



**FDA U.S. FOOD & DRUG
ADMINISTRATION**

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Re: Docket Nos. FDA-2013-P-1153, FDA-2013-P-1398, FDA-2014-P-0077

Dear Mr. Davis, Ms. Lynch, and Dr. Siegel:

This letter responds to the three above-referenced citizen petitions on nonproprietary naming of biosimilar products. As described below, the citizen petitions from the Generic Pharmaceutical Association (GPhA) and the Novartis Group of Companies (Novartis), including Sandoz International GmbH (Sandoz), request that biosimilar products share the same nonproprietary name as their reference products, whereas the citizen petition from Johnson & Johnson (J&J) requests that biosimilar products have nonproprietary names that are similar to, but distinguishable from, the nonproprietary names of their reference products or of other biosimilar products.

On January 13, 2017, the Food and Drug Administration (FDA or Agency) issued the final version of its guidance for industry *Nonproprietary Naming of Biological Products* (naming guidance or final naming guidance).¹ The final naming guidance describes FDA's current thinking that biosimilar products and their reference products should have distinguishable nonproprietary names, and sets forth a naming convention to accomplish this. Accordingly, the citizen petition submitted by J&J is granted to the extent it requests that biosimilar products have nonproprietary names that are similar to, but distinguishable from, the nonproprietary names of their reference products or of other biosimilar products, and the citizen petitions submitted by GPhA and Novartis are denied.²

¹ Available at <http://www.fda.gov/downloads/drugs/guidances/ucm459987.pdf>. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

² This response does not address whether the nonproprietary names of products determined to be interchangeable under section 351(k)(4) of the Public Health Service Act (42 U.S.C. 262(k)(4)) should be distinguishable from the nonproprietary names of their reference products. As explained below, the final naming guidance indicates that FDA is continuing to consider this issue.

I. BACKGROUND

A. Citizen Petitions

On September 17, 2013, GPhA submitted a citizen petition (FDA-2013-P-1153) (GPhA Petition) requesting that: (1) FDA implement its INN (international nonproprietary name)³ naming policy equally to all biologics; and (2) because all biologics approved under section 351(k) of the Public Health Service Act (PHS Act) (42 U.S.C. 262(k)) are demonstrated to be highly similar to and have no clinically meaningful differences from their reference products, further requesting that biosimilar products “share the same INN name as the RPP [reference protein product], just as comparable originator products produced by a change in a manufacturing process or facility (post-change product) share the same INN as the original RPP (pre-change product)” (GPhA Petition at 1).

On October 28, 2013, Novartis submitted a citizen petition (FDA-2013-P-1398) (Novartis Petition) requesting that “to encourage and protect the safe and rational use of all medicines, FDA require that a biosimilar, be identified by the same international nonproprietary name (INN) as the reference product” (Novartis Petition at 1) (emphasis in original). Novartis stated that it used the term “INN” in its Petition for simplicity, although the applicable term in the United States is the “United States Adopted Name” or “USAN” (Novartis Petition at 15, note 1). On May 5, 2015, Novartis amended its request slightly, reiterating that biosimilar products should generally have the same nonproprietary names as their reference products, but that, if a biosimilar were licensed without a brand name, the Food and Drug Administration (FDA) should assign a nonproprietary name that is the nonproprietary name of the reference product supplemented with a distinguishable suffix linked to the biosimilar sponsor so that the biosimilar can be distinguished from the reference product.⁴

In support of these requests, GPhA and Novartis assert:

- Unique INNs for biosimilar products would be detrimental to patient safety (Novartis Petition at 5; see also GPhA Petition at 9-10).
- “The global pharmacovigilance system works, products sharing INNs in the US and European biosimilars sharing INNs with the RPPs are successfully tracked” (GPhA Petition at 6). “INNs are not, and cannot, be the primary tool relied on for tracking and tracing” (Novartis Petition at 2).
- “NDCs [National Drug Codes] are one of the most effective methods for tracking products and educational efforts to promote reporting of NDCs will be far more productive than implementing unique INNs” (GPhA Petition at 10).
- “Assigning different INNs to products approved as biosimilars would unnecessarily put into question years of FDA’s practice of approving manufacturing changes of originator biologic products without a resulting change in the originator INN” (Novartis Petition at 3; see also GPhA Petition at 4-5).
- “Assigning different INNs to products which conform to an established compendial monograph in the US would be inconsistent with current regulations governing USP [United States Pharmacopoeia] names” (Novartis Petition at 4).

On January 7, 2014, J&J submitted a citizen petition (FDA-2014-P-0077) (J&J Petition) requesting that FDA “exercise its statutory naming authority or work through the [USAN] process to require biosimilars to bear nonproprietary names that are similar to, but not the same as, those of their reference products or of

³ For the purposes of this response, we use the term “nonproprietary name” to mean the name of a drug or biological product other than the proprietary or “brand” name. Examples of nonproprietary names include the international nonproprietary name (INN) designated by the INN Expert Committee of the World Health Organization (WHO), the USAN (the drug substance name selected by the United States Adopted Names Council (USANC or Council)), and the FDA-designated proper name.

⁴ Supplemental Submission to Citizen Petition FDA-2013-P-1398 (May 4, 2015).

other biosimilars" (J&J Petition at 1). J&J notes that it "also support[s] the adoption of a policy that would require distinguishable nonproprietary names for all innovative biologics going forward" (J&J Petition at 1, note 1).

In support of its request, J&J asserts that distinguishable nonproprietary names are critical for patient safety, as biosimilar products are not the same as their reference products and also not identical to other biosimilar products with the same reference product. "By conveying similarity *and* difference, distinguishable names will be an essential tool for effective pharmacovigilance and for reducing the risk of inadvertent switching between products (i.e., switching without or contrary to the intent of the prescriber)" (J&J Petition at 2). J&J discusses its experience with Eprex/Erypo outside the United States, particularly in Thailand, in which the market presence of several erythropoietin products with shared nonproprietary names "confounded [J&J's] ability to identify the product(s) responsible for the safety signal" (erythropoietin antibody-mediated pure red cell aplasia (PRCA)) (J&J Petition at 2 to 5). J&J also notes that "reference products and biosimilars may 'drift' ... after approval in clinically meaningful ways due to intentional or inadvertent manufacturing changes" (J&J Petition at 5). J&J cites previous FDA statements regarding the need for a "distinguishable, nonproprietary name for safety purposes" (J&J Petition at 9, citing Letter dated Sept. 18, 2008, from Dr. Torti, Principal Deputy Commissioner and Chief Scientist, FDA, to Rep. Pallone, at 3).

B. Development of FDA's Policy on Nonproprietary Naming of Biological Products

FDA requested public comments (in connection with a November 2010 hearing under 21 CFR part 15 on implementation of the new licensure pathway for biosimilar products and interchangeable products) on whether biological products, including biosimilar and interchangeable products, should be given distinguishing nonproprietary names to facilitate pharmacovigilance.⁵ In addition, FDA requested public input (in connection with a separate part 15 hearing held in May 2012) on FDA's plans for development of future policies regarding biosimilar products, including guidance on naming issues.⁶

FDA also has received comments on one or more of the GPhA, Novartis, and J&J Petitions from Amgen, Inc. (December 20, 2013, and March 11, 2015);⁷ Genentech, Inc. (January 30, 2014);⁸ Biotechnology Innovation Organization (BIO) (January 31, 2014);⁹ Pharmaceutical Research and Manufacturers of America (PhRMA) (February 3, 2014);¹⁰ AbbVie, Inc. (February 5, 2014);¹¹ American Pharmacists Association (APhA) (February 26, 2014), National Association of Chain Drug Stores (NACDS), and National Community Pharmacists Association (NCPA) (February 26, 2014);¹² Global Healthy Living Foundation (February 26, 2014);¹³ National Council for Prescription Drug Programs (NCPDP) (February 28, 2014);¹⁴ Momenta Pharmaceuticals, Inc. (March 4, 2014);¹⁵ Alliance for Patient Access (March 10,

⁵ See "Approval Pathway for Biosimilar and Interchangeable Biological Products; Public Hearing; Request for Comments" (75 FR 61497, October 5, 2010).

⁶ See "Draft Guidances Relating to the Development of Biosimilar Products; Public Hearing; Request for Comments" (77 FR 12853, March 2, 2012).

⁷ See FDA-2013-P-1398-0003 (Amgen 2014 Comment); FDA-2013-P-1398-0022 (Amgen 2015 Comment).

⁸ See FDA-2013-P-1398-0004 (Genentech Comment).

⁹ See FDA-2013-P-1153-0002 (BIO Comment).

¹⁰ See FDA-2013-P-1153-0009 (PhRMA Comment).

¹¹ See FDA-2013-P-1153-0010 (AbbVie Comment).

¹² See FDA-2013-P-1153-0012 (APhA, NACDS, and NCPA Comment).

¹³ See FDA-2013-P-1153-0011.

¹⁴ See FDA-2013-P-1153-0017 (NCPDP Comment).

¹⁵ See FDA-2013-P-1153-0014 (Momenta Comment).

2014);¹⁶ GPhA (March 19, 2014, and April 14, 2015);¹⁷ National Association of Boards of Pharmacy (March 19, 2014);¹⁸ Prime Therapeutics (September 4, 2014);¹⁹ Pharmaceutical Care Management Association (PCMA) (September 26, 2014);²⁰ and Mylan, Inc. (July 21, 2015).²¹

In addition, FDA has held “listening” meetings with several organizations interested in sharing their views on biological product nomenclature. The following meetings took place after the Petitions were submitted, and a summary of these meetings has been posted to the Petition dockets: Express Scripts (December 9, 2013);²² GPhA (January 9, 2014, July 24, 2014, and January 30, 2015);²³ NCPDP (May 1, 2014),²⁴ American Medical Association (July 9, 2014);²⁵ Hospira Inc. (August 12, 2014);²⁶ Patients for Biologics Safety and Access (PBSA) (October 31, 2014);²⁷ Amgen, Inc., and Actavis Generics (November 18, 2014);²⁸ and Biologics Prescribers Collaborative (December 9, 2014).²⁹

In March 2015, FDA approved Sandoz’ biologics license application (BLA) for Zarxio (filgrastim-sndz), the first biosimilar product approved in the United States. FDA explained that “filgrastim-sndz” was a “placeholder nonproprietary name” and that this name was not reflective of an Agency decision on a comprehensive naming policy for biosimilar and other biological products. FDA further explained that FDA intended to issue draft guidance on how current and future biological products marketed in the United States should be named.³⁰

In August 2015, FDA published for comment draft guidance on the nonproprietary naming of biological products.³¹ In the draft guidance, FDA stated that shared nonproprietary names are not appropriate for all biological products, because it is important to clearly identify biological products to improve pharmacovigilance and, for the purposes of safe use, to clearly differentiate among biological products that have not been determined to be interchangeable. The draft guidance described a naming convention to effectuate this policy: the nonproprietary names of biological products licensed under the PHS Act, including newly and previously licensed products, would consist of a core name (typically the name for the drug substance adopted by the USAN) with an FDA-designated suffix attached by a hyphen. The suffix would be part of the product’s proper name and would be used to differentiate it from other products, but

¹⁶ See FDA-2014-P-0077-0012.

¹⁷ See FDA-2013-P-1153-0015 (GPhA 2014 Comment); FDA-2013-P-1153-0038 (GPhA 2015 Comment).

¹⁸ See FDA-2013-P-1153-0016.

¹⁹ See FDA-2013-P-1153-0025 (Prime Therapeutics Comment).

²⁰ See FDA-2013-P-1153-0026 (PCMA Comment).

²¹ See FDA-2013-P-1153-0039 (Mylan Comment).

²² See FDA-2013-P-1153-0005.

²³ See FDA-2013-P-1153-0021, FDA-2013-P-1153-0031, and FDA-2013-P-1153-0037.

²⁴ See FDA-2013-P-1153-0017.

²⁵ See FDA-2013-P-1153-0028.

²⁶ See FDA-2013-P-1153-0023.

²⁷ See FDA-2013-P-1153-0032.

²⁸ See FDA-2013-P-1153-0019.

²⁹ See FDA-2013-P-1153-0036.

³⁰ See “FDA News Release: FDA approves first biosimilar product ZARXIO,” available at <http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm436648.htm>.

³¹ “Nonproprietary Naming of Biological Products; Draft Guidance for Industry; Availability,” 80 FR 52296 (Aug. 28, 2015). A copy of the draft guidance is available on regulations.gov (see Docket No. FDA-2013-D-1543-0002).

would otherwise be devoid of meaning. The nonproprietary name designated for originator biological products, related biological products,³² and biosimilar products would include a unique (i.e., product-specific) suffix. However, FDA explained that it was continuing to consider whether the nonproprietary name for an interchangeable product should include a unique suffix or should share the same suffix as its reference product.

The draft guidance further explained that FDA was continuing to consider the most effective regulatory approach to implement the naming convention for currently licensed products. The draft guidance stated that, in the near term, FDA intended to assign distinguishing suffixes to a limited group of: (1) biological products that are referenced by approved or publicly announced pending biosimilar applications and (2) any related products to those reference products through rulemaking. On the same day the draft guidance was issued, FDA published for comment a proposed rule to designate new nonproprietary names containing suffixes consistent with the naming convention described in the draft guidance for six products.³³ FDA is continuing to consider comments on the proposed rule.

