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U.S. Pharmacopeial Convention

July 24, 2014

Submitted Electronically
Division of Dockets Management (HFA-305)
United States Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Draft Guidance for Industry, Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product ("Draft Guidance"), 79 Fed. Reg. 27622 (May 14, 2014); Docket No. FDA-2014-D-0234

Dear Sir/Madam:

The United States Pharmacopeial Convention (USP) appreciates the opportunity to provide additional input to the Food and Drug Administration (FDA) on draft guidances related to the implementation of the Biologics Price Competition and Innovation Act of 2009 (BPCI Act, Title VVII.A of Public Law 111-48), including the above-captioned Draft Guidance. USP previously submitted comments to the docket following the public hearing held November 2-3, 2010, and in response to guidances released for public comment in March 2012 (USP comments submitted May 24, 2012, to docket no. FDA-2011-D-0618).

The Draft Guidance pertains to the design and use of clinical pharmacology studies to support regulatory decisions by FDA about whether a proposed therapeutic biological product is biosimilar to its reference product. As previously noted and detailed below, USP compendial quality standards play an important but defined role under Federal law. While USP standards are not directly pertinent to the assessment of clinically meaningful differences between a proposed drug and the applicable reference product, they may help FDA assess similarity with regard to certain key quality attributes of the product in question.

USP monographs contain as one component a test for Identity, or Identification, used to establish whether an article is that named in the *United States Pharmacopeia-National Formulary* (*USP-NF*). The USP Identity test is used to determine to which drugs/biologics a particular USP monograph standard applies. When two or more biologics, for example, fall under the same Identity test, they must conform to the compendial quality standards in the monograph, or risk being out of conformance with the applicable USP standard. Under Federal law, any nonconforming biologic risks being deemed misbranded or adulterated (Federal Food, Drug, and Cosmetic Act, §§501, 502).

In that context it is important to underscore, particularly as it relates to the Draft Guidance, that compendial identity is distinct and quite different from regulatory identity. In the United States, only FDA has the authority under various laws to clear a drug for marketing, or to determine that two drugs are the same, similar, identical, or interchangeable. Where two biologics share a compendial identity, 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. There is well-established precedent in this area; insulin, somatropin, and glucagon are all examples of non-interchangeable, multi-manufacturer drugs that share a single USP compendial standard.

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Thus, while an applicable compendial standard can help inform FDA's regulatory consideration, it is certainly not dispositive. This has long been reflected in FDA regulatory determinations, but deserves to be underscored again here. FDA has for example stated that it uses five criteria to characterize the sameness of an active ingredient.[1] Applicable USP standards play a role in the FDA criteria, but in the end only FDA can judge if sameness/identicality/interchangeability has been demonstrated. This has long been noted at FDA, as in the initial agency regulations implementing generic approval under Hatch-Waxman, where the role of USP standards for identity is noted, but with the qualifying statement that "FDA may prescribe additional standards that are material to the ingredient's sameness." 57 Fed. Reg. 17950, 17959 Col A (April 28, 1992).

In summary, regarding the Draft Guidance and the four assessments possibilities described on page 5, therein, applicable USP standards may be helpful for informing FDA's evaluation. But the distinctions between compendial and regulatory identity remain. Only FDA may make findings regarding the latter, and only FDA can determine on a case-by-case basis what role if any an applicable compendial standard should play in the Agency's deliberations.

Thank you for the opportunity to clarify the role and application of our standards, and why this role should not be confused with regulatory decisions regarding similarity or market access. If you have any questions I can be reached at (301) 816-8397 or tsm@usp.org.

Sincerely,

Tina S. Morris, Ph.D.
Vice President, Biologics & Biotechnology

[1] See Guidance for Industry: Immunogenicity-Related Considerations for the Approval of Low Molecular Weight Heparin for NDAs and ANDAs, Draft April 2014; see discussion re sameness of the active ingredient, page 3, including footnote 11. See also FDA rationale for the approval of generic enoxaparin, FDA response to citizen petition submitted on behalf of Aventis Pharmaceuticals (letter of July 23, 2010), discussion on pages 11-13 regarding the agency's five criteria for sameness, including the supportive but not dispositive role of applicable compendial standards.