefore its detection in a small (<200 patients) clinical study population was completely unexpected and is no basis for complacency about the risks of manufacturing biologics.

Advocates for identical non-proprietary names infer that, because product brand names have been widely used to date for biologic product adverse event reporting, no additional measures are required for identification of biologics in patient records. This inference rests on an assumption that brand names will continue to be used as the predominant means of identification as the biosimilars market matures. This is an unsupported claim, especially when brand names are not legally required for biologics.[185] In the absence of brand names for

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[179] Between 1998 and 2002 there was a 10- to 20-fold increase in the incidence of pure red cell aplasia in some European patients receiving subcutaneous Eprex®. This was ultimately tied to a formulation change. *See* Boven K et al., The increased incidence of pure red cell aplasia (PRCA) with an Eprex formulation in uncoated rubber stopper syringes, Kidney International 67:2348 (2005).

[180] Between 2007 and 2008, 246 fatal allergic-type reactions were reported among patients who received contaminated heparin in the U.S., and this was ultimately tied to adulteration of the active ingredient. *See* U.S. Gov't Accountability Office, Response to Heparin Contamination Helped Protect Public Health; Controls That Were Needed for Working With External Entities Were Recently Added, GAO-11-95 (2010).

[181] In 2010 a surprising increase in thromboembolic events (TEEs), a life threatening complication, was observed after administration of Octagam® to European patients, and this was eventually tied to a manufacturing issue. *See* EMA, CHMP Assessment Report: Octagam and Associated Names 4 (March 15, 2012), http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/05/WC500143742.pdf .

[182] In 2009 neutralizing antibodies were detected in 2 patients out of 187 patients treated with subcutaneous biosimilar epoetin alfa, of which one patient was diagnosed with PRCA. This issue was ultimately tied to an interaction of the product with its primary container. *See* Seidl A et al., Tungsten-Induced Denaturation and Aggregation of Epoetin Alfa During Primary Packaging as a Cause of Immunogenicity, Pharmaceutical Research 29:1454 (2012).

[183] EMA, Binocrit: European Public Assessment Report Scientific Discussion (Sept. 2007), http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000725/WC500053615.pdf.

[184] Macdougall IC et al., Antibody-Mediated Pure Red Cell Aplasia in Chronic Kidney Disease Patients Receiving Erythropoiesis-Stimulating Agents: New Insights, Kidney International 81:727 (2012).

[185] *See* SA Transcripts, Momenta Pharmaceuticals' CEO Discusses Q3 2013 Results - Earnings Call (Nov. 5, 2013), http://seekingalpha.com/article/1806372-momenta-pharmaceuticals-ceo-discusses-q3-2013-results-earnings-call-transcript ("As a reminder, our strategic goal is to develop fully interchangeable biologics."). S*ee also* BioCentury TV, Segment 4, Craig Wheeler interview (Feb. 16, 2014),

biosimilars, adverse event product identification would default to either the non-proprietary name or to an incorrect use of the originator brand name. This dynamic of attribution to the originator product has been documented for off-patent chemical drugs, and it is naïve to assume that it could not occur for a biologics market that includes multiple manufacturers' versions of the same originator product.

While distinguishable non-proprietary names will not prevent erroneous use of the originator brand names for safety reporting, they can help ensure that reporters and case investigators will consult prescribing and dispensing records to address what would have otherwise been a technically correct, but ambiguous non-proprietary name. Specifically, a patient medical record or adverse event report using the original core non-proprietary name (applicable to the biologic product class) would no longer be considered sufficient product identification. This would likely prompt a search for additional identifiers including a brand or manufacturer name, or the correct prefix or suffix associated with the distinguishable non-proprietary name.

Nonproprietary names can facilitate competition.

Non-proprietary names facilitate competition by permitting shared nomenclature and linking to practices used by payers and health care providers that group products for purposes of medication guidelines, compendia, coverage, reimbursement, and drug product selection. Traditionally, these grouping mechanisms have been primarily by identical active ingredient names for generic drugs, but there is no reason that they cannot be adjusted to accommodate related, but distinguishable names for biologics. For example, the WHO Anatomical Therapeutic Chemical (ATC) codes are used to communicate relationships among therapeutics for purposes of drug usage research, but are also used for other purposes.[186] For the erythropoeisis stimulating agent class of therapeutics the ATC Level 5 code B03XA01 includes all of the differentially named short acting epoetins in Europe (epoetin alfa, epoetin beta, epoetin theta, and epoetin zeta) as well as other epoetins sold elsewhere.[187,188] Indeed, this ESA ATC Level 5 code is often used for the purposes of defining the scope of tenders in European markets, and thus it is this ATC code that directly facilitates competition irrespectively of the distinguishable names for short acting epoetins.

