

September 21, 2018

Food and Drug Administration
Dockets Management Staff (HFA-305)
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Regarding: Docket No. FDA-2018-N-2689 “Facilitating Competition and Innovation in the Biological Products Marketplace; Public Hearing; Request for Comments”
Electronically filed

Dear Sir/Madam:

The United States Pharmacopeial Convention (USP) appreciates the opportunity to provide written comments in addition to the oral testimony we gave on September 04, 2018, during the public hearing on competition and innovation in the biological products marketplace, including facilitating greater availability of biosimilar and interchangeable products.

USP¹ is a scientific nonprofit organization dedicated to protecting and improving public health. We collaborate with the U.S. Food and Drug Administration (FDA) and stakeholders to develop public standards and related programs that support the quality of medicines, including biologics and drug ingredients. Public standards have an important role in helping ensure medicines quality, including enabling development and market entry.

Role of standards

USP has had a longstanding program in biologics standards development. For example, we have developed and maintained standards for insulin and have contributed to the development of an international public standard for this widely-used drug. These standards help give diabetic patients throughout the world confidence that the insulin they take is of reliable and consistent quality. As the range of insulin products available to patients has evolved over time with the introduction of new dosage forms and different insulin analogs, USP’s portfolio of standards has also evolved to demonstrate identity and potency for classes or families of insulin analogs. These have included system suitability standards used to demonstrate method resolution and performance that aid in addressing

¹ USP is governed by a Convention comprising over 450 leading organizations and institutions in health and science from the public sector; academia; industry; healthcare practitioners; and consumer and patient communities. USP’s public standards provide consistent benchmarks that help define the target for quality medicines for industry, also contributing to regulator, practitioner, and patient confidence in the integrity of these products. USP develops public standards through a collaborative and transparent process that brings together patients, practitioners, regulators, academia, and industry.

key analytical challenges associated with molecular variants, impurities and high-molecular species of insulins.

This approach of developing standards for molecular variants of products has also been applied to the measurement of high molecular species and aggregates potentially present in protein therapeutic samples. Proteins can be made up of combinations of single large molecules (e.g., monomers) as well as combinations of two or more molecules (e.g., dimers or oligomers). These can also combine to form even larger aggregates, the uncontrolled presence of which in a protein product has the potential to trigger immunogenicity and, thus, impact product safety. It is important to confirm that a chosen method for analyzing these aggregates is suitable for the task. USP reference standards can be used for this type of confirmatory activity. For example, USP provides a reference material specimen of filgrastim with known amounts of dimers, oligomers and aggregates. A manufacturer can use this reference material to verify that a particular chromatographic method for measuring these species in a filgrastim test sample (based on the known amounts of oligomers, dimers and aggregates in the reference material) is suitable for this purpose.

Performance standards for glycosylated monoclonal antibody products

Based on engagement with and input from stakeholders, and the FDA, we have focused in the past several years on the development of performance standards. USP's performance standards are developed using the same controlled process, quality systems and scientific review by staff and Expert Committees as other USP standards. In addition, their suitability for use will be established using multi-laboratory collaborative studies. These are broadly applicable to product families or classes and are intended to address common quality challenges associated with technologies and methodologies, thereby improving the efficiency of product development and characterization. For example, a common analytical challenge associated with monoclonal antibody products involves the ability to ascertain that a specific method can resolve relevant molecular variants. USP conducted extensive characterization of a monoclonal IgG antibody material using a variety of analytical methods and has made it available as a robustly-characterized performance standard. Manufacturers can use this standard as a system suitability standard to demonstrate the performance of methods in measuring molecular variants and low- and high-molecular impurities in monoclonal antibody drug substances. Among its established uses, this standard allows users to ensure that their system can adequately resolve and quantitate nonglycosylated heavy chains versus glycosylated heavy chains in monoclonal antibodies, using a capillary electrophoresis method described in General Chapter <129> in the *United States Pharmacopeia–National Formulary*.

For biologic and biosimilar companies, standards and tools that enable better measurements and characterization of products at early stages of development can contribute to a better understanding of product attributes and improve the efficiency of product development and characterization. These tools will also allow biosimilar

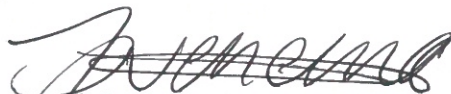
companies to set a baseline for analytical performance as they use a variety of different methods to establish similarity to a reference product. For example, attributes such as glycosylation patterns are important to address and control. Variations in these patterns can impact the safety and efficacy of a product, with implications on biological activity as well as the potential for immunogenicity. USP provides standards that enable users to assess variations in glycosylation. These include documentary and reference standards that address measurement and quantification of monosaccharide, oligosaccharide and sialic acid content in glycosylated products, allowing users to routinely measure and monitor the amounts of these species and show consistency in glycosylation patterns.

Collaborating to develop performance standards

USP continues to expand its performance standards program and engage stakeholders in a dialog to identify and prioritize development of performance standards that address critical challenges companies face throughout the product development cycle. In the last year we conducted roundtables with the Biotechnology Innovation Organization and the International Federation of Pharmaceutical Manufacturers and Associations, and identified a number of opportunities for standard development to support stronger biological manufacturing programs (see executive summaries from roundtables, <https://biologics.usp.org/white-papers-resources-trends-biologics-standards>). We believe that the USP approach to performance standards will support key areas identified in FDA's Biosimilar Action Plan, help maximize scientific clarity for the product development community, and facilitate the efficient development of biosimilar and interchangeable products using state-of-the-art science.

In conclusion, public quality standards support the priorities of all stakeholders including drug developers, drug manufacturers, and regulators by identifying quality attributes, creating predictability, and facilitating product innovation. USP is committed to actively gathering early and continued input-- including: industry, regulator, and other stakeholder views--before and during the development of a biologic standard. As the marketplace of biological products continues to expand and evolve, USP stands ready to work closely with FDA and other stakeholders to support the development and manufacturing of these critical drugs. For additional information, please do not hesitate to contact Elizabeth Miller, Pharm.D., Vice President, U.S. Public Policy and Regulatory Affairs, at ehm@usp.org; (240) 221-2064.

Sincerely,



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

