

February 3, 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: PhRMA Comments to Generic Pharmaceutical Association Citizen Petition

Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) submits these comments in response to the Citizen Petition filed with the Food and Drug Administration (FDA) by the Generic Pharmaceutical Association (GPhA) on September 19, 2013, docket no. FDA-2013-P-1153 (“GPhA petition”). In its Petition, GPhA requests that FDA implement its International Non-Proprietary Name (INN) naming policy equally to all biologics and argues that biosimilars should have the same INNs as their reference products.

PhRMA is a voluntary, non-profit association that represents the country’s leading pharmaceutical research and biotechnology companies, which are devoted to inventing medicines that allow patients to live longer, healthier and more productive lives. In 2012 alone, PhRMA members invested an estimated \$48.5 billion in discovering and developing new medicines, representing the vast majority of private investment in new biopharmaceutical products in the United States.

PhRMA respectfully requests that FDA deny the GPhA petition. PhRMA strongly believes that unique nonproprietary names for biologic products, in conjunction with clear and informative labeling of biosimilar products, are essential for effective pharmacovigilance and to ensure patient safety. Because use of the term “unique” may be a source of confusion among stakeholders, we will use the term “distinguishable” going forward.¹ Distinguishable nonproprietary names for all biologics will facilitate accurate attribution of any

¹ In some cases, “unique name” has been misinterpreted to mean a completely new, unrelated name instead of the intended meaning that a unique name will be either the first assignment of a completely new name (i.e., when an innovative biologic is first introduced on the market) or a name that consists of a common core plus a unique identifier. Therefore, “distinguishable” will be used going forward.

potential adverse events (thus preventing misattribution) and allow for the detection of any safety differences among and between biologics. Over time, as is true for small molecule drugs, the U.S. market will include multiple innovator biologics, interchangeable biosimilars, and biosimilars. As the market grows more complex, the current policy discussion around how best to track and accurately attribute adverse drug reactions is even more crucial. FDA policy in this area should reflect learnings from past pharmacovigilance challenges and implement durable naming policies that will increase the effectiveness of the pharmacovigilance system for all biologics over the short and long term. In addition, to avoid any potential confusion, a physician's decision as to which biologic is prescribed must be known to the dispensing pharmacy. It is therefore critical that FDA develop a naming policy that includes distinguishable names for all biologics.

Distinguishable nonproprietary names are necessary to facilitate timely identification and accurate attribution of adverse events. Given that biologics are often used to treat serious or life-threatening diseases that can require complex treatment regimens, patient's care and health outcomes may be jeopardized if either the safety or efficacy of products in their treatment regimen is called into question due to misattribution of product-specific adverse events.

The pharmacovigilance challenges of shared nonproprietary names are recognized by many global regulators. As discussed in our comments below, the naming approach in Europe does not directly apply to the United States. The projected increase over time in the number of innovative biologics and, in the future, both interchangeable and non-interchangeable biosimilars, presents an opportunity to develop forward-looking policies for the naming of biologics that improve the robustness of the existing pharmacovigilance system in the interest of all stakeholders, but especially patients. As discussed in our comments, we believe these policies are critical to facilitating the essential role that patients and physicians play in pharmacovigilance and spontaneous adverse event reporting.

PhRMA supports the implementation of a durable approach to naming by which the nonproprietary names of biologics that are similar to each other in structure and function are distinguishable, but morphologically related, and which prescribers and patients can more easily recognize, remember, and report accurately. In the long term, such a policy is in the best interests of patients, physicians and other prescribers, payers, and others.

I. Background

The Federal Food, Drug, and Cosmetic Act (FDCA) requires every drug, including every biologic drug, to include a nonproprietary or “established” name on its label.² In practice, the nonproprietary name is usually the United States Adopted Name (USAN), which is assigned by the United States Adopted Names Council. FDA has stated that in the absence of positive action by the agency, the USAN constitutes a product’s established name.³ Typically, a product’s USAN and INN, which is set by the World Health Organization (WHO), are the same, as the USAN Council and the WHO coordinate with one another and strive to assign identical names.

The Biologics Price Competition and Innovation Act (BPCIA), enacted in March 2010, gave FDA the new authority to approve biosimilar biologics, provided they are shown to be highly similar to a previously approved innovative reference product and provided there are no clinically meaningful differences between the biosimilar and the reference product in terms of safety, purity, or potency.⁴ FDA must deem a biosimilar “interchangeable” with its reference product if the agency determines that it can be expected to produce the same clinical result as the reference product in any given patient. In addition, for a product administered more than once, the safety and reduced efficacy risks of alternating or switching should not be greater than with repeated use of the reference product without alternating or switching.⁵

The BPCIA is silent regarding naming of biosimilars, leaving untouched FDA’s existing and robust authority to make decisions about product names based on its consideration of the relevant technical, scientific, and patient safety issues.