FDA has approved three additional biosimilar products following issuance of the draft guidance, and has designated nonproprietary names for each of these products consistent with the naming convention described in the draft guidance: Inflectra (infliximab-dyyb), biosimilar to Remicade (infliximab); Erelzi (etanercept-szzs), biosimilar to Enbrel (etanercept); and Amjevita (adalimumab-atto), biosimilar to Humira (adalimumab). FDA has not approved any interchangeable products.

Following careful consideration of comments, on January 13, 2017, FDA published the final naming guidance. Like the draft guidance, the final guidance states that biological products licensed under the PHS Act should bear a nonproprietary name that includes an FDA-designated suffix. The final guidance sets forth the naming convention FDA intends to use for biological products licensed under the PHS Act (the naming convention): FDA will designate nonproprietary names that consist of a core name (typically the name for the drug substance adopted by the USAN) with an FDA-designated suffix attached with a hyphen. Under this naming convention, the suffix designated in the nonproprietary name for newly and previously licensed originator biological products, related biological products, and biosimilar products will be a distinguishing suffix that is devoid of meaning and composed of four lowercase letters.³⁴ FDA is continuing to consider the appropriate suffix format for interchangeable products.

This naming convention will facilitate pharmacovigilance for originator, related, and biosimilar biological products containing related drug substances when other means to track a specific dispensed product are not readily accessible or available. Distinguishable nonproprietary names for originator, related, and biosimilar biological products will also facilitate accurate identification of these products by health care providers and patients. Further, distinguishing suffixes should help minimize inadvertent substitution of any such products that have not been determined to be interchangeable. Application of the naming convention to biological products licensed under the PHS Act should: (1) encourage routine use of

³² We use the term “related biological product” to mean a biological product submitted in a BLA under section 351(a) of the PHS Act for which there is a previously licensed biological product submitted in a different 351(a) BLA that contains a drug substance for which certain nomenclature conventions (e.g., USAN Guiding Principles) would be expected to provide for use of the same drug substance name.

³³ “Designation of Official Names and Proper Names for Certain Biological Products,” 80 FR 52224 (Aug. 28, 2015).

³⁴ As described in section II of the final naming guidance, the naming convention does not apply to certain biological products that also meet the definition of a device in section 201(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 321(h)), such as in vitro reagents (e.g., antibody to hepatitis B surface antigen, blood grouping reagents, hepatitis C virus encoded antigen) and blood donor screening tests (e.g., HIV and hepatitis C), and also does not apply to products for which a proper name is provided in regulations (e.g., 21 CFR part 640) or to certain categories of biological products for which there are well-established, robust identification and tracking systems to ensure safe dispensing practices and optimal pharmacovigilance (e.g., ISBT 128 for cord blood products and blood components).

designated suffixes in ordering, prescribing, dispensing, recordkeeping, and pharmacovigilance practices and (2) avoid inaccurate perceptions of the safety and effectiveness of biological products based on their licensure pathway, as described in detail in the guidance.

As described in the final guidance, FDA intends to designate nonproprietary names according to this naming convention at the time of licensure. FDA is continuing to consider the process for implementing the naming convention for previously licensed products but, in the near term, intends to assign distinguishing suffixes to a limited group of these products.³⁵ The guidance also states that FDA will accept submissions of prior approval labeling supplements that include proposed suffixes for use in the proper names of currently licensed biological products.

C. Legal Framework for Nonproprietary Names for Biological Products

The nonproprietary name, or “proper name,” of a biological product is different from a proprietary name, which generally is trademarked and registered for private use. Under the naming convention described in the final guidance, the “core” component of the proper name reflects certain scientific characteristics of the product, such as chemical structure and pharmacological properties, and assists health care providers in identifying the product’s drug substance. The suffix component of the proper name (and, when deemed necessary for safe use, a prefix component), distinguishes among originator, related, and biosimilar biological products that share the same core name.

1. Legal and Regulatory Background

For biological products licensed under the PHS Act, FDA designates the proper name in the license for use upon each package of the biological product (see section 351(a)(1)(B)(i) of the PHS Act and 21 CFR 600.3(k)). The USANC ordinarily will assign to a biological substance a name that the Council determines to be appropriate based on certain nomenclature principles. Prior to development of this naming convention, FDA would typically designate the USAN name as the product’s proper name on its license. Under this naming convention, FDA intends to attach a suffix (and, in some cases, a prefix) to the core (USAN) name. Although FDA typically designates the proper name of a biological product upon licensure, FDA also has the authority to designate proper names through regulation (see, e.g., 21 CFR part 640), or through approval of a supplemental application for a currently licensed product.

All biological products have a proper name; however, there is some ambiguity as to how the established name requirements of the Federal Food, Drug, and Cosmetic Act (FD&C Act) apply to biological products. Section 502(e) of the FD&C Act (21 U.S.C. 352(e)) requires drugs to include on the label the product’s “established name.” With respect to a drug or ingredient thereof, that term is defined in relevant part as: “(A) the applicable official name designated pursuant to [section 508 of the FD&C Act], or (B), if there is no such name and such drug, or such ingredient, is an article recognized in an official compendium, then the official title thereof in such compendium,³⁶ or (C) if neither clause (A) nor clause (B) of this subparagraph applies, then the common or usual name, if any, of such drug or of such ingredient.” In § 299.4 (21 CFR 299.4), FDA states that the established name of a drug ordinarily will be the official name or, if none exists, the compendium name or, if none exists, the common or usual name of the product.³⁷ Neither section 502(e) of the FD&C Act nor § 299.4 expressly addresses biological products licensed under the PHS Act.

Relatedly, section 508(a) of the FD&C Act (21 U.S.C. 358(a)) provides FDA with the authority to designate

³⁵ See *supra* note 33.

³⁶ Section 201(j) of the FD&C Act defines the term “official compendium” as “the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, official National Formulary, or any supplement to any of them.”

³⁷ See § 299.4(b) and (e) (21 CFR 299.4(b) and (e)).

the “official name” of any drug if the Agency determines that such action is “necessary or desirable in the interest of usefulness and simplicity.” Such official name “shall be the only official name of that drug . . . used in any official compendium published after such name has been prescribed or for any other purpose” of the FD&C Act. Section 508(b) and (c) set forth a procedure in which FDA reviews official names in compendia and may designate “a single official name” for various reasons, including when the existing “official name is unduly complex or is not useful for any other reason.”³⁸

Section 351(j) of the PHS Act states that “[t]he Federal Food, Drug, and Cosmetic Act, including the requirements under sections 505(o), 505(p), and 505–1 of such Act, applies to a biological product subject to regulation under this section, except that a product for which a license has been approved under subsection (a) shall not be required to have an approved application under section 505 of such Act.” Likewise, biological products meet the definition of a “drug” under section 201(g) of the FD&C Act, and FDA has long applied certain requirements of the FD&C Act to these products.³⁹ Although section 351(j) reflects Congressional intent for the FD&C Act to be generally applicable to biologics, the PHS Act and the established name requirement of section 502(e) of the FD&C Act provide distinct, and potentially conflicting, pathways for assigning nonproprietary names.

The Biologics Control Act of 1902 (1902 Act) first provided for Federal licensing of biologics,⁴⁰ predating the FD&C Act by 36 years, and the established name requirement of section 502(e) by 60 years. Relevant to nonproprietary naming, the 1902 Act required that “each package [of a biological product]⁴¹ . . . [be] plainly marked with the proper name of the article contained therein . . . ”⁴² The 1902 Act was reenacted by the PHS Act in 1944.⁴³ Currently, the law states that each package of a biological product must be “plainly marked with . . . the proper name of the biological product contained in the package.”⁴⁴ Since 1919, the biological product regulations have specified that the proper name is the name specified in the license of the product.⁴⁵ As described above, FDA has administered the PHS Act and its implementing regulations by designating the proper name at the time of licensure or by regulation.⁴⁶

By contrast, section 502(e) of the FD&C Act, which created the established name requirement, was

³⁸ According to § 299.4(e), FDA does not ordinarily designate an official name, except if: (1) the USAN or other official or common or usual name is unduly complex or is not useful, (2) two or more official names have been applied to a single drug or certain alike drugs, or (3) no USAN or other official or common or usual name has been applied to a medically useful drug.

³⁹ See, e.g., “Biological Products: Procedures and Review of Safety, Effectiveness, and Labeling,” 37 FR 16679 (Aug. 18, 1972) (“The review procedure proposed in this notice relies for legal authority on both the Federal Food, Drug, and Cosmetic Act and section 351 of the Public Health Service Act.”).

⁴⁰ Pub. L. 57-244, 32 Stat. 728 (1902).

⁴¹ The 1902 Act applied to “any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention and cure of diseases of man.” *Id.* Under current law, a biological product is defined as “virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings” (section 351(i)(1) of the PHS Act).

⁴² Pub. L. 57-244, section 1.

⁴³ Pub. L. 78-410, 58 Stat. 702 (1944).

⁴⁴ Section 351(a)(1)(b) of the PHS Act.

⁴⁵ Treasury Department, United States Public Health Service, Misc. Publication No. 10, Regulations for the Sale of Viruses, Serums, Toxins, and Analogous Products § 56 (1919); see also 42 CFR 22.81 (1938); 21 CFR 600.3(k) (2016).

⁴⁶ Responsibility for regulating biological products was transferred from the National Institutes of Health to FDA in 1972. Statement of Organization, Functions, and Delegation of Authority, 37 FR 12865 (June 23, 1972).

enacted in 1962 as part of the Kefauver-Harris Drug Amendments. The legislative history makes clear that the purpose of the established name was to encourage competition among drugs with the same “chemical structure” by providing a legal requirement that their label feature with sufficient prominence a nonproprietary name (determined by specified criteria)⁴⁷ in addition to any proprietary name.⁴⁸ We believe Congress did not intend for this provision to displace the Federal government’s role in naming biologics. As described above, since 1902, biologics were required to be identified by their proper name on the package. Since 1919, Federal regulations stated that this proper name must be the name specified in the license. The established name, by contrast, is determined by three different sources: the official name designated by FDA under section 508 of the FD&C Act or, if none exists, the compendium name or, if none exists, the common or usual name of the product. Accordingly, the established name requirement would be duplicative of the proper name and potentially conflicting.⁴⁹

As a matter of long-standing practice, FDA has identified the biological product nonproprietary name as the proper name, and it has distinguished biological products from those products that have established names. In regulations and guidance documents, FDA generally has recognized that there are different mechanisms to designate the nonproprietary name of drugs approved under the FD&C Act and biological products licensed under the PHS Act. For example, FDA’s labeling regulation provides that prescription drug labeling must include, among other things, the established name of the drug, if any, or, for biological products licensed under section 351 of the PHS Act, the proper name, including any appropriate descriptors.⁵⁰

2. FDA’s Interpretation of the Statutory and Regulatory Provisions Governing the Nonproprietary Names of Biological Products

Against this backdrop, FDA has interpreted section 351(a) and (j) of the PHS Act, section 502(e) of the FD&C Act, and its regulations in a manner that reconciles potential conflicts between these provisions and

⁴⁷ Before the 1962 Amendments, section 502(e) stated in relevant part that a drug would be misbranded “[i]f it is a drug and is not designated solely by a name recognized in an official compendium unless its label bears (1) the common or usual name of the drug, if such there be” 21 U.S.C. 352(e) (1958).

⁴⁸ S. Rep. 87-1744, at 18 (July 19, 1962) (“Many drugs are marketed under brand names which serve to identify a particular product coming from a particular source. It provides the incentive for the manufacturer to maintain quality surpassing the minimum. At the same time, the brand name does not sufficiently identify the chemical structure of the drug. The use of the generic or official name is important so that practitioners and pharmacists can turn to the official compendia and other literature to ascertain the qualities and specifications of the product, and the competing products.”); see Remarks of Senator Kefauver, 17 Cong. Rec. 5638 (April 12, 1962) (observing that the purpose of the legislation was to promote competition). Earlier versions of the bill used the term “official name” to describe the name required under section 502(e); as enacted, section 502(e) of the FD&C Act describes this name as the “established name,” and the “official name” is the name designated by FDA under section 508 of the FD&C Act. See H. Rep. 87-2526 (Oct. 3, 1962).

⁴⁹ This redundancy is emphasized by enactment of section 508 of the FD&C Act and its legislative history. See Remarks of Senator Kefauver, 17 Cong. Rec. 5642 (April 12, 1962). Regarding what is now section 508, Senator Kefauver explained that “[t]here is now no legal authority vested in the Secretary to determine official names of drugs. In most instances the manufacturers establish the common names as well as the brand names of drugs appearing in the official compendia.” *Id.* For biological products, however, the Federal government already designated the proper name in product’s license and had such authority since 1902.

