Biotechnology Industry Organization

January 31, 2014

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

Re: Docket No. FDA–2013-P-1153: BIO Comments to Generic Pharmaceutical Association Citizen Petition Requesting the Food and Drug Administration to Implement its INN Naming Policy Equally to all Biologics

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) respectfully submits these comments in response to the Generic Pharmaceutical Association (GPhA) Citizen Petition requesting the Food and Drug Administration (FDA) to "implement its INN naming policy equally to all biologics" and to require "all biologics approved under the Section 351(k) pathway…share the same INN [International Nonproprietary Name] as the RPP [reference protein product]" (the GPhA Petition).[1]

BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

The introduction of biosimilars into the marketplace raises novel and complex questions of science and law, and requires the updating of legal and regulatory frameworks to support overall public health and patient safety. BIO believes that a nonproprietary naming convention that ensures distinguishable product identification of all biological products best facilitates pharmacovigilance, ensures accurate attribution of adverse events to the right product, prevents inappropriate substitution and unintended switching, and supports tracing of products in the event of a recall; and thereby enhances patient safety. Accordingly, BIO respectfully requests that FDA deny the GPhA Petition.

Summary

For more than a decade, BIO has called for an open, transparent, and science-based dialogue regarding biosimilars. Many of our members are global leaders in the

[1] GPhA Citizens Petition, FDA Docket No. FDA–2013-P-1153. Available at http://www.regulations.gov/#!documentDetail;D=FDA-2013-P-1153-0001.

1201 Maryland Avenue SW
Suite 900
Washington DC 20024
202.962.9200 P
202.488.6306 F
bio.org

development and commercialization of biosimilars. BIO played a leading role in the effort to establish a statutory approval pathway for biosimilars. BIO supported the Biologics Price Competition and Innovation Act (BPCIA), which appropriately recognizes that biosimilars are not generic drugs, and, accordingly, carefully calibrates the goal of increasing access to medicines at competitive prices with scientific considerations to ensure the development and approval of safe and effective biosimilar products within a system that instills prescriber and patient confidence.[2] Leading scientific and regulatory authorities around the world have universally determined that treating biosimilars like generic drugs is inappropriate because biosimilars are similar to, but not the same as, their reference products.

Contrary to the GPhA Petition, we believe that a system that assigns the same name to products that are similar, but not the same, would create confusion for physicians and patients, hinder effective pharmacovigilance, and could jeopardize patient safety. We believe it is possible to craft a nonproprietary naming convention that both contributes to patient safety through enhanced product identification and improves access to medicines at competitive prices. Thus, BIO supports the development of a system under which nonproprietary names of biological products that are similar to each other in structure and function are distinguishable, but morphologically related, and which both prescribers and patients can easily recognize, remember, and report accurately. With appropriate education, such a system would introduce in the mind of the prescriber and patient not uncertainty – as alleged by GPhA – but rather the product identity and clarity that leads to greater prescribing confidence.

The Legal and Regulatory Principles of Biologics and Biosimilars Support Distinguishable Naming

The GPhA Petition mischaracterizes the current state of biologic and biosimilar naming conventions both in the United States and other highly regulated/ICH regions. By way of background, International Nonproprietary Names (INN) identify pharmaceutical substances or active pharmaceutical ingredients. Sponsored by the World Health Organization (WHO), the goal of the INN system "has been to provide health professionals with a unique and universally available designated name to identify each pharmaceutical substance."[3] For biologics, different substances are given different names. For therapeutic proteins, the defining factor in naming is the primary amino acid sequence. If two proteins have the same primary sequence but differ in glycosylation pattern, their names may be supplemented with distinguishable Greek suffixes. WHO

[2] *See*, Pub. L. 111-148 (March 23, 2010) (Patient Protection and Affordable Care Act, Title VII- Improving Access to Innovative Medical Therapies, amending the Public Health Service Act section 351).
[3] World Health Organization, *Guidelines on the Use of International Nonproprietary Names (INNs) for Pharmaceutical Substances*, WHO/PHARMS/NOM 1570 (2007). Available at: http://whqlibdoc.who.int/hq/1997/WHO_PHARM_S_NOM_1570.pdf.

also recognizes that further differentiation may be necessary if other aspects of the substance affect its activity.[4]

The U.S. Adopted Names (USAN) Council and similar bodies in other countries usually adopt the INN as their national drug substance name. The USAN Council is sponsored by the American Medical Association (AMA), the American Pharmacists Association (APhA), the United States Pharmacopeial (USP) Convention, and includes an FDA representative. When a product comes before FDA for regulatory approval, FDA provides an "interim established name" that serves as the nonproprietary name until USP designates an official nonproprietary name by monograph title. Typically, the FDA and USP adopt the USAN, which generally is the INN.