II. Distinguishable but Morphologically Related Nonproprietary Names for Biologics are Essential for Effective Pharmacovigilance.

The cornerstones of effective pharmacovigilance are attribution of safety signals to the correct product, on the one hand, and the ability to both aggregate and disaggregate related products as warranted, on the other hand. In the absence of distinguishable nonproprietary names for biologics, and depending on the types and accuracy of information provided in the adverse event report, manufacturers, physicians, and health authorities may not be able to

² FDCA § 502(e)(1)(A), 21 U.S.C. § 352(e)(1)(A). Section 351 of the Public Health Service Act (PHSA) uses the phrase “proper name” rather than “established name,” but the agency generally treats the terms as synonymous.

³ See, e.g., FDA, “Guidance for Industry: Contents of a Complete Submission for the Evaluation of Proprietary Names” (Feb. 2010), at 18, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075068.pdf>.

⁴ PHSA §§ 351(i)(2), (k), 42 U.S.C. §§ 262(i)(2), (k).

⁵ PHSA §§ 351(i)(3), (k), 42 U.S.C. §§ 262(i)(3), (k).

identify the specific product within a class of products associated with a specific adverse event. This in turn could impede or delay effective analysis and correction of the problem. Shared nonproprietary names may also hinder detection of a safety signal associated with only one product or a subset of products. At the same time, nonproprietary names that are not completely different – but are instead morphologically related - would help facilitate the aggregation of data to detect class-wide safety issues. In contrast, identical nonproprietary names within a class of similar, but not identical, products present a risk to patients in that a serious issue related to one product may impede patient access to other products in the class if the issue cannot be quickly and definitively attributed to the correct product. Because biologics are often used to treat patient populations that are amongst the most vulnerable with diseases for which there may be few treatment options, prompt attribution of adverse events is critical. Thus, distinguishable but related nonproprietary names for biologics could prevent misattribution of issues to uninvolved products in the class while also permitting aggregation to detect class effects.

A. Product Identifiers Other Than Distinguishable Nonproprietary Names Are Not Currently Sufficient for Effective Pharmacovigilance

FDA requires that the adverse event reports submitted by manufacturers contain (1) an identifiable patient, (2) an identifiable reporter, (3) a suspect product, and (4) an adverse experience or fatal outcome suspected to be due to the suspect product. But FDA does not require any particular method of identifying the suspect product.⁶ The MedWatch form (3500A) used for mandatory reporting of adverse events by manufacturers contains fields for the name and strength of the product (including the manufacturer name, if known), the dose, frequency and route of the product, the indication, the lot number (if known), the NDC number (if known), and expiration date (if known).⁷ Similarly, for voluntary reporting by physicians and patients, the MedWatch form (3500) provides a space to identify the name of the product, the manufacturer of the product, the lot number, and the NDC number, but completion of any one of these or all these fields is not required to report the event.⁸ The information reported through the MedWatch program is collected by FDA in the FDA Adverse Event Reporting System (FAERS), which serves as the principal support for FDA's postmarketing safety surveillance for drugs and biologics.

⁶ See FDA, "Draft Guidance for Industry: Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines" (Mar. 2001), at 8-9.

⁷ FDA, Form FDA 3500A (Feb. 2013), at 1, <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf>.

⁸ FDA, Form FDA 3500 (Feb. 2013), at 1, <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf>; FDA, Form FDA 3500B (Apr. 2013), at 1, <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM349464.pdf>. See FDA, Instructions for Completing Form 3500, <http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/ucm149236.htm>.

We also support physician and pharmacist education about robust adverse event reporting practices and exploration of novel reporting mechanisms as well as the importance of accurate record keeping. There is, however, an urgent need to develop policies specifically designed to improve the current pharmacovigilance system and the robustness of spontaneous adverse event reports (e.g., MedWatch / FAERS) independent of ongoing improvements to active surveillance systems (e.g., Sentinel).

Further, empirical evidence strongly suggests that adverse event reports follow the nonproprietary name – rather than the National Drug Code (NDC) or manufacturer name – even where there is very strong circumstantial evidence that the adverse event *could not be* attributable to the company receiving the report.⁹ A recent study of adverse event data for several small molecule drugs established that product name (brand or nonproprietary) is often the only meaningful product-specific information provided in the FAERS data. Indeed, while NDCs might in theory be a precise method of tracking products, this empirical study suggested the NDC rarely appears in the FAERS database: NDC numbers were included in less than 0.01% of all adverse event records in the de-duplicated FAERS database.¹⁰ FDA officials have themselves informally confirmed the lack of NDC numbers in the FAERS database.¹¹

The lack of NDC numbers in pharmacovigilance databases may result from a failure of the NDC numbers to follow the products to the physician and other prescriber and the patient level. A survey of physicians conducted by the Alliance for Safe Biologic Medicines found that more than 99% of physicians record a product name, not the NDC, in the patient record. Physicians and other prescribers do not always take the additional steps necessary to go back and identify the NDC number when reporting adverse events.¹² A separate analysis found that NDCs are often not reported back to prescribers when the patient obtains the prescribed drug from a retail pharmacy.¹³

⁹ Lietzan, E., et al., “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) (2013).