⁵⁰ See 21 CFR 201.57(a)(2), 208.20(b)(1); see also “Prescription Drug Product Labeling; Medication Guide Requirements,” Final Rule, 63 FR 66378 at 66380 (Dec. 1, 1998) (noting that “[s]ection 208.20(a)(7) and (b)(1) now require that a Medication Guide contain the established or proper name of the drug *in order to recognize the terminology used for biologicals.* (See 21 CFR 600.3(k))” (emphasis added); “Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products,” Final Rule, 71 FR 3922 at 3937 (Jan. 24, 2006) (in comments concerning the highlights section of labeling, noting that “the final rule requires that the statement be placed on its own line directly below the established name of the product (proper name of the product for biological products) rather than on the same line as the proprietary name”).

further FDA's mission to protect the public health. The interaction between these statutory and regulatory provisions and the naming convention described in the final guidance generally will fall within one of three categories. After describing these three categories, we explain why our interpretations are both consistent with the applicable statutory and regulatory provisions and further critical public health goals.

First, in cases where there is no official name or USP monograph that potentially could apply to the product, section 502(e)(3)(C) states that the established name will be determined by the drug's common or usual name. For biological products, FDA considers the common or usual name to be the proper name assigned to the product in its license (including any designated suffix).⁵¹

As explained in the final naming guidance, the proper name of a biological product will typically consist of a core name, which is the USAN for the biological substance connected to an FDA- designated suffix with a hyphen. This approach is consistent with § 299.4(e), which states in relevant part:

The Food and Drug Administration will not routinely designate official names under section 508 of the act. As a result, the established name under section 502(e) of the act will ordinarily be either the compendial name of the drug or, if there is no compendial name, the common and usual name of the drug. Interested persons, in the absence of the designation by the Food and Drug Administration of an official name, may rely on as the established name for any drug the current compendial name or the USAN adopted name listed in USAN and the USP Dictionary of Drug Names.

FDA recognizes that USANs, which typically are assigned to a biological substance rather than a particular biological product, do not at this time include distinguishing suffixes. Notably, the regulation does not expressly address its application to biological products, which are assigned nonproprietary names in their licenses on a product-by-product basis. Thus, for a biological product with a proper name that features a suffix, the USAN will be part of, but not the entirety of, the common or usual name (and proper name). By incorporating the USAN into the proper name, however, the naming convention described in the final guidance is consistent with both the language and intent of this regulation.⁵²

Second, in certain cases, USP has published monographs for biological products. As described above, section 502(e)(3)(B) of the FD&C Act states that "if there is no [official name for a drug] and such drug, or such ingredient, is an article recognized in an official compendium, then the official title thereof in such compendium" constitutes the established name. A biological product is "an article recognized" in an official compendium only if its proper name matches the official title of a monograph, and it otherwise meets the identity and definition set forth in the monograph. Thus, at the time FDA is licensing a biological product, under FDA's interpretation of section 502(e), such a monograph would apply to the newly licensed biological product only if FDA designates a proper name in the license for the biological product that matches the official title of the relevant USP monograph, and the biological product otherwise meets

⁵¹ Given the widespread use of the proper name designated in the license in the health care setting, FDA considers the proper name to be the common and usual name of the biological product. Notably, the proper name is the name used throughout a biological product's labeling, including its prescribing information and on the principal display panels of the carton and container labeling. The name also is reflected in the Purple Book, displayed in drug information, and generally displayed as a drug name in electronic databases used to order, prescribe, dispense, and administer medicines to patients.

⁵² We also note that the preamble to the proposed rule for § 299.4(e) explained that "[f]or noncompendial drugs, a USAN will be the 'established name' because it is likely to be the drug's common and usual name. . . ." "Designated Names; Revocation of List of Official Names of Drugs," 47 FR 31008 at 31009 (July 16, 1982) (emphasis added). As recognized by this language, for noncompendial drugs, the USAN might not always constitute the common or usual name described in section 502(e)(3)(C) of the FD&C Act. For the naming convention described in the final guidance, the USAN will not constitute the entire common or usual name of a particular biological product.

the identity and definition set forth in that monograph.⁵³ Thus, if FDA assigns a proper name to the biological product that differs from the monograph's official title —for example, because the proper name features a suffix and the official title does not — the product would not be “an article recognized” in a USP monograph within the meaning of section 502(e)(3)(B). Accordingly, the established name of the product would be the common or usual name, which would be the proper name assigned in the product’s license for the reasons described above.⁵⁴

Finally, in certain cases, FDA may elect to assign official names (which may include a suffix) to biological products, in which case the established name is the official name under section 502(e)(3)(A). As described above, FDA has published a proposed rule to designate nonproprietary names containing suffixes consistent with the naming convention described in the draft guidance for six products.

The approach described above best reconciles the complex, and potentially conflicting, statutory and regulatory provisions regarding the nonproprietary naming of biological products.⁵⁵ Importantly, FDA’s approach preserves the Federal government’s long-standing role in designating the proper name of biological products. As explained above, FDA is aware of no evidence that section 502(e) of the FD&C Act was intended to displace the Federal government’s role in designating the proper name of biological products. Rather, Congress intended section 502(e) to serve an entirely different purpose by taking nonproprietary naming out of the control of drug manufacturers and increasing competition among certain drugs with the same chemical structure. Accordingly, FDA has interpreted the relevant statutory and regulatory provisions to allow the Agency to continue to exercise its authority to name biological products. Further, as described in detail below, FDA’s approach helps ensure the safe use of biological products and provides a critical tool for effective pharmacovigilance of these products.

Novartis argues that under section 502(e)(1)(A)(i) and (e)(3)(B) of the FD&C Act, if there is a USP monograph for a biological product, a “biosimilar will be deemed misbranded unless its label bears the official title recognized in USP-NF” unless FDA supersedes the existing compendial name using notice-and-comment rulemaking under section 508 of the FD&C Act (Novartis Petition at 5).⁵⁶ Under the approach described above, however, the established name of a biosimilar is the proper name designated in the license. Accordingly, the product would not be misbranded under section 502(e). We note further that the approach urged by Novartis — that the Agency defer to nonproprietary names established by USP, a nongovernmental body, without exercising its independent judgment — would be untenable for biological products. Such an approach would be inconsistent with FDA’s independent role in designating the proper name during licensure of a biological product. In exercising this authority, FDA intends to use its scientific judgment to assign proper names that help ensure safe use and adequate pharmacovigilance of these products.

D. Biologics Price Competition and Innovation Act of 2009 (BPCIA Act): Overview and Legislative History Regarding Naming

⁵³ C.f., 21 CFR 299.5 (Prohibiting a drug from using the name recognized in an official compendium, “unless such drug complies in identity with the identity prescribed in an official compendium under such recognized name.”).

⁵⁴ FDA notes that this approach to interpreting section 502(e) of the FD&C Act does not apply to non-biological-product drugs approved under section 505 because those drugs do not have a proper name that is assigned by FDA at the time of licensure or through regulation. C.f., Letter to Thomas P. Koestler, Ph.D. from Janet Woodcock, M.D., FDA Docket No. 96-P-0459, at 17-18 (Nov. 2, 1998) (stating that cyclosporine drug products that met monographs for “cyclosporine oral solution” and “cyclosporine capsules” could not use “microemulsion” in the established name).

⁵⁵ See *Watt v. Alaska*, 451 U.S. 259, 267 (1981) (noting that “repeals by implication are not favored” and that courts “must read the statutes to give effect to each if we can do so while preserving their sense and purpose” (internal quotations marks and citations omitted)).

⁵⁶ See also Novartis Petition at 4 (assigning different INNs to products that conform to an established compendial monograph in the United States would be inconsistent with current regulations governing USP name).

The BPCI Act was enacted as part of the Patient Protection and Affordable Care Act on March 23, 2010. The BPCI Act creates an abbreviated licensure pathway for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed biological reference product. The objectives of the BPCI Act are similar to those of the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98–417) (commonly referred to as the “Hatch-Waxman Amendments”), which established abbreviated pathways for the approval of drug products under the FD&C Act. The implementation of an abbreviated licensure pathway for biological products can present challenges, given the scientific and technical complexities associated with the larger and typically more complex structure of biological products, as well as the processes by which such products are manufactured. Most biological products are produced in a living system such as a microorganism, or plant or animal cells, whereas small molecule drugs are typically manufactured through chemical synthesis. Although the BPCI Act has some conceptual similarities with the generic drug approval pathway established by the Hatch-Waxman Amendments to the FD&C Act, the statutory approval standards for generic drugs and for biosimilar and interchangeable products differ in significant ways that reflect the scientific differences between small molecule drugs and biological products.⁵⁷

Section 351(k) of the PHS Act, added by the BPCI Act, sets forth the requirements for an application for a proposed biosimilar product and an application or a supplement for a proposed interchangeable product. Section 351(i)(2) of the PHS Act defines *biosimilarity* to mean “that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that “there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product” (see section 351(i)(2) of the PHS Act). A 351(k) application must contain, among other things, information demonstrating that the biological product is biosimilar to a reference product based upon data derived from analytical studies, animal studies, and a clinical study or studies, unless FDA determines, in its discretion, that certain studies are unnecessary in a 351(k) application (see section 351(k)(2) of the PHS Act). To meet the additional standard of “interchangeability,” an applicant must provide sufficient information to demonstrate biosimilarity, and also to demonstrate that the biological product can be expected to produce the same clinical result as the reference product in any given patient and, if the biological product is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the 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 (see section 351(k)(4) of the PHS Act). Interchangeable products may be substituted for the reference product without the intervention of the prescribing health care provider (see section 351(i)(3) of the PHS Act).

The BPCI Act did not amend any of the naming-related provisions in the PHS Act or the FD&C Act or otherwise direct how FDA must name biosimilar and interchangeable products. The GPhA Petition asserts that the absence of a provision in the BPCI Act addressing naming of biosimilar and interchangeable products limits FDA’s “specific authority” to require a separate INN for these products (see GPhA Petition at 2). A commenter suggests that Congress’s silence on naming was an endorsement

⁵⁷ For example, under the FD&C Act, an application for a generic drug must generally demonstrate that it contains the “same” active ingredient; dosage form; route of administration; strength; and, with certain exceptions, labeling as its reference listed drug (RLD) (section 502(j)(2), and (j)(4) of the FD&C Act). With rare exceptions, an approved generic drug is “therapeutically equivalent” to its RLD, which means that it can be substituted with the full expectation that it will produce the same clinical effect and safety profile as the prescribed RLD (see 21 CFR 314.3(b); see also Approved Drug Products with Therapeutic Equivalence Evaluations vii-viii (36 ed. 2016)). In contrast, under the BPCI Act, for example, biosimilar products are required to be, among other things, “highly similar to,” but not the “same” as, the reference product (section 351(i)(2) and (k)(2) of the PHS Act). The BPCI Act does not include express reference to substitution in the definition of “biosimilar” (see section 351(i)(2) of the PHS Act). The BPCI Act defines the terms “interchangeable” or “interchangeability” in reference to a product that is shown to meet the statutory criteria for demonstration interchangeability in section 351(k)(4) to mean that the “biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product” (see section 351 (i)(3) of the PHS Act).

of FDA's 2006 World Health Organization (WHO) submission, in which FDA stated, in part, that "INNs should not be used to differentiate products with the same active ingredient(s) when credible scientific data demonstrate that no pharmacologically relevant differences exist."⁵⁸ Several other commenters note that Congress' silence preserves FDA's existing authority to adopt a naming framework that features distinguishing names for biosimilar products.⁵⁹

As described above, FDA has long possessed statutory authority to assign nonproprietary names (i.e., proper names) to biological products.⁶⁰ Neither the PHS Act nor the FD&C Act directs how similar biological products must be named in relation to one another,⁶¹ and, in light of this ambiguity, FDA has discretion to exercise its statutory naming authority in a manner that is not arbitrary and capricious or manifestly contrary to the statute.⁶² To the extent that Congress's silence on naming in the BPCI Act should be given any legal weight, case law suggests that it would be viewed as an endorsement of this status quo.⁶³ Here, the status quo is that FDA has the authority and discretion to designate nonproprietary names for biological products. Further, several bills before Congress proposing to establish a biosimilar approval pathway addressed the naming issue, with some calling for biosimilar products and their reference products to have identical names and others calling for unique names.⁶⁴ Congress ultimately settled on statutory silence, lending further support to the conclusion that it intended to leave untouched FDA's discretion to determine an appropriate naming framework.⁶⁵

⁵⁸ Prime Therapeutics Comment at 3, note 2; Novartis Petition, appendix A.

⁵⁹ See, e.g., BIO Comment at 4-5, PhRMA Comment at 3.

⁶⁰ See section 351(a)(1)(B)(i) of the PHS Act and 21 CFR 600.3(k). As several commenters have pointed out, FDA has exercised its naming authority to require distinguishable nonproprietary names in past instances when the Agency believed that safety considerations compelled distinguishing names for related, but distinct biological products (see, e.g., tbo-filgrastim and ziv-aflibercept).