There currently is no international consensus on nonproprietary naming of biosimilars, with naming policies inconsistent at the global level. Japan and Australia have each developed separate and distinct regulations for the approval of biosimilars and nonproprietary naming conventions. The European Medicines Agency (EMA) has allowed biosimilar products to use the same nonproprietary name as the reference product.[5] However, in 2012 the European Commission (EC) introduced a directive requiring EU member states to ensure that biological medicines are clearly identified by name of the product and batch number. It is a legal requirement for European Union Member States to take all necessary measures to clearly identify the biological medicines that are prescribed, dispensed and sold in their country. Member States are empowered to impose implementing requirements on doctors, pharmacists, and other healthcare professionals, including requiring prescribing by brand name.

Japan adopted a separate and distinct nonproprietary naming convention. In Japan biosimilar products are given the same base nonproprietary name as the reference product, followed by the designation "biosimilar" and a number indicating the order in which biosimilars have been approved. Brand names for biosimilars must include the nonproprietary base name followed by the letters "BS" along with dosage form, product strength, and manufacturer.

---

[4] World Health Organization, *WHO Informal Consultation on International Nonproprietary Names (INN) Policy for Biosimilar Products Geneva 4-5 Sept. 2006*, INN Working Doc. 07.211 (2006). Available at: http://www.who.int/medicines/services/inn/BiosimilarsINN_Report.pdf.

[5] EMA procedural advice for biosimilar applications also allows biosimilars to use a different nonproprietary name if merited by INN rules ("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."). European Medicines Agency, *EMA Procedural Advice for Users of the Centralised Procedure for Similar Biological Medicinal Products Applications*, 940451/2011, p. 11. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/04/WC500125166.pdf.

The Australian Therapeutics Goods Administration (TGA) adopted a distinguishable naming system whereby the suffix "sim-" would be added to the nonproprietary name of biosimilar products followed by a three letter code issued by the WHO INN Committee.[6]

The WHO has recognized problems with applying the current INN system to biosimilars, especially as more biosimilars enter the market, including that regulators are likely to run out of Greek letters for glycosylated biosimilars and the use of identical INNs may lead to inadvertent and medically inappropriate switching at the pharmacy. [7] In furtherance of its mandate to ensure clear identification of pharmaceutical substances, both chemical and biological, the WHO continues to discuss and explore the need for a systematic way of identifying biosimilars from different sources. At the WHO 56th Consultation on International Nonproprietary Names for Pharmaceutical Substances (the Consultation) the TGA proposed their system for distinguishable names as a prelude to the closed door meeting held on *Discussion on INN Proposal for Similar Biological Products (SBPs)* attended by biological experts of the INN Expert Committee and representatives from worldwide regulatory agencies.[8]

Given this background, FDA has ample precedent to develop a policy of, and to assign, distinguishable nonproprietary names for biosimilars. Furthermore, FDA has clear authority to do so. Several bills that proposed establishing a biosimilar approval pathway addressed the naming issue, with some calling for biosimilars and their reference products to have identical names and others calling for unique names.[9]

---

[6] Australia Therapeutic Goods Administration, *Evaluation of Biosimilars*, Vol. 1, p. 15 (July 2013). Available at: http://www.tga.gov.au/pdf/pm-argpm-biosimilars.pdf.