¹⁰ *Id.* at 6. Similarly, the study found that other product-specific information is infrequently included in the FAERS database: less than a quarter (23%) of adverse event reports have the marketing application field (i.e., NDA or BLA number) populated; only 10% of adverse event reports have the lot number field populated; and the manufacturer name associated with an adverse event report is the name of the reporting manufacturer, regardless of whether the adverse event reporter has attributed the adverse event to the wrong product. *Id.* at 1, 6, 11.

¹¹ FDA, Part 15 Public Hearing on Approval Pathway for Biosimilar and Interchangeable Biological Products, Transcript, Docket No. FDA-2010-N-0477 (Nov. 2, 2010), at 169 (statement by the Director of FDA’s Office of New Drugs that “while the reporting system may include a field for NDC number, I think it’s very rare that we get that level of information”).

¹² Dolinar, R., “It’s all about the name: What is the imperative of adopting unique names for biologic and biosimilar therapeutics?” *FDLI’S FOOD AND DRUG POLICY FORUM* 2(22):1, 6 (2012).

¹³ Zelenetz A., et al., “NCCN biosimilars white paper: Regulatory, scientific, and patient safety perspectives,” *J. NATL. COMPR. CANC. NETW.* 9(Supp. 4):S1, S14 (Sept. 2011).

B. The Ability to Accurately Attribute Adverse Events to Specific Biologics is Critical to Patient Safety

The ability to identify and accurately attribute adverse events to a specific product is critical to effective pharmacovigilance. The adverse events associated with biologics can have significant clinical consequences, and some adverse events may be rare and difficult to detect in any reasonable premarket testing program. In addition, small but meaningful clinical differences between biosimilars and their reference products may be detectable only after approval of the biosimilar, due to the complexity and heterogeneity of biologics. Because biosimilars will be only “highly similar” to (not the “same as”) their reference products and will be approved on the basis of abbreviated clinical data packages, important information about their efficacy and safety profiles could emerge after their approval. Further, meaningful differences between a biosimilar and its reference product may *develop* after approval, as a result of changes in the manufacture, or unintentional drift in quality characteristics, of the biosimilar, the reference product, or both.

The inability to identify the specific product associated with a specific adverse event, or misattribution impedes and delays root cause analyses, jeopardizing patient safety. For instance, in response to a 2010 Congressional inquiry about adverse events associated with generic anti-epileptic drugs, the agency admitted it was unable to attribute the events to the correct drug.¹⁴ Anti-epileptic drugs have been associated with more significant substitution risks than other generic products.¹⁵ Within therapeutic classes, the generic anti-epileptic drugs on the market have the same nonproprietary names as each other and as their reference product. Congress requested information on adverse events associated with these drugs due to concern about reports of unexpected side effects when patients switched among different manufacturers’ versions of the same therapeutic agent. In its response, FDA admitted that it could not fully provide this information because “[i]n the absence of drug manufacture information included in the [Adverse Event Reporting System] report, the adverse event could not be attributed to a particular drug product.”¹⁶

To give another example, the Government Accountability Office (GAO) concluded that the lack of identifying information in adverse event reports significantly impeded FDA’s oversight of the 2008 heparin crisis. FDA received multiple adverse event reports involving severe allergic reactions associated with heparin. Ultimately, FDA identified the contaminant as oversulfated chondroitin sulfate, which was present in an active pharmaceutical ingredient sourced from a factory in China. But in reviewing FDA’s response to the issue, GAO concluded that the lack of identifying information in adverse event reports significantly hindered

¹⁴ FDA, “Information Regarding Anti-Epileptic Drugs: U.S. Food and Drug Administration in Response to Requests in Senate Report No. 111-39 and House Agriculture Committee Report No. 111-279” (2011).

¹⁵ *Id.* at 2.

¹⁶ *Id.* at 4.

FDA's efforts to link adverse events to contaminated products. Specifically, of the 94 adverse event death reports FDA received, only 13 included lot numbers and nearly two-thirds of the voluntary reports did not list the heparin manufacturer.¹⁷ Because the multiple heparin products marketed by different manufacturers share the same nonproprietary name, the adverse event reports provided no information about the identity of the heparin administered in the absence of a lot number or manufacturer information.

