



U.S. Pharmacopeia  
The Standard of Quality<sup>SM</sup>

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Division of Dockets Management (HFA-305)  
Food and Drug Administration  
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Subject: Comments of USP on “Approval Pathway for Biosimilar and Interchangeable Biological Products; Request for Comments”  
Docket No. FDA -2010-N-0477  
75 *Fed. Reg.* 61497 (October 5, 2010)

Dear Sir/Madam:

The United States Pharmacopeial Convention (USP) appreciates the opportunity to provide input as the Food and Drug Administration (FDA) proceeds with implementation of the Biologics Price Competition and Innovation Act of 2009 (BPCI Act). These comments supplement the testimony of USP’s Chief Executive Officer, Roger L. Williams, M.D., at the November 2-3 Public Hearing that was also noticed in the above-referenced *Federal Register*.

USP is an independent, volunteer-based, scientific, nonprofit standards-setting organization that since 1820 has worked to advance public health through public standards and related programs. USP standards help ensure the quality, safety, and benefit of medicines and foods. As noted by FDA Commissioner Hamburg at USP’s Convention this past April, USP has a special relationship with FDA, including a shared “common public health mission” and longstanding statutory ties. Our quality standards for drugs and biologics are official in the law and enforced by FDA, as described below.

The BPCI Act creates an additional approval pathway targeted specifically at biological products that FDA (the HHS Secretary) can determine to be biosimilar and also possibly interchangeable compared to a reference product. Like all approved drugs and biologics, these approved biosimilar and interchangeable products will be subject to USP compendial requirements in applicable monographs and general chapters in the *United States Pharmacopeia (USP)* and *National Formulary (NF)*, which are official compendia of the United States as described in the Federal Food, Drug, and Cosmetic Act (FDCA).

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Congress and FDA have long recognized USP as an entity that “develops drug product standards with the help of professionals from academia, the medical community, the pharmaceutical industry, and the FDA,” whose book of standards(*United States Pharmacopoeia* and *National Formulary*, presented as a combined publication *USP-NF*) is an “official compendium” recognized in US law.<sup>1</sup> An overarching point emphasized throughout these comments pertains to the historic partnership USP has maintained with FDA over the years. This relationship is critical for understanding USP’s role, including with regard to implementation of the BPCI Act.<sup>2</sup>

The initial focus of our comments in Section I is on the historic role of USP in providing quality standards for both drugs and biologics, initially as a pharmacopeia containing voluntary standards, and then additionally in the past century as *USP* and *NF* gained recognition under federal law with mandatory standards included in the adulteration and misbranding provisions of the FDCA.

Section II provides USP’s comments on scientific considerations, focusing on the ways in which the *USP-NF* and USP’s Council of Experts can continue to be helpful to FDA as USP fulfills its multifaceted role in giving nonproprietary names to biological products and other drugs and establishing standards for the identity, strength, quality, and purity of such articles through USP’s monographs and General Chapters.

With regard to the specific questions identified by FDA for input, these comments are most responsive to A. Biosimilarity (issues 1-3 regarding differences and similarity), and C. Patient Safety and Pharmacovigilance (issue 3 regarding nonproprietary names).

## **I. USP’s COMPENDIAL ROLE IN FEDERAL LAW**

USP’s role in setting uniform, voluntary standards for the quality of drugs and biologics has been ongoing for nearly 200 years. The first *United States Pharmacopoeia* published in 1820 provided recipes for compounding pharmacists. *USP* subsequently evolved into a book of specific chemical formulas and tests and assays for purity and other quality attributes, all aimed

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<sup>1</sup> *U.S. v. Barr Laboratories*, 812 F.Supp. 458, 465-466 (D.N.J. 1993). See also this language cited favorably by FDA in its Appellee brief submitted to the D.C. Circuit May 18, 2005, in *Novartis v. Leavitt*, No. 04-5414, brief pp. 17-18 and fn #9; subsequent decision in which FDA prevailed reported at 435 F.3d 344 (D.C. Cir. 2006); role of USP addressed at pp. 350-352.

