

February 28, 2014

Federal Trade Commission  
Office of the Secretary, Room H-113 (Annex X)  
600 Pennsylvania Avenue NW, Washington, DC 20580  
Submitted electronically to <https://ftcpublic.commentworks.com/ftc/biologicsworkshop/>  
Re: Workshop on Follow-On Biologics: Project No. P131208

Dear Colleagues:

Thank you for the opportunity to discuss drug naming at the Federal Trade Commission's (FTC's) recent workshop on Follow-On Biologics. The United States Pharmacopeial Convention (USP) appreciates FTC's efforts to help ensure access to quality medicines. We look forward to being a continued resource on standards and science. For your convenience we summarize our remarks.

### I. USP's Perspectives on Biosimilar Naming

The prospect of biosimilars approved through the new 351(k) Biologics License Application (BLA) pathway has renewed interest in the role of naming. Since USP began publishing the *United States Pharmacopeia* in 1820, our government has been able to rely upon that compendium (now the *United States Pharmacopeia-National Formulary (USP-NF)*) to provide "convenient and definite"<sup>1</sup> names for medicines. What hasn't changed over these years is USP's role in naming that ultimately promotes the public health: these approaches are already in place to apply to biosimilar medicines.

USP has extensive experience in the naming of biologics, including naturally derived biologics (e.g. heparins and enzyme extracts), as well as recombinant protein therapeutics like somatropin, glucagon, and the insulins. Legal recognition of standards works hand in hand with that scientific understanding. In brief, if one looks at medicines and how they have evolved over the nearly 200 years that USP has been around, one sees USP's time tested approach for linking a nonproprietary name on the label of a medicine to the publicly available standards of identity and quality that stand behind it. USP standards—recognized in law—are a critical, but by no means all-comprehensive set of parameters that describe attributes and quality of an article in commerce. They can potentially be a helpful resource of relevance to regulatory licensing decision making, including in the biologics area, but are not intended for that purpose, hence:

1. A USP monograph identity test may cover multiple articles in commerce that share the same nonproprietary name, but have not necessarily been found to be similar or identical or interchangeable by the Food and Drug Administration (FDA) (one example being Somatropin; there are multiple growth hormones, all sharing the same nonproprietary name, with differing brand names). This does not mean they are one and the same drug; only that they are subject to one and the same USP standard for quality.
2. FDA retains the sole authority with regard to licensing and market access. If two articles are subject to the same USP monograph standards, including compendial standards for identity, that can help inform FDA's review and approval process (such as the Agency's evaluation of "sameness" in the case of Enoxaparin), but it does not constrain or impinge on FDA's essential regulatory role.

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<sup>1</sup> Preface to the *Pharmacopoeia of the United States of America*, December 1820.

## II. Drug Naming in the United States

The USP compendium's role was specified in the original Federal Food, Drug, and Cosmetic Act (FDCA) in 1938, and is articulated in that law's adulteration and misbranding provisions:

- **FDCA 201(j), 501(b):** A drug/biologic “shall” be deemed 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 standards set forth in such compendium.”
- **FDCA 502(e)(3):** If USP has an applicable monograph, the drug/biologic is deemed misbranded unless its label bears the “official title” (naming) recognized in *USP-NF*.

It is important to note that USP's broad role in naming applies to both drug substances and products, and to all drugs, including biologics licensed by FDA under the Public Health Service Act. USP's role in naming is carried out as follows:

- At the time when FDA approves a drug or biologic for marketing, if there are already applicable USP standards, the “official title” in the USP monograph is the nonproprietary name designated for the drug substance and product. Under the FDCA, a drug with a name recognized in *USP-NF* must comply with USP's standards of identity or be deemed adulterated or misbranded or both.
- When FDA approves a drug and there is no applicable USP standard—which is likely in the case of New Drug Application (NDA) or a BLA, for example—FDA provides an “interim established name” that serves as the nonproprietary name (official, established or proper name) until USP creates an applicable monograph. While it rarely happens that a USP Expert Committee would approve a monograph containing a nonproprietary name in the title that differs from that in the FDA license (e.g. a BLA ‘proper’ name), particularly in light of the collaborative role of USP, FDA and other organizations on nomenclature issues (see below), it is possible, and contemplated in law. Congress did give FDA a means to designate an official title for use in *USP-NF*; but it cannot be done in an NDA or BLA – the only way to change the USP designation is by using notice and comment rulemaking (FDCA 508).
- USAN/INN: In terms of broader nomenclature aspects, during the drug development process (prior to FDA approval or licensure of a medicine), manufacturers may seek a name for drug substances from the United States Adopted Names (USAN) Council. USAN is sponsored by the American Medical Association, the American Pharmacists Association, and USP, with active participation by FDA. Separately, the assignment of International Nonproprietary Names (INN) is sponsored by the World Health Organization (WHO). USAN works very closely with INN, but they are independent of each other, and neither has a specified role in the FDCA. Just as with interim established names given by FDA, USP will generally approve the USAN name for a drug substance in a monograph quality standard, but the final authority for naming rests with the USP Expert Committee. In distinguishing the roles of USP and USAN, it is important to note that about 75% of the drug substances named in USAN never make it to market; and unlike the case with USP monograph standards, a USAN name is not developed with related tests and assays, such as for identity, that can be used to link a particular article with that name.