C. The European Model is Not Directly Applicable to the United States

The effectiveness of product identification in the European pharmacovigilance system relies, in part, on the fact that biosimilars bear distinct product names in Europe. Although Europe does not require biosimilar products to have distinguishable nonproprietary names, it does require distinct product names. For all medicinal products, including biosimilars, the name of the product is either (1) a proprietary name or (2) the common or scientific name accompanied by a trade mark or name of the marketing authorization holder.¹⁸ Biosimilars, which are centrally authorized, thus have distinguishable product names, providing a mechanism to distinguish between and among innovative biologics and biosimilars.¹⁹

A recent study found that the specific biologic was identifiable in 96.2% of adverse event reports involving biologics for which a biosimilar was available in Europe, due to the inclusion of either the biologic's brand name or the biologic's nonproprietary name as well as the manufacturer name.²⁰ In contrast, in the United States, reliance on identifying products by brand name could present risks. *First*, brand names are not required under U.S. law. *Second*, it remains to be seen whether adverse event reporters will consistently identify a biologic's proprietary name after the introduction of biosimilar competition. *Third*, in the FAERS database the reporting manufacturer is associated with the report by default, i.e. the manufacturer listed for a given adverse event report is the manufacturer who submitted the report. Therefore, when the manufacturer is reporting an adverse event to FDA that was reported to the manufacturer by a third party (e.g. a patient or physician), that manufacturer will be associated with the adverse event report even if the initial reporter incorrectly attributed the event to the manufacturer.

¹⁷ GAO, "Food and Drug Administration: Response to Heparin Contamination Helped Protect Public Health; Controls That Were Needed for Working with External Entities Were Recently Added," GAO-11-95 (Oct. 2010), at 35-36.

¹⁸ Committee for Human Medicinal Products (CHMP), European Medicines Agency (EMA), "Guideline on the Acceptability of Names for Human Medicinal Products Processed Through the Centralised Procedure" CHMP/328/98, Rev. 5 (Dec. 2007); CHMP, EMA, "EMA Procedural Advice for Users of the Centralised Procedure for Similar Biological Medicinal Product Applications," EMA/940451/2011 (Mar. 2013), at 10-11.

¹⁹ Council Directive 2001/83 Art. 1(20), as amended; Commission Regulation (EC) No 726/2004, 2004 O.J. (L36) 1, 12.

²⁰ Vermeer, N., 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. 36(8):617 (2013).

D. Effective Pharmacovigilance is Particularly Critical for Biologics

Given these experiences and pharmacovigilance challenges with generic drugs and the greater complexity of biologics (both in terms of the products themselves and in terms of the regulatory relationship between a biosimilar product and its reference product and the lack of regulatory relationship between biosimilar products that share a reference product), we believe there is a demonstrated need for FDA to implement a naming policy that makes deliberate attempts to address known weaknesses in the current pharmacovigilance system and to improve the ability to identify and track biologics. The timely detection and attribution of safety signals to the correct product is particularly critical for biologics.

The immunogenicity risk presented by biologics is greater than that associated with chemically synthesized products, and immunogenicity can have significant adverse clinical consequences. The ability to detect emerging safety risks quickly is critically important because a narrow therapeutic window exists for detecting antibody development and amending the treatment protocol to forestall further antibody-mediated complications.²¹ Of particular relevance, adverse events associated with biologic immunogenicity often manifest with a delayed onset. With the introduction of biosimilars to the U.S. market in the future, the environment will become more complex, thus providing the impetus to implement naming policies to address known weaknesses and further strengthen the existing pharmacovigilance systems in the United States.

As the introduction of biosimilars in the United States and the continued entry of new innovator biologic medicines increase competition, treatment options for patients will expand over time. We expect to see an increase in the number of patients using a biologic for the first time as well as an increase in the number of patients switched from one product to another. As a result, we expect that simply by the nature of an increase in the number of biologics, we will likely see a corresponding increase in the number of adverse event reports and, potentially, differences in the types of adverse event reports as the environment becomes more complex. Shared names across products that are not the same may mask an increase or qualitative change in adverse events with respect to one product but not others. Adverse events from similar products will inherently be pooled in the event of shared nonproprietary names, and this pooling may mask a small, but nevertheless statistically significant, rate increase for a particular product,

²¹ See, e.g., Casadevall, N., "Antibodies against rHuEPO: Native and recombinant," *NEPHROL. DIAL. TRANSPLANT.* 17(Supp. 5):42, 46 (2002); Hartung, H.P., et al., "Significance of neutralizing antibodies to interferon beta during treatment of multiple sclerosis: Expert opinions based on the proceedings of an international consensus conference," *EURO. J. NEUROL.* 12(8):588, 592-593 (2005).

and importantly, real public health consequences. This pooling of adverse events among products may also mask causal associations that would help researchers identify root causes.²²

III. Distinguishable But Morphologically Related Nonproprietary Names for Biologics Would Support, Not Jeopardize, Patient Safety.