[7] It is also worth noting that most regulatory authorities recognize the risks of appropriate substitution of biologic medicines (interchangeability refers to the scientific/regulatory decision made by a regulatory body such as FDA; substitution refers to policies governing dispensing of products at the pharmacy and provider level). Across the European Union (EU), decisions on prescribing, including substitution are made at the national level. Currently, in general, most EU Member States expressly prohibit substitution. In some EU jurisdictions, substitution is usually not permitted because no biologic has been added to the list of medicines that indicates what products pharmacists are required or permitted to substitute. Substitution is permitted in Poland, Denmark and Germany. However, Denmark and Germany restrict substitution to "duplicate biologics" (those identical to each other, manufactured by the same company, and approved on the basis of the same marketing dossier) or "parallel biologics" (identical biologics imported from one member state to another, which are made by the same manufacturer, but marketed by different companies). In Sweden and the UK, where doctors prescribe by brand, substitution is permitted for INN-only prescriptions. France recently passed a law permitting pharmacists to substitute a biosimilar for the prescribed reference product as long as the prescribing physician has not marked the prescription as "non-substitutable." In addition, substitution is only permitted when initiating a course of treatment, and if the biosimilar belongs to the same "group" as the prescribed product. *See*, Allen & Overy, *Biosimilar Substitution in France: No Way Back?* (Jan. 8, 2014). Available at: https://www.aohub.com/aoos/viewContent.action?key=Ec8teaJ9Var1ljrCiNzUiF7eOOGbnAEFKCLORG72fHz0%2BNbpi2jDfaB8lgiEyY1JAvAvaah9lF3d%0D%0AzoxprWhI6w%3D%3D&nav=FRbANEucS95NMLRN47z%2BeeOqEFCt8EGQ%2FHLCIrtYuIY%3D&uid=frsvcLdHNrI%3D&popup=HxapDW%2FMKd4%3D&freersslink=true.

[8] *See*, World Health Organization, *Executive Summary: 56th Consultation on International Proprietary Names for Pharmaceutical Substances Geneva, 15-17 April 2013*, INN Working Doc. 13.335 (Sept. 2013). Available at: http://www.who.int/medicines/services/inn/56th_Executive_Summary.pdf.

[9] *See*, *e.g.*, H.R. 1548, 111th Cong. (2009), § 101(a)(2) & H.R. 5629, 110th Cong. (2008), § 101(a)(2) (requiring FDA to ensure that a biosimilar's labeling has a name that "uniquely" identifies the product); S. 1505, 110th Cong. (2007), §§ 2(a)(2), 3(a)(1) & H.R. 1956, 110th Cong. (2007), §§ 2(a)(2), 3(a) (requiring

Congress rejected both approaches; the BPCIA does not address naming. It thus leaves FDA free to develop a naming convention for biosimilars based on the Agency's existing authority and scientific and public health expertise.

FDA's authority to develop a policy of, and to assign, distinguishable nonproprietary names resides in the FDCA. Section 502(e)(1)(A) of the FDCA provides that a drug (including a biologic) is misbranded unless its label bears the "established name" of the drug.[10] By statute, the "established name" is (per FDCA § 502(e)(3), 21 U.S.C. § 352(e)(3)): (1) the applicable official name that FDA designates pursuant to section 508 of the FDCA; or, if none, (2) the official title of the drug or ingredient in an official compendium; or, if none, (3) the "common or usual name" of the drug.[11] Section 508, in turn, provides 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."[12] Specifically, the Agency may exercise its section 508 naming authority when it determines that (among other things) the USAN or other official or common or usual name "is unduly complex or is not useful for any other reason" *or* no USAN or other official or common or usual name has been applied to a medically useful drug.[13] Also, FDA could deem biosimilar labeling that bore the same non-proprietary name as its reference product misleading and therefore misbranded.[14] FDA may thus exercise its naming authority at its own initiative, in the interest of usefulness, either to change an existing name or to name a product that does not already have a name.

Where an established name as defined in section 502(e) does not already exist, FDA may designate a "provisional" or "interim" established name outside of section 508. In 2006, the D.C. Circuit affirmed FDA's view that "because that statute [FFDCA] is silent as to the result when none of the [section 502(e)(3)] categories is met, it is up to agency to fill the statutory gap."[15] Finding that the categories of established names set out in section 352(e)(3) do not exhaust the potential categories of nonproprietary names, the Court held that "FDA's designation of 'interim' or 'provisional' established names outside the § 352(e)(3) triad appears both consistent with the statutory structure

---

"unique" nonproprietary names for therapeutic protein products); H.R. 1038, 110th Cong. (2007), § 3(a)(2) & S. 623, 110th Cong. (2007), § 3(a)(2) (requiring FDA to designate a name for a biosimilar that is the same as that of its reference product, if the agency designates an official name for a biosimilar under section 508 of the FFDCA).