⁶¹ In its comments, Mylan argues that, because "strength always relates to a specific active ingredient," the "same strength" requirement of section 351(k)(2)(A)(i)(IV) of the PHS Act means "there would be no rational basis for requiring a biosimilar to have the 'same strength' as the reference product if the two products contain different active ingredients identified by different non-proprietary names" (Mylan Comment at 13). Mylan further argues that section 505B(m)(1) of the FD&C Act (21 U.S.C. 355c(m)(1), which states that a biosimilar product should be considered to have a new active ingredient for purposes of the pediatric assessment requirements of section 505B, would be made superfluous by distinguishable names for biosimilars, "since a product with a new non-proprietary name, by definition, contains a new active ingredient" (*Id.* at 14). Mylan appears to argue that both provisions reflect congressional intent that biosimilar products and reference products share the same active ingredient (except for purposes of section 505B), which Mylan then argues is probative of Congress's intent regarding nomenclature. Neither argument is persuasive. Both cited provisions of the BPCI Act address requirements that are wholly unrelated to the naming of biosimilar products. Further, both provisions must be read in context with section 351(i) of the PHS Act, which defines biosimilar products as, among other things, being "highly similar" to their reference products, not the "same" as their reference products.

⁶² *Mayo Found. for Med. Educ. & Research v. United States*, 62 U.S. 44, 55 (2011); *Chevron U.S.A. Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837, 843 (1984).

⁶³ See *Wyeth v. Levine*, 555 U.S. 555, 574-75 (2009) (concluding that Congress's failure to enact an express preemption provision in the FD&C Act for claims related to prescription drug labeling during the 70-year history of the Act was "powerful evidence" weighing against implied preemption).

⁶⁴ Compare, e.g., H.R. 1427, 111th Cong. § 3(a)(2) (2009) (proposed section 351(k)(6) of the PHS Act), with H.R. 1548, 111th Cong. § 101(a)(2) (2009) (proposed section 351(k)(10) of the PHS Act).

⁶⁵ See Letter dated November 13, 2013, from Senators Hatch, Eshoo, Alexander, Barton, Enzi, and Hagan to Commissioner Hamburg stating that "we want to assure you that it was the intent of Congress to provide the FDA with the flexibility to establish a science-based policy for nonproprietary naming of drug substances, and not to encourage the FDA to adopt a policy of either identical or differentiated naming. It is not the role of Congress to predetermine decisions that should be based on scientific evidence." FDA notes, however, that not all members of Congress agreed with that assessment. See Letter dated October 23, 2013, from Senators Rockefeller, Harkin, McCain, Nelson, Schumer, and Wyden to Commissioner Hamburg opining that "[i]f biosimilars are unable to share

II. DISCUSSION

A. Need for Distinguishable Nonproprietary Names for Biological Products, Including Biosimilar Products

With the passage of the BPCI Act, which established an abbreviated licensure pathway for products demonstrated to be biosimilar to or interchangeable with an FDA-licensed reference product, a growing number of biological products will be entering the marketplace. In addition, the option remains for an applicant to request licensure for a related biological product in a BLA submitted under section 351(a) of the PHS Act (i.e., a “stand-alone” BLA). As a result, the biological product marketplace will be much larger and qualitatively different than previously existed, which has led FDA to carefully consider how to best provide for safe use and pharmacovigilance of biological products.

A key question in this regard is whether the same or distinguishable nonproprietary names should be used for this class of products. As discussed below, FDA has determined that identical nonproprietary names are not appropriate for originator, related, and biosimilar biological products because of the need to clearly identify and differentiate among biological products to facilitate safe use and pharmacovigilance.

Accordingly, under the naming convention described in the final guidance, these products will have distinguishing nonproprietary names.⁶⁶

By differentiating these biological products from one another, the naming convention will help minimize inadvertent substitution. Inadvertent substitution may lead to unintended switching or alternating of biological products that have not been determined by FDA to be interchangeable. The designation of distinguishable nonproprietary names for these products will also facilitate pharmacovigilance in the setting of multiple biological products containing related drug substances. Application of the naming convention to biological products licensed under the PHS Act will also: (1) encourage routine use of designated suffixes in ordering, prescribing, dispensing, and recordkeeping practices and (2) avoid inaccurate perceptions of the safety and effectiveness of biological products based on their licensure pathway (which could be a possibility if, for example, suffixes were only required for biosimilar products).

Nonproprietary names are extensively used in ordering, prescribing, dispensing, and billing systems in the United States, and other product-specific identifiers, such as proprietary names or NDCs may not be available. Therefore, a naming convention that provides for distinguishing nonproprietary names will facilitate product-specific identification and differentiation amongst biological products that share the same “core” nonproprietary name component. For reference products and their corresponding biosimilar products, as well as for “stand-alone” BLAs for related biological products, a shared core name (typically the USAN drug substance name, when available) will indicate a relationship among the products, while the distinguishing suffixes will indicate that the products are distinct. To ensure the suffix is clearly understood to be part of the nonproprietary name and that the full name would be incorporated into electronic prescribing, ordering, dispensing, and billing systems in the United States, the suffix will be appended to the core name with a hyphen. The placement of the identifier as a suffix, rather than a prefix, should result in biological products with the same core name being grouped together in electronic databases to help health care providers locate and identify these products.

the same active ingredient name as the brand originator product, we believe the Congressional intent behind the [BPCI Act] would be undermined as would the safety and accessibility of affordable biosimilars.”

⁶⁶ As noted by the Petitioners, a small number of biological products licensed under the PHS Act currently have shared nonproprietary names (see Novartis Petition at 10, Table 1, which also includes certain products approved under the FD&C Act). FDA is continuing to consider the process for implementation of the naming convention described in the final guidance to previously licensed biological products, including products that currently share the same nonproprietary name. This naming convention also will apply to biological products that are approved under the FD&C Act on or before March 23, 2020, when such biological products are deemed to be licensed under section 351 of the PHS Act on March 23, 2020 (see section 7002(e)(2) through (e)(4) of the BPCI Act).

1. *Distinguishable Nonproprietary Names Should Help Ensure Safe Use*

GPhA and Novartis maintain that assigning unique nonproprietary names to biosimilar products would compromise patient safety (see GPhA Petition at 9-10, Novartis Petition at 5-7). FDA disagrees, for the reasons explained in this section and section II.B.3 of this response.

Assigning nonproprietary names that include a distinguishing suffix for originator products, biosimilar products, and related biological products will help health care providers and others accurately identify and differentiate among these products. This should increase the likelihood that the intended biological product will be prescribed and that a different product will not be inadvertently substituted for the prescribed product at the dispensing level. This will help ensure safe use for all biological products, including biosimilar products.

First, inadvertent switching between biological products that have not been shown to be interchangeable may affect immune response. In some instances, immune responses to therapeutic proteins may pose safety and efficacy issues. For example, immune responses can lead to significant clinical consequences, such as pure red cell aplasia; inhibition of the efficacy of therapeutics; and reactions, including serum sickness and anaphylaxis.⁶⁷ Individual patients can vary in their immune responses to protein products, and these differences can be caused by the same genetic components that have an impact on sensitivity to small changes in structure.⁶⁸ Thus, switching or alternating of biological products not determined by FDA to be interchangeable may raise unique safety concerns related to immunogenicity.

Second, a biosimilar product may be licensed for fewer than all of the indications or routes of administration previously approved for its reference product, and may be packaged in a different delivery system. Accordingly, inadvertent substitution of a biosimilar product could, in some cases, result in a patient receiving a product for a use for which it has not been approved (potentially compromising safety or efficacy), or a product with a different delivery system than the patient is expecting or accustomed to (potentially leading to medication errors when administering the product).

Third, the option remains for an applicant to request licensure for a “related biological product” in a BLA submitted under section 351(a) of the PHS Act (i.e., a “stand-alone BLA”) for which the applicant was not required to submit comparative data to any other biological product in support of licensure. Such products may also have different indications, dosage forms, or strengths from originator biological products. Thus, inadvertent prescribing or substitution of one such product for another could compromise safety or efficacy or lead to medication errors.

For these reasons, providers must be able to readily and reliably identify precisely which biological product they are prescribing to their patients, especially when the patient is already being treated with a biological product. Similarly, pharmacy staff must be able to understand precisely which product is prescribed to avoid inadvertently substituting a biosimilar product, a related biological product, or an originator biological product for the prescribed product.

The risks associated with inadvertent prescribing or dispensing would be exacerbated if related biological products or biosimilar products that have not been determined to be interchangeable with another biological product were to share an identical nonproprietary name with that product. Specifically, health care providers or pharmacists may assume, based on their knowledge of and experience with small-

⁶⁷ FDA's guidance for industry *Immunogenicity Assessment for Therapeutic Protein Products* (August 2014), available at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm338856.pdf>.

⁶⁸ Buck D., S. Cepok, S. Hoffmann, et al., “Influence of the HLA-DRB1 Genotype on Antibody Development to Interferon Beta in Multiple Sclerosis.” Archives of Neurology, 68(4):480-487, 2011.

molecule drugs, that biological products with the same nonproprietary name are fully substitutable.⁶⁹ In a recent survey of more than 400 pharmacists, “the majority of respondents (58%) believed that products sharing non-proprietary scientific names could be safely switched from a reference biological medicine to its biosimilar during a course of treatment and the same result would be expected with either of the products.”⁷⁰ Further, much of the prescribing in inpatient settings where biological products are commonly used is done by nonproprietary name rather than the proprietary or “brand” name,⁷¹ and electronic prescribing, ordering, and dispensing systems may use the product’s nonproprietary name as the primary or only means of product identification.⁷²

Incorporation of a distinguishing suffix in the nonproprietary names of biological products should increase the likelihood that the intended biological product will be prescribed and will not be inadvertently substituted at the dispensing level.⁷³ Specifically, incorporation of these suffixes into the nonproprietary

⁶⁹ A generic drug and its corresponding reference listed drug share the same nonproprietary name, reflecting the requirements that a generic drug has the “same” active ingredient as its reference listed drug. Moreover, with rare exceptions, a drug product that has met the approval standard for a generic drug under section 505(j) of the FD&C Act is designated as “therapeutically equivalent” to the reference listed drug (see FDA’s *Approved Drug Products with Therapeutic Equivalence Evaluations*, commonly referred to as the “Orange Book”). In contrast, given the complexity of biological products, it is not scientifically appropriate to conclude that such products are substitutable without the intervention of the prescribing health care provider in the absence of an FDA determination of interchangeability.

⁷⁰ *Naming and labelling of biologicals- the perspective of hospital and retail pharmacists*. Generics and Biosimilars Initiative Journal, Volume 5, 2016, Issue 4. (December 16, 2016).

⁷¹ Our evaluation of current electronic prescribing systems used in health care systems, together with our review of current guidelines published by pharmacy organizations, suggest that the use of nonproprietary names in prescribing is dominant in the inpatient setting and also likely to be substantial in clinic settings where biological products are commonly used. The American Society of Hospital Pharmacists (ASHP), an organization that enjoys wide membership and influence on inpatient hospital pharmacy practice, provides guidelines on preventing medication errors with chemotherapy and biological products. See ASHP Guidelines on Preventing Medication Errors with Chemotherapy and Biotherapy (ASHP 2014), item 7, page 234, and item 2 on page 236. In those guidelines, ASHP states that “When ordering chemotherapy agents the generic name (as approved by the United States Adopted Names (USAN) program) should be used. Brand names are not acceptable unless they aid in identifying combination drug products or a particular drug formulation (e.g. to distinguish between liposomal and nonliposomal product formulations).” Also, a recent survey of inpatient and outpatient e-prescribing programs in six major health care systems found that many relied predominantly or solely on the nonproprietary name to identify products because multiple educational and pharmacy practice organizations recommend using the nonproprietary name. The researchers further recommended that electronic systems should be consistently designed to embrace the use of the nonproprietary name as the product identity for the sake of consistency within and across health care systems. See Computerized Prescriber Order Entry Medication Safety (CPOEMS): Uncovering and Learning from Issues and Errors at page 49 (Brigham and Women’s Hospital, Harvard Medical School, Partners HealthCare 2014), available at <http://www.fda.gov/downloads/Drugs/DrugSafety/MedicationErrors/UCM477419.pdf>.

⁷² A review of the electronic systems that are commonly (and increasingly) used to prescribe, order, and dispense medications finds that there is substantial variation in how drugs are identified within health care institutions. Some exclusively list products by nonproprietary name, some prioritize the nonproprietary name, and some list both the brand and nonproprietary name. See *Computerized Prescriber Order Entry Medication Safety (CPOEMS): Uncovering and Learning from Issues and Errors* (Brigham and Women’s Hospital, Harvard Medical School, Partners HealthCare 2014).