Distinguishable but morphologically related nonproprietary names would not jeopardize patient safety. Regulators and researchers would maintain the ability to aggregate data across a product class to detect safety signals. And use of distinguishable nonproprietary names is not expected to lead to prescribing errors.

Distinguishable but morphologically related nonproprietary names would facilitate, rather than prevent, aggregation of data. The suggestion that “unique” names would lead to disaggregation of safety data is a misinterpretation of either the nature of what is meant by “unique” names (i.e., distinguishable but morphologically related) or the manipulability of adverse event databases. The use of a common core, preceded or followed by a unique identifier, would allow both product aggregation (cores together, without inclusion of an identifier) and product disaggregation (separation according to core INN plus identifier).

We share GPhA’s concern about disassociation of U.S. and international safety signals and therefore recommend that FDA implement a naming policy that allows the agency to fulfill its mandate to promote and protect public health while making reasonable effort to implement a system that is compatible with the WHO process to harmonize naming protocols around the world. The WHO recognizes the need for a unique identifier of a biosimilar and believes that it is preferable that the INN programme be used to address this need.²³ As these discussions evolve, it is reasonable to expect that regulatory authorities use this opportunity to update their approaches to naming in the interest of improving the robustness of both country-specific and global pharmacovigilance systems. In the meantime, it is technologically possible to pool adverse event data even if the nonproprietary names are different. And an interest in international harmonization, and the aggregation of data globally, does not justify giving biosimilars the same nonproprietary names as their reference products. In fact, it argues for increased emphasis on the ability of the INN, the only internationally adopted identifier, as a definitive data point in pharmacovigilance efforts. The other available identifiers in the United States (i.e., brand name, NDC, manufacturer name, HCPCS code, J codes) are either not relevant to ex –U.S. systems (e.g., NDC, J and HCPCS codes), not required or permitted by some

²² See, e.g., Bennett, C., et al., “Pure-red cell aplasia and epoetin therapy,” *NEW ENG. J. MED.* 351:1403, 1404 (2004) (“[t]he most common reasons for exclusion from the study were . . . the use of multiple epoetin products (44 cases)”).

²³ WHO, 55th Consultation on International Nonproprietary Names for Pharmaceutical Substances (16-18 October 2012) http://www.who.int/medicines/services/inn/55th_Executive_Summary.pdf

countries (e.g., China does not permit the use of brand names for biosimilars or generics²⁴ while the United States does not require brand names for generics or biosimilars), or may differ from country to country (e.g., manufacturer's name). A number of jurisdictions have already selected for some biologics nonproprietary names that differ from their INNs; these include the United States, Australia, and Japan. Use of product NDC number or proprietary name for tracing, as GPhA recommends, would similarly fail to facilitate pooling of international data. Realizing the need for a globally acceptable and durable naming strategy for biosimilars, the WHO has signaled that it may give biosimilars a distinguishable name in the form of an INN with qualifier going forward.²⁵

Most biologics are injected or administered intravenously by healthcare providers. The administering healthcare providers or infusion centers would be aware of the various biosimilars and reference products available and would be unlikely to overmedicate. Similarly, it is unlikely a physician would prescribe two biologics that shared a common core for a patient's outpatient use. It is more probable that inadvertent and inappropriate substitution of two non-interchangeable biologics would occur where they share the same nonproprietary name. And in fact, evidence from the American Pharmacists' Association, suggests that use of prefixes may reduce the potential for dispensing errors due to pharmacist use of pull-down menus.²⁶

In thinking about ways to guard against inappropriate or errors in substitution of biologics, PhRMA is supportive of FDA's reported efforts to develop a reference guide for FDA-approved biologic medicines, assuming that this reference guide is intended to make clear to users (e.g., pharmacists) FDA's determination of interchangeability, or lack thereof, of FDA-approved biosimilars to their reference products. PhRMA believes that such a reference guide, if properly constructed and updated in a timely manner, would be one of several options that should be considered as the FDA seeks ways to educate stakeholders on the scientific and regulatory relationship between a biosimilar or interchangeable biologic and its reference product and the lack of these relationships between different biosimilars and interchangeable biologics. In addition to a reference guide and distinguishable names for biologics, PhRMA strongly urges the FDA to approach the labeling of biosimilars in a way that makes it clear that the product is a biosimilar and the basis for approval of the biosimilar (i.e., the studies that were conducted with the biosimilar and descriptions of how the studies inform a finding of the absence of clinically relevant differences between the biosimilar and the reference product).

²⁴ Notice on Further Circumscribing the Administration of Drug Names (CFDA No. 99 2006).