[10] The PHSA refers to packages marked with a product's "proper name." PHSA § 351(a)(1)(B)(i), 42 U.S.C. § 262(a)(1)(B)(i). FDA has generally treated "proper name" as synonymous with "established name."

[11] FFDCA § 502(e)(3), 21 U.S.C. § 352(e)(3).

[12] FFDCA § 508(a), (c), 21 U.S.C. § 358(a), (c).

[13] FFDCA § 508(c), 21 U.S.C. § 358(c); 21 CFR § 299.4(e).

[14] FFDCA § 502(a), 21 U.S.C. § 352(a) (providing that labeling is misbranded if it is "false or misleading in any particular").

[15] Appellee brief submitted to the D.C. Circuit (May 18, 2005), in *Novartis v. Leavitt*, 435 F.3d 344 (DC Cir. 2006), at 32 ("The district court correctly concluded that, because FDA did not designate an official name pursuant to 21 U.S.C. § 352(e)(3)(A), and because that statute is silent as to the result when none of the categories is met, it is up to agency to fill the statutory gap. FDA did so here by adopting an interim established name.") (internal citations omitted).

and reasonable."[16] An interim name remains in effect until FDA designates a nonproprietary name under section 508 or, absent that, until a nonproprietary name is listed in an official compendium.[17]

Consistent with this naming authority, FDA has designated distinguishable nonproprietary names for biologics.[18] And the Agency implicitly recognized this authority in its October 2010 Notice announcing a Part 15 hearing on implementation of the BPCIA, when it asked for comments on whether, if each biological product were given a unique non-proprietary name, a distinguishing prefix or suffix should be added to the name of a related biological product.[19]

The Science of Biologics and Biosimilarity Supports Distinguishable Naming

Congress, in enacting the BPCIA, recognized that the generic drug legal and regulatory construct is inappropriate for biosimilar products due to scientific differences between the two classes of products. In order to receive regulatory marketing approval, a generic drug application (Abbreviated New Drug Application (ANDA)) must by statute and regulation contain information to show that the proposed drug product is the same as a drug previously approved under section 505(c) of the Federal Food, Drug, and Cosmetic Act (FFDCA) (reference product) with respect to active ingredient(s), dosage form, route of administration, strength, labeling, and conditions of use, among other characteristics, and is bioequivalent.[20] Biosimilars on the other hand are not by definition direct copies of the reference product or of each other in the case of multiple biosimilars of the same reference product. Due to the complex structure of biologics and the associated manufacturing processes, biosimilars, in order to qualify for regulatory marketing approval, must be shown on the basis of analytical non-clinical and clinical data to be "highly similar" to an innovator/reference biologic in terms of structural characteristics with an absence of clinically meaningful differences, understood to mean having equivalent efficacy and non-inferior safety.[21] In fact, minor differences with the active ingredient (e.g., N- or C- terminal truncations or differences in post-translational modifications) are expected and permitted provided that such differences are not expected to affect safety and effectiveness and are justified and explained by the Sponsor.

In addition, most generics are considered therapeutically equivalent (*i.e.,* interchangeable) with their reference product, meaning that the effects of both drugs

---

[16] *Novartis v. Leavitt*, 435 F.3d 344, 352 (D.C. Cir. 2006).
[17] *Id.*; FFDCA § 502(e)(3), 21 U.S.C. § 352(e)(3); PHSA § 351(a)(1)(B)(i), 42 U.S.C. § 262(a)(1)(B)(i).
[18] For example, FDA designated distinct interim names for botulinum toxin biologics (e.g., onabotulinumtoxinA, abobotulinumtoxinA, incobotulinumtoxinA), Zaltrap (ziv-aflibercept), Granix (tbo-filgrastim), and Kadcyla (ado-trastuzumab emtansine).
[19] 75 Fed. Reg. 61497, 61499 (Oct. 5, 2010).
[20] FFDCA § 505(j), 21 U.S.C. § 355(j).
[21] PHSA § 351(i)(2). The biosimilar must also share "the same mechanism or mechanisms of action for the condition or conditions of use prescribed, recommended, or suggested in the proposed labeling" as the reference product. PHSA § 351(k)(2).

