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U.S. Pharmacopeial Convention

February 13, 2017

Also submitted electronically to oira_submission@omb.eop.gov and https://www.regulations.gov

Office of Information and Regulatory Affairs
Office of Management and Budget
Attn: FDA Desk Officer

Re: OMB Control No. 0910-New, "Nonproprietary Naming of Biological Products" Docket No. FDA-2013-D-1543

Dear FDA Desk Officer:

The United States Pharmacopeial Convention (USP) respectfully submits comments on the Food and Drug Administration's (FDA) Final Guidance, Nonproprietary Naming of Biological Products (Final Guidance).

I. Legal and Regulatory Framework for Naming Medicines

USP acknowledges FDA's commitment to implement the Biologics Price Competition and Innovation Act (BPCIA) as well as the complexity and effort it takes to issue related Guidances and Rules. USP continues to be supportive of FDA's goals of enhancing pharmacovigilance, preventing medical errors, and ensuring the quality of medicines, and efforts to implement the BPCIA, the Public Health Service Act (PHSA), and the Federal Food, Drug, and Cosmetic Act (FDCA). USP encourages FDA to work with USP and other stakeholders as it implements policies surrounding nonproprietary naming of biologic products so that economic and regulatory costs are well understood and addressed and to achieve shared goals of improving patient safety and ensuring the quality of medicines.

In support of these goals and in an effort to help set forth a solution, USP submitted comments on FDA's Draft Guidance and FDA's Proposed Rule related to Naming of Biological Products (See Attachment A). As noted in our comments and those comments of other stakeholders, USP plays an essential role in designating nonproprietary names for medicines that has long been codified in the FDCA, working in cooperation with FDA and stakeholders. Those names are part of a well-established system that protects patients by ensuring medicines to USP's public quality standards. Disrupting the well-established and understood system could have unintended economic and public health consequences.

USP wants to reiterate our willingness to work with FDA as envisioned in the BPCIA and the FDCA to ensure that the link between naming and the quality of biologics is retained. This will allow practitioners, patients and industry to continue to rely upon USP public quality standards as a benchmark for medicine quality. These standards have helped to protect patient safety for nearly 100 years, while also facilitating competition.

II. Potential Public Health and Economic Impacts

Public comments on the Draft Guidance and Proposed Rule represented a wide range of patient, practitioners, healthcare facilities, manufacturers, insurers, and health plans, with diverse views about potential impact to patient safety, costs, and drug prices. USP encourages FDA and the Office of Management and Budget (OMB) to evaluate how the proposal could impact the naming of medicines, with resultant potential economic costs to regulated and nonregulated entities.

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- The naming system set forth in the Final Guidance may require hospitals, payers, providers, and others to engage in substantial information technology redesign and reprogramming. For example, hospital systems may have to modify medicine dictionaries in systems such as physician order entry, automated dispensing systems (e.g., Pyxis), and other systems and medical devices that rely upon incorporation of drug nomenclature.

- In addition to the private sector, affected entities could also include Federal, state, and local government health agencies including Medicare and Medicaid, and Veterans Administration and Department of Defense healthcare programs.

- The Final Guidance naming system may increase the cost of treatments for diseases that have significant morbidity and mortality rates and rely upon biologics, like insulins for diabetes. This is an important consideration when these medicines present a significant percentage of healthcare costs; for example, insulin makes up the largest share of gross spending for biologics in Medicare Part D.[1] Other biologic products administered in hospitals are also significant healthcare cost drivers.

In summary, USP encourages FDA and OMB to fully evaluate and understand the impact of the naming system outlined in the Final Guidance and is prepared to assist in any evaluation.

Thank you for the opportunity to share our views. If you have any questions, please feel free to contact Elizabeth Miller, Vice President, US Public Policy and Regulatory Affairs, at EHM@usp.org, (240) 221-2064.

Sincerely,

Jaap Venema, Ph.D
Executive Vice President and Chief Science Officer

[1] Medicare Payment Advisory Commission, October 7, 2016, Biosimilars in Medicare Part D, slide 6 (Insulin makes up the largest share of gross spending for biologics in Part D); http://medpac.gov/docs/default-source/meeting-materials/biosimilarsinmedicarepartd_oct16_pres_sec.pdf?sfvrsn=0 (accessed February 8, 2017).

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Attachment A

November 12, 2015

Also submitted electronically to http:/www.regulations.gov

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

Subject: Comments of USP on FDA's Proposed Rule, "Designation of Official Names and Proper Names for Certain Biological Products," Docket No. FDA-2015-N-0648.

Dear Sir/Madam:

The United States Pharmacopeial Convention (USP) appreciates the opportunity to comment on the Food and Drug Administration's (FDA) Proposed Rule, "Designation of Official Names and Proper Names for Certain Biological Products" (Proposed Rule). Under the Proposed Rule, FDA seeks to utilize Section 508 of the Federal Food, Drug, and Cosmetic Act (FDCA) to designate nonproprietary names, including distinguishing suffixes, for six specific biological products. The Proposed Rule implements the general approach set forth in FDA's Nonproprietary Naming of Biological Products Draft Guidance for Industry (Draft Guidance), FDA Docket No. 2013-D-1543.

USP and FDA share a common public health mission and the goal of improving patient safety across all medicines.[1] As we noted with respect to the Draft Guidance,[2] and as further explained below, FDA's proposed naming approach could create unintended consequences, including increased complexity and ambiguity—potentially placing patients at risk.

FDA's approach represents a significant departure from the existing, scientifically based nonproprietary naming system for drugs, including biological products, that has served patients, healthcare practitioners, and the public so well for over a century. This useful and simple system relies upon a single nonproprietary name for multiple products that share the same identity, as defined by USP's compendial standards.

FDA's designation of individual "official names" for the six products at issue in the Proposed Rule, and its overall approach in the Draft Guidance, runs counter to this longstanding naming convention. By employing different names for products that meet the same identity standard, FDA is using nonproprietary names for a purpose for which they were not intended (essentially no longer making them nonproprietary).

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[1] The long partnership between FDA and USP is further discussed at FDA-USP: Partners in Public Health at http://www.usp.org/sites/default/files/fda-exhibit/

[2] *See*, USP's Comments to the Draft Guidance at http://www.regulations.gov/#!documentDetail;D=FDA-2013-D-1543-0061.

This diminishes the nonproprietary name's usefulness and simplicity and may cause confusion in both scientific and healthcare settings.

USP has set forth below a comprehensive set of comments that highlight the following key concepts:

1. USP's well-established monograph system links naming with key identity and quality attributes of drugs, including biologics. The basic principle behind this system is that drugs that share the same identity, as set forth in the *United States Pharmacopeia-National Formulary* (*USP-NF*) monograph, also share the same nonproprietary name. The system is not intended to denote differences in regulatory status between products that, by virtue of having a common identity, share the same name and quality standard.

2. USP believes that designating manufacturer-specific official names as set forth in the Draft Guidance and Proposed Rule runs contrary to FDCA Section 508 goals of "usefulness and simplicity." As discussed in USP's comments to the Draft Guidance, USP believes there are ways of mitigating the concerns that prompted the Proposed Rule and Draft Guidance without disrupting well-established naming conventions nationally and internationally. USP continues to encourage FDA to consider labeling and other solutions as alternatives to the naming approach proposed in the Draft Guidance and Proposed Rule.

3. Whether FDA elects to follow longstanding naming conventions or adopts a new approach as described in the Proposed Rule and the Draft Guidance, the USP monograph system remains critical to, and embedded in, the regulatory system for drugs set forth in the FDCA and implemented by FDA. USP is prepared to work with FDA—as envisioned by the FDCA and reflected in our longstanding partnership—to ensure that the critical link between drugs and their public compendial standards is maintained.

Thank you for your consideration of these comments. If you have any questions, please contact Tina Morris, Ph.D., Senior Vice President, Science-Global Biologics, at tsm@usp.org or (301) 816-8397.

Sincerely,

Jaap Venema, Ph.D.
Executive Vice President and Chief Science Officer

I. USP'S Public Standards for Biologics

USP has played a key role in setting public quality standards for the identity, purity, quality, strength, packaging and labeling for drugs, including biologics, for nearly 200 years. Through this legally-recognized role, USP helps ensure that the medicines patients receive are of high quality, safe and effective. Public standards for medicines, including biologic medicines, are fundamentally important to all stakeholders and particularly the public at large. A public quality standard allows independent determination that a product has been made according to regulatory expectations for identity, purity, quality, and strength regardless of the manufacturer or manufacturing process. In today's increasingly globalized pharmaceutical marketplace, there is a critical need for a common public standard to assure the quality and consistency of biologic medicines moving in national and global commerce.

USP's standard-setting role historically has applied to biologics just as it has to non-biologic drugs. Biologics were first included in the *USP-NF* following the passage of the 1902 Biologics Act and in response to the health challenge posed in the 19th century by diphtheria. An antitoxin was developed to build up immunity in humans, but in 1901 contaminated diphtheria antitoxin was found to be the cause of a tetanus outbreak in New Jersey. Congress responded with passage of the Biologics Act, which was reenacted in 1944 as part of the recertification of the Public Health Service Act (PHSA). In 1904, the United States (U.S.) Surgeon General urged USP to adopt a standard for diphtheria antitoxin in *USP-NF*. USP responded and diphtheria antitoxin became the first official biological product admitted to the compendium.

Since that time, USP has established many scientifically based standards for a large and growing number of biologic substances and products across a broad variety of product classes -- from small peptides to very complex mixtures, including naturally derived, synthetic, and recombinant protein products, as well as advanced therapies (cells and tissues). Many of these products are essential medicines that are made by multiple manufacturers. Below are a number of examples of several biologics that have long been recognized in the *USP-NF* (Figure 1).