²⁵ WHO, Executive Summary, "57th Consultation on International Nonproprietary Names for Pharmaceutical Substances, Geneva, 22-24 October 2013," INN Working Doc. 13.340, at 5-6, *available at* http://www.who.int/medicines/services/inn/57th_Executive_Summary.pdf?ua=1.

²⁶ Senior, M., "The name game: Will innovators' latest battlefield kill biosimilars?," *THE RPM REPORT* 22, 23 (Sept. 2013).

IV. Public Health Authorities, Including FDA, Now Recognize the Pharmacovigilance Challenges Presented by Shared Nonproprietary Names for Biosimilars.

With the inevitable increase in market complexity that comes with the introduction of biosimilars, there is an emerging global consensus that biologics must be distinguishable by name for pharmacovigilance purposes. For example, in Japan and under a recent proposal in Australia, the nonproprietary name of a biosimilar is the nonproprietary name assigned to the biologic modified by a specified formula.²⁷ Although Europe does not require biosimilar products to have distinguishable nonproprietary names, it does require distinct product names. In Europe, centrally authorized biosimilars thus have distinguishable product names, enabling distinctions to be made between and among innovative biologics and biosimilars.²⁸

The WHO is currently re-considering the issue as well, in view of the need for accurate pharmacovigilance and the broad use of nonproprietary names for substitution decisions. GPhA relies on the 2006 discussion at the WHO on biosimilar naming, which preceded the approval of the first wave of biosimilars. Upon the conclusion of that discussion, the WHO determined that a unique naming process was not necessary for biosimilars. Rather, assignment of INNs to biosimilars should be based on considerations of molecular characteristics and pharmacological class. For epoetins and other glycoproteins, the WHO recommended that amino acid differences be denoted by prefixes in the INN name (*e.g.*, “darbepoetin”) and that glycosylation differences be indicated by unique Greek letters (*e.g.*, epoetin α , epoetin β).²⁹ The WHO also recommended that a reference product and a biosimilar with different glycosylation patterns use different INNs.³⁰

²⁷ Australian regulators have proposed requiring the nonproprietary name of a biosimilar to be the Australian Biological Name (ABN) of the reference product followed by “sim” and a three-letter unique identifier, *e.g.*, “infliximab simfam.” See Australia Therapeutic Goods Administration, “Naming Conventions for Biosimilars” (July 30, 2013), <http://www.tga.gov.au/industry/pm-argpm-biosimilars-10.htm>.

For a biosimilar, the Japan accepted name (JAN) is determined by applying the following formula: JAN of the reference product + “[” + JAN of the reference product *minus* “rDNA,” if any + “Biosimilar” + the order number of the biosimilar product + “]”, *e.g.*, Filgrastim (rDNA) [Filgrastim Biosimilar 2]. If, however, the “essence” of a simple biosimilar protein were “identical” to that of the reference product, the biosimilar would be given the same nonproprietary name as the reference product.

²⁸ Council Directive 2001/83 Art. 1(20), as amended; Commission Regulation (EC) No 726/2004, 2004 O.J. (L36) 1, 12.

²⁹ Jelkmann, W., “Biosimilar epoetins and other ‘follow-on’ biologics: Update on the European experiences,” *AM. J. HEMATOL.* 85:771, 775 (2010) (citing WHO, “International Nonproprietary Names (INN) for Biological and Biotechnological Substances” (2007)).

³⁰ WHO, “50th Consultation on International Nonproprietary Names for Pharmaceutical Substances Geneva, 18-20 May 2010,” Executive Summary, INN Working Doc. 10.271 (March 2010), <http://www.who.int/medicines/services/inn/50thExecutiveSummary.pdf>

This discussion is, however, nearly a decade out of date and – as noted – it preceded the first wave of biosimilar approvals. Regulators now have experience with multiple biosimilars within product classes, and, as noted, a consensus is emerging among those regulators that distinguishable names are desirable. The WHO itself has since formally acknowledged that shared nonproprietary names may complicate pharmacovigilance efforts and lead to inappropriate substitution of products not deemed to be interchangeable. Further, there have been indications that the WHO may re-evaluate its approach to INNs or biosimilars and recommend unique global qualifiers for all biosimilars. For example, in 2009 a WHO official stated:

Spontaneous reporting still remains the cornerstone of pharmacovigilance but has several weaknesses. Often, only the international non-proprietary name (INN) is used as the sole product identifier and in the case of several products with the same INN (originator, plus generics or biosimilars) it may be difficult to trace the exact manufacturer of the product. A much better traceability of products is needed, particularly in the case of biosimilars.³¹

In 2010, the WHO released guidelines on similar biotherapeutics products that concluded that biosimilars, even when they share the same nonproprietary name, should nevertheless be “clearly identifiable by a unique brand name.”³² At a meeting of the WHO in October 2012, the Chair of the WHO INN Expert Group indicated after discussion that the present naming scheme for biosimilars “is not satisfactory and that action is required.”³³ One option being considered is adding a “unique biological qualifier” to the INNs of biosimilars.³⁴ As a WHO official has recognized, often the INN is the sole product identifier used in pharmacovigilance, and the use of the INN in pharmacovigilance efforts should be considered when creating policy.³⁵

³¹ WHO, “Biosimilar medicines and safety: New challenges for pharmacovigilance,” WHO DRUG INFORMATION 23(2): 87, 91 (2009) (citation omitted), <http://apps.who.int/medicinedocs/documents/s16240e/s16240e.pdf>.