### III. Nonproprietary Name Provides Link to USP's Publicly Available Quality Standards

Critical to the naming process is the link of the name on the label of a medicine (both the drug substances/ingredients, and drug product) to USP's quality standards. The nonproprietary name links to the applicable USP monograph, which has an identity test<sup>2</sup> 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 quality. And the reverse also is true. If a new product links to the identity test in a monograph, the monograph name and standards apply.

### IV. Expert Committees are USP's Decision Makers

Behind the nonproprietary name and public USP standard are scientific experts who create these standards. These experts ensure that the name of the medicine and the monograph tests are linked. These experts serve on USP's Nomenclature, Safety, and Labeling Expert Committee and they make decisions on monograph titles for drug substances, typically adopting the USAN name, and drug products through standardized taxonomies. They also are scientific experts who serve on other topic-specific Expert Committees who review and approve monograph tests and specifications. Typical deliberations by the USP Expert Committees include:

1. Consideration of existing USAN name(s) and compendial standards in other pharmacopeias where they may exist
2. Consideration of proposed test(s), their specificity and resolving power in the context of the article identity and scope of the entire monograph
3. Reconciliation with previous and existing naming approaches in the compendium for biological medicines

### V. USP Experience to Date and Scientific Considerations

USP has extensive experience in naming biologics, including naturally derived biologics (e.g. heparins and enzyme extracts), as well as recombinant protein therapeutics like somatropin, glucagon, and the insulins. In several of these cases, including somatropin, multiple non-interchangeable products share the same official title and monograph specifications. USP does have an official drug substance monograph for Filgrastim. Should the recently approved TBO Filgrastim meet the identity test in the USP Filgrastim monograph, the manufacturer would be obliged to submit a Supplemental Biologics License Application (SBLA) to bring the article into conformance with the official title and quality standards in that monograph, otherwise it would risk being deemed misbranded and possibly adulterated as well. (The manufacturer would also have the option of working with USP to revise the monograph to accommodate its product).

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<sup>2</sup> Per USP General Notices, 5.40. Identity: a compendial test titled Identity or Identification is provided as an aid in verifying the identity of articles as they are purported to be, e.g., those taken from labeled containers, and to establish whether it is the article named in *USP–NF*. The Identity or Identification test for a particular article may consist of one or more procedures. When a compendial test for Identity or Identification is undertaken, all requirements of all specified procedures in the test must be met to satisfy the requirements of the test. Failure of an article to meet all the requirements of a prescribed Identity or Identification test (i.e., failure to meet the requirements of all of the specified procedures that are components of that test) indicates that the article is mislabeled and/or adulterated.

## VI. Role of Post-Translational Modifications and Resolving Power of Analytical Technology

Glycosylation is a non-template driven post-translational process that can add considerable structural and functional complexity to the synthesis of a biomolecule and can be highly variable based on changes in the synthesis environment. Glycosylation has received much attention as a contributing factor to molecule identity aside from primary sequence (e.g. Epoetin). While USP currently does not yet have an official product or substance monograph that considers glycosylation as a quality attribute, USP experts have considered this issue in general guidance (<1084> Glycoprotein and Glycan Analysis – General Considerations). One of the key considerations is whether the glycosylation has to be considered as a critical quality attribute of the molecule in question, e.g. is necessary for proper structure and function, and hence especially in the latter case should be considered a key part of the molecule identity (for most biologics, a functionality or bioactivity test is part of molecule identity).

It must also be considered that the level of differences in glycosylation patterns, especially once entering the realm of so-called microheterogeneity, is highly dependent on the resolving power of analytical approaches that have only recently become available. As a practical example, Epoetin  $\alpha$  and  $\beta$  cannot be distinguished by gel-based isoelectric focusing analysis, which was considered state-of-the-art technique for glycan analysis available at the time of first licensure of the innovator products. And both also have the same bioactivity – in fact the first international standard for Epoetin was a mixture of  $\alpha$  and  $\beta$ . It should also be pointed out that sophisticated testing and specification-setting approaches for highly complex and polydisperse completely carbohydrate-based multi-manufacturer biologics do already exist, e.g. in the case of low molecular weight heparins like Enoxaparin Sodium. In the case of Enoxaparin, the USP monograph now covers several interchangeable generics under the same name.

Thank you for the opportunity to share our views. Please let us know if you have any additional questions. Ms. Angela Long can be reached at (301) 816-8382 or [agl@usp.org](mailto:agl@usp.org) and Dr. Tina Morris can be reached at (301) 816-8397 or [tsm@usp.org](mailto:tsm@usp.org).

Sincerely,



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