Figure 1. Example Biologic Monographs

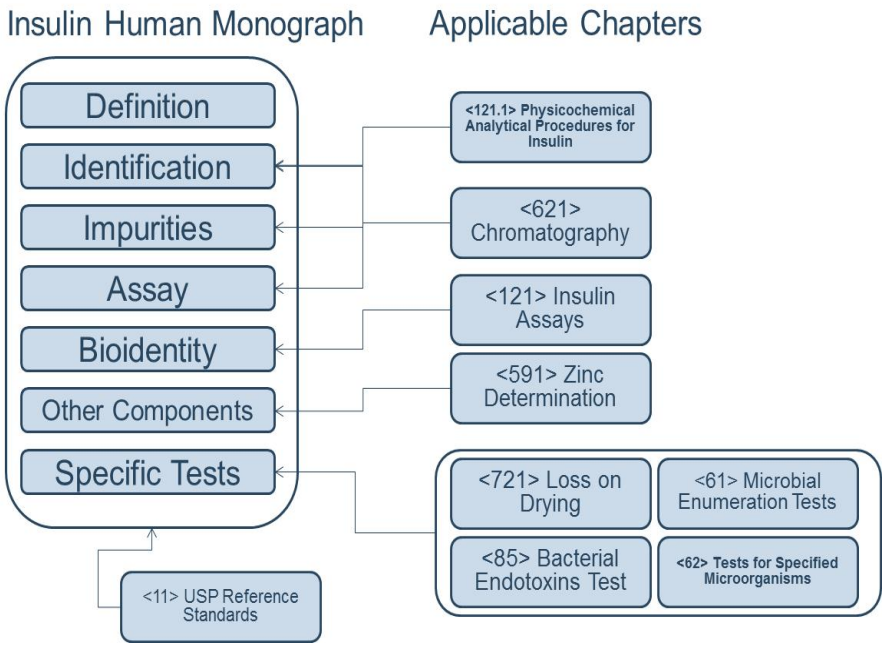
Product	Monograph in USP official since	Multi-Manufacturer products under the same official title?	Drug Substance and Drug Product Standards?
Insulin	1980, USP14, transferred from NF	yes	yes
Insulin Human	1985, USP21	yes	yes
Glucagon	1965, USP17	yes	yes
Somatropin	2005, USP28	yes	yes
Heparin	1950, USP14	yes	yes
Enoxaparin Sodium	2008, USP31	yes	yes
Pancrelipase	1980, USP14, transferred from NF	yes	yes

Recent cases of adulterated or substandard medicines occurring at a global scale affect biologics of all classes and licensure pathways—just because a drug is made by only a single or a few legitimate manufacturers in the U.S., does not mean that adulterated or substandard versions of this medicine could not enter the marketplace.[3] In these situations the availability of a public standard for independent testing is crucial as testing capability must extend beyond the affected manufacturer and the regulator. USP provides these public standards which, as detailed below, represent a multi-tiered set of reliable analytical tools that are based first and foremost on determining the identity of a drug and linking it to a scientifically based, useful, and simple name.

USP develops its standards through Expert Committees consisting of leading scientific expert volunteers from around the world. For the 2015-2020 cycle, USP has established four Expert Committees for Biological Standards, which draw additional advice from specialized Expert Panels formed on an ad hoc basis to deliberate specific scientific issues. In the course of the last cycle, USP formed over 25 biologics Expert Panels totaling more than 700 independent scientific experts. USP's Biological Expert Committees includes active participation by Government Liaisons, primarily from FDA but also other governmental agencies, and closely collaborate with USP's Nomenclature and Labeling Expert Committee which is responsible for USP's naming decisions.

USP's approach to setting quality standards for biologics substances and products includes product-specific monographs as well as general chapters that support and complement these monographs. The monographs and general chapters work in concert with each other as set forth below in Figure 2.

Figure 2. Insulin Human Monograph and Applicable Chapters



[3] 2012 Rituximab adulteration case: http://www.fda.gov/ICECI/CriminalInvestigations/ucm294706.htm.

USP monographs provide tests for critical quality attributes that define the biologic, as demonstrated in the left side of Figure 2. Biologic drug products and their ingredients can now be associated with comprehensive and specific testing expectations that have associated standardized procedures, acceptance criteria, and reference materials, covering both physicochemical attributes and biological activity (potency). Procedures are established based on common understanding of appropriate performance criteria for which the reference materials are confirmatory when testing is conducted.

While biologics are analytically more challenging and generally require more extensive combinations of tests than chemical medicines, USP's approach of combining common quality and testing expectations with product-specific ones can provide the complete set of measurement tools necessary for evaluating constantly evolving modern biologic medicines. As an example, the recently developed modern USP standards for Heparin Sodium contain five identification tests, including a very sophisticated ^{1}H-NMR procedure. These standards have proven effective in protecting the U.S. supply of unfractionated heparin and the entire supply of advanced low molecular weight heparin products such as Enoxaparin sodium through the starting material testing requirements in *USP-NF* monographs. USP is currently working side-by-side with FDA to further develop this portfolio of standards in anticipation of the possible reintroduction of heparin from bovine sources, so that applicable public standards will be available as soon as these drugs enter the marketplace. In this way, USP's compendial standards complement and support FDA's regulatory approaches to protect public health.

In order to preserve and further strengthen this multi-tiered safety net for all biologics, maintaining the integrity of the established naming systems will be of particular importance. An integral part of these systems is the clear link between the identity of a drug and a nonproprietary name that is scientifically based, useful and simple.

II. USP's Compendial Role in Federal Law

USP standards contained in the *USP-NF* have long been recognized in the FDCA, the relevant provisions of which apply equally to biologics and non-biologic drugs. The many references to *USP-NF* standards in the FDCA, and their use by FDA in regulating biologic and non-biologic drugs alike, underscore the importance of these standards to FDA's regulatory framework and the need to ensure that changes to FDA's approach to nonproprietary names preserve the overall structure and proper functioning of the current well-established naming system.

A. Specific Provisions Related to USP under the FDCA, BPCIA, and PHSA

The Biologics Price Competition and Innovation Act (BPCIA) creates an additional licensure pathway under the PHSA for biological products that FDA determines to be biosimilar to or interchangeable with a reference product according to criteria specified in the statute. USP's standards play a vital role as FDA proceeds to implement the BPCIA, just as they have historically played a role under the other provisions of the PHSA and the FDCA. The role of USP standards arises both in FDA's review and approval process and in FDA's evaluation of whether marketed products are misbranded or adulterated.

1. Approval and Licensure Pathways

USP standards are pertinent and helpful to applicants and FDA in the context of the application process for both NDAs and BLAs.[4] This is consistent with the direction from Congress that FDA "shall take measures to minimize differences in the review and approval of products required to have approved biologics license applications under section 351 of the PHSA (42 U.S.C. 262) and products required to have approved new drug applications under section 505(b)(1) of the FDCA (21 U.S.C. 355(b)(1)."[5]

FDA has long indicated, for example, that meeting USP standards for identity will be accepted as part of the required demonstration that an active ingredient in a generic drug product is the same as that of a reference listed drug under the FDCA.[6] For example, in the recent case of Enoxaparin Sodium (a low molecular weight heparin), FDA stated "*Instead, we adopted a more flexible approach, stating that we would "consider an active ingredient (in a generic drug product) to be the same as that of the reference listed drug if it meets the same standards for identity. We further stated that, in most cases, the standards for identity are described in the USP, although we might prescribe additional standards that are material to the ingredient's sameness. In the case of enoxaparin, there is a USP monograph and there are additional standards that are material to enoxaparin's sameness*."[7]

This is consistent with USP's longstanding view that *USP-NF* standards may help assess similarity with regard to certain key quality attributes of the product, including identity. However, of critical importance to the discussion of the Proposed Rule (and Draft Guidance), the fact that two drug products (including two biologics) share a compendial identity and therefore a nonproprietary name does *not* mean they are one and the same drug for approval/licensure purposes. Looking at it the other way, the fact that two products are not one and the same product for approval/licensure purposes does not mean that they cannot share compendial identity and a single nonproprietary name. FDA's Proposed Rule blurs this key distinction between compendial identity and regulatory status.

2. Compliance

USP standards also play a prominent role in FDA compliance and enforcement through the adulteration and misbranding provisions in FDCA Sections 501 and 502, both directly (through references in the FDCA to an official compendium) and indirectly (through FDA's use of USP standards as part of its authority to require current good manufacturing practices (GMPs)). Any drug, including a biologic product, that is recognized in *USP-NF* must conform to compendial standards relating to nonproprietary naming and identity, and strength, quality and purity, or risk being deemed adulterated and/or misbranded.

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[4] Reference to USP standards may satisfy relevant requirements for applicants: *See, e.g.*, the CMC (chemistry, manufacturing and controls) part of the technical section, regarding specifications and analytical methods necessary to assure identity, strength, quality and purity. 21 C.F.R. §§ 314.50(d)(1)(i), 314.50(d)(1)(ii)(a).

[5] FDA Modernization Act of 1997, § 123(f), Pub. L. No. 105-115.

[6] *See* preamble to FDA's final rule implementing Title I of the Hatch-Waxman amendments, 57 FedReg 17950, 17959 col. A (April 28, 1992).

[7] FDA's July 23, 2010, response to the Citizen Petition of Saventis Pharmaceuticals (enoxaparin) in Docket No. FDA-2003-P-0273, p. 10.