<sup>2</sup> The history of interactions between USP and FDA is detailed in Attachment 1, which is incorporated by reference in these comments: *FDA-USP: Partners in Public Health*, a brochure from an ongoing exhibition (through October 1, 2011) at the Charles Rice Museum & Library, at USP’s headquarters in Rockville. The paper provides background on the history of FDA and USP, including a list of shared leadership (p. 13), an overview of 8 landmark drug acts passed by Congress starting in 1848 (p. 4), and summaries of 14 initiatives over the years (beginning on p. 7), including: creation of a Vitamin Advisory Board in 1932 and an Insulin Advisory Committee in 1941; the formation of the United States Adopted Names Council in 1964; shared efforts to strengthen compendial standards, including formation of a Compendial Liaison Staff Office in the Bureau of Drugs in 1974; formation in 1991 of a Joint FDA-USP Advisory Panel on Simplification and Improvement of Injection Labeling, which culminated in 2010 in a new standard for labeling on injectable medications; work on a glycerin monograph identification standard beginning in 2006; and updated standards to address heparin contamination beginning in 2008.

at fostering consistency in the strength, quality, and purity of manufactured ingredients, finished products, and dispensed medicines. The evolution continued with the decision to admit biologics, following passage of the 1902 Biologics Act and in response to the request of the U.S. Surgeon General to adopt a compendial standard for diphtheria antitoxin.

Over the course of its history, USP has had no role in enforcement.<sup>3</sup> However, throughout the 19<sup>th</sup> century various pharmacy and medical professional groups, and state governments -- and particularly Boards of Pharmacy-- increasingly recognized USP standards and exercised enforcement authority based on those standards. In 1848, Congress turned to USP as a means of documenting quality of a medicinal article in the Import Drugs Act. By the beginning of the 20<sup>th</sup> 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 FDCA (1938 Federal Food, Drug, and Cosmetic Act), most notably in both the adulteration and misbranding provisions. To this day, those provisions specify USP's role in creating nonproprietary names and related standards for identity, as well as standards for strength, quality and purity.

#### A. Role of USP Standards for NDAs, BLAs, & FDA

Before examining the USP-related adulteration and misbranding provisions in detail, it is helpful to appreciate the vital role USP's compendial standards will play as FDA proceeds to implement the BPCI Act, just as they continue to play under the other provisions of the Public Health Service (PHS) Act and the FDCA.

1. USP compendial standards play a prominent role in FDA compliance and enforcement, by helping to inform the adulteration and misbranding provisions of the FDCA, both directly (as an official compendium) and indirectly (through FDA's authority to require current good manufacturing practices).
2. USP standards are also pertinent and helpful to applicants and FDA, in the context of the application process for both NDAs and BLAs.<sup>4</sup> This is consistent with the direction

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<sup>3</sup>Although USP does not enforce its standards (see USP General Notices §2.30), the applicable *USP* or *NF* standard applies to any article marketed in the United States that (1) is recognized in the compendium and (2) is intended or labeled for use as a drug or as an ingredient in a drug. The applicable standard applies whether or not such articles add the designation "USP" or "NF." See General Notices §3.10.10. A drug product, drug substance, or excipient may use the designation "USP" (or "NF") in conjunction with its official title or elsewhere on the label only when (1) a USP monograph is provided for the particular drug or biologic, and (2) the article complies with (a) the identity prescribed in the specified compendium, as well as (b) standards for strength, quality, or purity (unless clearly labeled to show any differences). See General Notices §3.20. The General Notices presents the basic assumptions and definitions for interpreting and applying *USP-NF* compendial standards; a copy of General Notices from the current compendium is provided in Attachment 2. (*USP 34*, published and released November 1, 2010; official May 1, 2011).