are expected to be identical, and, therefore it does not matter, in nearly all circumstances, which drug a patient receives at any given time. This therapeutic equivalence is viewed as a property intrinsic to the "sameness" of the active ingredient, subject to additional requirements relating to the biodistribution attributes of the final dosage form. In contrast, biosimilars are highly similar, but not clinically identical, to their reference products, and as reflected by the two different standards set forth in the BPCIA, interchangeability is not intrinsic to a biosimilar's analytical attributes and the equivalence of biodistribution. Further, FDA may affirmatively designate a biosimilar as interchangeable only after an additional determination that: (1) it can be expected to produce the *same* clinical results as the reference product *in any given patient*; and (2) for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.[22] The scientific and legally distinct standard for interchangeable biologics versus biosimilars means that a non-interchangeable biosimilar is not held to the interchangeability standard in regulatory review and thus one cannot claim that this non-interchangeable biosimilar has the features of an interchangeable biologic.

Accordingly, adopting a generic drug naming convention for biologics – as urged by GPhA – simply fails to recognize these fundamental scientific differences between generic drugs and biosimilars.

The GPhA Petition also does not adequately or accurately address the contextual scientific differences between comparability assessments for manufacturing changes made to an existing biological product and biosimilarity exercises performed to demonstrate the initial quality, safety, and efficacy relationship between a biosimilar and its reference product. A comparability assessment for intra-manufacturer changes is performed to confirm the established safety and efficacy profile of a marketed biological product after well-defined, incremental process changes have been made by the manufacturer, taking into consideration an extensive process and product history linked to clinical experience. Scientific considerations for these comparability assessments, based on the extensive experience of manufacturers and international regulatory authorities, are outlined in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) document entitled, *Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process* (Q5E).[23]

Both the FDA and the EMA note that the scientific principles outlined in ICH Q5E underlie the scientific framework of the biosimilarity exercise.[24, 25] However, FDA and the

---

[22] PHSA § 351(k)(4) (emphasis added).
[23] FDA, Guidance for Industry: *Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process*, (2005).
[24] FDA, Draft Guidance for Industry: *Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product*, p. 3 (2012). Retrieved electronically at:

European Commission also clearly explain that the demonstration of comparability before and after a manufacturing change is a contextually different exercise from the establishment of similarity between two products made by different manufacturers using different cell lines, manufacturing processes, facilities and equipment, the latter of which requiring more extensive and comprehensive data.[26]

A biosimilarity assessment, which is performed to establish the safety and efficacy profile of a biosimilar product derived from an independently designed manufacturing process where no process history exists and a link to clinical experience has to be established, requires comparative quality, pre-clinical and clinical data with a reference product. Members of the Biosimilar Medicinal Products Working Party (BMWP) at the EMA explained:

> …data requirements for the latter [a biosimilar product] are higher [than those of the comparability exercise required for changes in the manufacturing process of a given biological product] and, at least in the EU, always include clinical studies because, due to the completely independent manufacturing processes, some differences between the biosimilar and the reference product can be expected, and the potential impact of these differences on safety and efficacy cannot be predicted from analytical assessment alone...[27]

Similarly, FDA explains:

> Demonstrating that a proposed product is biosimilar to a reference product typically will be more complex than assessing the comparability of a product before and after manufacturing changes made by the same manufacturer. This is because a manufacturer who modifies its own manufacturing process has extensive knowledge and information about the product and the existing process, including established controls and acceptance parameters… Therefore, even though some of the scientific principles described in ICH Q5E may also apply in the demonstration of biosimilarity, in general, more data and information will be needed to establish biosimilarity than would be needed to establish that a

---

http://www.fda.gov/downloads/Drugs/GuidanceCompliance RegulatoryInformation/Guidances/UCM291134.pdf on January 17, 2014.

[25] EMA, Draft *Guideline on Similar Biological Medicinal Products* (CHMP/437/04 Rev 1), (2013).

[26] European Commission, *What you Need to Know about Biosimilar Medicinal* Products, Consensus Information Paper, p. 11 (2013). Retrieved electronically at: http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/biosimilars_report_en.pdf on January 17, 2014.

[27] Weise M, et al., *Biosimilars – why terminology matters*, Nature Biotechnology 29, pp. 690-693 (2011). doi:10.1038/nbt.1936. Retrieved electronically at: http://www.nature.com/nbt/journal/v29/n8/pdf/nbt.1936.pdf on January 17, 2014.

manufacturer's post-manufacturing change product is comparable to the pre-manufacturing change product.[28]

Therefore, based upon the contextual scientific differences of the comparability assessment and biosimilarity exercise, it is entirely consistent to argue that a comparable product produced by the same manufacturer need not be distinguished from its predecessor batches by virtue of non-proprietary naming, while a similar drug substance produced by a different manufacturer should be distinguished from its reference product.