Payers are presumably sensitive to the potential implications of differentiated names to competition. Nevertheless, a recent survey of U.S. based private payers indicated that a majority of respondents support differentiated names for biosimilars (i.e. the same INN but with an extra detail to show it is a biosimilar); in that same survey, a majority of US and EU based specialists who prescribe biologics support differentiated names for biosimilars.[189]

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http://www.biocenturytv.com/player/3203440019001/3197851279001 ("You don't want to have to force companies to have proprietary brand names [such] that they have to build large sales forces.").

[186] *See* WHO Collaborating Center for Drug Statistics Methodology, ATC Structure and Principles, http://www.whocc.no/atc/structure_and_principles/ (accessed Feb. 22, 2014).

[187] WHO Collaborating Center for Drug Statistics Methodology , at http://www.whocc.no/atc_ddd_index/?code=B03XA01&showdescription=yes (last visited Feb. 25, 2014).

[188] *See* list of epoetin brands included in B03XA01, The-medication.com. , Drug information, http://www.the-medication.com/?cat=atc&s=B03XA01 (accessed Feb. 25, 2014).

[189] *See* BioTrends Research Group, Biosimilars Advisory Service, US and EU Payer Perspectives 104 (July 2013) (Only 7% of 60 payers surveyed believed biosimilars should have identical names to the reference products, with the

While it is not possible to draw conclusions about the historical impact of naming on generic uptake in the United States, it is possible to evaluate the relevance of naming to uptake of biosimilar products in other markets. Biosimilar products with distinguishable names have been licensed in several developed economies including Europe, Japan and Australia. These regions also include classes of biosimilars sharing the same non-proprietary name, so it is possible to perform some comparison of market uptake in these settings.

It is important to note that a legal framework that proactively allows for automatic pharmacy substitution does not exist in any of those regions[190], and that biosimilars are associated with brand or trade names and are marketed to prescribers and payers on the basis of value (including price). In this context, there are many confounding variables impacting market uptake, including whether the biologic is used in acute or chronic care, the existence of multiple non-reference product competitors, and a diversity national and regional coverage and reimbursement policies.[191]

Australia represents a situation where uptake of biosimilars may be compared between product classes with shared non-proprietary names (e.g., filgrastim) and with distinguishable names (e.g., epoetin). Such comparisons will always have the caveat that filgrastim is generally used in acute care for chemotherapy support, whereas epoetin is used in both acute care and chronic care settings. The latter will tend to lag in uptake, because practitioners and payers are more reluctant to switch patients who are stable on a biologic critical to the maintenance of their health (e.g., anemia management for chronic renal failure).

We have examined the market uptake dynamics for filgrastims and epoetins in Australia and see no compelling evidence that the distinguishable names for epoetins have impeded competition. The comparisons in Australia are very time sensitive because the uptake of biosimilar epoetin lambda initially lagged for several years before rapidly accelerating in 2013. A fair-minded analysis of the factors impacting the initial uptake of the biosimilar Novicrit® (epoetin lambda) from 2010 to 2012 would take into account the marginal reimbursement incentives for use of the lower cost product and a somewhat unfavorable product label.[192]

Nevertheless, in the most recent quarter for which data are available (Q4, 2013) the uptake of Novicrit® reached 27.0% unit share relative to its reference product (up from 1.3% in the Q3 of

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vast majority (78%) believing they should have similar names, "i.e. the same INN but with extra detail to show it is a biosimilar." (What is your opinion on how biosimilar molecules should be named (non-proprietary names)?) .

[190] Many countries in the EU simply prohibit pharmacy-level substitution, thus requiring the pharmacist to obtain consent for a biosimilar from the physician. Recently passed legislation in France, however, allows patient initiation with biosimilars on a limited basis and does require that the pharmacist communicate to the physician the exact product dispensed.

[191] *See* Grabowski H et al., Biosimilar competition: Lessons from Europe, Nature Reviews Drug Discovery. Published online 21 Jan. 2014; doi:10.1038/nrd4210 (Jan. 2014).

[192] The Australian reimbursement review concluded that Novicrit was not therapeutically interchangeable with other products in the class, because "… epoetin lambda can only be administered intravenously, whereas the other PBS-subsidised erythropoiesis stimulating agents can be administered intravenously and subcutaneously, and the subcutaneous route of administration accounts for a significant proportion of use of the PBS-subsidised erythropoiesis stimulating agents. This means that these drugs are not sufficiently similar in their clinical use." *See* PBAC Public Summary Document (July 2010), http://www.health.gov.au/internet/main/publishing.nsf/Content/22C8C4368FC0D8C1CA257BF0001D7BE7/$File/Epoetin%20lambda%20NOVICRIT%20Novartis2.pdf.