⁷³ FDA has previously incorporated distinguishing features in the nonproprietary names of biological products that contain drug substances related to those found in previously licensed products to help minimize medication errors by: (1) preventing a patient from receiving a product different from what was intended to be prescribed and (2) reducing confusion among health care providers who may consider use of the same nonproprietary name to mean that the biological products are indistinguishable from a clinical standpoint. For example, FDA has used three-letter prefixes to distinguish Granix (tbo-filgrastim) from Neupogen (filgrastim) and Zaltrap (ziv-aflibercept) from Eylea (aflibercept). As explained in the final naming guidance, FDA now thinks that the distinguishing element should be connected to the core name as a suffix rather than as a prefix for the majority of products (so that products with related drug

product names listed in prescribing, ordering, and dispensing systems should assist prescribers in selecting the specific intended product, pharmacists in dispensing the correct product, and health care providers in administering the correct product. The presence of a distinguishing suffix should also serve as a reminder to health care providers that biological products containing drug substances with the same “core” name should not simply be assumed to be substitutable for each other. Instead, health care providers and information technology specialists who program electronic databases may consult the Purple Book (Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations), an online resource that lists all FDA-licensed biological products by their nonproprietary name and clearly identifies products that have been approved as biosimilar to or interchangeable with a particular reference product.⁷⁴ Finally, the consistent use of a distinguishing suffix for originator, related, and biosimilar biological products would remove ambiguity about the identity of the intended biological product. If a core name was used without such identifier, it may be unclear which of several biological products was intended to be ordered, prescribed, dispensed, or reported.

2. Distinguishable Nonproprietary Names Should Enhance Pharmacovigilance

Pharmacovigilance is the collection, detection, assessment, monitoring, and understanding of adverse effects associated with pharmaceutical products. Novartis “agrees that for pharmacovigilance purposes all drug products and biologics must be tracked” (Novartis Petition at 3). However, Novartis asserts that “a tracking system does not require, nor would it be helped by, unique INNs for biosimilars” (Novartis Petition at 3). Novartis maintains that the proprietary name of a product is more useful for tracking and tracing specific products, along with the NDC, manufacturer name, and batch and lot numbers. Further, Novartis opines that “[i]f there are any weaknesses in the current system with regard to the traceability of a specific product to an adverse event, such weaknesses are not related to the INN and must be addressed for all currently approved products” (Novartis Petition at 3; see also GPhA Petition at 3 and 6).

J&J maintains that “[t]he inability to identify the product a patient received or, after a patient has been switched between or among products, to identify which product that a patient received is responsible for an adverse event, will harm public health. Signals arising from a single product will take longer to detect. And when signals are detected, regulatory action (e.g., warnings, recalls) against an entire class of useful products may be necessary because the responsible product(s) is not known” (J&J Petition at 7). FDA disagrees with GPhA’s and Novartis’s assertion that a pharmacovigilance system would not be helped by distinguishable nonproprietary names for biosimilar products. It is FDA’s view that assigning a nonproprietary name that includes a distinguishable suffix to originator, related, and biosimilar biological products would improve pharmacovigilance for these products in both “active” and “passive” postmarketing surveillance systems.⁷⁵

The Agency considers appropriate pharmacovigilance fundamentally important for all biological products.

substances appear next to each other when products are sorted alphabetically by nonproprietary name), and that distinguishing prefixes should be reserved for special situations where the presence of a distinguishing suffix alone may not be sufficient to assure safe use.

⁷⁴ Similarly, FDA’s current thinking is that the labeling of biosimilars should prominently state that they have been approved as biosimilars to their reference products. See, e.g. the “Highlights of Prescribing Information” section of the FDA-approved labeling of Amjevita (adalimumab-atto), available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761024lbl.pdf, which states that “AMJEVITA (adalimumab-atto) is biosimilar* to HUMIRA (adalimumab).” See also the draft guidance for industry *Labeling for Biosimilar Products* (March 2016) at pages 8 to 9, available at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm493439.pdf>.

⁷⁵ See, e.g., Amgen 2014 Comment at 32-33 (“In the absence of distinguishable product names and product-specific billing codes there would not be an unique, verifiable identifier associated with an administered medicine in physician office and hospital out-patient setting. This could undermine the effectiveness of both the SRS [spontaneous reporting systems] and AS [active surveillance] systems.”).

Although safety of drug and biological products is rigorously assessed prior to approval, manufacturer-specific safety issues may arise post-approval with any marketed product, and therefore a robust pharmacovigilance program is essential to help ensure patient safety, which in turn enhances patient and prescriber confidence when using newly approved products. To ensure continued safe use of a biological product, appropriate pharmacovigilance requires that FDA be able to track adverse events to a specific manufacturer's biological product (and, as appropriate, to a lot or manufacturing site for a particular biological product), and that surveillance systems be sensitive to detect safety signals that could be related to product changes over time so that the Agency and the manufacturer can act swiftly and in a targeted manner to identify and address any problems that may arise (see Amgen 2014 Comment at 21-24; see also BIO Comment at 9-10). If the Agency cannot identify a biological product's manufacturer, remedial action (including recall) may implicate a broader set of products than would otherwise be necessary were more targeted information available, which may restrict patient access to safe and effective products for which no safety problem exists.

Pharmacovigilance systems, both active and passive, vary in their use of identifiers to differentiate between biological products, and may include the proprietary (brand or trade) name, proper name, manufacturer name, NDC number, lot number, and billing codes. Novartis and GPhA assert that the proprietary (brand) name of a product is more useful than the nonproprietary name for tracking and that biosimilar products with a unique manufacturer name, NDC, lot number and brand/trade name "will be readily distinguishable in the same manner as originator products are today" (see Novartis Petition at 3 and GPhA Petition at 4 and 7; see also Prime Therapeutics Comment at 6 to 7, Mylan Comment at 26, and Attachment to Momenta Comment at 16). These Petitioners and several commenters further discuss the utility of certain product-specific identifiers in the context of passive postmarketing surveillance, active postmarketing surveillance, pooling of safety data, and other pharmacovigilance considerations. We address each of these issues below.

a. Passive postmarketing surveillance

FDA uses the FDA Adverse Event Reporting System (FAERS), a "passive" surveillance system that compiles mandatory adverse event reports from manufacturers and voluntary reports submitted directly to FDA by health professionals and patients. FDA currently requires a minimum of four elements (identifiable patient, identifiable reporter, suspect product, and an event or fatal outcome) when a suspected adverse event related to use of drug or biological product is reported in FAERS.⁷⁶ However, many adverse event reports do not identify the suspect product by its proprietary name, and the overwhelming majority of reports do not include NDC numbers. Further, as discussed below, the availability of these identifiers (even when accurately reported) is insufficient to address concerns regarding pharmacovigilance. Accordingly, we believe that the use of nonproprietary names that include an FDA-designated suffix would offer a mechanism to improve product identification.

Surveillance systems such as FAERS have traceability weaknesses, which are primarily related to adverse event reports missing information such as the proprietary or trade name, nonproprietary name, NDC, manufacturer name, lot number, or relevant clinical information.⁷⁷ Similarly, reports submitted to the Vaccine Adverse Events Reporting System (VAERS) often specify a vaccine type (e.g., influenza vaccine),

⁷⁶ See the guidance for industry *Postmarketing Adverse Experience Reporting for Human Drug and Licensed Biological Products: Clarification of What to Report*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071981.pdf>.

⁷⁷ Dal Pan GJ, Lindquist M, and Gelperin K, "Postmarketing Spontaneous Pharmacovigilance Reporting Systems," Chapter 10, in *Pharmacoepidemiology*. 5th ed, edited by B.L. Strom and S. Hennessy. Etobicoke (Canada): John Wiley & Sons; 2012.

but do not specify the manufacturer, lot number, or other identifying information.⁷⁸ However, we disagree with GPhA's view that "education of physicians and pharmacists to include NDCs, manufacturer names, and other relevant identifiers on all safety reports" would be viable alternative approaches to distinct nonproprietary names (GPhA Petition at 3, see also Novartis Petition at 3). Although FDA has issued guidance to improve the quality of adverse event reports,⁷⁹ many reports continue to lack key information and product identification in such reports can be unreliable.⁸⁰ Among other things, this may reflect that health care providers who submit adverse event reports do not have information such as the NDC or manufacturer name readily available to them at the time of reporting. In addition, many adverse event reports are submitted to manufacturers or the Agency by consumers who likewise may not have access to such information at the time of reporting.⁸¹ Proprietary names, even when included in such reports, may not reliably identify the product that is the subject of the spontaneous adverse event report since misattribution to the originator product can occur with adverse event reporting.⁸² These traceability weaknesses are applicable to all currently approved products, and we have no data to suggest that product identifiers such as the lot number or NDC are more or less likely to be reported for biosimilar products compared to the originator product.⁸³

We do not agree with Novartis's assertion that products that "share INNs ha[ve] not resulted in any unique traceability issues" (Novartis Petition at 3), because such products can present challenges with traceability. The inability to track an adverse event to a specific product or products amongst several that share a single nonproprietary name could inhibit identification of an increase in adverse event reports associated with a particular product, especially one with a relatively small market share.⁸⁴ Although

⁷⁸ Although there are statutory requirements for recording and reporting certain information for vaccines (see 42 U.S.C. 300aa-25(a)), spontaneous adverse event reports may still contain incomplete information, and it is resource intensive to obtain the necessary information.

⁷⁹ See Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiology Assessment, March 2005. Available at <http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126834.pdf>. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. See also Specifications for Preparing and Electronically Submitting ICSRs and ICSR Attachments to FAERS, June 2013. Available from:

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM153588.pdf>.

⁸⁰ Getz KA, Stergiopoulos S, Kaitin KI. "Evaluating the Completeness and Accuracy of MedWatch Data." Am J Ther. 2014;21(6): 442-446.

⁸¹ See "FAERS Reporting by Healthcare Providers and Consumers by Year (as of November 2015)" available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070456.htm>.

⁸² See Bohn J, Kortepeter C, Muñoz M, Simms K, Montenegro S, Dal Pan G. Patterns in Spontaneous Adverse Event Reporting Among Branded and Generic Antiepileptic Drugs, Clin Pharm and Therapeutics 2015 May;97(5):508-517.

⁸³ We also recognize that there are inherent limitations to a voluntary reporting system for adverse events associated with the use of a drug, including but not limited to underreporting, duplicate reporting, and reporting biases. Furthermore, for any given report, the reported adverse event(s) may not be causally related to the product(s) reported to have been taken. The event may have been related, for example, to the underlying disease being treated, to other medical conditions, or to another product taken at the same time. The number of cases reported to FAERS cannot be used to calculate the incidence rates, to estimate drug risk for a particular product, or to compare risks between products. Accordingly, it is important to have complementary tools for pharmacovigilance, including active postmarketing surveillance.

⁸⁴ See, e.g., BIO Comment at 12 ("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

reported product characteristics and other information in the text of narrative in a case report may sometimes facilitate identifying the specific product, this information is often missing or insufficient. For example, the nonproprietary name “somatropin” (both an INN and USAN) is associated with at least 10 proprietary product names. FDA evaluated a sample of adverse event reports from FAERS associated with the primary suspect product reported as “somatropin,” and found that for about 20 percent of these reports, we were unable to readily track a case to a specific product. We believe that designating a nonproprietary name that incorporates a distinguishing suffix would improve product identification in adverse event reports.

As reflected in the above example, proprietary names may not be used routinely on spontaneous adverse event reports (particularly for secondary suspect or concomitant medications) because national health and patient safety organizations recommend the use of nonproprietary names for prescribing.⁸⁵ Thus, events may be reported to FAERS by health care providers using a product’s nonproprietary name.⁸⁶ Manufacturers also may elect to market a drug or biological product without a proprietary name, so the nonproprietary name may be the only identifier available for those products. Research on adverse event reporting for drugs has found that after generic entry, there is often a substantial increase in the number of reports that cannot be attributed to any manufacturer or that are mistakenly attributed to the reference listed drug even as the market share decreases for that product.⁸⁷ In addition, a manufacturer may market more than one product with the same or similar proprietary name, resulting in uncertainty when trying to identify a specific product.

NDC numbers can be used to identify manufacturer-specific information about a product, but are infrequently provided in spontaneous adverse event reports.⁸⁸ These numbers may not be available to the

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.”); PhRMA Comment at 8 to 9; Amgen 2014 Comment at 25.

⁸⁵ For example, United States Pharmacopeia (available from:

<http://us.vocuspr.com/Newsroom/ViewAttachment.aspx?SiteName=USPharm&Entity=PRAsset&AttachmentType=F&EntityID=96750&AttachmentID=787d5f50-d639-482b-8689-81bc1a4c0adb>; Institute for Safe Medication Practices (ISMP) guidelines for standard order sets (available from: <http://ismp.org/tools/guidelines/StandardOrderSets.asp>); American Society of Health-System Pharmacists (ASHP) guidelines on preventing medication errors in hospitals (available from: http://www.ashp.org/s_ashp/docs/files/medmis_gdl_hosp.pdf); and Larson CM and Saine D in the Medication Safety Officer’s Handbook (2013, Chapter 7, Safety in the Medication Use System, p 191).

⁸⁶ FDA previously has observed that “[d]ue 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.” (FDA Memo to File re: BLA 125294 for tbo-filgrastim, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/125294Orig1s000NameR.pdf (Ref. ID 3169145); see also BIO Comment at 13-14).