These provisions apply to all drug products, including biologics. The PHSA states explicitly that the requirements of the FDCA apply to biological products just as they apply to non-biological drug products, except that FDA licensure of a biologic under the PHSA obviates the need for an applicant to seek FDA approval of an NDA or ANDA.[8] In short, the USP monograph standards provide mandated benchmarks for determining whether a drug product is adulterated or misbranded (and therefore potentially unsafe and/or ineffective).

FDA's practice is consistent with these FDCA requirements, as it has applied the USP compendial standards to determine whether a drug, including a biologic, is adulterated and/or misbranded, as well as whether a product that does not comply with an existing *USP-NF* monograph should be approved in the first place.

B. USP Role in Naming and the FDCA's Misbranding and Adulteration Provisions

"Branded" (or "proprietary") drug names are used to distinguish drugs and biological products in the market. Drug substances and drug products also receive a *nonproprietary* name. The key feature of nonproprietary names under the well-established USP system is that they are designed to link under common names, products that share common attributes relating to identity. This link, in turn, dictates the common compendial quality standards applicable to each product bearing the same name.

A drug's nonproprietary name as reflected in the *USP-NF* informs the manufacturer's obligations under (1) the FDCA's misbranding provisions (by identifying the name that must be included on the labeling under FDCA Section 502(e)(i)(A)); and (2) the statute's adulteration provisions (by identifying the specific compendial standards the product must meet under FDCA Section 501(b)).

Under FDCA Section 502(e)(1)(A)(i) (21 U.S.C. 352(e)(1)(A)(i)), a drug is misbranded unless its label bears, to the exclusion of any other nonproprietary name, the product's "established name."[9] FDCA Section 502(e)(3) (21 U.S.C. 352(e)(3)) specifies that the "established name" of a drug or ingredient is:

> (A) The official name designated by FDA in accordance with section 508 of the FDCA;
>
> (B) The official title used for the drug or ingredient in an **official compendium such as *USP* or *NF***, if FDA has not designated a name under (A) [emphasis added]; or
>
> (C) If no name has been established under (A) or (B), the common or usual name of the drug or ingredient.

[8] *See,* 42 U.S.C. § 262(j). *See also* FDA, "Frequently Asked Questions About Therapeutic Biological Products" ("Biological products subject to the *PHS Act* also meet the definition of *drugs* under the [FDCA]" (emphasis in original) (last updated July 7, 2015).

[9] For biologics, Section 351 of the PHSA uses the term "proper name" instead of "established name," but FDA generally treats the terms as synonymous. See *Guidance for Industry, Product Name Placement, Size, and Prominence in Advertising and Promotional Labeling* (Nov. 2013) n. 4 *(*using the term "established name" to refer to both "established names" under the FDCA and "proper names" under the PHSA).

Under FDCA Section 502(e)(3)(B), if a drug, or ingredient, is an article recognized in an official compendium (*USP-NF*), the "official title" used for a drug or ingredient in the *USP–NF* becomes the established name.[10] Furthermore, if an official name is established by FDA in accordance with FDA Sections 502(e)(3)(A) and 508, it shall be the only official name used in the *USP-NF*.[11] In short, the *USP-NF* name – whether it is established by USP itself or by FDA through the section 508 process – is a critical component of the misbranding provisions of the FDCA.

USP-NF names likewise are critical to FDA enforcement of the adulteration provisions of the FDCA. Under FDCA Section 501(b), a drug or device shall be deemed to be adulterated if it "purports to be or is represented as a drug **the name of which is recognized in an official compendium**, and its strength differs from, or its quality or purity falls below, the standard set forth in such compendium. Such determination as to strength, quality, or purity shall be made in accordance with the tests or methods of assay set forth in such compendium."[12]

In addition to the specific statutory language above, FDA regulations concerning compendial names establish a pivotal role for *USP-NF* standards of identity, and reinforce the interconnection between USP's naming authority in 502(e) and the compendial adulteration standards in 501(b). Specifically, 21 C.F.R. § 299.5 provides that:

> (a) The name by which a drug is designated shall be clearly distinguishing and differentiating from any name recognized in an official compendium unless such drug complies in identity with the identity prescribed in an official compendium under such recognized name.
>
> (b) **The term drug defined in an official compendium means a drug having the identity prescribed for a drug in an official compendium.**
>
> (c) A statement that a drug defined in an official compendium differs in strength, quality, or purity from the standard of strength, quality, or purity set forth for such drug in an official compendium shall show all the respects in which such drug so differs, and the extent of each such difference.

Furthermore, under the adulteration provisions of the FDCA, Section 501(a)(2)(B) (21 U.S.C. 351(a)(2)(B)), relating to GMPs, states that an article is adulterated:

> "if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that

[10] In practice, drugs and biologics obtain an FDA-approved nonproprietary name upon approval of an NDA or BLA and such are considered "interim established names," that exists until USP designates a name. *See, Novartis v. Leavitt*, 435 U.S. 344 (D.C. Cir. 2006). Because both FDA and USP work closely as part of USAN on naming beginning with the early stages of drug development, and follow the same established naming principles, typically the name designated by USP is consistent with the interim name assigned by FDA.

[11] 21 U.S.C. § 358(a) ("Any official name designated under this section for any drug or device shall be the only official name of that drug or device used in any official compendium . . . .").

[12] 21 U.S.C. § 351(b).

such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess . . . ."

This statutory provision and the related GMP provisions in FDA's regulations and other authorities are complementary to each other and further articulate the role of USP standards of identity, and strength, quality, and purity.[13]

Taken together, the references to *USP-NF* standards throughout the FDCA and FDA's regulations confirm the fundamental role of the USP in FDA's regulatory framework. This system has as its centerpiece the nexus between the nonproprietary name assigned to a product and the standards by which the product is measured as a result. Put simply, (i) if a drug has the same identity as a drug recognized in *USP-NF* it must use the compendial name (whether that name is established by FDA or by USP), and (ii) once a drug uses the compendial name it must meet the compendial standards for strength, quality and purity. The name and the standards used to guide FDA's enforcement of the misbranding and adulteration provisions of the statute (including GMP requirements) are therefore inextricably intertwined.

III. The Proposed Rule and Section 508

Under the Proposed Rule, FDA is proposing to utilize Section 508 of the FDCA to designate nonproprietary names by including distinguishing suffixes for six biological products that fall under one of the following categories: (1) A reference product for an approved or publicly disclosed section 351(k) application – filgrastim (BLA 103353), pegfilgrastim (BLA 125031), epoetin alfa (BLA 103234), and infliximab (BLA 103772); (2) a related biological product to one of these reference products – tbo-filgrastim (BLA 125294); and (3) a biosimilar product – filgrastim-sndz (BLA 125553).

A. Section 508 of the FDCA

FDCA Section 508[14] gives the FDA the authority to designate an official name for drugs if it "determines that such action is necessary or desirable in the interest of usefulness and simplicity."[15] As discussed above, Section 508(a) also specifies that any official name designated under that section shall be the only official name of that drug used in an official compendium published after such name has been prescribed, thus preserving the linkage

[13] *See, e.g.,* FDA Compliance Policy Guide 420.000 ("Performance of Tests for Compendial Requirements on Compendial Products") ("[W]hen an official product purports to conform to the standards of the USP/NF the manufacturer must assure that each batch conforms to each monograph requirement."); 21 C.F.R. § 211.165(a).

[14] Section 508 also states that before FDA initiates a rulemaking proceeding to designate an official name for a drug already identified and recognized in an official compendium, it shall transmit in writing to the official compendium where the drug is identified and recognized the agency's request for an official name and allow the compendium 180 days to make a recommendation in response. 21 U.S.C. § 358(c). In addition to submitting comments on the Proposed Rule, USP recognizes Section 508 affords USP a specific timeframe for making naming recommendations.

[15] 21 U.S.C. § 358(a). *See, also* Proposed Rule, Designation of Official Names for Certain Biological Products, Docket No. FDA-2015-N-0648, p. 7 (Proposed Rule).

between the drug and its associated *USP-NF* quality standards even in cases where FDA chooses the nonproprietary name.[16]

Section 508 and FDA's regulation promulgated thereunder contemplate that FDA may publish names under the provisions of Section 508 when the Agency determines, among other things, that: (1) The USAN or other official or common or usual name is unduly complex or is not useful for any other reason; or (2) Two or more official names have been applied to a single drug, or to two or more drugs that are identical in chemical structure and pharmacological action and that are substantially identical in strength, quality, and purity.[17] FDA in practice and through its own regulation provides that FDA "will not routinely designate official names under section 508" of the FDCA.[18]

As set forth in USP's comments to the Draft Guidance, and as described above, USP has an established approach for setting standards and designating nonproprietary names for biologics that is scientifically based and has protected patients for over a century. USP believes that designating each drug substance and product that meet the same identity as set forth in the *USP-NF* with the same nonproprietary name already adheres to the criteria of usefulness and simplicity set forth in Section 508.

The Proposed Rule would deviate from these well-established conventions by conferring different nonproprietary names on products that meet the same compendial identity standards. Moreover, notwithstanding FDA's common practice of deferring to compendial names, the Draft Guidance suggests that FDA intends for its proposed approach to apply broadly with respect to all biologic products. We believe FDA's proposal, both in general and in connection with the products at issue in the Proposed Rule, to be contrary to the goals of clarity, usefulness, and simplicity in the assignment of nonproprietary names.

B. Specific Products and their Relation to USP Standards

Filgrastim provides a useful example of how USP's current naming conventions work, and how the Proposed Rule would disrupt those well-established conventions. USP has an official monograph for Filgrastim.[19] The Filgrastim monograph shows how (1) the USP monograph system links the nonproprietary name to the quality standards that FDA relies on under the FDCA to protect the public health; and (2) the existing system is premised on the understanding that two different products (such as the Amgen filgrastim reference product and the Sandoz filgrastim biosimilar) may have the same nonproprietary name.