2012).[193] This compares with the uptake of the leading biosimilar filgrastim (Nivestim®) which in Q4 of 2013 reached a cumulative 22.3% unit share relative to its reference product, Neupogen®, and other biosimilars. Cumulatively, the three biosimilar versions of Neupogen® in Australia reached 31.9% unit share of the market with these biosimilars and their reference product in the same quarter.[194]

These uptake figures may also be compared with the more mature European markets where a study commissioned by the EC showed that biosimilars from three classes (somatropins, filgrastims, and epoetins) achieved 19.2% overall uptake relative to their reference products in the 12 months leading up to June 2011.[195] Another analysis of European sales data through Q4 of 2011 showed that biosimilar epoetin uptake in France, Italy and the UK did not exceed 20% of the epoetin alfa market segment while uptake of biosimilar filgrastims in these countries ranged from 45% to 87% by the end of 2011.[196] Thus, uptake of biosimilar epoetins in Europe was generally lower than uptake of filgrastims, and this was attributed by Grabowski to "both medical considerations and reimbursement policies."[197]

These data show that the 2013 market share of epoetin lambda in Australia was commensurate with the 2011 market share of epoetin biosimilars in Europe. (This is fair basis of comparison given time lag in approvals between EU and Australia). Furthermore, the slower uptake of biosimilar epoetins relative to filgrastims in Australia is directionally aligned with the relatively slower uptake of epoetins in Europe. Therefore, there is no obvious deficit in uptake of biosimilar epoetin lambda in Australia and the evidence does not support that uptake of this product has been impacted by its non-proprietary name.

Biosimilar competition in Japan has been very successful by the above-mentioned European and Australian benchmarks, notwithstanding Japan's practice to emphasize distinguishable names. After launching in 2010, biosimilar epoetin kappa (epoetin alfa BS1) achieved 65% value market share in 2012 relative to its reference product, ESPO (epoetin alfa).[198] These data illustrate that distinguishable nomenclature does not impede competition, and that other market forces and coverage and reimbursement policies dominate.

Finally, while Europe has generally acceded to the use of the same INN for biosimilar and reference products, there is one exception that can serve as a comparator. Retacrit® (epoetin zeta) was authorized by EU in 2007 as the second biosimilar to epoetin alfa. The Retacrit® sponsor has described isolated situations where tendering in 3 markets (Romania, Spain and Italy) was restricted only to the products named "epoetin alfa." A more detailed understanding of how epoetin tenders are normally structured in Europe, and as that relates to these markets, shows that any inference between distinguishable naming and market exclusion is overstated.

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[193] Amgen analysis based on IMS data.
[194] *Id*.
[195] Euopean Commission, What you need to know about Biosimilar Medicinal Products, Consensus Information Paper 2013 (2013) at Figure One (showing 11% biosimilar market share and 46% reference product market share (with 43% share from non-reference products which should be excluded from the analysis for a direct comparison between markets)).
[196] *See* Grabowski H et al., Biosimilar competition: Lessons from Europe, Nature Reviews Drug Discovery. Published online 21 Jan. 2014; doi:10.1038/nrd4210 (Jan. 2014).
[197] *Id*.
[198] EvaluatePharma Sales Data, accessed Nov. 21, 2013.

The evidence across Europe suggests that tenders for biologic medicines are customarily held at ATC Level 5 (namely, all short-acting ESAs without reference to INN) and, less commonly, at ATC Level 4 (all ESAs, including short-acting and long-acting without reference to INN). Importantly, ATC coding has no relationship to INN. Even if a sponsor can point to individual tenders in the past that have been constructed on other principles, it is difficult to see how such past incidences can be generalized given how tendering policy has evolved over the past years in Europe.

In order to be included in tender negotiations, a sponsor must ensure both a current regulatory approval (EMA centralized or Member State mutual recognition) and approved reimbursement status. Romania has implemented changes within its Ministry of Health and a new reimbursement list is under development. It is likely that sponsors have been unable to finalize reimbursement status that serves as a pre-requisite for tendering bids in the country.

In both Spain and Italy, the legal and policy basis of tenders has been evolving over recent years, but there is little evidence that naming has been central to this policy evolution. In Italy, tenders for ESAs operate principally at the ATC Level 5 level and thus include biosimilars and multiple reference products.

From Amgen's own experience in Spain, tender groups for ESAs currently refer to product INN but include multiple INNs sharing common root names (i.e. epoetin alfa, epoetin beta, epoetin theta, epoetin zeta as well as long-acting ESA products such as darbepoetin alfa). In a recent tender in Spain, epoetin alfa was not accepted for consideration demonstrating the multivariate acceptance criteria.

In conclusion, there may be isolated EU tenders that can be identified which have excluded products; however this is invariably the result of local processes including regulatory approvals, national reimbursement status, ATC codes and clinical datasets rather than any systematic policy decision that ties tender design to non-proprietary naming. Thousands of tenders are held across Europe each year, many at regional and local levels; it is always possible to identify a small number of tenders that are not appropriately designed or conducted. Whilst the legal and policy framework for tenders continues to evolve at European, national and regional levels, Amgen sees no evidence that naming policy plays any significant role.

Indeed, with the possible exception of poorly structured tenders that also disadvantaged other legitimate competitors, there is no compelling evidence that the existence of a distinguishable INN has impacted the competitive position of the biosimilar epoetin zeta in Europe. The biosimilar epoetin alfa recently withdrew from the UK market leaving epoetin zeta as the only biosimilar competitor there.