Additionally, the GPhA Petition does not account for the scenario wherein multiple biosimilar or interchangeable biosimilar products share a single reference product. To demonstrate biosimilarity, a step-wise, head-to-head similarity exercise between the putative biosimilar and its reference product is performed, which results in an empirical relationship between the two products. It is important to note, though, that multiple products from different manufacturers may seek and ultimately demonstrate biosimilarity with a common reference product. In this vein, it is critical to note that it is scientifically unjustified to assume with respect to biologics that, if product A is biosimilar to product B, and product B is biosimilar to product C, then product A must also be similar to product C. In the absence of data that directly compares the quality, safety, and efficacy attributes of multiple biosimilars sharing the same reference product, there can be no expectation or conclusion of biosimilarity between those products. Multiple biosimilar products sharing the same nonproprietary name would imply a relationship between those products that would not have been established, which presents a confusing and potentially hazardous situation for patients, prescribers, and dispensers. Therefore, in the event that multiple biosimilar or interchangeable products are available for a single reference product, the need for distinguishable names for all biological products becomes even more important, because biosimilarity or interchangeability will generally have been designated between one reference product and one other product, not among all biosimilars or interchangeable products.

Finally, the GPhA Petition fails to address significant scientific considerations related to changes accumulated throughout the lifecycles of biological products. Scientifically justified manufacturing changes performed throughout the lifecycles of biological products, for both biosimilars and their reference products, may result in incremental changes to those products. Such incremental product changes, when compounded over time, are sometimes referred to as "drift", but are better characterized as "product evolution" for each given product with the resulting potential for "product divergence" among a set of originally related products.

---

[28] FDA, Draft Guidance for Industry: *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*, pp. 5-6 (2012). Retrieved electronically at: http://www.fda.gov/downloads/Drugs/GuidanceCompliance RegulatoryInformation/Guidances/UCM291128.pdf on January 17, 2014.

It is important for policy makers to understand that product evolution is not a reflection of lack of control by the individual biologic manufacturers: each incremental change must be justified and any unexpected shifts in quality must be investigated and controlled. Rather, in this context "divergence" is an emergent property of multisource biologic manufacturing that may occur due to the absence of a systemic mechanism to constrain product changes with respect to each other.

While all manufacturing changes must be scientifically justified through comparability assessment of the resultant product with its immediate precursor product, it is not clear that the product evolution observed over the lifecycle of a biosimilar product will match that of its reference product (or vice versa). The reality of product evolution and divergence supports the need for distinguishable names, which will ensure that manufacturers of biosimilars and their reference products retain the flexibility to make scientifically justified changes to their manufacturing processes.

Distinguishable Naming Ensures Accurate Product Identification and Effective Pharmacovigilance

The GPhA Petition reflects lack of understanding and recognition of the heightened importance of post-market monitoring for biologics and biosimilars and the need to ensure accurate product identification. Biologics, as large molecules synthesized in living cells, have increased structural complexity that can affect a product's function and clinical safety and efficacy, as compared to small molecule drugs which are chemically synthesized. In addition, while some variability is inherent in all biologically synthesized products and is expected to occur over a product's lifecycle, it is not the case, as claimed by GPhA, that biosimilar batches will necessarily fall within the historical ranges of the reference product. On the contrary, biosimilar products may exhibit additional structural differences as manufacturers of biosimilars will not have access to the innovator company's proprietary data, cell lines, or manufacturing process. These differences have important pharmacovigilance implications.

In order to receive marketing approval, biologics manufacturers must demonstrate that their product is safe, pure, and potent.[29] In addition, because of the complex nature of biological products and the need to ensure continued safety and efficacy, biologic manufacturers have distinct post-market regulatory requirements from small molecule manufacturers. Products may be subject to comparability testing if there are changes in the manufacturing process, equipment, or facilities used in production.[30] Biologic manufacturers must also submit distribution reports that include bulk lot, fill lot, and label lot numbers for each dosage of product domestically distributed. These reports are due every six months, and FDA can request additional information.[31]

---

[29] PHSA § 351(a).
[30] FDA, Guidance for Industry: *Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process*, (2005).
[31] 21 C.F.R. § 600.81.