<sup>4</sup>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 CFR §§314.50(d)(1)(i), 314.50(d)(1)(ii)(a). FDA also specifies that reference standards from official sources like USP can be used in applications without further characterization, whereas the characterization burden for standards from other sources is substantial. *Guidance for Industry:*

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 Public Health Service Act (42 U.S.C. 262) and products required to have approved new drug applications under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(b)(1)).” (FDA Modernization Act of 1997, §123(f), Pub. L. No. 105-115.) 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 is the same as that of a reference listed drug under the FDCA.<sup>5</sup>

3. USP also shares with FDA the understanding that biologics are a subset of drugs, and that all of the drug regulatory authority of the FDCA – other than what type of license to issue, a BLA or NDA – applies to PHS biologics. Since FDA took over responsibility for the regulation of biological products in 1972, they have been subject to the regulatory and compliance provisions of the FDCA, including the adulteration and misbranding sections (FDCA §501 and §502).<sup>6</sup> This understanding was confirmed by Congress in 1997 with enactment of Public Health Service Act §351(j), which was unaffected by the BPCI.<sup>7</sup>

#### B. Overall Working of the BPCI Act and New Biosimilar Pathway

USP’s role under the new PHS Act §351(k) biosimilars pathway arises both under the adulteration and misbranding provisions of the FDCA, as well as in the context of application review and approval (such as with regard to weighing in FDA’s consideration of whether an article is “highly similar,” i.e. issues of sameness and identity). Before turning to the application of FDCA §§501 and 502, we recognize that the overall working of the BPCI Act is critical for informing how FDA should implement the law, as well as the role of stakeholders such as USP. Key observations on the scope and mechanism of the new 351(k) pathway include the following:

1. The new (k) pathway is not exclusive; applicants can also choose to utilize the 351(a) approval pathway if they do not wish to obtain an FDA determination of biosimilarity or

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*Analytical Procedures and Methods Validation – CMC Documentation* (August 2000), p. 4 (availability of draft guidance announced at 65 Fed. Reg. 52776 (August 30, 2000)).

<sup>5</sup> See preamble to FDA’s final rule implementing Title I of the Hatch-Waxman amendments, 57 Fed. Reg. 17950, 17959 col. A (April 28, 1992); see also FDA’s July 23, 2010, response to the Citizen Petition of Aventis Pharmaceuticals (enoxaparin) in Docket No. FDA-2003-P-0273, p. 10.

<sup>6</sup> See for example the preamble to the initial GMP final rule, which states that PHS Act 351 “does not affect, modify, repeal or supersede” the FDCA, and that FDA “has consistently interpreted these provisions to be additive . . . . Thus, for example, the [IND provisions of the FDCA] apply to biological products . . . [and] the Commissioner believes it is consistent with both laws to apply current good manufacturing practices to biological drug products.” 43 Fed. Reg. 45014, 45027 col. A (September 29, 1978).

<sup>7</sup> “The Federal Food, Drug, and Cosmetic Act applies to a biological product subject to regulation under this section, except that a product for which a license has been approved under subsection (a) shall not be required to have an approved application under section 505 of such Act.” PHS Act §351(j). See also FDA regulations, Part 310 – New Drugs, 21 CFR §310.4(a): “If a drug has an approved license under section 351 of the Public Health Service Act (42 U.S.C. 262 *et seq.*) or under the animal virus, serum, and toxin law of March 4, 1913 (21 U.S.C. 151 *et seq.*), it is not required to have an approved application under section 505 of the act.”

interchangeability. However, by 10 years after enactment, all biologics that come within the definition of “biological product” (now expanded to include proteins) will have to seek FDA approval under PHS Act §351(a) or (k); the existing options under the FDCA will be sunset. BPCI Act §7002(e)(1-3).