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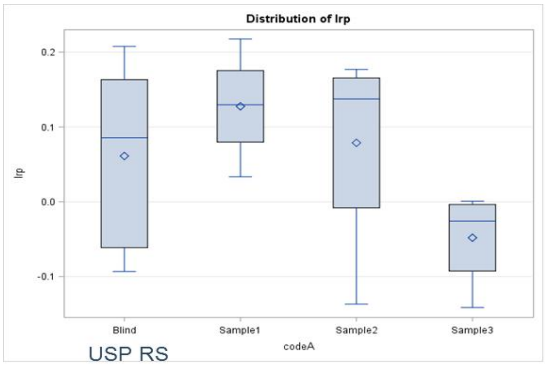
[16] *Ibid*.
[17] FDCA § 508(c) and 21 C.F.R. § 299.4(e)(1) and (2).
[18] 21 C.F.R. § 299.4(e). 21 C.F.R. § 299.4(e) states, "The Food and Drug Administration will not routinely designate official names under section 508 of the act. As a result, the established name under section 502(e) of the act will ordinarily be either the compendial name of the drug or, if there is no compendial name, the common or usual name of the drug."
[19] USP has yet to create a monograph for infliximab and pegfilgrastim (in development). USP's monograph proposal for epoetin alpha was proposed in Pharmacopeial Forum 41(5) under the monograph title of Epoetin. This recommendation by the USP Nomenclature and Labeling as well as the responsible biologics Expert Committee is based on the assessment that the proposed monograph does not include tests that could distinguish between the alpha and beta variants of epoetin and thus can be applicable to both.

USP's official drug substance monograph for Filgrastim was developed based on the innovator product (BLA 103353) and was first published for public comment in *PF36(5)*. The monograph became official on December 1, 2013 in *USP 36-NF 31 Supplement 2,* and is supported by two USP Reference Standards (RS): USP Filgrastim RS and USP High Molecular Weight Filgrastim RS. The monograph contains three requirements for identification:

- It meets the requirements in the Assay (Figure 3).
- The retention time of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained as directed in the test for Organic Impurities, Related Compounds (Figure 4).
- Peptide Mapping (Figure 5).

USP laboratories recently have evaluated three batches of the Sandoz Filgrastim biosimilar Filgrastim-sndz (BLA 125553) against the requirements of the monograph, including identity. The results for identity are summarized in Figures 3, 4, and 5 below and clearly demonstrate that the monograph is applicable.

Figure 3. Identification A - Meets Assay Requirements



Box Plot of Log Relative Potency by Sample

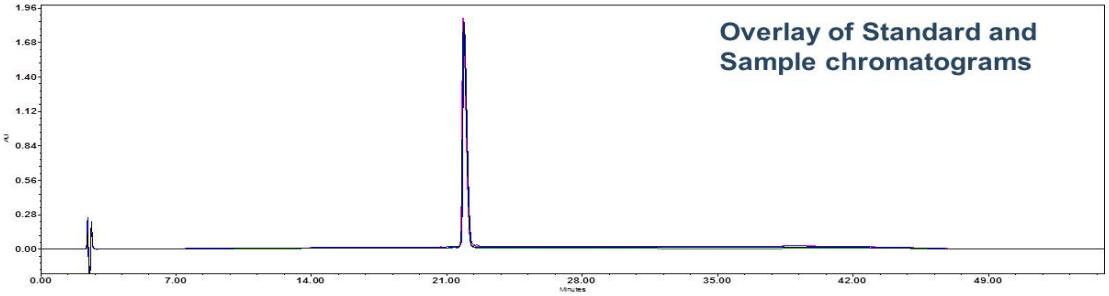
Sample	Relative Potency (Geometric Mean of Individual Plates)
Batch 1	102.86
Batch 2	98.82
Batch 3[2]	92.96

Identification A requires that the material meet the monograph acceptance criteria for assay: "The mean estimated potency is NLT 80% and NMT 125% of the stated potency."[20] It is important to note that "Identification A" via the application of a bioassay is a bioidentity test that applies a potency assay as a measure of molecule functionality. The USP Filgrastim RS for this purpose was calibrated against the existing WHO International Standard for Filgrastim. As shown above, the three batches meet the assay requirements of the monograph.

[20] Analysis of the relative potency shows that the Filgrastim-sndz is not statistically different than the USP RS when using both the USP RS and WHO International Standard as the reference. Batch 3 shows lower relative potency than the other 2 batches;, though statistically different than the USP RS, it is within the acceptable limits of the USP RS.

The next identification test is the reverse phase HPLC. Figure 4 below shows the test results and again the products meet the requirements.

Figure 4. Identification B – Reverse Phase HPLC

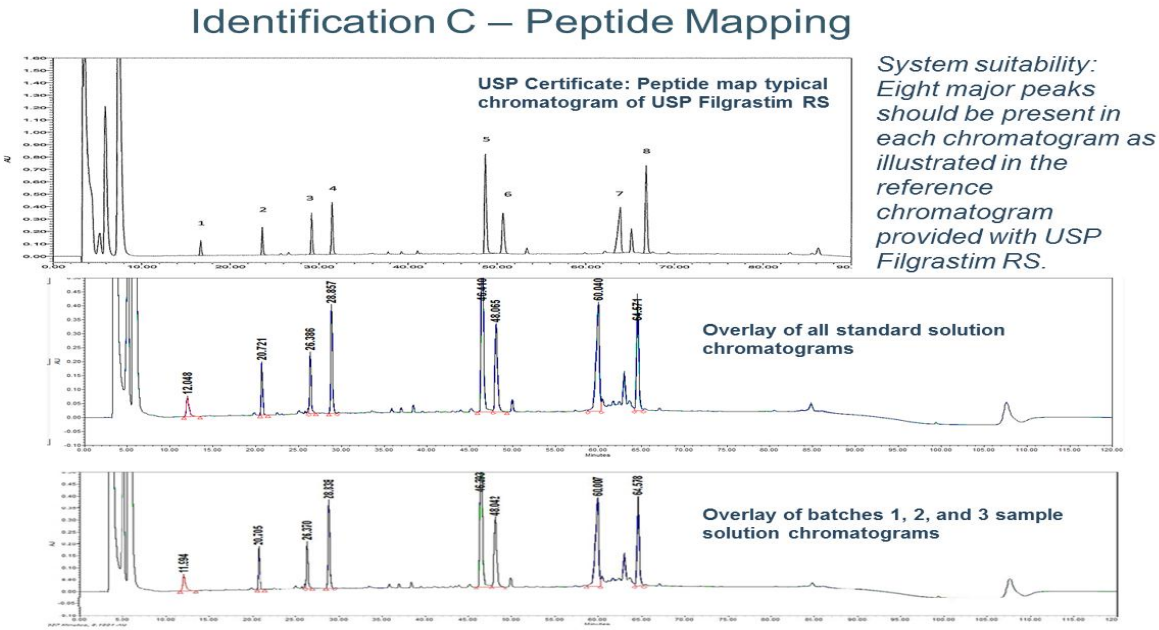


Identification B-Related compounds (RP-HPLC)	
Name	**RT (min) of Major peak**
USP Filgrastim RS	21.895
Filgrastim_Sndz_B237997	21.860
Filgrastim_Sndz_B269450	21.838
Filgrastim_Sndz_B269451	21.848

As shown above in an overlay chromatogram and described in the table below, the chromatographic profiles, as well as the retention times for the USP RS and the three tested batches of Filgrastim-sndz match and thus meet the requirements specified in the monograph.

Peptide Mapping is the third identification test. As shown in Figure 5 below, all 3 batches of Filgrastim-sndz tested provide a match to the peptide signature of the USP Filgrastim RS and fulfill the system suitability requirements of the test.

Figure 5. Peptide Mapping



Though not presented here, USP has additional data demonstrating that the Sandoz Filgrastim-sndz product complies with all requirements of the current official USP Filgrastim drug substance monograph. Under the current naming system and following sound scientific principles, the innovator product and the biosimilar have the same compendial identity and should share the same nonproprietary name.[21]

IV. Summary and Alternative Solutions

USP believes that the current nonproprietary naming system best serves the Section 508 goals of usefulness and simplicity. As set forth is USP's Chapter <1121> *Nomenclature* – a chapter developed in close cooperation with FDA to ensure coordination and consistency between USP and FDA in drug naming – "the value of designating each drug substance with one and only one nonproprietary name is important in terms of achieving simplicity and uniformity in drug nomenclature."

Names must be useful, simple, concise, and devoid of nonessential information to allow them to be easily read and understood by practitioners and minimize the potential for medication errors. USP has a long history of creating a taxonomy system that practitioners understand and depend upon to make rational decisions at the time of patient treatment.

The Proposed Rule would undermine the existing scientifically based, useful, and simple naming system that has served patients, practitioners and the public health so well for over a century. Furthermore, FDA's departure from the basic principles underlying the current nonproprietary naming system could create confusion and disharmony in the global marketplace. USP's comments to the Draft Guidance describe some potential effects of FDA's proposed approach on the global pharmaceutical marketplace, on prescribers and dispensers of drug products, and on the data systems that are critical to the effective cataloguing and tracking of drug products. *See* Attachment A at 14.

Nevertheless, if FDA chooses to exercise its authority under Section 508 with respect to the products described in the Proposed Rule (and/or others), the critical link between drugs and *USP-NF* quality standards should and will be maintained. This link is recognized to be essential even if FDA chooses an official name for a drug product. FDCA Section 508(a) states that an FDA-selected official name must be integrated into the compendial system; the statute does not envision a Section 508-named product untethered to the compendial standards that inform FDA's enforcement authority under the FDCA. USP is prepared to work with FDA to ensure the continued strength of the monograph system under any naming regime to ensure our shared public health mission is achieved.[22]

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[21] The current official title of the USP Filgrastim monograph also is consistent with USAN (1990) and INN.