⁸⁷ See Bohn J, Kortepeter C, Muñoz M, Simms K, Montenegro S, Dal Pan G. Patterns in Spontaneous Adverse Event Reporting Among Branded and Generic Antiepileptic Drugs, Clin Pharm and Therapeutics, 2015 May;97(5):508-517. See also Lietzan EF, Sim LE, and Alexander EA. Biosimilar Naming: How Do Adverse Event Reporting Data Support the Need for Distinct Nonproprietary Names for Biosimilars? FDLI Food and Drug Policy Forum 2013;3(6): 1-18 (available at <http://www.fdl.org/docs/members-only/lietzan-faers-bio-final-3-27-13.pdf?sfvrsn=0>); see also PhRMA Comment at 5 (“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 [citing Lietzan article]... 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.”), and BIO Comment at 11.

⁸⁸ See, e.g., Lietzan EF, Sim LE, and Alexander EA. Biosimilar Naming: How Do Adverse Event Reporting Data Support the Need for Distinct Nonproprietary Names for Biosimilars? FDLI Food and Drug Policy Forum 2013;3(6): 1-18.

reporter either at the time of reporting or upon follow-up with the reporter. We agree that, as Amgen notes, “[i]t is particularly unlikely that AEs [adverse events] related to immunogenicity will be reported using an NDC, because these events can occur weeks or months after the biologic has been administered and the packaging has been discarded” (Amgen 2014 Comment at 45). FDA agrees that “[n]onproprietary names play an integral role in attribution of adverse events, because they are the only product-identifying information that routinely appears in adverse event reports” (Genentech Comment at 6). Nonproprietary names with distinguishing suffixes can assist in pharmacovigilance in passive postmarket surveillance systems where a product’s nonproprietary name is commonly recorded, while other identifiers like NDC numbers and lot numbers are not. Thus, distinguishable nonproprietary names for originator, related, and biosimilar biological products would provide another critical tool in uniquely identifying products and facilitating more precise adverse event reporting for these products.⁸⁹

GPhA and Novartis opine that requiring a biosimilar and its reference product to use different nonproprietary names would interfere with “pooling of safety data, detection of class effects and appropriate and timely response to safety alerts,” and would “necessarily decouple biosimilars approved in the [US] from safety data of the same products elsewhere in the world,” thereby impeding global pharmacovigilance (Novartis Petition at 7; see also GPhA Petition at 9 to 10).

FDA does not share these concerns. Distinguishable nonproprietary names for originator, related, and biosimilar biological products following the format described in the final guidance would preserve the ability to detect both product-specific safety signals and class effects, and would facilitate prompt evaluation of safety signals in passive (and active) postmarketing surveillance systems. In the absence of distinguishable nonproprietary names, there would be “forced pooling” of safety data on biological products that would impair the ability to detect safety signals associated with a specific product.⁹⁰ As J&J recognizes in its Petition: “[p]harmacovigilance systems must be sensitive enough to detect problems in a group of related products (i.e., biosimilars and their shared reference product), a subset of those products, or an individual product” (J&J Petition at 5). Thus, the use of proper names with distinct FDA-designated suffixes would not impede the “pooling of safety data, detection of class effects and appropriate and timely response to safety alerts.”

We recognize, however, that there may be operational challenges. For example, the selection of individual product names for the purposes of pooling or creating a class of products will depend on retrieval search tools and database structures for capturing INNs, USANs, and FDA-designated proper names.⁹¹ Foreign sources will continue to report adverse events by their INN (which may be different from the FDA-designated proper name or USAN). Although distinct suffixes offer the capability to drill down to a specific product in pooled data, unless foreign sources adopt similar nomenclature or database structures use a global unique product identifier, it may take additional effort to link a product marketed in other countries to a product marketed in the United States if that product is identified by different nonproprietary names (and possibly one or more different proprietary names) in other countries. Therefore, regulators, researchers, or others analyzing these data would need to use care when identifying and selecting individual products from United States and global safety reporting systems and other databases, to ensure that these sources contain comprehensive listings of nonproprietary names,

⁸⁹ See, e.g., Genentech Comment at 10 (noting that the NDC number, batch number, and lot number appear in only a small percentage of adverse event reports. Even when available, a distinct nonproprietary name will still provide an important back-up mechanism for identification if there is an error in transcription of these numbers); Amgen 2014 Comment at 43 (“To improve the robustness and accuracy of pharmacovigilance in a multisource biologics setting reporters should be encouraged to submit multiple, distinguishable identifiers... The brand name, if it exists for a product, is a potentially useful identifier. But, given the apparent bias of reporters towards incorrectly using the originator brand in spontaneous AE reporting, additional identifiers are required.”).

⁹⁰ See, e.g., BIO Comment at 12; see also PhRMA Comment at 9.

⁹¹ Assuming the product class is already correctly identified and grouped, there should be no impact on pooling or detecting class effects when using an established product class.

including INN, USAN, and FDA-designated proper names. FDA is considering how to minimize concerns related to the global impact of INNs that would differ from the FDA-designated proper name.⁹² We note that FDA participates in activities to harmonize global reporting and analysis of adverse events. Furthermore, license holders who have an approved product in the United States are required to report serious and unexpected adverse events, whether foreign or domestic.⁹³ In addition, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use recently harmonized the periodic reporting requirements to provide the global postmarket safety experience of an active substance available worldwide.⁹⁴

Novartis and GPhA maintain that the European experience with pharmacovigilance of EU-approved “biosimilars” supports their view that distinguishable nonproprietary names are not necessary for product identification (see Novartis Petition at 3; see also GPhA Petition at 6, 8, and 4, citing Vermeer presentation to the European Medicines Agency (EMA)). FDA is aware that most biosimilar products approved in Europe share INNs, and at least one study suggested that the practice of sharing of INNs does not appear to present unique challenges in Europe for identifying specific products.⁹⁵ However, in Europe, applications for medicinal products are required by the EMA to include a proprietary name, which is defined as a “brand name, or common name together with a trade mark or name of the manufacturer, or scientific name together with a trade mark or name of the manufacturer” (e.g., Filgrastim Hexal),⁹⁶ whereas biological products may be licensed and marketed in the United States without a brand name. FDA does not require a drug or biological product to use a proprietary name. Further, as previously noted, electronic ordering, prescribing, dispensing, and billing systems in the United States extensively use nonproprietary names, and may use such names as the primary or only means of identification. Accordingly, differences between the European and U.S. regulatory and health care environments make reliance on brand names as a primary means of achieving product-specific pharmacovigilance inadequate here.

Finally, it should be noted that GPhA incorrectly asserts that “when an adverse event is reported to FDA that triggers a need to investigate, the Agency typically contacts the physician and then checks with the pharmacist to determine the product's manufacturer and precise batch information. This specific information, not the product's INN, enables FDA and the actual manufacturer to investigate possible causes of the adverse event” (GPhA Petition at 7; see also Momenta Attachment at 19). In the last calendar year alone, FAERS received more than 1.7 million adverse event reports, of which more than 95 percent were submitted by manufacturers. FDA recommends that manufacturers “make a reasonable

⁹² See, e.g., PhRMA Comment at 9 (“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... 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”); see also Prime Therapeutics Comment at 8.

⁹³ See 21 CFR 600.80.

⁹⁴ Referred to as the Periodic Benefit Risk Evaluation Report (PBRER), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM299513.pdf>.

⁹⁵ A cross-sectional study of postmarket adverse event reports submitted to EudraVigilance between 2004-2010 revealed that for three products with an approved biosimilar (epoetin alfa, somatropin, and filgrastim), the specific suspect product was nearly always (96.2%) identifiable. Vermeer NS, Straus SM, Mantel-Teeuwisse AK, 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;36:617-625. A product was considered identifiable if the report contained the brand name or the INN plus the name of the marketing authorization holder.

⁹⁶ See: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31965L0065:EN:HTML>. See also Genentech Comment at 9; PhRMA Comment at 7; Amgen 2015 Comment at 2.

attempt to obtain complete information for case assessment during initial contacts and subsequent follow-up, especially for serious events.”⁹⁷ Although we request that manufacturers collect and report complete information, it is the nature of spontaneous reporting that key information is not always available (e.g., a vial containing the lot number may have been discarded), or the reporter may not respond to requests for follow-up information. When analyzing the reports in FAERS, FDA relies on multiple data elements for analysis. Depending on the nature of the safety issue, FDA may contact reporters to obtain follow-up information such as the lot number; however, the Agency does not have the resources to investigate missing data on all adverse event reports.

b. Active postmarketing surveillance

Active surveillance systems and spontaneous reporting systems (i.e., passive postmarketing surveillance) form a robust and integrated approach to pharmacovigilance. For active postmarketing surveillance, FDA uses the Sentinel System and other electronic health care databases. Through its Mini-Sentinel pilot, FDA created a distributed system used to better understand potential events by querying privately held electronic health care data, which consists primarily of administrative and claims data from health plans covering well over 100 million individuals. In addition, FDA leverages other types of electronic health care data, including electronic health records, inpatient data from collaborating hospitals, and data from numerous registries. The findings are analyzed in conjunction with other data, including data from passive surveillance systems such as FAERS.

At this time, successful use of Sentinel and other electronic health care databases for adverse event tracking relies on the standardized coding systems for capturing drug information in billing records. These coding systems vary based on the setting in which a drug is dispensed. Administrative health care claims databases capture data in a standardized format from three types of health care billing claims:⁹⁸ (1) prescription claims (NCPDP) from pharmacies, (2) medical claims (CMS1500) from physician offices, and (3) hospital claims⁹⁹ (CMS1450) from inpatient or ambulatory care facilities associated with a hospital. All three of these billing claims use different coding schemes. Prescription claims from outpatient pharmacies use NDCs. Medical and hospital claims use CPT/HCPCS¹⁰⁰ codes, billing codes required by the Centers for Medicare & Medicaid Services (CMS) and most insurers, to identify drug administration and medical procedure history. Specific drug claims are typically coded using “J” or “Q” codes in HCPCS.

Many therapeutic biological products are administered in settings such as physician offices or outpatient facilities where administrative and billing data do not routinely include product identifiers such as brand name, manufacturer name, NDC number, or lot number.¹⁰¹ Thus, active pharmacovigilance systems that

⁹⁷ See *supra* note 79.

⁹⁸ NCPDP (National Council for Prescription Drug Programs), CMS1500, and CMS1450 refer to the form type used to submit the claim for billing purposes.

⁹⁹ The common data model that Mini-Sentinel uses contains hospital discharge diagnosis and procedure codes (and does not contain drug administration data unless it is billed separately).

¹⁰⁰ HCPCS (Healthcare Common Procedure Coding System) consists of two principal subsystems, referred to as Level I and Level II. Level I is comprised of CPT (Current Procedural Terminology) codes, a numeric coding system maintained by the American Medical Association to identify medical services and procedures furnished by physicians and other health care professionals. Level II is a standardized alphanumeric coding system maintained by CMS that is used primarily to identify products, supplies, and services not included in the CPT codes.

¹⁰¹ See, e.g., Amgen 2014 Comment at 46 (“most therapeutic biologics are dispensed and administered in the hospital outpatient or physician office setting where NDCs are rarely used for either dispensing records or for billing transactions. Payer tracking systems do not regularly record the NDCs of biologics dispensed in the hospital outpatient and physician office settings, and Federal claims databases do not include routinely NDCs”); Vora JB. “Evaluation of Medical Specialty Medications: Utilization and Management Opportunities,” Commissioned by CVS Caremark; (April 8, 2014), p.3 (estimating that just over 50 percent of biological products, by value, are currently reimbursed under a medical benefit). Available at regulations.gov (FDA-2015-N-0648-0013).

use administrative and billing data have limited ability to track biological products that share the same nonproprietary name to the manufacturer.¹⁰² In ambulatory care facilities, such as physicians' offices, hospitals, and clinics, FDA's active post-market surveillance generally relies on HCPCS billing codes because NDCs generally are not available in billing records in these settings. HCPCS billing codes shared by more than one product do not distinguish a specific product. However, beginning January 1, 2016, CMS has required claims for separately paid biosimilar biological products to include a modifier that identifies the manufacturer of the specific product. Thus, the modifier distinguishes among biosimilar products that appear in the same HCPCS code but are made by different manufacturers.¹⁰³ The modifiers will enable FDA to rely on billing data to conduct active surveillance on individual manufacturers' products. The use of distinguishable nonproprietary names provides a mechanism for claims administrators to accurately select the correct modifier and verify that it is assigned in the claim for the administered biosimilar product. Therefore, a distinguishing suffix could aid in ensuring products, ordering systems, and billing codes are accurately linked to product-specific modifiers within HCPCS codes for biosimilar products.

GPhA states that "[s]ome have raised the concern that the Sentinel System does not always draw from databases that capture NDCs. We note, however, that the Sentinel System has little utility (Positive Predictive Values of less than 50%) in identifying even the most clinically pronounced outcomes of an immunogenic reaction, anaphylaxis and other hypersensitivity reactions. Thus, we believe it premature to point to the Sentinel System as a reason to change the current naming system, as development continues and the system can already accommodate NDCs" (GPhA Petition at 11).