2. The new (k) pathway may not be abbreviated, since the statutorily required demonstration for licensure is much more detailed than the “safe, pure, and potent” showing required under 351(a). It has long been known that a showing of equivalence between two products may entail greater study than a showing of inequivalence between a medicine and a placebo. Careful attention to sound science, study design and reliance on optimal public standards, expressed either in FDA or USP documents, can facilitate a reduction in the number of studies needed to allow a showing of either biosimilarity or interchangeability.
3. Despite the array of extensive and detailed elements required to obtain a 351(k) BLA, the HHS Secretary nevertheless retains considerable discretion to make the (k) pathway both attractive to applicants and consistent with the agency’s public health mission,<sup>8</sup> including the specific authority of 351(k)(2)(A)(ii) to determine that any of the required data elements related to biosimilarity (including analytical studies, animal studies, or human clinical studies) are “unnecessary.”
4. USP also agrees with, and supports, the position of FDA stated in the *Federal Register* notice of October 5, 2010 (75 Fed. Reg. page 61497 col. C) that “The BPCI Act aligns with FDA’s longstanding policy of permitting appropriate reliance on what is already known about a drug, thereby saving time and resources and avoiding unnecessary duplication of human or animal testing.”
5. It is not noteworthy that there is no distinct provision for naming (k) biologics in the new law; rather, as discussed below, this is already provided for in the drug regulatory provisions of which PHS Act (a) and (k) and the FDCA are all an integrated whole.

These principles provide important context for the comments below.

### C. USP Role in Naming; Identity; Strength, Quality and Purity

The misbranding provision of the FDCA, §502, is a logical starting point for examining the naming of biologics, as well as USP’s role in the related issue of identity, and standards for strength, quality and purity. §502 provides that a drug/biologic is deemed misbranded “unless its label bears, to the exclusion of any other nonproprietary name . . . the established name . . .” §502(e)(1). FDCA §508 in turn provides FDA with authority to designate official names. Unless FDA has designated an “official name *for any drug*” by notice and comment rulemaking

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<sup>8</sup> FDA’s statutory mission includes (1) *promoting public health* by “promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner,” as well as (2) *protecting public health* by “ensuring that . . . human and veterinary drugs are safe and effective . . .” FDCA §903(b).

(§508(a); emphasis added), which is rarely if ever done, for either NDA “established” names or BLA “proper” names, the “established name” for “an article recognized” in *USP* is “the official title” in *USP*. §502(e)(3).<sup>9</sup> The courts and FDA have been very clear about the application of this provision. Unless FDA establishes the “official” nonproprietary name of a drug/biologic by means of a §508 rulemaking, then the *USP*-specified name prevails, even if *USP* assigns the name after FDA has already licensed a drug or biologic under the FDCA (NDA) or PHS Act (BLA). In such a case, the name given in an NDA or BLA is considered an “interim established name” that exists only unless and until *USP* designates a name.<sup>10</sup> Accordingly, the existing drug regulatory provisions of the PHS Act and FDCA already contain comprehensive naming authority for any biologics that may be approved under the new 351(k) pathway.

Turning from the issue of naming to the related issues of identity and quality standards, the adulteration provision, FDCA §501(b), provides that a drug/biologic is deemed adulterated if:

*First*, “it purports to be or is represented as a drug the name of which is recognized in an official compendium”, and

*Second*, “its strength differs from, or its quality or purity falls below, the standards set forth in such compendium.” (The provision further provides that the “determination as to strength, quality, or purity shall be made in accordance with the tests or methods of assay set forth in such compendium . . . .”)