III. Questions related to Biosimilar Competition in the United States and in Other Countries

III.1. What, if any, predictions made in the FTC's 2009 FOB Report should be revised in light of more recent data available on approved biological products or biosimilar development programs?

Key points

- The 2009 FOB report says biosimilars cost $100M-$200M to develop; that cost estimate is low.
- The 2009 FOB report says only two to three companies will seek approval of a biosimilar for a given reference product; while that estimate is true for some reference products, more recent reports indicate that up to 10 companies may be interested in developing a biosimilar of any given reference product that is available in the US.
- The report also assumes only "large companies with substantial resources" will develop biosimilars; we have already seen many creative partnerships arise that contradict this conclusion.
- The report claims that a lack of automatic substitution will slow uptake of biosimilars; a recent statement from Express Scripts and experience in Europe contradict this assertion.

The 2009 FOB report estimates regarding the cost to develop a biosimilar are low.

Estimates for development cost must be upwardly adjusted to account for inflation. Using the GDP Deflator,[199] translating the FTC's original estimate into 2013Q4 dollars would increase the cost of biosimilar development to $107M-$214M for development. According to Sandoz, the cost of developing a generic small molecule is around $2-3 million, whereas biosimilars have been estimated to cost around $100-250 million to reach approval, largely due to the clinical studies and comparability exercise required to demonstrate biosimilarity.[200]

The 2009 FOB report says only two to three companies will seek approval of a biosimilar for a given reference product; while that estimate is true for some reference products, we are seeing up to 10 companies developing a biosimilar of any given reference product that is available in the US.

While many companies are developing biosimilars for the U.S. market, there are many more companies who are developing biosimilars for other regions that may choose to attempt development for the U.S. market. For example, one article lists as many as 11 developers of a biosimilar version of Rituxan.[201] BioTrends' 2013 analysis found 28 developers of a biosimilar version of Rituxan, 29 developers of a biosimilar version of Herceptin, 17 developers of a biosimilar version of Enbrel, 15 developers of a biosimilar of Avastin, 13 developers of a biosimilar version of Humira, and 12 developers of a biosimilar of Remicade.[202] It is unclear at

[199] Federal Reserve Bank of St Louis, Gross Domestic Product: Implicit Price Deflator (GDPDEF) (Jan. 30, 2014), http://research.stlouisfed.org/fred2/series/GDPDEF/.
[200] Novartis website, http://www.novartis.com/innovation/focused-diversification/differentiated-generics.shtml (accessed Feb. 26, 2014).
[201] Biosimilars: 10 Drugs to Watch,. Genetic Engineering & Biotechnology News (April 29, 2013), http://www.genengnews.com/insight-and-intelligence/biosimilars-10-drugs-to-watch/77899804/.
[202] BioTrends Research Group (March 2013).

this time how many of these developers will successfully gain FDA approval, but even if a small percentage is successful, the number of entrants will be well above "two to three."

The report also assumes only "large companies with substantial resources" will develop biosimilars; we have already seen many creative partnerships that contradict this conclusion.

Hospira (a generics and biosimilars company) signed an agreement with NovaQuest (a private equity firm) to develop biosimilars of three products.[203]

Hospira also has a long-established partnership with Celltrion (formerly a contract manufacturing organization) to develop biosimilar mAbs, the first of which was granted marketing authorization by the European Commission on 9/10/2013.[204]

Coherus Biosciences (a startup only established in 2010[205]) announced a partnership with Baxter (a diversified healthcare products company with over 50,800 worldwide employees[206]) on 9/3/2013 to develop and commercialize a biosimilar version of etanercept.[207]

Momenta (a company with a market capitalization of only $1B) is developing a portfolio of up to six biosimilars in collaboration with Baxter[208] and one on its own.[209]

In Europe, most biosimilars products have been successfully marketed via co-marketing partnerships involving 2 to 4 companies pooling their resources and expertise.[210] It is reasonable to expect that such companies and others will display similar levels of creativity and flexibility for accessing the U.S. market.

[203] Press Release, NovaQuest Capital Management, Hospira and NovaQuest Co-Investment I, L.P. Enter Into Collaborative Arrangement (April 29, 2013), http://www.novaquest.com/hospira-and-novaquest-co-investment-i-l-p-enter-into-collaborative-arrangement/.

[204] EMA, Remsima/Inflectra EPARs (Sept. 2013), http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002576/WC500150872.pdf.

[205] Coherus Biosiences, Company story, http://www.coherus.com/about-us/company-story/ (accessed Feb. 25, 2014).

[206] Baxter, Corporate overview, http://www.baxter.com/about_baxter/company_profile/corporate_overview.html (accessed Feb. 25, 2014).

[207] News Release, Coherus Biosciences, Hospira and NovaQuest Co-Investment I, L.P. Enter Into Collaborative Arrangement (Sept. 3, 2013), http://www.coherus.com/press-releases/baxter-and-coherus-biosciences-announce-collaboration-to-develop-and-commercialize-biosimilars/.