[22] USP notes that while historically, the title specified for a monograph has been the official title for such article, there has been at least one instance when USP established an "official title" that was different than the monograph title. For example, Polyethylene Glycol NF Monograph has a specific labeling requirement for the official title. It reads: "Labeling: Label it to state, as part of the official title, the average nominal molecular weight of the Polyethylene Glycol. Label it to indicate the name and quantity of any added antioxidant." USP could leverage a combination of its *General Notices and Requirements to the USP-NF*, general chapters, and/or monograph labeling provisions to establish official titles (with different suffixes) for products covered by a single monograph.

As USP discusses in its comments to FDA's Draft Guidance (Attachment A at 14-15), we believe that the goals that FDA seeks to accomplish through changes to nonproprietary names for biosimilars and their RLDs can be accomplished through other means. For example, USP has pointed to labeling changes (separate from changes to the nonproprietary name itself) as a way of differentiating among products to address potential practitioner and patient confusion and ensure effective pharmacovigilance.

Specifically, USP proposes that FDA work with USP to leverage its recognized role in the misbranding and adulteration provisions of the FDCA by considering including the suffix, if one is determined to be needed, in USP monograph labeling requirements without designating it as part of the nonproprietary name. In addition to providing a resolution achievable under the FDCA, such a solution would be consistent with the WHO approach to the naming of biological products, thus resulting in one uniform global naming system. We strongly urge FDA to consider this labeling solution, and other solutions, as a way of addressing its concerns about safe use and pharmacovigilance while maintaining the integrity and effectiveness of the current naming system.

ATTACHMENT A

U.S. Pharmacopeial Convention

October 26, 2015

Also submitted electronically to http:/www.regulations.gov

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

8494 15 OCT 26 P 2:43

Subject: Comments of USP on Nonproprietary Naming of Biological Products Draft Guidance for Industry, Docket No. FDA-2013-D-1543

Dear Sir/Madam:

The United States Pharmacopeial Convention (USP) appreciates the opportunity to comment on the Food and Drug Administration's (FDA) "Nonproprietary Naming of Biological Products" Draft Guidance for Industry" (Draft Guidance). The Draft Guidance describes FDA's proposal that all biological products bear a nonproprietary name that includes a product-specific FDA-designated suffix. Along with the Draft Guidance, FDA issued a Proposed Rule, "Designation of Official Names and Proper Names for Certain Biological Products," that sets forth proposed names for six products based on the naming convention proposed in the Draft Guidance. USP will be commenting separately on the Proposed Rule.

USP shares FDA's goal of improving patient safety across all medicines. Throughout our nearly 200-year history we have worked to ensure that patients receive high-quality, safe and effective medicines. USP achieves this through our legally recognized role in setting public standards for the identity, purity, quality, strength, packaging, and labeling of drugs and biologics. As part of this role, USP is involved in a well-established drug naming system, which includes naming of biologics. USP remains committed to fulfilling this role as we have since the beginning of drug approval and biologic licensing laws in the United States.

USP acknowledges FDA's efforts to advance the successful implementation of the Biologics Price Competition and Innovation Act (BPCIA). We understand that the naming approach for biologics in the Draft Guidance reflects FDA's interest in preventing inadvertent substitution of and facilitating pharmacovigilance for biological products. At the same time, USP believes it is critically important to maintain a uniform and scientifically based naming approach that does not create unintended risks for patients and practitioners.

USP has set forth below a comprehensive set of comments that highlight the following key concepts: (1) USP has a well-established approach for setting standards for biologics and biotechnology-derived products that includes drug substances and drug products; (2) there is a scientifically based existing nonproprietary naming system, in which USP is a participant, for drugs and biologics that has protected patients for over a century; (3) USP appreciates FDA's challenge of ensuring safe use and facilitating pharmacovigilance, however, the use of a

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nonproprietary naming system to convey regulatory status could result in unintended consequences by employing the system in a way that was not intended; and (4) USP encourages FDA to consider alternative labeling solutions to the naming convention proposed in the Draft Guidance.

We appreciate FDA's efforts to address the challenges of implementing the biosimilars pathway, including naming, and acknowledge that these challenges are complex and often defy easy solutions. We stand ready to work collaboratively with FDA and stakeholders, using our current compendial process and legal recognition to help ensure that USP's quality standards continue to support and work in concert with the Agency's regulatory efforts to advance our common goal of protecting and promoting the public health. Our comments are further detailed below.

Thank you for your consideration of these comments.

If you have any questions, please feel free to contact Tina Morris, Senior Vice President, Science Global Biologics, at tsm@usp.org or (301) 816-8347.

Sincerely,

Jaap Venema, Ph.D.
Executive Vice President and Chief Science Officer

I. USP'S LEGALLY RECOGNIZED ROLE IN ADVANCING PUBLIC HEALTH

USP is a scientific nonprofit organization that since 1820 has worked to advance public health through standards that help ensure the quality, safety, and benefit of medicines. USP develops its standards through Expert Committees consisting of leading scientific expert volunteers.

Public standards ensure product quality and consistency and are a critical part of the overall safety net that protects our medicines and the patients who use them. A public quality standard allows independent determination that a product has been made according to regulatory expectations for identity, strength, quality, and purity regardless of the manufacturer or manufacturing process.

The critical importance of a scientific public standard has long been recognized by patients, practitioners, regulatory agencies, and Congress. Starting in 1848, Congress turned to USP as a means of documenting the quality of a medicinal article in the Import Drugs Act. By the beginning of the 20th century, a specific role for USP standards was included in federal law–first in the adulteration provision of the 1906 Food and Drugs Act, and later in various provisions of the modern Federal Food, Drug, and Cosmetic Act (FDCA, 1938), most notably in both the adulteration and misbranding provisions. These provisions and others specify USP's role in creating nonproprietary names and related standards for identity, as well as standards for strength, quality, purity, packaging, and labeling.

USP's role in naming has clear statutory recognition under the FDCA. Under section 502(e), a drug is misbranded unless its label bears, to the exclusion of any other nonproprietary name, the established name. Section 502(e)(3) specifies that the "established name" of a drug or ingredient is: (A) The official name designated by FDA in accordance with section 508 of the FDCA; (B) The official title used for the drug or ingredient in an **official compendium such as *USP* or *NF***, if FDA has not designated a name under (A); or (C) If no name has been established under (A) or (B), the common or usual name of the drug or ingredient. Under this provision, unless FDA has designated an "official name" under section 508, the "official title" used in the *United States Pharmacopeia and National Formulary (USP–NF)* becomes the established name. In order to designate an official name under section 508, FDA must go through a rulemaking process. FDA in practice and through its own regulation provides that FDA "will not routinely designate official names under section 508" of the FDCA.[1] If FDA does designate an established name under section 508, that name is to be used as the official name in the *USP-NF*.

Complementary to the naming provisions in Section 502 and 508, under FDCA 201(j) and 501(b) a drug "shall be deemed adulterated" if it purports to be, or is represented as, a drug

[1] 21 CFR § 299.4(e). 21 CFR § 299.4(e) states, "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 or usual name of the drug."

the name of which is recognized in an official compendium, and its strength differs from, or its quality or purity falls below, the standards set forth in such compendium.

These provisions apply to biologics just as they do to all other drugs, whether such biologics are approved under the FDCA or licensed under the Public Health Service (PHS) Act. This is confirmed in the case of PHS Act biologics by PHS Act Section 351(j), which states that all PHS Act biological products are subject to the FDCA, other than the requirement of having an approved application under FDCA Section 505. Accordingly, a biological product that is licensed under the PHS Act nevertheless is subject to FDCA regulatory requirements, including notably the adulteration and misbranding provisions in Sections 501, 502 and 508.

The Biologics Price Competition and Innovation Act (BPCIA, 2009) creates an additional licensure pathway under the PHS Act for biological products that FDA determines to be biosimilar to or interchangeable with a reference product according to criteria specified in the statute. Like all other approved and licensed biologics, these biosimilar and interchangeable products must comply with the provisions described above: they must bear the established name as designated by USP or FDA, and must conform to compendial standards related to strength, quality or purity or risk being deemed adulterated and/or misbranded.

II. EXISTING WELL-ESTABLISHED NONPROPRIETARY NAMING SYSTEM FOR DRUGS AND BIOLOGICS

Clear, consistent, and scientifically based names for drug substances and drug products are essential to helping practitioners, patients, and consumers use medications safely. Since USP began publishing the *United States Pharmacopeia* in 1820, our government and the public have relied on that compendium (now published together with the *National Formulary* as *USP–NF*) to provide nonproprietary names for medicines. USP's role in naming applies to both drug substances and drug products, and to all drugs, including biologics. USP has extensive experience in the naming of biologics, including naturally derived biologics (e.g., heparin), as well as recombinant protein therapeutics such as Filgrastim, Somatropin, Glucagon, and insulins. Despite the changes that have occurred over the years in the way these medicines are developed, manufactured, licensed, and/or administered, USP's role in naming has not changed; it is and has always been to provide scientifically based names that ultimately promote public health.