For marketing approval, a biosimilar manufacturer must demonstrate that its product is "highly similar" to an approved reference product. Similarity will need to be demonstrated through a combination of structural characterizations; comparative functional assays; comparative animal toxicity, Pharmacokinetics (PK), Pharmacodynamics (PD), and immunogenicity studies; and clinical testing designed to address any remaining biosimilarity uncertainty.[32] However, there are limits to the degree that biosimilarity can be established through preclinical methods. Furthermore, in the not uncommon case where minor differences are found, there are limits to the certainty that such differences will not have clinical consequences. It is well established that clinical trials may not be powered to detect the rare adverse events associated with new products.[33] In the post-market, as more patients use products in less controlled settings, critical safety and efficacy information is learned through post-market safety surveillance and outcomes research. This information will be increasingly important as biologics and biosimilar use becomes more widespread.

Furthermore, adverse events associated with biologics, including immunogenicity risks, can have significant clinical consequences. FDA staff has noted that "[t]racking adverse events associated with the use of reference and biosimilar products will be difficult if the specific product or manufacturer cannot be readily identified, and appropriate strategies must be developed to ensure the implementation or robust, modern pharmacovigilance programs for biologics."[34] A robust and modern pharmacovigilance system for biologics depends on the accurate identification of individual products and an ability to link exposure to possible adverse outcomes. Distinguishable names will help to ensure that adverse events are traced to the correct product and facilitate the collection of more timely and accurate adverse event data in order to inform critical decisions about the use of biologics.

In addition, because - whether brand or nonproprietary names - are widely used in prescribing and in adverse event reporting, the use of shared nonproprietary names could impede efforts to identify the particular products associated with adverse event reports. Adverse events reporters often incorrectly attribute adverse events by assuming the event is associated with the innovative product, when in fact the patient likely took a generic product with the same nonproprietary name.[35] Studies have shown that meaningful product identifying information (*i.e.*, information beyond product brand or nonproprietary name) is usually not included in FDA's adverse event report systems

---

[32] FDA, Draft Guidance for Industry: *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (Feb. 2012). Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf.

[33] Jesse Berlin, et al., *Adverse Event Detection in Drug Development: Recommendations and Obligations Beyond Phase 3*, Am. J. Public Health, Vol. 98, No. 8, 1366–1371 (August 2008). Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2446471/pdf/0981366.pdf.

[34] Steven Kozlowski, et al., Developing the Nation's Biosimilar Program, 365 New Eng. J. Med. 385, 387-88 (2011).

[35] Erika F. Lietzan, et al., *Biosimilar Naming: How do Adverse Event Reporting Data Support the Need for Distinct Nonproprietary Names for Biosimilars?*, Food and Drug Policy Forum, Vol. 3, Issue 6, p. 5 (March 27, 2013).

or included in reports provided by both mandatory and voluntary adverse advent reporters.[36]

The National Drug Code (NDC), a 10-digit numerical code, does not serve same function as a distinguishable name, as argued in the GPhA Petition. First, evidence demonstrates that in the majority of cases, the NDC number is not provided in the adverse event reporting database.[37] Second, biologics are likely to be administered by physicians in their office or in the inpatient setting. NDCs are not typically used in practice settings, and in particular are not commonly used in physician offices or the inpatient setting.[38] Third, the reporting of adverse events by NDC is highly likely to involve error. In addition, the use of brand names alone is also insufficient as nonproprietary names are often used by healthcare professionals and are currently permitted as the only product identifier provided in pharmacovigilance systems.[39]

Distinguishable names also provide for easy data aggregation and disaggregation. Distinguishable names may mitigate against the forced pooling of adverse events that occurs when adverse events are reported by nonproprietary name alone allowing manufacturers to better detect and investigate safety signals relevant to their specific products, and permitting researchers and regulators to analyze pharmacovigilance data for both product specific and class wide safety signals. This is of critical importance for effective pharmacovigilance. For example, without distinguishable names, a major (*e.g.*, two fold) increase in adverse event rates associated with a biosimilar that has only a small (*e.g.*, 5%) market share compared with the innovator would present in pharmacovigilance systems as very small (5%) increase in event rates that might escape detection and/or be assumed to represent chance variation. With distinguishable names, the two-fold increase is much more likely to be apparent. Even if the small increase were noted, not being able to identify which product had the problem could delay problem identification and corrective measures. This, in turn, may expose patients either to higher risks or to loss (withdrawal or warnings) of the entire class of drugs due to a problem with one.