[208] Momenta, Biosimilars and Potentially Interchangeable Biologics: Development Program, http://www.momentapharma.com/pipeline/development-program.php (accessed Feb. 25, 2014).

[209] Momenta Form 8-K, filed 12/20/13 (http://ir.momentapharma.com/secfiling.cfm?filingID=1104659-13-91364&CIK=1235010.

[210] *See* EMA, European Public Assessment Reports (EPARs), http://www.ema.europa.eu/ema/. For example, the molecule developed as XM-02 is currently marketed in Europe as Tevagrastim (by Teva), ratiograstim (by ratiopharm), and Biograstim (by CT Arzneimittel) and at one point was also marketed as Filgrastim ratiopharm (by ratiopharm). As another example, the molecule developed as CT-P13 is currently marketed in Europe as both Remsima (by Celltrion, Egis, and Orion Pharma) and Inflectra (by Hospira).

The report claims that a lack of automatic substitution will slow uptake of biosimilars; a recent statement from Express Scripts and experience in Europe contradict this assertion.

Specifically, the 2009 report says, "The lack of automatic substitution between an FOB product and a pioneer biologic drug will slow the rate at which an FOB product can acquire market share and thereby increase its revenues." Of note, the 2009 FOB report was written in a context of a pathway that did not include provisions for approval of an interchangeable biologic, meaning that the 2009 FOB report could not fully assess the impact of the BPCIA including a pathway for FDA to approve an interchangeable biologic and the substitution that accompanies such an approval.

In a December 2013 research note, Ronny Gal (Bernstein Research) summarized Express Scripts' position as follows: "**It does not take substitution.** Express [Scripts] relies on P&T committee of independent experts to tell it what it needs to cover (e.g. differentiated medicine or two of the following five drugs in less differentiated categories). Within the parameters set by the P&T, it has room to make choices. Biosimilars will act as low cost brands with the P&T committee giving PBM's a choice which product to cover." The same note also elaborated that Express Scripts' chief trade relations officer, Everett Neville, "[i]s reasonably confident payor efforts to block specific drugs will be successful, with most existing and virtually all new patients transitioned to the preferred drugs."[211] While some payors will be able to drive biosimilars uptake through utilization management techniques, broad uptake of biosimilars will be successfully driven by physician and patient acceptance, not automatic substitution (as also discussed in section III.3 below).

Furthermore, experience in Europe (although not directly applicable to expectations for the US) calls into question the report's claim. Automatic substitution is neither allowed nor practiced on any substantial scale in any of the 28 EU Member States.[212] Despite this lack of automatic substitution, biosimilars have achieved—in a relatively short period of time—substantial market shares, in some cases even higher than the share of the original reference product.[213]

III.2. What has been the competitive effect of the market entry of biosimilar competitors in countries with drug regulatory approval standards comparable to those of the U.S. FDA, such as the EU, Australia, or New Zealand? After such entry, have reference biologic manufacturers lowered their prices, offered discounts, engaged in enhanced marketing activities, or increased innovation or next-generation developments?

Key points

- A European Commission report says biosimilars in Europe have been successful without interchangeability or allowing pharmacists to overturn physicians' decisions.

[211] Gal A et al., Biosimilars: Notes from Long View on Biosimilars Conference; Moving Beyond Regulatory - Heading into Commercialization, Bernstein Research (Dec. 13, 2013) (emphasis in original).
[212] *See Supra* note 192.
[213] Press Release, Sandoz, Zarzio® overtakes Neupogen® and Granocyte® to become most prescribed daily G-CSF in Europe (July 22, 2013), http://www.sandoz.com/media_center/press_releases_news/global_news/zarzio_reg_overtakes_neupogen_reg_and_granocyte_reg_to_become_most_prescribed_daily_g-csf_in_europe_.shtml (stating "Zarzio® (filgrastim) has become the first biosimilar to overtake both its reference product (Amgen's Neupogen®) and European market leader (Chugai's Granocyte®) and is now the most prescribed daily G-CSF in Europe and the #1 biosimilar daily G-CSF globally.").

- Sales impact from biosimilars—like that of generics—is not uniform across Europe: varying by brand, country, and distribution channel.
- At this stage, one cannot establish a causal relationship between the arrival of biosimilar medicines and biotechnology innovation, because biosimilars are new relative to the timeframe of biotechnology innovation.

A European Commission report says biosimilars in Europe have been successful without interchangeability or allowing pharmacists to overturn physicians' decisions.

"Overall, biosimilar medicines are starting to provide the benefits that they were expected to bring – giving physicians and patients an additional treatment option while affording payers a broader range of tools to better manage healthcare expenses."[214] Experience in Europe, where biosimilars have been on the market the longest, demonstrates that price competition has increased as additional products become available. It is worth noting that this occurs without designation of interchangeability or approval of automatic substitution.