The distinction between *Identity*, and *Strength, Quality* and *Purity*, has proved significant. A drug or biologic may vary from compendial standards for strength, quality or purity, “if its difference in strength, quality, or purity from such standards is plainly stated on the label.” §501(b). No such variance is allowed in the case of *Identity*. The fact that the role of *USP*

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<sup>9</sup> FDA has recognized that a “proper name” for a biologic product is synonymous with the “established name” for drug products. See, e.g., FDA Guidance for Industry, “Product Name Placement, Size, and Prominence in Advertising and Promotional Labeling,” p. 1 fn 2 (January 1999).  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070076.pdf>

<sup>10</sup> “The *USP* Nomenclature Committee acts under its own schedule, so that its designation of a name qualifying under §352(e)(3)(B) need not coincide with the FDA’s approval of a drug.” *Novartis v. Leavitt*, 435 F.3d 344, 352 (D.C. Cir. 2006). FDA expanded in greater detail on the role of *USP* in its Appellee brief submitted to the D.C. Circuit in *Novartis v. Leavitt*, and the court examined the agency’s explanation of its naming policy (see 435 F.3d at pp. 350-352). As FDA stated persuasively in its brief, in the absence of either a 508 Rulemaking name, or *USP* name, FDA “may use an interim nonproprietary name that does not fit into any category listed in 21 U.S.C. §352(e)(3). If at a later time a particular name does satisfy a category listed in section 352(e)(3), the manufacturer may be required to change the name.” Appellee (HHS/FDA) brief submitted to the D.C. Circuit May 18, 2005, in *Novartis v. Leavitt*, No. 04-5414, pp. 17-18. The FDA brief further described the process by citing a journal article written by an FDA official, Dr. Dan Boring: Names established by FDA at the time of product launch “are subsequently evaluated, however, by the *USP*’s Nomenclature Committee for conformance with the *USP*’s nomenclature conventions when a compendial monograph is submitted to the *USP*. It is possible that the designated established name is unacceptable as a monograph title and another term will be required by the *USP*. Usually, there are ongoing negotiations between the drug sponsor, FDA, and *USP* regarding new terms, but the final decision rests with the *USP*. If the *USP* insists on a different name, the sponsor must comply and the product must be relabeled to use the compendial established name.”

From *The Development and Adoption of Nonproprietary, Established, and Proprietary Names for Pharmaceuticals*, 31 *Drug Information Journal* 621, 626-27 (1997). See JA 1683-84. FDA brief at p. 18.

compendial standards is implicit with regard to standards of Identity (is it, or is it not, the drug addressed in the compendium?) does not diminish the legal force and standing of the requirement.<sup>11</sup>

The role of these statutory compendial standards of Identity, and Strength, Quality and Purity, is reflected in a longstanding FDA regulation (**emphases added**):

**21 CFR §299.5 Drugs; compendial name:**

(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.<sup>12</sup>

These federal laws and regulations pertaining to the USP role in naming and identity, as well as strength, quality and purity, are reflected in USP General Notices, §2.30 “Legal Recognition.”

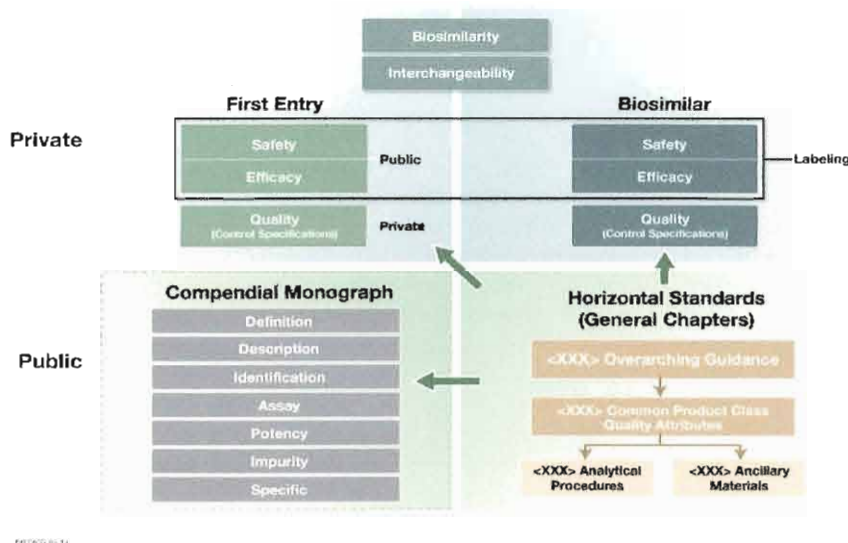
## **II. USP’S STANDARDS FOR BIOLOGICS**

USP has a well-evolved approach for setting standards for biologics and biotechnology-derived that includes both “vertical standards” (*USP* monographs) as well as “horizontal standards” (general chapters) that support and complement these monographs (Figure 1; see following page).