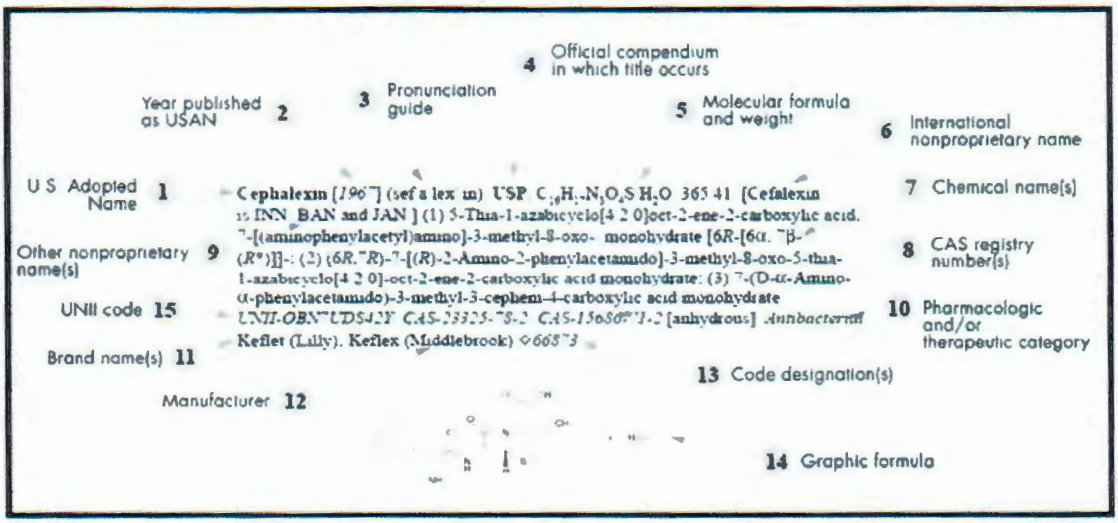
As medicines have evolved over the past nearly 200 years and the understanding of science has advanced, the time-tested approach of linking the official title in the *United States Pharmacopeia (USP)* on the label of a medicine to publicly available quality standards has created a single, consistent and reliable system proven to benefit public health. A USP monograph for a medicine helps ensure that what's on the label is actually in the bottle—that is, that the product is what it is purported to be, and in the right purity and strength. It does this by connecting the name of an article to a fixed standard of identity and quality (scientific criteria that uniquely identify the article).

USP's role in naming is part of a larger well-established naming system that has global significance. This system ensures the scientific consistency of nonproprietary names from the early drug development stage through the marketing of a drug or biologic. This system

involves the USP, FDA, and others working together to ensure a single naming convention, which to date has resulted in the establishment of well over 10,000 nonproprietary names for drugs and biologics.
This system starts early in the drug development stage (long before FDA approval or licensure of a medicine), when manufacturers seek an approved name for a drug substance. At an international level, the assignment of the International Nonproprietary Names (INN) is sponsored by the World Health Organization (WHO). In the United States, the United States Adopted Names (USAN) Council provides nonproprietary names for active ingredients. Founded in 1961, USAN is sponsored by the American Medical Association, the American Pharmacists Association, and USP, with active participation by FDA. Decisions reached by the USAN Council are unanimous and the results have been published by USP continually since 1963 in the *USP Dictionary of USAN and International Drug Names*.

Below is a USP-USAN Dictionary Entry that identifies all the names, codes, and identifiers that help link together all the relevant information on a given substance (Figure 1). This information includes a unique ingredient identifier (UNII) for each substance, generated by the joint FDA/USP Substance Registration System (SRS) which supports health information technology initiatives.

Figure 1.



In practice, this naming system is a very collaborative effort. USAN works closely with INN so that in most situations these names are aligned and a USAN name will be afforded INN status and vice versa. Neither USAN nor INN is recognized in federal law, and about 75% of the drug substances named by these organizations never actually make it to market.

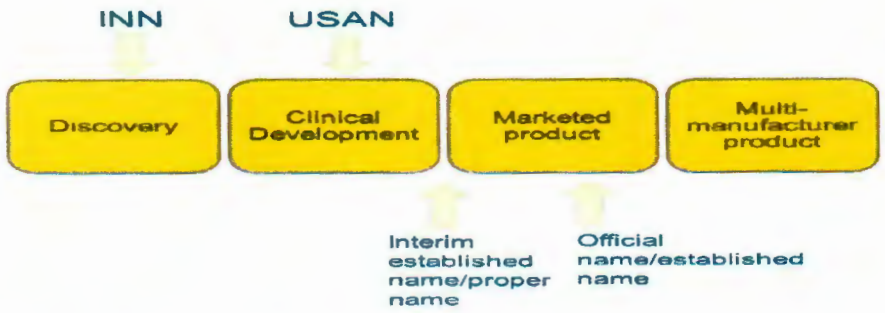
As USP develops a drug substance monograph for an approved product and creates an official title, it will generally align with the USAN nonproprietary name for the drug substance as USP is active in determining this name as part of USAN and shares an aligned scientific approach. USP will also establish a nonproprietary name for the drug product, as USAN names only drug substances. Like USAN and INN, USP, through its scientific expert

committees responsible for naming decisions, bases naming on the scientific attributes of the article which comprise its identity.[2]

When FDA approves a drug or licenses a biologic for marketing and there is already an applicable USP standard, the official title in the USP monograph is the designated nonproprietary name. When FDA approves a drug and there is no applicable USP standard—which is likely in the case of a New Drug Application (NDA) or Biologics License Application (BLA)—FDA assigns an interim established name that serves as the nonproprietary name (official established or proper name) until USP creates an applicable monograph.[3]

This link between INN, USAN and USP, and FDA's long-standing practice and policy to rely on the nonproprietary drug names established by USAN and USP, creates a clear and well-understood progression of naming activities throughout the drug lifecycle (Figure 2).

Figure 2.



Together these activities create a comprehensive, uniform system that works in concert with the naming provisions of the FDCA in the US, and in most cases results in global consistency across names.

[2] The USP Nomenclature, Safety and Labeling (NSL) Expert Committee is the decision-making body that designates official titles for the *USP—NF*. The committee does so in close consultation with the relevant expert committees that review and approve the associated monograph tests and specifications. The NSL Expert Committee in the review process carefully considers and works to align with existing INN and USAN names. FDA Government Liaisons actively participate in the NSL Expert Committee.

[3] Recent case law confirmed that FDA's long standing practice of assigning a name upon drug approval results only in an "interim" established name until an established name is provided in *USP-NF*. *Novartis v. Leavitt*, 435 F.3d 344 (D.C.Cir. 2006).

III. NAMING AND USP'S QUALITY STANDARDS FOR BIOLOGICS

USP has a well-evolved approach for setting standards for biologics and biotechnology-derived products that includes *USP* drug substance and drug product monographs as well as general chapters that support and complement these monographs. USP standards and associated Reference Standards define identity, strength, quality, and purity for both the biologic drug substance (active pharmaceutical ingredient) and the drug product. These standards also specify the established name for both the substance and product. They cover multiple manufacturers regardless of regulatory status; they evolve over time as science and regulations evolve, and they are part of globally harmonized approaches.

1. Drug Names Provide a Critical Link to Public Quality Standards

As the monographs below demonstrate, USP standards apply at both the drug substance (Insulin Human) level and the drug product (Insulin Human Injection) level, with the nonproprietary name for the product grounded in the drug substance name. This link provides critical assurance to patients, providers, and other stakeholders that a drug is what it purports to be and meets the standards for strength, quality, and purity that are provided in the compendia.

Insulin Human

$C_{257}H_{383}N_{65}O_{77}S_6$ 5807.57

Insulin (human) [11061-68-0].

DEFINITION

Insulin Human is a two-chain peptide hormone consisting of 51 amino acids, and its structure corresponds to native insulin produced *in vivo* by the beta cells of the pancreas. The A-chain is composed of 21 amino acids, and the B-chain is composed of 30 amino acids. It is either produced by methods based on recombinant DNA technology or derived by enzymatic modification of insulin from porcine pancreas to change the amino acid sequence appropriately. The presence of host cell DNA in Insulin Human is process-specific. The capability of the process to clear host-derived DNA requires validation and is determined by validated methods. Its potency is NLT 27.5 USP Insulin Human Units/mg, calculated on the dried basis.

[NOTE—One USP Insulin Human Unit is equivalent to 0.0347 mg of pure Insulin Human.]

Insulin Human Injection

DEFINITION

Insulin Human Injection is an isotonic, sterile solution of Insulin Human in Water for Injection. It has a potency of NLT 95.0% and NMT 105.0% of the potency stated on the label, expressed in USP Insulin Human Units/mL.

IDENTIFICATION

- **A.** The retention time of the major peak of *Sample solution A* or *Sample solution B* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve and dispense in the unopened, multiple dose container provided by the manufacturer. Store in a refrigerator, protect from sunlight, and avoid freezing.
- **LABELING:** Label it to indicate that it has been prepared with Insulin Human produced by methods based on recombinant DNA technology or that it is derived by enzymatic modification of insulin from porcine pancreas. Label it to state that it is to be stored in a refrigerator and that freezing is to be avoided. The label states the potency in USP Insulin Human Units/mL.
- **USP REFERENCE STANDARDS** ⟨11⟩
  USP Endotoxin RS
  USP Insulin Human RS

The label below demonstrates how the nonproprietary name specified in the monograph (Insulin Human Injection) links that product to USP's publicly available quality standard, which includes identification tests and appropriate acceptance criteria for purity, potency, and strength. This connection between the nonproprietary name on the label and the USP standard behind it provides traceability to publicly available quality tests and criteria that define the drug's identity and other critical quality attributes.

Insulin Human Injection

DEFINITION
Insulin Human Injection is an isotonic, sterile solution of Insulin Human in Water for Injection. It has a potency of NLT 95.0% and NMT 105.0% of the potency stated on the label, expressed in USP Insulin Human Units/mL.