Sales impact from biosimilars—like that of generics—is not uniform across Europe: varying by brand, country, and distribution channel.

While IMS data do not cover all distribution channels or net prices (i.e., including discounts), an IMS study commissioned by the European Commission found wide variances in uptake of biosimilars in the channels covered across both countries and therapeutic categories, ranging from 0% to 94% market share.[215] Importantly, such variation across European countries in terms of biosimilar market penetration is not fundamentally different than the variations seen in terms of generic penetration. Even though biosimilar uptake in Europe has varied from country to country (i.e., due to the fragmented and variable nature of the European market), we know from the much more extensive adoption of generics in the U.S. as compared to Europe that uptake and/or variation in uptake from Europe is likely not directly predictive of experience in the US.

At this stage, one cannot establish a causal relationship between the arrival of biosimilar medicines and biotechnology innovation because biosimilars are new relative to the timeframe of biotechnology innovation.

Biosimilars have only been on the market in Europe since 2006 and are not yet available in the world's largest drug market (the US), while drug discovery and development typically takes on the order of 15 years. For example, Amgen's second generation versions of epoetin alfa and filgrastim preceded the approval of the first-generation biosimilars in Europe by more than 10 years. Furthermore, because biosimilars have to date only been approved in Europe for a small

[214] European Commission, What You Need to Know about Biosimilar Medicines: Process on Corporate responsibility in the Field of Pharmaceuticals Access to Medicines in Europe, Consensus Information Paper 2013 (2013), http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/biosimilars_report_en.pdf.
[215] IMS, Biosimilar accessible market: Size and biosimilar penetration (April 2012)(*see,* e.g., pages 28, 30, 32), http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/biosimilars_imsstudy_en.pdf.

set of reference products,[216] correlations between arrival of a biosimilar and originator innovation are limited in number and only anecdotal.

III.3. Are there empirical models that could predict the nature of U.S. biosimilar or interchangeable biologics competition based on existing biologic product competition in Europe, Australia, New Zealand, or other countries? Are there empirical models that could predict the nature of U.S. biosimilar or interchangeable biologics competition based on existing competition in specialty drug markets? What factors increase or detract from robust competition between reference biologic and biosimilars or interchangeable biologics in other countries?

Key points

- While there are no empirical models for biosimilars uptake in the US, Milliman has developed an actuarial model to understand the effect of biosimilars on employers' healthcare costs.
- Our experience across European markets has informed Amgen that physician and patient education is a critical success factor in fostering a successful biosimilars market.

There are no empirical models for biosimilars uptake in the US, because the dynamics of such a market are unprecedented.

Frank Kopenski (of Milliman, Inc.) developed an actuarial model to understand the effect of biosimilars on employers' healthcare costs and found that total healthcare costs could decrease by between 0.1%-0.6% due to biosimilars uptake, depending on certain assumptions. This actuarial model is not designed to predict the overall U.S. biosimilars market.[217] There are other examples of models[218] that have been published outside of the peer-review system, but these largely lack transparency (e.g., in the percentage of patients who would take a biosimilar), have verifiable factual errors (e.g., in the number of biosimilars approved in Europe), and reach conclusions that are well outside the mainstream (e.g., that biosimilars will lead to a 67% savings).

Our experience across European markets has informed Amgen that physician and patient education is a critical success factor in fostering a successful biosimilars market.

In drawing lessons from biosimilars market experience in the EU, it is important to note that unlike payors in Europe, the majority of U.S. payors do not have enough dominance in their respective geographic markets or networks to be able to unilaterally and absolutely drive physician prescribing behavior. In other words, while some payors will use formulary management techniques to drive prescribing behavior, the majority of U.S. patients are covered

[216] To date, biosimilars have been approved in Europe in five therapeutic/molecular classes. Four of these classes are regulated as biologics by the PHSA in the US (ESAs, G-CSFs, anti-TNF mAbs, and FSH), and one of these classes (hGH) is regulated by the FDC&A biologics in the US.

[217] Kopenski, F, Milliman, Understanding biosimilars and projecting the cost savings to employers (Dec. 2011), http://us.milliman.com/uploadedFiles/insight/health-published/understanding-biosimilars.pdf. (Please note that, although this study was commissioned by Amgen, the author remained independent and exercised total editorial control.)

[218] *E.g.*, Frazee S, Garavaglia S, Houts J, Express Scripts, Ten-Year Potential Savings from Biosimilars in California (Sept. 26, 2013), http://www.gphaonline.org/media/cms/Biosimilars_CA_white_paper_092613.pdf.

by payors who use formulary management techniques to only shape prescribing behavior. Thus, for the majority of U.S. patients, their physicians still retain at least some ability to make the most appropriate medical decisions for each patient. Because of these cases reflecting the majority of patients, our research suggests physician/patient education on the merits of biosimilars will improve the present value (i.e., the cumulative sum of future sales, discounted to reflect their current value) of the biosimilars market by 13-22%.[219] In other words, while payors will take measures to encourage uptake of biosimilars, we expect that successful uptake of biosimilars will also rely upon physician and patient acceptance through education.