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<sup>11</sup> The role of compendial Identity is reflected in the legislative history of the FDCA, in the context of a House provision that would have specified that in cases where a drug that is not represented in a compendium, and also differs from the identity “which it purports or is represented to possess,” it would be considered adulterated. The provision was deleted in conference, but only because it was deemed “surplusage,” since in such cases “as well as in the case of drugs recognized in an official compendium, if the identity differs from that which it purports or is represented to possess, they would either be considered to be adulterated under section 501(d) or misbranded under section 502, or both.” Statement of the Managers on the part of the House, Conference Report accompanying S. 5, H. Report No. 2716, June 11, 1938, p. 24, contained in “Vol. 6 Legislative History of the Food, Drug, & Cosmetic Act,” p. 425.

<sup>12</sup> Compare USP General Notices regarding Identity (§5.40), and labeling in the event of differences (§3.20; in the event of varying Identity, an article must have a different name than is recognized in USP; in the event of varying strength, quality or purity, the difference must be clearly stated on the label).



**Figure 1: USP horizontal and vertical standards, as they apply to biological products in the marketplace**

This approach can facilitate FDA’s consideration of biosimilar products. The components of the approach are discussed in more detail in the sections below, as are the role of USP reference materials.

**A. USP Vertical Standards: Monographs**

USP monographs (vertical standards) and associated reference standards define identity, strength, quality and purity (considered by FDA, and under law, to be equivalent requirements under both the FDCA and PHS Act). These standards in turn apply both to the biologic drug substance (active pharmaceutical ingredient) and drug product. As described in the lower left quadrant of Figure 1, a USP monograph provides tests for critical quality attributes that define the biologic in terms of these criteria and can form part of a comparison exercise that determines sameness.

Recently, the role of a USP monograph in this regard was referred to in FDA’s response to Sanofi-Aventis’ Citizen’s Petition where monograph tests formed an important part of the physicochemical characterization exercise that led to a determination of sameness.<sup>13</sup> While enoxaparin sodium is an FDCA-regulated drug, the case nonetheless highlights the potential importance and utility of a USP standard in the evaluation of either biosimilarity or interchangeability.

USP has been setting monograph standards for biologics and biotechnology-derived articles of all classes, from highly purified small peptides like insulin and glucagon (which are both multi-manufacturer products) to highly complex biological mixtures like pancreatin or heparin. The

<sup>13</sup> “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’ . . . ‘Other criteria for showing physicochemical equivalence can also be used that capture broad characteristics of enoxaparin, including, among other things, certain tests and acceptance criteria described in the USP monograph.’” Docket no. FDA-2003-P-0273 (pp. 10, 12)



flexible monograph<sup>14</sup> mechanism allows the accommodation of multi-source materials as well as the application of different, yet equivalent, procedural approaches to the determination of established quality attributes for a given molecule. USP has been developing, and continues to develop, monographs for products where biosimilars already exist in other markets—for example, erythropoietin and filgrastim (monograph proposal in *Pharmacopeial Forum (PF)* 36(5))—and USP looks forward to further collaboration with manufacturers and FDA in the development of these standards. Ensuring harmonization of national unitage with the World Health Organization’s International Units is also critical, and USP intends to continue its collaboration with WHO in furtherance of this goal as well. USP has recently very carefully examined the role of the biological potency test, resulting in a suite of general chapters that speaks to the USP potency test (see Figure 2, tier 1, Guidance and Information). This is a landmark effort that reflects a multiyear, science based, highly collaborative effort that fully updates—and corrects previous errors in—this critical test for any biologic that cannot be fully characterized.

