VIA ELECTRONIC SUBMISSION

January 27, 2020

Food and Drug Administration
Division of Dockets Management
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2019-D-5255 for "Clinical Immunogenicity Considerations for Biosimilar and Interchangeable Insulin Products"; Draft Guidance for Industry

Dear Sir/Madam,

The United States Pharmacopeia (USP)[1] appreciates the opportunity to comment on FDA's draft guidance, "Clinical Immunogenicity Considerations for Biosimilar and Interchangeable Insulin Products." We incorporate by reference our comments submitted to FDA's docket on "Increasing Access and Facilitating the Efficient Development of Insulin Biosimilar and Interchangeable Products."[2]

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) provides that on March 23, 2020, an application for a biological product approved under section 505 of the Federal Food, Drug, and Cosmetic Act will be deemed to be a license for the biological product under section 351 of the Public Health Service Act (PHS Act). This provision directly impacts insulin products, allowing those with deemed biologics license applications (BLAs) to be used as reference products for potential biosimilar and interchangeable insulin products licensed under section 351(k) of the PHS Act.

The draft guidance states the Agency's updated position that generally, if a comparative analytical assessment supports a demonstration of "highly similar" for a proposed biosimilar or interchangeable insulin product, there would be little or no residual uncertainty regarding immunogenicity. Thus, a comparative clinical immunogenicity study generally would be unnecessary to support a demonstration of biosimilarity or interchangeability.

USP supports FDA's updated stance, which is based on extensive product understanding, scientific data, and clinical evidence. This recommendation regarding clinical immunogenicity studies should effectively reduce the burden for potential BLA holders to bring new biosimilar and interchangeable insulin products to market. Reduced clinical study costs, coupled with the potential for increased competition among insulin products, should appreciably reduce barriers to develop insulin and is

[1] USP is an independent, scientific, nonprofit organization dedicated to improving health through the development of public standards for medicines, foods, and dietary supplements. Through a longstanding collaboration with FDA, we have worked continuously to benefit public health through accessible quality medicines.

[2] *See* USP comments on "The Future of Insulin Biosimilars: Increasing Access and Facilitating the Efficient Development of Insulin Biosimilar and Interchangeable Products; Public Hearing; Request for Comments" (Docket No. FDA-2019-N-1132) submitted May 31, 2019.

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in line with the objectives of the BPCI Act to improve access to innovative medical therapies.

In addition to this announcement about clinical immunogenicity studies, other tools and approaches can help facilitate increased access to safe and reliable insulins for patients. For example, USP standards are important tools for developing a robust comprehensive and comparative analytical assessment for drug products, including biological products. USP has worked closely with FDA, industry, and other stakeholders to develop public standards for insulin that help ensure product quality and support regulatory predictability as science evolves, regardless of the source (i.e., sourced naturally from animals, made recombinantly). Since the introduction of the first official USP insulin standard in 1941, USP has developed numerous science-based public quality standards that have been continuously updated to accommodate subsequent technological advances and regulatory changes associated with insulin. Insulin standards establish reliable and validated analytical results for identity, purity, and potency of various insulin products. A list of USP insulin drug substance monographs, drug product monographs, and general chapters is included in the Appendix.

FDA's draft guidance, "Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations"[3] states that comprehensive comparative analytical data are necessary to build the foundation for a development program for a proposed biosimilar product. It also states that an application submitted under section 351(k) of the PHS Act must contain, among other things, information demonstrating that the biological product is biosimilar to a reference product based upon data derived from analytical studies that demonstrate that the biological product is highly similar to the reference protect notwithstanding minor differences in clinically inactive components. USP's insulin standards provide a source of reliable and relevant tests, materials, and specifications for the analytical assessment of insulins. The standards provide information specifically developed to describe some of the critical physio-chemical properties of insulin products. For example, the use of compendial test methods, such as quantitative chromatographic analyses, in concert with a verified Insulin USP Reference Standard, provides assurances when determining the identity and potency of an uncharacterized insulin product.

Through the work of our expert committees, USP continues to maintain and revise the current library of insulin monographs and related General Chapters <121> *Insulin Assays* and <121.1> *Physicochemical Analytical Procedures for Insulins* to provide reliable tests and specifications useful for characterization of critical product quality attributes of insulin products.

We look forward to continuing to collaborate with the Agency, the public, and industry to develop and continuously evolve science-based public quality standards to help ensure the quality of insulin.

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[3] FDA draft guidance, "Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations, at https://www.fda.gov/media/125484/download (May 2019).

Again, thank you for the opportunity to comment. For more information, please contact Elizabeth Miller, Pharm.D., Vice President, U.S. Public Policy and Regulatory Affairs, at ehm@usp.org; (240) 221-2064.