The Sentinel System and other electronic health care databases for active postmarketing surveillance provide a pharmacovigilance tool that is complementary to passive postmarketing surveillance systems such as FAERS. For example, the databases queried by the Sentinel System are not dependent on recognition that a clinical event is drug related and thus not subject to the same underreporting or reporting bias. These databases also have a large number of exposures. These systems also allow FDA to make inferences about whether a particular drug is likely to be associated with a given outcome because we can find all the exposures to a particular drug and the clinical outcomes that occur in association with that drug, controlling for confounding factors, in a specific population. And, over time, the coding of adverse event outcomes in electronic data systems will be more readily identifiable with improvements in implementing standardized codes for medical outcomes (e.g., ICD-10-CM codes). When coupled with the improved ability to identify the biological products that is afforded by a naming convention that provides product-specific information, over time our ability to use active surveillance to detect, characterize, and understand safety data is expected to continue to improve.

Notwithstanding our expectations for improvements in active surveillance, our current capabilities allow us to calculate incidence rates and make inferences about whether a particular drug is associated with a given outcome. Experience has shown that, in the circumstances where certain drugs share the same nonproprietary name, data on individual products would be useful in attaining a product-specific understanding of adverse events and a more complete understanding of a given safety issue. For example, intravenous iron dextran products are thought by some in the medical community to differ in their rates of anaphylaxis. Because these products are grouped under one HCPCS code and share the same nonproprietary name, however, it has not been possible to fully investigate this hypothesis using electronic health care systems. In contrast, FDA was able to successfully detect differences in the rate of

¹⁰² See, e.g., Amgen 2014 Comment at 48 ("For AS [active surveillance], the NDC is useful primarily for biologics dispensed to patients by pharmacies, but it lacks utility for physician office or hospital administered biologics"); Amgen 2014 Comment at 36 ("It is important to consider that product brand names are irrelevant for active surveillance, and what matters is whether a unique billing code is assigned for an administered product.").

¹⁰³ See "Part B Biosimilar Biological Product Payment and Required Modifiers," available at <https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/Part-B-Biosimilar-Biological-Product-Payment.html>.

anaphylaxis between the other intravenous iron products that have unique nonproprietary names and individual HCPCS codes.¹⁰⁴

We note that an assessment of potential approaches to distinguish between biological products and enable product-specific active postmarketing surveillance viewed unique nonproprietary names as the best option without implementing new methodologies.¹⁰⁵ FDA concurs with the analysis that other alternatives would involve significant changes to health care system infrastructure.

c. Drug Supply Chain Security Act (DSCS Act)

The Drug Supply Chain Security Act (DCSC Act)¹⁰⁶ was enacted as Title II of the Drug Quality and Security Act (DQS Act) on November 27, 2013. GPhA proposes that “[p]assage of the [DSCS Act] changes the legal, regulatory and practical landscape. It likely answers completely many, if not all, of the arguments made in the [J&J] Petition and the Amgen Comments or renders them premature” (GPhA 2014 Comment at 11). GPhA contends that “[u]nder the Act, a national system for tracking and tracing of biologic and biosimilar medicines, as well as other drugs covered by the DQS Act, with substantial uniformity, will be in-place in less than one year, by January 15, 2015... The system, in either paper or electronic form, will from the outset be capable of use for all tracking and tracing purposes, including pharmacovigilance” (*Id.*). GPhA further asserts that the “requirement of the DQSA, that proprietary or established names are sufficient for use as ‘transaction information,’ itself refutes the argument that that ‘distinguishable names will be an essential tool for effective pharmacovigilance’ ” (*Id.*).

The DSCS Act, commonly referred to as the “track and trace” legislation, will enhance FDA’s ability to help protect consumers from exposure to drugs that may be counterfeit, stolen, contaminated, or otherwise harmful. The system will improve detection and removal of potentially dangerous drugs from the drug supply chain to protect U.S. consumers. However, it is not sufficient to identify and conduct surveillance of adverse events for biological products. Generally speaking, the DSCS Act does not require product tracing information¹⁰⁷ to be passed beyond a “dispenser” (in many cases, the pharmacy), nor must a dispenser’s dispensing records be captured as part of the DSCS Act product tracing requirements. Several exemptions to the statutory definition of “transaction” in section 581(24)(B) of the FD&C Act (21 U.S.C. 360eee(24)(b)) would limit the tracing of a product beyond the sale to the dispenser. The term “transaction” excludes the “dispensing of a product pursuant to a prescription executed in accordance with section 503(b)(1)” of the FD&C Act (see section 581(24)(B)(iv) of the FD&C Act). The term also excludes “intracompany” transfers of a product between affiliates and distribution among hospitals under common control (see section 581(24)(B)(i)-(ii) of the FD&C Act). Due to these exceptions, the person administering a biological product may not have access to the product tracing information for that product. In the inpatient setting, it is possible that some institutions will associate product tracing information from their pharmacies with individual patients’ records, but this practice would not be required by the DSCS Act. The DSCS Act also does not require tracing of products administered directly to patients in a physician’s office, because health care providers are not subject to the DSCS Act’s product tracing requirements.¹⁰⁸

¹⁰⁴ Wang, C., Graham, D., Kane, R., et al. Comparative Risk of Anaphylactic Reactions Associated with Intravenous Iron Products. *JAMA* 2015. 314(19): 2062-2068.

¹⁰⁵ Hennessy S, Leonard CE, Platt R, “Assessing the Safety and Comparative Effectiveness of Follow-on Biologics (Biosimilars) in the United States.” *Clin Pharmacol Ther.* 2010;87:157-159.

¹⁰⁶ 21 U.S.C. 360eee et seq.

¹⁰⁷ For purposes of this response, “product tracing information” refers to the “transaction information,” “transaction history,” and “transaction statement” described in section 581 of the FD&C Act.

¹⁰⁸ In some instances, a physician administering a biological product that the physician purchased from a wholesale distributor or manufacturer may have access to tracing information for that product. The term “dispenser” includes health care providers who administer drugs (see section 581(3) of the FD&C Act). Licensed health care providers, such as physicians, generally are exempt from the requirement that they capture records of product tracing information (see section 582(d)(5) of the FD&C Act), but the wholesale distributor, manufacturer, or repackager from

In addition, the use of standardized numerical identifiers (SNIs) that are part of the product identifier established by the DSCS Act, which will be phased in across the supply chain through November of 2020, does not ensure identification of biological products because, in some instances, the product identifier may not be imprinted on the actual unit of product dispensed to the patient, such as when a biological product is sold to dispensers in packages of multiple vials (see section 582(b)(2) (21 U.S.C. 360eee-1(b)(2), 582(e)(2), and 581(11)(A)-(B) of the FD&C Act). Moreover, the actual “package” of a product might be discarded before it is administered to a patient, so the product identifier may not be available at the time an adverse event is reported. In addition, for the product identifiers to be useful for pharmacovigilance, the patient or physician likely would need to decipher the product identifier’s SNI and record it manually into a patient record by reading the product identifier on the label or electronically by using equipment capable of reading the information contained in the barcode.

Although its comments are not entirely clear, GPhA appears to be arguing that the use of a proprietary or nonproprietary name, when combined with other information in the transaction information (e.g., the product’s NDC), allows “complete” tracing of a product from the manufacturer to the “ultimate user” (see GPhA 2014 Comment at 18). As described above, however, the product tracing information may not be available to the person administering the drug, nor will it include the dispensing of the product to the end user. Thus, even though the product’s transaction information would distinguish biosimilars from their reference products, it is not clear that this information would be available to the person reporting an adverse event or to a manufacturer who investigates an adverse event.

To the extent GPhA is arguing that the use of distinguishable nonproprietary names for different biological products is inconsistent with the requirements of the DSCS Act, the argument is unfounded. Nothing in the DSCS Act affects the statutory and regulatory provisions, described above in section I.C.1 of this response, that address the nonproprietary names of biological products.

3. Distinguishable Nonproprietary Names Are Not Generally Needed for Post-Manufacturing Change Products

The GPhA and Novartis Petitions contend that the “highly similar” standard that proposed biosimilars must meet (along with other applicable requirements) to obtain approval derives from, and is conceptually the same as, FDA’s approach to evaluating postapproval manufacturing process changes for a given biological product. These Petitioners argue that just as FDA does not require the nonproprietary name of a biological product to be changed to reflect product differences following a manufacturing process change, it is not necessary or appropriate to require distinguishing nonproprietary names for biosimilars (GPhA Petition at 4; Novartis Petition at 3).¹⁰⁹

In fact, these circumstances are quite different. First, FDA expects that a biosimilar product will be created using cells of a different lineage than those used for its reference product (or other biosimilars to the same reference product), as the cell lines generally are proprietary and/or patented. FDA also expects a biosimilar product will be developed using a different process than the reference product (or other biosimilars to the same reference product). In contrast, although some within-manufacturer changes involve multiple major process changes, many are small adjustments to one part of a highly defined process. We expect that, in most cases, the extent of differences between a biosimilar and its reference product will be greater than is typically the case between versions of a given manufacturer’s product before and after a manufacturing process change. Within-manufacturer changes thus do not generally

whom they purchased the product generally would be required to provide the product tracing information. Because physicians are not subject to the DSCSA’s product tracing requirements, however, they would not be required to keep or use the tracing information in any particular manner under the DSCS Act.

¹⁰⁹ Conversely, these Petitioners argue that if we were to require biosimilars to have distinct proper names from their reference products, we would be obligated to require proper names of biological products to be changed following manufacturing process changes.

raise the same safe-use problems described above.

Furthermore, pre- and post-change products typically only overlap on the market for a limited time; once the supplies of the pre-change product are no longer available, only the post-change product will be dispensed. Accordingly, there generally would be little, if any, public health benefit to requiring pre- and post-change products to bear distinguishing nonproprietary names. In fact, changing the nonproprietary product name following every process change would likely be quite confusing to both health care providers and patients, because a product marketed under the same brand name by the same sponsor would not have a single, consistent nonproprietary name over time.¹¹⁰

B. Other Considerations Regarding Distinguishable Nonproprietary Names

1. *Distinguishable Nonproprietary Names for Biological Products Would Not Communicate Regulatory Status*

Novartis expresses the concern that assigning unique nonproprietary names to biosimilars would imply that the nonproprietary name is intended to communicate an aspect of the product's regulatory status, "such as interchangeability or lack thereof" (Novartis Petition at 2). Novartis further contends that assigning distinguishing nonproprietary names to biosimilars for purposes of preventing inadvertent substitution "would necessarily create an inappropriate implication that all products with the same [nonproprietary names] are by definition interchangeable" (Novartis Petition at 6). Novartis contends that it should be FDA's determination and subsequent listing of a product as biosimilar to or interchangeable with another that should inform health care providers of the product's regulatory status, not the products' nonproprietary names (Novartis Petition at 5). In contrast, GPhA appears to contend that the proper names *should* convey an aspect of the products' regulatory status. Specifically, GPhA contends that "[s]hared [nonproprietary names] between a biosimilar and its [reference product] accurately reflect the regulatory determination that there are no meaningful clinical differences between these products and thus indicate that both produce the same clinical outcome" (GPhA Petition at 9).

FDA agrees with Novartis that the nonproprietary names of originator biological products, related biological products, and biosimilars should not be used to convey, or relied upon to determine, whether products are biosimilar to each other, and believes that the naming convention described in final guidance furthers this goal. Specifically, FDA expects that, by assigning suffixes to biological products irrespective of their licensure pathway — not just biosimilars — the nonproprietary name will serve only to identify the product. That is, the nonproprietary name would convey that the biological product contains a related drug substance (as reflected by the shared core name) but is distinct from any other biological product with the same core name but a different suffix. As more products are assigned nonproprietary names under the naming convention, and as more biosimilars are licensed with FDA-approved labeling containing biosimilarity statements,¹¹¹ health care providers who prescribe and dispense these products will become educated both about the naming convention and that the product's labeling, the Purple Book, or other appropriate resources should be consulted to determine which products with nonproprietary names that share a common core element have been determined by FDA to be biosimilar to a reference product.¹¹² FDA also will monitor implementation and use of the naming convention in the health care system carefully, and will engage in educational and outreach efforts on the naming convention as necessary.

¹¹⁰ That said, in special circumstances FDA might require a post-change product to be distinguished by name (potentially both proprietary and nonproprietary names) from a pre-change product. This could be appropriate, for example, if the change results in a lack of comparability and the manufacturer wants to keep both pre- and post-change products on the market.

¹¹¹ See *supra* note 74.

¹¹² As explained in the final guidance, FDA continues to consider the appropriate format for the suffix of interchangeable products, i.e., whether the suffixes of such products could or should be shared with those of their reference products. FDA has not yet approved any interchangeable products.