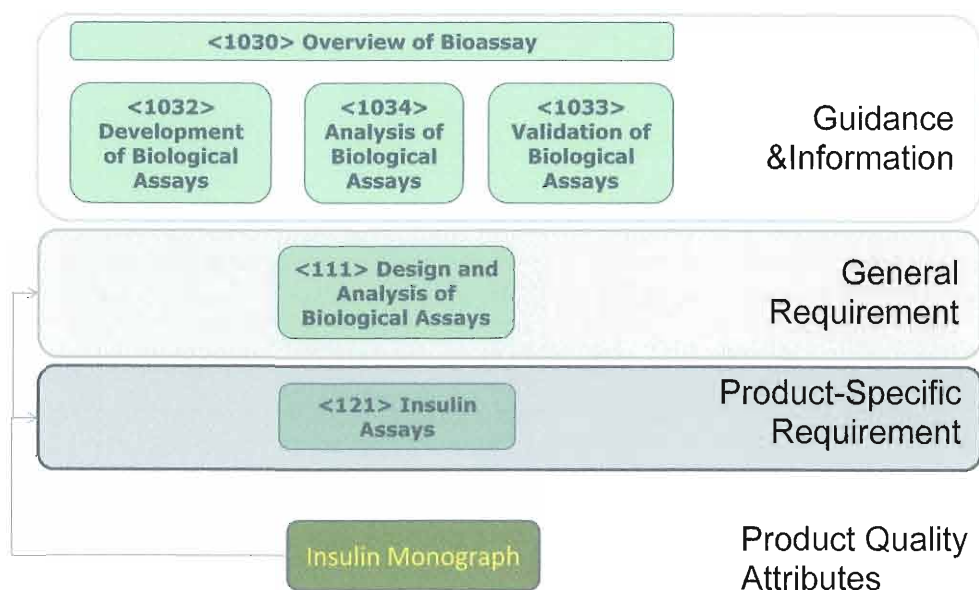
Clearly submission of a monograph to USP and its finalization by any manufacturer may have considerable bearing on FDA’s decision-making for either a biosimilar and/or interchangeable biologic, and how this evolves merits close coordination between FDA and USP.

#### B. USP Horizontal Standards: General Chapters

Scientifically sound and broadly applicable public procedures can form the basis for the consistent evaluation of any biologic. USP General Chapters for biologics provide procedures and acceptance criteria that are representative of current scientific industry practice and assure that key attribute measurements are done in a consistent and appropriate manner. This pertains to the assessment of primary structure (e.g. Harmonized Chapter *Peptide Mapping* <1055>), post-translational modifications (*Glycoprotein and Glycan Analysis – General Considerations* <1084>) and, very importantly, also extends to the correct determination of strength or potency via biological assays (see example in Figure 2, on the following page) and in connection with established WHO International Standards (IS). USP also establishes and maintains important standards that speak to the limitation of harmful impurities (*Bacterial Endotoxins Test* <85>) as well as the quality control of key process and ancillary materials used in biologics manufacturing (*Protein A Quality Attributes* <130>).

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<sup>14</sup> The ‘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.



**Figure 2: USP standards for biological potency determination, insulin example**

Biological products can be divided into different molecular classes based on their structure and function, e.g. peptide hormones, enzymes, glycosaminoglycans, immunoglobulins, and others. For many of these molecule classes, established platform approaches exist in terms of manufacturing, regulatory expectations (often reflected in FDA guidance to industry), and consequently analytical characterization and quality control. USP uses the class chapter approach to reflect this and appropriately link horizontal and vertical standards: as outlined in the lower right quadrant of Figure 1, first an overarching general chapter speaks broadly to a product class, then a more specific general chapter addresses critical quality attributes, and finally general chapters that provide procedures with/without reference materials for both critical quality attributes and ancillary materials. These general approaches, as noted in Figure 1, undergird specification of the private or public monograph. As FDA will discern, they can be enormously time-saving for both the Agency and industry. USP works carefully to involve all parties, including other pharmacopoeias in this in many ways, and all of this information is readily available to FDA.