Because of the unique nature of biologics and their manufacturing process, it is not enough to solely argue for better pharmacovigilance systems for all marketed products. While BIO strongly supports a uniform, national standard for supply chain traceability, as well as adverse event reporting education improvements, we also believe that distinct nonproprietary names are an important and necessary component of an effective pharmacovigilance system for biologics.

---

[36] *Id*. at 5.
[37] *Id*. at 13.
[38] Engelberg Center for Health Care Reform at Brookings, Discussion Guide: *Developing Systems to Support Pharmacovigilance of Biologic Products*, p. 5 (Nov. 15, 2013).
[39] *See*, Steinman et al., *What's in a Name? Use of Brand versus Generic Drug Names in United States Outpatient Practice*, 22 J. Gen. Intern, Med. 645 (May 2007).

Recent FDA naming decisions (discussed below) support the broader conclusion that the use of distinguishable nonproprietary names will help post-marketing safety monitoring, allowing better traceability of medicines in the case of an adverse event. And contrary to the GPhA Petition, international developments, discussed above, demonstrate that there is no single international naming consensus and that pharmacovigilance and patient safety concerns are shared by all regulators.

Distinguishable Naming Furthers Patient Safety

A cornerstone of patient safety, the combined ability to prevent prescribing errors (including inappropriate substitution) and accurately attribute adverse events, depends upon the ability of patients, prescribers, and dispensers of medication to identify specific products. BIO believes that distinguishable nonproprietary names for all biological products are necessary to not only protect patients but also to further efforts that promote and enhance patient safety.

GPhA and other opponents of distinguishable naming have argued that assigning distinguishable nonproprietary names to related but non-identical biological products would lead to prescriber confusion, double-dosing, or dispensing errors, thereby jeopardizing patient safety. This stands in direct opposition to the policy adopted by FDA in several recent approvals of biological products under section 351(a) of the Public Health Service Act (42 U.S.C. §262) that share similarities with other innovative biologics, in which the Agency has indicated that distinguishable nonproprietary names may help to promote patient safety.

Specifically, for the Teva product tbo-filgrastim, the FDA Biological Product Naming Working Group concluded:

> …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… unique nonproprietary names will facilitate postmarketing safety monitoring by providing a clear means of determining which "filgrastim" product is dispensed to patients.[40]

Also in the tbo-filgrastim Biological Product Naming Working Group report, FDA concludes that nonproprietary names have a role distinct from that of proprietary names:

---

[40] FDA, Biological Product Naming Working Group *Memorandum: BLA 125294 – [xxx]-filgrastim,* (2012). Accessed electronically at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/125294Orig1s000NameR.pdf on January 18, 2014.

> Due to the fact that health care providers may use nonproprietary names instead of proprietary names when prescribing and ordering products, and pharmacovigilance systems often do not require inclusion of proprietary names, the use of distinct proprietary names is insufficient to address these concerns.[41]

FDA made the same determination with identical justification for the Sanofi product Zaltrap (ziv-aflibercept), which is closely related to Regeneron's Eylea (aflibercept).[42]

Conclusion

BIO appreciates this opportunity to comment on the GPhA Petition requesting the Food and Drug Administration (FDA) to "implement its INN naming policy equally to all biologics" and to require "all biologics approved under the Section 351(k) pathway…share the same INN [International Nonproprietary Name] as the RPP [reference protein product]". For all the reasons above, we respectively request FDA to deny the GPhA Petition and implement a nonproprietary naming convention that ensures distinguishable product identification of all biological products in order to best facilitate pharmacovigilance, ensure accurate attribution of adverse events to the right product, prevent inappropriate substitution and unintended switching, and support tracing of products in the event of a recall; and thereby enhancing patient safety. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Tom DiLenge
General Counsel

/S/

Sara Radcliffe
Executive Vice President, Health

[41] *Id*.
[42] FDA, Biological Product Naming Working Group, Memorandum: BLA 125418 – Zaltrap ([xxx]_aflibercept) manufactured by sanofi-aventis, U.S., LLC, (2012). Accessed electronically at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/125418Orig1s000NameR.pdf on January 18, 2014.