III.4. Based on the experiences in other countries, does competition from biologics influence investments in research and development for new biologics, improvements to existing biologics, and the timing and rollout of new and/or improved biologics? Does the market experience with generic drugs provide insights into these issues.

Key points

- Because research and development for biologics is global, one cannot look to "other countries" for experience to determine a correlation between competition and development.
- Globally speaking, competition from biosimilars does not reduce innovation or the continued investment in new biologics.
- The experience with generic drugs in the U.S. provides only limited insight into the likely dynamics between biosimilars uptake and biologics innovation.

Because research and development for biologics is global, one cannot look to "other countries" for experience to determine a correlation between competition and development.

Biologics development is expensive (greater than $1B per molecule[220,221,222]) and time consuming (on the order of 15 years per molecule), so innovative companies rarely develop a biologics medicinal product for just one country or even region. Rather, innovators discover and develop biologic medicines and then sell these medicines in various countries and generally seek to reach as many markets as possible.

Globally speaking, competition from biosimilars has no apparent impact on innovation or the continued investment in new biologics.

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[219] This unpublished analysis was conducted by IMS and commissioned by Amgen and is based on a combination of market research, historical European adoption dynamics, and best credible assumptions about how adoption will take place in the US. For example, IMS market research suggests approximately 87% of US lives are covered by plans that have a stated desire to manage biosimilars but lack sufficient control to use the most strict of utilization management techniques to mandate biosimilars adoption without physician consent.

[220] $1.3B, according to Eli Lilly in 2012. *See* https://lillypad.lilly.com/entry.php?e=1424, accessed 2/14/2014.

[221] $4B-$11B, according to Matthew Herper of Forbes in 2012. Herper M., The Truly Staggering Cost Of Inventing New Drugs, Forbes.com LLC (Feb. 10, 2012), http://www.forbes.com/sites/matthewherper/2012/02/10/the-truly-staggering-cost-of-inventing-new-drugs/.

[222] The cost is an estimated $1.2B for a biologic, according to Tufts Center for the Study of Drug Development in 2006. *See* Tufts Center for the Study of Drug Development, Research Milestones: Research Milestones, Drug Policy and Strategy Analyses to Inform R&D and Strategic Planning Decisions, http://csdd.tufts.edu/research/research_milestones (accessed Feb. 25, 2014).

Amgen is a good example of a company that is committed to R&D both to advance new originator medicines and to develop biosimilars.

The health care market is very different today from when generic drugs first entered. Some have suggested that prior to the arrival of generic competition, investment in innovation was less than robust. Whether or not that suggestion bears out, it is clear that investment in biotech innovation is significant today. Furthermore, competition among innovators is robust, and subsequent innovative products are able to challenge the first-in-class products for market share.[223] Biosimilars are simply another competitor in a tightly cost-constrained economic environment. Limited resources make expanding R&D efforts beyond their current levels unlikely, regardless of how many new competitors enter. Thus, the implications of biosimilar competition are very different from what some suggest occurred after the arrival of generic drugs.

It is worth noting that the development of biosimilars is itself innovative. The learnings gained by developing highly similar and/or interchangeable biosimilars may inform subsequent development of new products and improvements on existing products.

The experience with generic drugs in the U.S. provides only limited insight into the likely dynamics between biosimilars uptake and biologics innovation.

If you only need to invest approximately $10 million to get a fully therapeutically equivalent generic, the small size of that investment shapes generic pricing, uptake, and the residual value of innovator brand equity (and value of any marginal innovation) in a particular way. Generics can be priced very low and need not recoup much absolute return on investment, so there is little incentive for any party to differentiate or innovate within the non-patent protected segment of the market.

If you need to invest approximately $100-250 million to develop a biosimilar, and an additional amount to develop an interchangeable biologic, the biosimilar uptake and resulting originator innovation behavior will follow different dynamics. Biosimilar developers may decide that differentiating a biosimilar affords opportunities to compete both with the innovator and other biosimilars developers and thus provides a better return on their investment than pursuing interchangeability. For biologics administered in a physician's office or hospital outpatient setting (i.e., the majority of currently marketed biologics), interchangeability might only be used as a differentiator to obtain preferred prescribing and formulary status, rather than to drive automatic pharmacy substitution per se. Originators will continue investing in their brands because of higher residual value. All of these possibilities will likely lead to the U.S. biosimilars market having a very different dynamic than the U.S. generics market.

[223] Anti-TNFs embody this competition. Enbrel was FDA approved in 1998, while Humira wasn't approved until 2002. FDA, Drugs @ FDA, http://www.accessdata.fda.gov/scripts/cder/drugsatfda/) (accessed Feb. 25, 2014).

III.5. What data or empirical evidence exist in Europe or other countries regarding immunogenicity or other serious adverse events, if any, caused by substitution or switching between biosimilar and reference biologics?