³² Expert Committee on Biological Standardization, WHO, “Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs)” (2009), at 29, http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf

³³ WHO, Executive Summary, “55th Consultation on International Nonproprietary Names for Pharmaceutical Substances, Geneva, 16-18 October 2012,” INN Working Doc. 13.329, at 4.

³⁴ WHO, Executive Summary, “57th Consultation on International Nonproprietary Names for Pharmaceutical Substances, Geneva, 22-24 October 2013,” INN Working Doc. 13.340, at 5-6, available at http://www.who.int/medicines/services/inn/57th_Executive_Summary.pdf?ua=1.

³⁵ See, e.g., WHO, “Biosimilar medicines and safety: New challenges for pharmacovigilance,” WHO DRUG INFORMATION 23(2): 87, 91 (2009).

Since 2006, FDA itself has repeatedly expressed concern about the impact of shared names on pharmacovigilance efforts and patient safety. For example, in a 2007 letter to the Senate Committee on Health, Education, Labor and Pensions, FDA stated that the biosimilar pathway should recognize “the potential impact on pharmacovigilance and prescribing and require that these products be assigned a distinguishable, non-proprietary name for safety purposes.”³⁶ FDA again stated its view that biosimilars should “be assigned a distinguishable, non-proprietary name for safety purposes” in a 2008 letter to the House Subcommittee on Health.³⁷ FDA noted that biosimilars “present issues with pharmacovigilance (for example, post-market surveillance and withdrawal based on class or specific product concerns)” and emphasized its concern that “patients not be exposed to an avoidable safety risk by being switched to a product not known to be interchangeable with the product they are currently receiving.”³⁸ And at the 2010 public hearing to obtain input on the implementation of the BPCIA, FDA specifically requested comment on whether biosimilars and related products should be given unique nonproprietary names to facilitate pharmacovigilance.³⁹

In addition, FDA has recently required distinguishable nonproprietary names for three innovative biologics: Zaltrap (ziv-aflibercept), Granix (tbo-filgrastim), and Kadcyra (ado-trastuzumab emtansine). The action packages for those approvals suggest that the random prefixes were scrutinized for the potential of medication error.⁴⁰ With respect to tbo-filgrastim, FDA 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

³⁶ Letter of Michael O. Leavitt, Secretary, U.S. Department of Health and Human Services, to Senator Edward Kennedy (June 26, 2007).

³⁷ Letter of Frank M. Torti, M.D., M.P.H., Principal Deputy Commissioner & Chief Scientist, FDA, to Representative Frank Pallone, Jr. (Sept. 18, 2008).

³⁸ *Id.*

³⁹ FDA, Approval Pathway for Biosimilar and Interchangeable Biological Products; Public Hearing, 75 Fed. Reg. 61497, 61499 (Oct. 5, 2010).

⁴⁰ FDA, Administrative and Correspondence Documents, BLA 125418 Zaltrap (ziv-aflibercept) (2012), http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/125418Orig1s000Admincorres.pdf [“Zaltrap Review”]; FDA, Proprietary Name Review for BLA 125294 tbo-filgrastim, http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/125294Orig1s000NameR.pdf [“Tbo-filgrastim Review”]; FDA, Administrative and Correspondence Documents, BLA 125427 Kadcyra (ado-trastuzumab emtansine) (2013), http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/125427Orig1s000Admincorres.pdf [“Kadcyra Review”].

indistinguishable from a clinical standpoint. FDA also has concluded that unique nonproprietary names will facilitate postmarketing safety monitoring. . . . Due to the fact that health care providers may use nonproprietary names instead of proprietary names when prescribing . . . , and pharmacovigilance systems often do not require inclusion of proprietary names, the use of distinct proprietary names is insufficient to address these concerns.⁴¹

Similarly, for ziv-aflibercept, FDA concluded “a different nonproprietary name would minimize the possibility of medication errors and reduce confusion among healthcare practitioners who may consider use of the same nonproprietary name to mean the biological products are indistinguishable.”⁴² PhRMA believes that FDA’s approach to applying a random three-letter identifier with a common core may be a helpful model for the naming of all biologics, including biosimilars, going forward.