IDENTIFICATION
- **A.** The retention time of the major peak of *Sample solution A* or *Sample solution B* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ADDITIONAL REQUIREMENTS
- **PACKAGING AND STORAGE:** Preserve and dispense in the unopened, multiple-dose container provided by the manufacturer. Store in a refrigerator, protect from sunlight, and avoid freezing.
- **LABELING:** Label it to indicate that it has been prepared with Insulin Human produced by methods based on recombinant DNA technology or that it is derived by enzymatic modification of insulin from porcine pancreas. Label it to state that it is to be stored in a refrigerator and that freezing is to be avoided. The label states the potency in USP Insulin Human Units/mL.
- **USP REFERENCE STANDARDS** ⟨11⟩
  USP Endotoxin RS
  USP Insulin Human RS

2. Non-Proprietary Naming in Evolving Multi-Manufacturing Environments

For many decades, USP has been setting monograph standards for biologics and biotechnology-derived articles of all classes, from highly purified small peptides like insulin and glucagon to highly complex biological mixtures like pancreatin or heparin. Many of these monographs are for biologics from multiple manufacturers that have shared the same nonproprietary name, even as the product and associated regulatory expectations have evolved over time. The flexible monograph[4] mechanism allows for accommodation of multi-source materials as well as application of different, yet equivalent, procedural approaches to the determination of established quality attributes for a given molecule.

It is important to note that the fact that products share the same compendial name does not mean that they are comparable or interchangeable and does not confer regulatory status. Only the relevant regulator has the authority under various laws to clear a drug for marketing or to determine that two or more drugs are the same, similar, or interchangeable. USP monograph tests establishing identity may cover multiple articles in commerce that

[4] The USP 'flexible monograph' allows different tests, procedures, and/or acceptance criteria, depending on characteristics that do not affect the primary safety and efficacy of a drug; e.g., different Impurity tests to account for different impurities arising from different routes of production.

share the same nonproprietary name but have not been found to be similar or interchangeable by FDA.

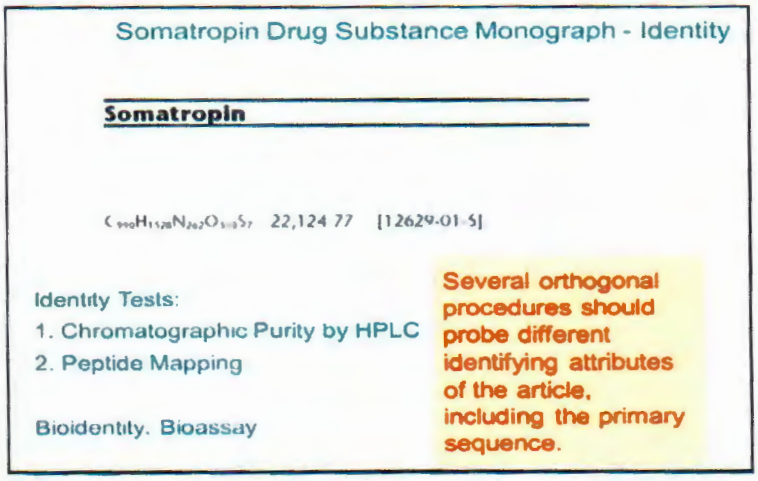
Examples include Glucagon, a long-established diabetes medicine that has been on the U.S. market since 1960. As illustrated below, it was originally a naturally derived product, but currently it is a recombinant biotechnology product made by multiple manufacturers, licensed as non-interchangeable (Figure 3). Most recently, in May 2015, through the advances of organic chemistry, it has also been licensed in the United States as a completely synthetic peptide, also licensed as non-interchangeable. Along with these developments, both national and international standards have evolved to allow the maintenance of appropriate and common quality expectations for products under the same name with shared key quality attributes, most importantly substance identity.

Figure 3.

Throughout these developments, the products have continued to share the same nonproprietary names, which are the official titles specified in the USP monographs: for the Glucagon drug substance the official title is *Glucagon,* and for the drug product the official title is *Glucagon for Injection*. These nonproprietary names/official titles are scientifically based—the shared nonproprietary name for the drug substances reflects the fact that they are the same chemical entity (in the case of Glucagon, share the same unmodified primary protein sequence). They also share other key common attributes that define quality, strength, and purity. This is important, because in a typical USP drug substance monograph several tests directly probe the substance identity and establish what the drug is and whether the standard applies.

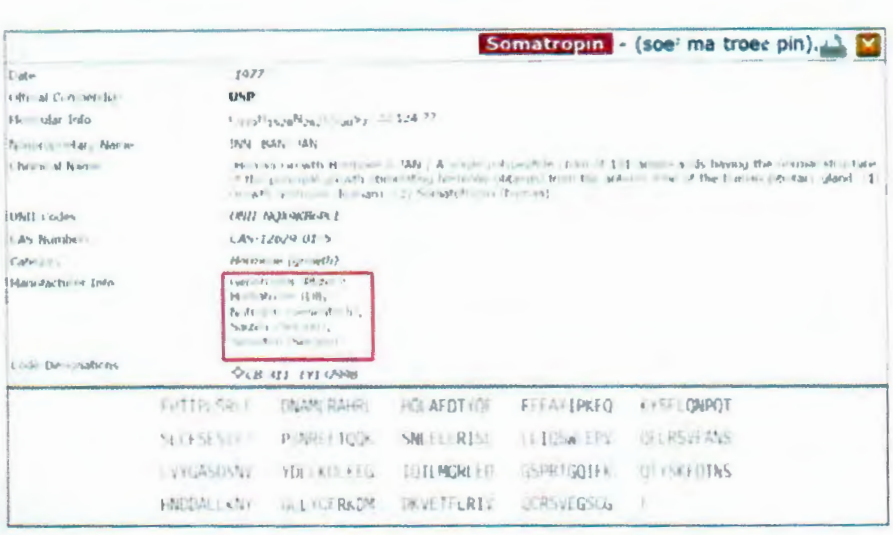
Another example of a multi-manufacturer biologic is Somatropin, human growth hormone. USP has both an official drug substance monograph (*Somatropin*) and a drug product monograph (*Somatropin for Injection*). As with Glucagon, these monographs contain key quality attributes that link directly to the nonproprietary name. For example, the current modern USP drug substance monograph contains three separate and orthogonal tests for identity, and at least one of them directly probes the primary structure, as shown below (Figure 4).

Figure 4.



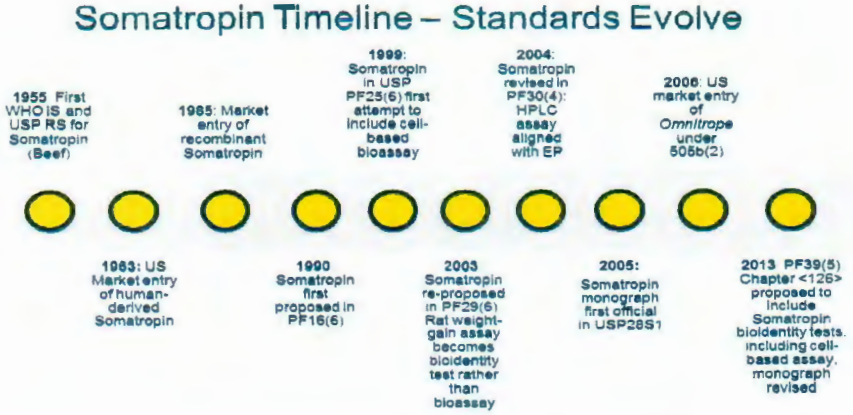
The excerpt from the USP-USAN Dictionary shown below illustrates how Somatropin drug substances from different manufacturers in the US market that share this common identity share the same nonproprietary name as well as the same UNII or substance registration code, as maintained by FDA and USP (Figure 5).

Figure 5.



Like Glucagon, Somatropin is a biological medicine that has evolved over time. As with Glucagon, USP's current modern standards for Somatropin have evolved with the science and in international dialog, as the timeline below illustrates (Figure 6).

Figure 6.



The third, most recent relevant example is Filgrastim, human granulocyte-stimulating factor, used in the chemotherapy recovery of cancer patients. USP's drug substance monograph follows the same approaches established above for Somatropin and Glucagon. The modern monograph covers key quality attributes of the Filgrastim molecule relevant to both the innovator molecule and the recently licensed biosimilar Filgrastim-sndz.[5] In the Filgrastim monograph, as shown below, identity is covered by three tests, one of which is peptide mapping that links directly to the primary amino acid sequence of the substance.

Filgrastim

$C_{845}H_{1404}N_{229}O_{241}S_7$ 18,799 daltons
[121181-53-1]

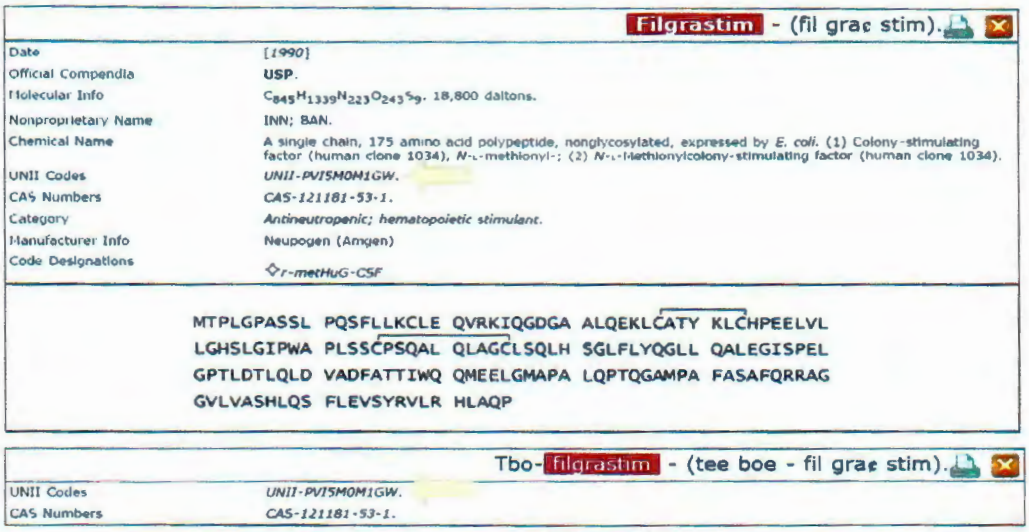
DEFINITION
Filgrastim is a recombinant form of human granulocyte colony-stimulating factor (r-metHuG-CSF). It is a single chain, 175 amino acid nonglycosylated polypeptide produced by *Escherichia coli* bacteria transfected with a gene encoding a methionyl human granulocyte colony-stimulating factor. When prepared as a drug substance, it contains NLT 0.9 mg/mL of Filgrastim. Formulation contains one or more suitable buffering and/or stabilizing agents. The presence of host cell DNA and protein in Filgrastim is process-specific. The capability of the process to clear host-derived DNA and protein requires validation and is determined by validated methods. It has a biological potency of NLT 80% and NMT 125% relative to standard on a mass-to-mass basis.