Key points

- No ICH country other than the U.S. has adopted a legal framework that proactively allows for pharmacy-level automatic substitution of biosimilar medicines.
- Because only few biosimilars have been approved in highly regulated markets, the absence of large-scale immunogenicity concerns made evident by switching among biosimilars and their reference product is not instructive.
- Immunogenicity is a concern common to all biologics.
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Aside from the section of U.S. law allowing FDA to approve an interchangeable biologic, no ICH country has adopted a legal framework that proactively allows for pharmacy-level automatic substitution (i.e., as we know it in the U.S.) of biosimilar medicines.

In fact, a dozen European countries have laws in place explicitly prohibiting automatic substitution of biologics. To date, no biosimilars have been approved in any highly-regulated market that would allow for substitution of the reference product during a course of therapy without the physician's consent.

Because only few biosimilars have been approved in highly-regulated markets, the absence of large-scale immunogenicity concerns made evident by switching among biosimilars and their reference product is not instructive.

Europe is the highly regulated market that has seen the most biosimilar entrants and competition. Prior to 2014, the European experience has been primarily with three product classes, of which two (somatropins and filgrastims) have not been historically associated with serious class-based or serious product-specific immunogenicity issues. Therefore, absence of evidence of large-scale switching issues with these two product classes over the course of their limited off-patent experience is not necessarily a surprise and is not instructive of the broader policy questions.

Importantly, even in the case of somatropins, the European Commission notes in their consensus report on biosimilars, "Work has been done on switches from an originator reference medicine to a biosimilar medicine that was undertaken by Skåne University Hospital (Malmö, Sweden) in 2009. Ninety-eight pediatric patients who were receiving human growth hormone were selected for a switch from a reference medicine to a biosimilar medicine, out of a larger population of 130 patients. 15 children experienced an adverse event in the course of the switch (most commonly pain at the injection site), though none were deemed "serious" by hospital personnel. Four children were switched back to the originator reference medicine."[224]

[224] European Commission, What You Need to Know about Biosimilar Medicines: Process on Corporate responsibility in the Field of Pharmaceuticals Access to Medicines in Europe", Information Paper 2013 (2013), http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/biosimilars_report_en.pdf.

The third class of European biosimilars (epoetins) is more susceptible to serious immunogenicity issues, as evidenced by clusters of severe immune-induced anemia in Europe in 1998-2002 and in Thailand in the mid- 2000's.[225,226] There is no evidence in Europe that carefully controlled switching among commercially approved biosimilars and reference product epoetins has caused problems, but it is noteworthy that Europe experienced a situation in which two clinical trial patients who were being treated with a biosimilar epoetin acquired neutralizing antibodies due to a manufacturing problem specific to the biosimilar product.[227] That biosimilar epoetin is currently marketed with a restricted condition of use (omitting the most immunologically sensitive subcutaneous route of administration). Therefore, Europe's experience with switching of biosimilar epoetins under immunologically sensitive conditions of use has really been limited to the single other biosimilar (epoetin zeta). Epoetin zeta includes the subcutaneous route of administration on its label.[228]

In the context of its experiences with the 1998-2002 epoetin immunogenicity cluster and the "near miss" with the biosimilar clinical trial (described immediately above), the EU recently recognized inadequate pharmacovigilance was a potential problem and has adopted new provisions to address this problem.

Immunogenicity is a concern common to all biologics.

The outbreak of PRCA in Europe in 1999-2001 wasn't attributed to switching but does illustrate that immunogenicity issues may not be clinically manifested until 6-67 months after a patient initiates therapy with the causative biologic.[229] Broadly speaking, immunogenicity concerns with biologics can be due to the biological medicinal product, the patient, or both. Furthermore, immunogenicity of biosimilars will be important to understand long-term post-approval, since the clinical data and experience in a biosimilar development program is both abbreviated relative to the experience with a marketed reference product and is not expected to be evaluated in all indications for which the biosimilar may be approved.

[225] Casadevall N et al., Pure Red-Cell Aplasia and Antierythropoietin Antibodies in Patients Treated with Recombinant Erythropoietin, New England J. Medicine 346:469 (2002).
[226] Fotiou F et al., Impact of illegal trade on the quality of epoetin alfa in Thailand, 31 CLIN. THERAP. 31:336, 337 (2009).
[227] Seidl A et al., Tungsten-Induced Denaturation and Aggregation of Epoetin Alfa During Primary Packaging as a Cause of Immunogenicity, Pharmaceutical Research 29:1454 (2012).
[228] *See* EMA, Retacrit EPAR Variation Assessment Report 4 (June 23, 2011), http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000872/WC500116652.pdf (noting the prior approval of the SC route of administration for indications of renal anemia).
[229] Casadevall N et al., Pure Red-Cell Aplasia and Antierythropoietin Antibodies In Patients Treated with Recombinant Erythropoietin, N Engl J Med, 346:469 (2002).