The BPCIA left untouched FDA’s residual authority to ensure distinct nonproprietary names, including its well-established authority to assign interim established names, its participation in the USAN Council and consequent ability to influence USANs, and its statutory authority to assign an official name under section 508 of the FDCA. Moreover, the FDA has ensured distinct nonproprietary names on many occasions. In addition to the three examples in the preceding paragraphs, it has required unique established names in other cases where there was a concern about medication errors, confusion among healthcare providers as to whether the same nonproprietary name meant the products were indistinguishable, and/or inappropriate substitution. For example, FDA designated distinguishable established names for botulinum toxin biologics.⁴³

V. FDA Can Assign Distinct Nonproprietary Names to Biologics on a Prospective Basis.

GPhA raises the question whether FDA can, consistent with administrative law principles, require distinguishable names for biosimilars without requiring them for innovative biologics (including those already on the market from different manufacturers with the same

⁴¹ Tbo-filgrastim Review, *supra*, at 2-3/58 (Memorandum from Biological Product Naming Working Group (Aug. 2, 2012), at 1-2).

⁴² Zaltrap Review, *supra*, at 41/164 (Memorandum from Melanie Pierce, CDER (July 17, 2012), at 1).

⁴³ See, FDA, FDA Alert, “Information for Healthcare Professionals: OnabotulinumtoxinA (marketed as Botox/Botox Cosmetic), AbobotulinumtoxinA (marketed as Dysport) and RimabotulinumtoxinB (marketed as Myobloc),” (Aug. 2009),

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm174949.htm>.

nonproprietary name) and without requiring name changes following manufacturing changes. PhRMA believes that there is a rational basis for FDA to adopt a policy requiring distinguishable but related nonproprietary names for all biologics from this point forward. We disagree that there is a rational basis for a policy requiring name changes following manufacturing changes when there is no change in regulatory status of the product. While comparability exercises and biosimilarity exercises share some common principles, the intent of the exercises differs significantly. The comparability exercise is performed by the manufacturer to confirm the established safety and efficacy profile after well-defined, incremental process changes. A manufacturer that modifies its own process draws on its extensive – and typically proprietary – knowledge about the product and the manufacturing process. This wealth of experience enables manufacturers to better anticipate the effect of process parameter changes, especially where the potential for clinical implications exist. Further, most comparability exercises involve the assessment of a single, or a few, changes to a process, not a change in nearly all elements of the process. In contrast, a biosimilarity exercise is designed to establish the safety and efficacy profile of a biosimilar from an independently designed manufacturing process where no process history exists and a link to clinical experience has to be established.

The risk of misattribution of adverse events does not exist following a manufacturer's change to its own product. In the event that a major process change is implemented there is typically limited overlap of the pre- and post-change products on the market, and therefore there is no requirement for distinguishable nomenclature to aid a given manufacturer in tracking its own product adverse events. We disagree, therefore, that a new nonproprietary name would be needed in the case of a manufacturing change to a licensed product. There is no meaningful risk of misattribution of adverse events in the case of one company's own product. In contrast, biosimilars remain on the market concurrently with other products. And biosimilars – unlike innovative products – may be subject to automatic substitution (depending on state law) for their reference products, once they are found interchangeable by FDA, creating a risk of misattribution of adverse events. A biologic's nonproprietary name should therefore be assigned prior to approval and should remain unchanged regardless of later manufacturing or labeling changes, such as an interchangeability determination. As indicated above, we agree with GPhA that the agency may wish to consider — in consultation with stakeholders — how to implement a naming policy that ensures that all biologics (innovative, biosimilar, and interchangeable) have distinguishable names.

Finally, we believe FDA can apply its policy prospectively only, including – if desired – a policy of assigning distinguishable, nonproprietary names to all biologics. Although a handful of approved therapeutic protein products currently share nonproprietary names, to our knowledge all of those products have unique proprietary names, and none is subject to automatic substitution. There is therefore no meaningful risk that the physician or patient will misattribute the adverse event. In any case, none of the products currently sharing nonproprietary names was

approved under the biosimilar pathway, and it is reasonable for FDA to adopt a new regulatory scheme prospectively with the implementation of the new authority to approve biosimilars.

VI. Conclusion

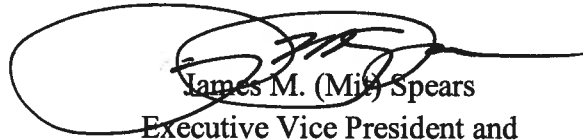
Distinguishable, morphologically related, nonproprietary names for all biologics are essential for effective pharmacovigilance and to ensure patient safety.

If you have any questions, please do not hesitate to contact us.

Respectfully submitted,



Bill Chin
Executive Vice President,
Scientific & Regulatory Affairs



James M. (Mike) Spears
Executive Vice President and
General Counsel