Approaching characterization, and ultimately comparability, by product class as much as possible affords important advantages: it gives the opportunity to establish and define acceptable assay approaches in important areas like potency determination, detection of common process impurities, or characterization of known, class-specific post-translational modifications. These approaches, in turn, are linked to general and public (compendial) procedures that are not reliant on a single manufacturer's experience. The class approach helps define and establish critical quality attributes that are common to a class of molecules rather than an individual product and hence can help focus and delineate scientific discussions around product identity and uniqueness.<sup>15</sup>

<sup>15</sup> As an example, USP is in the process of establishing an expert panel to create *Quality Attributes of Therapeutic Monoclonal Antibodies* <129> to apply these principles to this very important class of molecules. In the area of low molecular weight heparins (LMWH) the existing USP expert panel is already working on *Anti-Factor IIa and Anti-*

### C. USP Reference Materials

Measurement science (metrology) strongly allies the procedures of a private control specification or a public monograph with a well-studied and collaboratively tested physical reference material. The public availability of this reference material is critical to the public standards in *USP* and *NF*, including the vertical and horizontal standards for biologics described above. Access to this reference material would be highly useful for applicants proceeding under any approval pathway for a biologic at FDA, including the new (k) pathway. The public reference material also serves as an ongoing resource to all licensees to perform quality testing, and can be utilized by FDA for compliance testing.

### Conclusion

As FDA considers how to implement the provisions of the BPCI Act, USP urges FDA to consider USP's complementary role to FDA, and how USP can assist FDA in advancing the provisions of the BPCI Act. USP's standards for biologics, both vertical and horizontal, as well as its growing work in class standards, offer great capacity for advancing the analytical component of the triad of studies that may be used to demonstrate a showing of either biosimilarity or interchangeability in the new (k) pathway. USP's legal role in establishing names for biologic products also can work effectively in support of FDA's efforts to ensure appropriate pharmacovigilance for biosimilar and interchangeable products.

From the beginning in 1820, USP has spoken to consistency and appropriate product performance and these are grounded in a science-based understanding of what might be termed 'continuing equivalence.' Continuing equivalence is a key question for all drugs and biologics, including biosimilars, which relies on a need to show that over time (and barring intentional change) marketed products are equivalent to the clinical trial material on which the determination of safety and efficacy is based. The role of public standards—both documentary and physical—in assuring this cannot be overestimated

USP also works in many other ways, as a neutral convenor, to bring together policy makers, governmental representatives, manufacturers and practitioners and patients to consider key questions such as those coming before the FDA in its implementation of the BPCI Act and exploring ways to resolve them. USP may be able to assist FDA by working in this capacity as well. We pledge USP's resources now on behalf of the Convention, Board of Trustees, Council

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*Factor Xa Assays for Low Molecular Weight Heparins <208> and Low Molecular Weight Heparin Molecular Weight Determinations <209>* which are class-specific procedural Chapters that will establish consistency in how LMWH products are analyzed in terms of potency and molecular weight distribution, two critical product attributes. Class standards fully support individual API and product monographs for individual medicines, aid comparability and facilitate the establishment of appropriate acceptance criteria.

of Experts and staff in assisting FDA in implementing this legislation in accordance with our role in law.

Sincerely,

A handwritten signature in black ink, appearing to read "R. Williams", with a long horizontal flourish extending to the right.

Roger L. Williams, M.D.  
Chief Executive Officer  
Chair, Council of Experts

**Attachments**

1. *FDA-USP: Partners in Public Health*, brochure from an ongoing exhibition (through October 1, 2011) at the Charles Rice Museum & Library, USP, Rockville, MD.
2. *General Notices and Requirements, USP34-NF29*.