2. *Distinguishable Nonproprietary Names for Biological Products Would Not Disrupt Pharmacy Systems*

GPhA asserts that “the use of unique biosimilar non-proprietary names would disrupt the current pharmacy systems (where the U.S. established name would not be the same as its INN, and may not even match its USAN and this poses its own safety risks by interfering with the existing safety alert functions used today to protect patients” (GPhA Petition at 10; see also APhA, NACDS, and NCPA Comment). NCPDP commented that the “current industry norms for product classification enable decision making by both clinical and administrative users. Having the same root generic active moiety name for all products with the same chemical ingredient is a core principle in identifying products that should be associated with one another. For example, the National Library of Medicine’s RxNorm uses the active ingredient, among other things, to group products that are conceptually equivalent” (NCPDP Comment at 5-6). With respect to the RxNorm (which uses the descriptor “USAN + dosage form + strength” to facilitate standardized electronic prescribing information), Amgen notes that a “prescriber using RxNorm would be unable to specify the drug product intended for a particular patient if non-proprietary names were shared among biosimilars” (Amgen 2014 Comment at 45, note 209). NCPDP recommended that “biosimilar products maintain the same non-proprietary name for the root active moiety as their reference biologic counterparts” rather than using unique individual nonproprietary names, and further recommended that the “FDA and stakeholders consider solutions to retool such [electronic] systems to allow for tracking by NDC identifier. In addition, given the different systems and process standards used in inpatient and outpatient settings, best efforts must be made to ensure that solutions work for all practice settings.” (NCPDP Comment at 5-6).

With the introduction of more biological products, it is important to initiate and encourage routine use of suffixes in ordering, prescribing, dispensing, recordkeeping, and pharmacovigilance practices for biological products irrespective of their licensure pathway. A distinguishable suffix for originator, related, and biosimilar biological products would provide a consistent mechanism that is readily available and recognizable for patients and health care professionals, including providers and pharmacists, to correctly identify biological products. Regular use of such suffixes should help minimize inadvertent substitution and certain medication errors by helping to prevent a patient from receiving a product different from what was intended to be prescribed, and should facilitate manufacturer-specific pharmacovigilance by providing a means of determining which biological product was dispensed to a particular patient. With respect to NCPDP’s recommendation that “biosimilar products maintain the same non-proprietary name for the root active moiety as their reference biologic counterpart,” we note that under the naming convention, shared core names will indicate a relationship among products, while the products’ suffixes will indicate that the products are distinct.

An FDA-designated proper name for a biological product is not required to exactly match the USAN and/or INN. However, we recognize that if the USAN and/or INN do not match the FDA-designated proper name, then there is a need to ensure that the datasets that populate the nonproprietary name field for electronic ordering and dispensing systems, claims and adverse event databases, and electronic health records contain the distinguishing suffix as part of the nonproprietary name.¹¹³ To help with the implementation of

¹¹³ FDA has learned from its experience with Kadcyla, the breast cancer drug that FDA approved in February 2013. Kadcyla was approved with an FDA-designated proper name (ado-trastuzumab emtansine) that incorporated but did not exactly match its USAN (trastuzumab emtansine) because use of the Kadcyla USAN (trastuzumab emtansine) may cause confusion with Herceptin (trastuzumab) and result in medication errors (the dosing for Herceptin is significantly higher than for Kadcyla) and potential harm to patients. Shortly after approval, FDA was made aware that some drug information publications, compendia references, health information systems, and Web sites were using the Kadcyla USAN, which does not include the “ado” prefix and hyphen. Because of this risk of name confusion between Kadcyla and Herceptin, FDA issued an FDA Safety Alert to notify U.S. health providers in May 2013 (see

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm350817.htm>.) FDA subsequently modified its internal processes to ensure that FDA-designated nonproprietary names are available in reference files that are used to populate electronic data systems, including electronic prescribing and dispensing

the naming convention, FDA will continue to maintain a reference file on the National Library of Medicine's Daily Med Web site. These technical files can be accessed by the companies that generate and operate electronic pharmacy databases and can be used to ensure that nonproprietary names are accurately displayed. We intend to continue working with informatics stakeholders to maintain these reference files on nonproprietary names for biological products and to ensure that new and revised names are displayed accurately and consistently in all systems.

3. Stakeholder Concerns About Effect of Distinguishable Nonproprietary Names on Health Care Providers

GPhA and Novartis argue that assigning unique nonproprietary names to biosimilars would compromise patient safety (GPhA Petition at 9-10, Novartis Petition at 5-7). GPhA argues that although shared nonproprietary names would accurately reflect the regulatory determination that there are no clinically meaningful differences between a biosimilar and its reference product, "requiring a biosimilar and its [reference product] to use different [proper names] would, instead, inaccurately suggest that these products have meaningful clinical differences for patients" (GPhA Petition at 9).¹¹⁴ GPhA believes this could lead to prescriber errors "if, for example, a physician inadvertently double dosed a patient by prescribing highly similar products because he thought, based on their different [proper names], that they contained different active ingredients" (*Id.* at 9). Novartis notes that FDA has recommended against the use of prefixes and suffixes in proprietary names because of their ability to lead to confusion (Novartis Petition at 6).

GPhA and Novartis also express the concern that assigning distinguishing nonproprietary names to biological products could make prescribing by nonproprietary name (rather than brand name) more prevalent. These Petitioners argue that prescribing by nonproprietary name is more likely to lead to confusion because nonproprietary names are not specifically reviewed by FDA for their potential to create medication errors (GPhA Petition at 9, Novartis Petition at 6-7).

FDA disagrees. For the reasons discussed above in section II.A.1 of this response, the risks associated with inadvertent prescribing or dispensing would be exacerbated if related biological products and biosimilar products that have not been determined to be interchangeable with their reference products shared identical nonproprietary names with originator products.

Although GPhA appears to contend that if biosimilar products and their reference products shared identical nonproprietary names health care providers would accurately infer only that these products have no clinically meaningful differences, FDA is concerned that health care providers could mistakenly assume that such products are *fully substitutable* with, and not just biosimilar to, each other, because this is the case for most small-molecule drugs with identical established (i.e., nonproprietary) names.¹¹⁵ Furthermore, use of distinguishing suffixes would be highly unlikely to cause clinician confusion leading to double dosing because the nonproprietary names of biological products containing related drug substances would still share the same core name; only the suffixes would vary.

FDA understands that implementing the naming convention retrospectively (i.e., changing the nonproprietary names of previously licensed products) will take time, and that in the meantime, several previously licensed biological products would continue to share identical nonproprietary names. Novartis argues that this discrepancy could convey the mistaken impression that previously licensed products

systems, that rely directly on FDA as the source. There may be other stakeholders, including the electronic database vendors and the USNC, that FDA could partner with to ensure that nonproprietary names are universally displayed accurately.

¹¹⁴ See also Mylan Comment at 17.

¹¹⁵ See *supra* note 70 and accompanying text.

sharing the same nonproprietary name — products for which FDA has made no comparability determination — have been determined by FDA to be interchangeable with each other, “negatively impact[ing] the safe and rational use of these...medicines” (Novartis Petition at 6). Any such confusion is unlikely, because the prescribers and pharmacists who prescribe and dispense these products would be unlikely to attach new meaning to their shared nonproprietary names simply because the nonproprietary names of newly licensed biological products have distinguishing suffixes. Finally, FDA will monitor implementation and use of the naming convention in the health care system carefully, and will address any confusion that arises as a result through targeted outreach efforts.

Regarding GPhA’s and Novartis’s concerns about the use of nonproprietary names in prescribing, FDA first observes that prescribing by nonproprietary name is already common. Many generic drug products and products marketed under applications approved through the pathway described by section 505(b)(2) of the FD&C Act (21 U.S.C. 355(b)(2)) do not have brand names. Also, as discussed previously, many electronic prescribing, ordering, and dispensing systems use the drug or biological product’s nonproprietary name as the primary or only means of product identification.

Furthermore, FDA’s implementation of the new naming convention for biological products will include FDA review of the distinguishing suffix proposed for inclusion in the nonproprietary name for potential medication errors. FDA acknowledges that omitting or overlooking prefixes and suffixes in proprietary names of drug products has led to errors in which the wrong product has been dispensed, and it is possible that similar errors could occur if a distinguishing suffix incorporated into the nonproprietary names of biological products were overlooked or omitted. However, we expect this type of error would be *more* likely, not less, if biological products containing related drug substances shared identical nonproprietary names.¹¹⁶ Also, as more products are assigned nonproprietary names under the naming convention, health care providers who prescribe and dispense these products would increasingly expect to see suffixes in the nonproprietary names of all biological products, making any errors associated with leaving off or overlooking the suffix less common. And, most importantly, we expect that the widespread and growing use of electronic health records and computerized prescribing systems would diminish the potential for such errors. Electronic systems can link biosimilar products to reference products in a format that lends itself to ready use and selection by clinicians and pharmacists at all points in the prescribing, ordering, and dispensing process.

Accordingly, having considered the Petitioners’ concerns, FDA continues to believe that, as discussed in section II.A.1 above, incorporation of a distinguishing suffix in the nonproprietary name of a biological product would reduce (not increase) the likelihood of medication errors associated with the prescribing of biological products by their nonproprietary names.

4. Stakeholder Concerns About Effect of Distinguishable Nonproprietary Names on Patient Access

Novartis argues that assigning different nonproprietary names to biosimilars could unintentionally communicate increased caution or unfounded risk (see Novartis Petition at 2). Novartis and GPhA contend that distinguishing nonproprietary names could inhibit market competition and frustrate the core BPCI Act goal of expanding patient access to biologics (see GPhA Petition at 3-4, 9-10; Novartis Petition at 7). FDA disagrees.

First, FDA expects, based on comments received from physician and patient groups, that distinguishing nonproprietary names for substantially all biological products (including but not limited to biosimilars) would augment acceptance and uptake of biosimilars. The naming convention will help health care providers and patients more readily and accurately identify and differentiate among biological products containing related drug substances, and should give physicians and patients increased confidence that the

¹¹⁶ See section II.A.1.

prescribed product will be correctly dispensed and a different product will not be inadvertently substituted at the dispensing level.

FDA also does not agree that distinguishing names would inappropriately convey increased caution or unfounded risk. As discussed elsewhere in this response, biological products (in contrast to small-molecule drugs) have characteristics that make distinguishing nonproprietary names appropriate. Furthermore, as discussed in the final guidance, the inclusion of an FDA-designated suffix in the nonproprietary name of products licensed under section 351(a) or 351(k) of the PHS Act should have the added benefit of helping to avoid inaccurate perceptions of the safety and effectiveness of any subset of biological products based on their licensure pathway.

5. Nonmeaningful Suffixes

Although FDA's draft guidance proposed that suffixes be devoid of meaning, FDA asked for comment on whether suffixes should be devoid of meaning or meaningful (e.g., derived from the name of the license holder).¹¹⁷

FDA has concluded that the format of the suffixes designated under this naming convention should not be derived from the license holder's name. Such a suffix format could confuse health care providers and patients as to the license holder's identity if ownership of the product changes following licensure, potentially detracting from our pharmacovigilance goals. Alternatively, if FDA on a regular basis designated new suffixes following changes in BLA ownership, whether on its own initiative or in response to license holders' requests, this too could result in confusion amongst health care providers and patients who could mistakenly conclude that the new suffix indicated a material change in the product or discontinuation of the product, as opposed to merely a change in ownership.¹¹⁸ Furthermore, while suffixes derived from the names of license holders may produce suffixes that are generally more likely to be memorable than suffixes that are unique to each product and devoid of meaning, the increasing prevalence of electronic systems in the ordering, prescribing, and dispensing process reduces the potential utility of such memorability.¹¹⁹ Finally, suffixes that are devoid of meaning are potentially compatible with the "Biological Qualifier" (BQ) scheme proposed by the World Health Organization (WHO) in 2015,¹²⁰ whereas suffixes derived from the name of the license holder and shared across the license holder's product line would not be. We recognize that such compatibility may benefit both U.S. and international pharmacovigilance efforts.

¹¹⁷ "Nonproprietary Naming of Biological Products; Draft Guidance for Industry; Availability," 80 FR 52296 (Aug. 28, 2015).

¹¹⁸ As described in section I.B, FDA is continuing to consider the process for implementing the naming convention for previously licensed products but, in the near term, intends to assign distinguishing suffixes to a limited group of these products. To minimize potential confusion, FDA intends to work with stakeholders to educate the prescribing and dispensing communities on the nature of this one-time change in nonproprietary name.

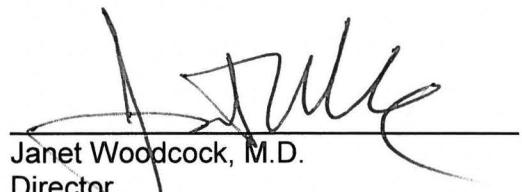
¹¹⁹ For example, health care providers using a prescribing system organized by nonproprietary name would need to accurately select the desired product from a list of products whose names have the same core components but different suffixes, but would generally not need to write the desired product's full nonproprietary name, including the FDA-designated suffix, from memory.

¹²⁰ The WHO has proposed a product identification scheme for biological products in which a unique identification code (the BQ) would be assigned to all biological substances consisting of four random consonants (and potentially including a two-digit checksum). The BQ scheme would be administered by the WHO INN Secretariat and would be available for use by individual regulatory authorities, including the FDA. See *Biological Qualifier: an INN Proposal* (World Health Organization, October 2015), available at http://www.who.int/medicines/services/inn/WHO_INN_BQ_proposal_2015.pdf?ua=1.

III. CONCLUSION

For the reasons given in this response, the GPhA and Novartis Petitions are denied, and the J&J Petition is granted to the extent it requests that biosimilar products have nonproprietary names that are similar to, but distinguishable from, the nonproprietary names of their reference products or of other biosimilar products.

Sincerely,



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