IDENTIFICATION
- **A.** It meets the requirements in the *Assay*.
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained as directed in the test for *Organic Impurities, Related Compounds*
- **C. Peptide Mapping**
  (See *Biotechnology-Derived Articles—Peptide Mapping* ⟨1055⟩.)

[5] See, http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125553Orig1s000ChemR.pdf.

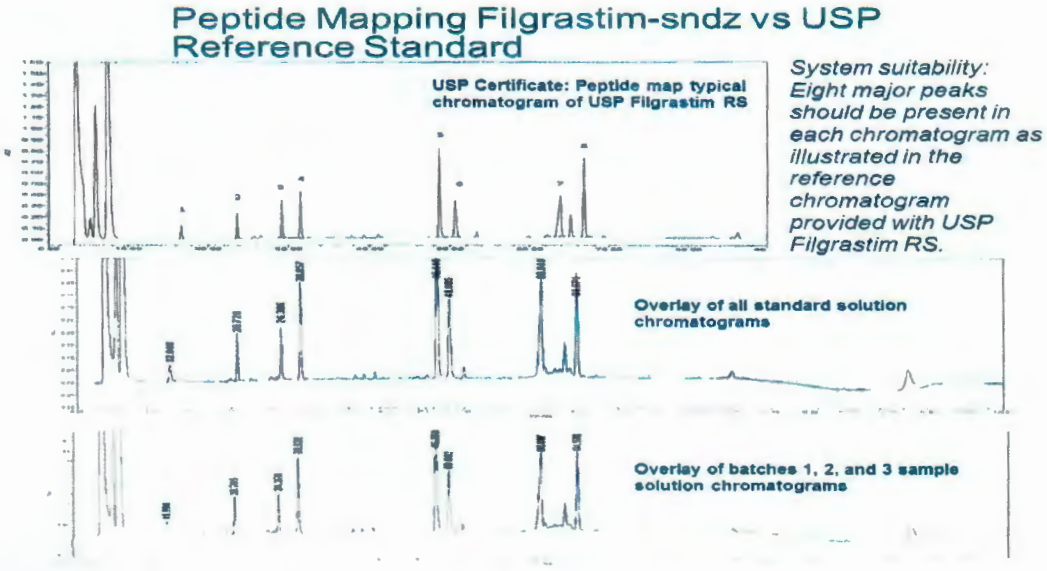
It is important to note that all currently US-licensed Filgrastim products (including tbo-Filgrastim, brand name *Granix*) again share the same UNII code for substance, as shown below (Figure 7).

Figure 7.



USP laboratories have recently analyzed three drug substance lots of the Filgrastim-sndz biosimilar and confirmed that the material conforms with all requirements of the USP *Filgrastim* drug substance monograph (see Figure 8, detailed findings will be presented in USP's comments to FDA's Proposed Rule). Under the time-tested approach used for Glucagon, Somatropin, and many other products, because the Filgrastim-sndz drug substance meets the identity specified in the monograph, the official title *Filgrastim* would apply as the nonproprietary name.

Figure 8.



Maintaining linkage of the same nonproprietary name to products with the same key quality attributes, especially with regard to molecule identity and potency, has been and continues to be an important component of advancing the global scientific quality understanding and the public health impact of these products. The table below describes international agreement on key standards for these and other products under the same name for key attributes such as potency (Figure 9).

Figure 9.

Substance	Potency	Compendia	International Standard	Source	Harmonized Tests?	Labeling
Insulin Human	28.82 IU/mg 28.82 USP U/mg	USP and EP, USP unit =IU	yes	Recombinant	Mostly, EP: no bioassay	Units
Somatropin	3 IU/mg 3 USP U/mg	USP and EP USP unit = IU	Yes	Recombinant, mass assigned	Mostly, EP: no bioassay	mg
Glucagon	1 IU/mg NLT 0.8 USP U/mg	USP and EP USP and IU are assumed equivalent	Yes	Porcine	Mostly, EP: no bioassay	mg and U, assuming 1U/mg
Filgrastim	NLT 0.9 $x10^9$ IU/mg of protein	USP and EP, IU in both	Yes	Recombinant	Mostly	mg

This table also reflects the important links between these common names and compendial and internationally recognized reference materials. Biological activity plays a key role in the establishment of molecule identity, the so-called bioidentity, and establishment of reliable bioassay data is heavily reliant on the availability of appropriate reference materials. Establishment of appropriate measurement chains for these standards relies on scientifically based naming for related and identical substances.

IV. IMPLICATIONS OF FDA'S PROPOSED APPROACH

The Draft Guidance proposes that all newly licensed and previously licensed biological products be given a "proper name" consisting of a core name and a unique FDA-designated suffix attached with a hyphen. According to the Draft Guidance, such a naming convention would help prevent inadvertent substitution and promote safe use by signifying that related biological products may not have been licensed for the same route of administration or packaged with the same delivery system, and that such products have not been determined to be interchangeable. Additionally, the Draft Guidance indicates that FDA believes such a convention would facilitate pharmacovigilance for biological products.

USP appreciates the challenge of ensuring safe use and facilitating pharmacovigilance in the implementation of the new licensure pathway for biosimilar and interchangeable biological products under BPCIA. However, USP is concerned that in attempting to address some of these challenges through the nonproprietary naming system, which was never designed or intended to serve such purposes, the proposal in the Draft Guidance could create unintended consequences.

The nonproprietary naming system was intended to establish simple and scientifically useful names and has never been intended to convey regulatory status. Establishing nonproprietary names based on shifting regulatory expectations, as proposed by FDA in the Draft Guidance, could dilute well-established scientific principles and understanding of drug and biologic substances and products. This would also be a departure from establishing such names based on well-established scientific principles for chemical and biological entities with defined properties. This has implications globally as well as in the US, as many established drugs and biologics are linked to existing internationally harmonized efforts that are increasingly important in a global pharmaceutical marketplace.

Additionally, the proposal in the Draft Guidance could have the unintended effect of creating confusion, potentially placing patients in harm's way through medication errors and disruption of pharmacy systems. Some commentators have expressed the possibility that prescribers and dispensers may not be able to recall non-distinctive suffixes.

Manufacturing and pharmacy organizations have also expressed a concern that different nonproprietary names could affect data transfer within the US and abroad and that even small, seemingly inconsequential changes in product descriptions could have the potential to create significant consequences within healthcare systems.

The proposal could also create obstacles to global trade and harmonization, creating requirements that are viewed by other countries as an unfair restraint of trade, balkanizing national approaches, and making it more difficult to create globally interoperable systems.

It is not possible to predict to what extent these issues might occur. However, given the uncertainty and potential risks created by deviating from the existing long-standing and well-recognized naming system, USP urges FDA to consider whether its goals might be achieved through other mechanisms.

V. POTENTIAL SOLUTIONS

As discussed above, USP has a recognized role in the misbranding and adulteration provisions of the FDCA. USP's labeling requirements are also separately recognized in FDCA 502(g). These statutory provisions clearly distinguish between compendial naming on the one hand, and compendial labeling requirements. FDA regulations also reflect the distinction between the role of the nonproprietary name (official title) on the label and other labeling requirements that include information and text in addition to the established name of the drug or ingredients.[6]

USP believes that labeling is potentially one avenue for addressing the concerns that prompted the approach in the Draft Guidance, without the unintended consequences noted above. Specifically, we would propose the inclusion of a suffix in USP labeling requirements, without designating it as part of the nonproprietary name, to ensure that the qualifier remains closely linked to the name and can be used to identify and trace products back to their manufacturers.

[6] 21 CFR § 201.10(a), (g)(1)-(2)), & (i), (Drugs; statement of ingredients); 21 CFR § 201.50 (Statement of Identity) (2015).

In addition to providing a resolution achievable under the FDCA, USP believes that such a solution would facilitate a common global approach to the naming of biological products that would be built on and consistent with existing, accepted scientific principles. USP continues to support the efforts of the WHO's INN expert group in the context of international nonproprietary naming, specifically the recent WHO INN Biological Qualifier (BQ) proposal.[7] Under the BQ proposal, unlike the proposal in the Draft Guidance, the BQ suffix would not be made part of the INN, thus maintaining existing naming systems.

Again, we appreciate FDA's efforts to address the challenges of implementing the biosimilars pathway, including naming, and remain committed to working collaboratively with the Agency to advance our common goal of protecting and promoting the public health.

[7] See, http://www.who.int/medicines/services/inn/bq_innproposal201506.pdf.pdf?ua=1.