Sincerely yours,

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Appendix

Table 1 – USP Insulin Drug Substance Monographs

Insulin Drug Substance Monograph	Reference Standard	Date of Admission of First Standard (Official date)	Date of Most Recent Revision
Insulin	Insulin Pork (50 mg); Insulin (Beef) (50 mg); Endotoxin (10,000 USP Endotoxin Units); High Molecular Weight Insulin Human (8.4 mg)	*USP 19-NF 14 S4* May 1, 1978	Revision Bulletin Posting Date: March 29, 2019; Official Date: May 1, 2019
Insulin Human	Endotoxin (10,000 USP Endotoxin Units); Insulin Human (100 mg); Insulin Pork (50 mg)	*USP 21-NF 16* Jan. 1, 1985	*USP 39-NF 34* Official Date: May 1, 2016
Insulin Apsart	Insulin Aspart (7.62 mg)	First published in: *USP 37-NF 32* Jan. 6, 2014; Official in: *USP 41-NF 36* May 1, 2018	*USP 40-NF 35 S2* Official Date: Dec 1, 2017
Insulin Lispro	Insulin Lispro (5.73 mg); Endotoxin (10,000 USP Endotoxin Units); Insulin Human (100 mg)	*USP 26-NF 21* April 1, 2003	Interim Revision Announcement (IRA) Posting Date: Nov. 30, 2018; Official Date: Jan. 1, 2019
Insulin Glargine	Insulin Glargine (15.06 mg); Insulin Glargine for Peak Identification (3.2 mg) (Mixture of Insulin Glargine and 0A-Arg-Insulin Glargine)	*USP 38-NF 33* May 1, 2015	IRA Posting Date: Sept. 30, 2016; Official Date: Nov. 1, 2016

Table 2 – USP Insulin Drug Product Monographs

Insulin Drug Product Monograph	Reference Standard	Date of Admission of First Standard (Official Date)	Date of Most Recent Revision
Extended Insulin Zinc Suspension	Insulin (Beef) (50 mg); Endotoxin (10,000 USP Endotoxin Units); Insulin Pork (50 mg)	*USP 17* Sept. 1, 1965	Revision Bulletin Posting Date: Mar. 29, 2019; Official Date: May 1, 2019 (Omission of USP Insulin Beef RS)
Human Insulin Isophane Suspension And Human Insulin Injection	Insulin Human (100 mg); Endotoxin (10,000 USP Endotoxin Units)	*USP 30-NF 25 S1* Aug. 1, 2007	IRA Posting Date: Nov. 30, 2018; Official Date: Jan. 1, 2019
Insulin Zinc Suspension	Insulin (Beef) (50 mg); Endotoxin (10,000 USP Endotoxin Units); Insulin Pork (50 mg)	*USP 16* Oct. 1, 1960	Revision Bulletin Posting Date: Mar. 29, 2019; Official Date: May 1, 2019 (Omission of USP Insulin Beef RS)
Insulin Lispro Injection	Endotoxin (10,000 USP Endotoxin Units); Insulin Lispro (5.73 mg)	*USP 26-NF 21 S1* April 1, 2003	IRA Posting Date: Nov. 30, 2018; Official Date: Jan. 1, 2019
Insulin Injection	Insulin (Beef) (50 mg); Endotoxin (10,000 USP Endotoxin Units); Insulin Pork (50 mg)	*USP XI S2* Dec. 31, 1941 (Interim Revision Announcement No. 4)	Revision Bulletin Posting Date: Mar. 29, 2019; Official Date: May 1, 2019 (Omission of USP Insulin Beef RS)
Extended Insulin Zinc Suspension	Insulin (Beef) (50 mg); Endotoxin (10,000 USP Endotoxin Units); Insulin Pork (50 mg)	*USP 17* Sept. 1, 1965	Revision Bulletin Posting Date: Mar. 29, 2019 Official Date: May 1, 2019 (Omission of USP Insulin Beef RS)
Prompt Insulin Zinc Suspension	Insulin (Beef) (50 mg); Endotoxin (10,000 USP Endotoxin Units); Insulin Pork (50 mg)	*USP 17* Sept. 1, 1965	Revision Bulletin Posting Date: Mar. 29, 2019; Official Date: May 1, 2019 (Omission of USP Insulin Beef RS)

Insulin Drug Product Monograph	Reference Standard	Date of Admission of First Standard (Official Date)	Date of Most Recent Revision
Insulin Aspart Injection	Insulin Aspart (7.62 mg)	*USP 37-NF 32 S1* Aug. 1, 2014	IRA Posting Date: Nov. 30, 2018; Official Date: Jan. 1, 2019
Isophane Insulin Human Suspension	Endotoxin (10,000 USP Endotoxin Units); Insulin Human (100 mg); Insulin Pork (50 mg)	*USP 23-NF 18 S2* May 15, 1995	IRA Posting Date: Nov. 30, 2018; Official Date: Jan. 1, 2019
Insulin Human Injection	Endotoxin (10,000 USP Endotoxin Units); Insulin Human (100 mg); Insulin Pork (50 mg)	*USP 21-NF 16* Jan. 1, 1985	*USP 38-NF 33 S2* Official Date: Dec. 1, 2015
Insulin Lispro Injection	Endotoxin (10,000 USP Endotoxin Units); Insulin Lispro (5.73 mg)	*USP 26-NF 21 S1* April 1, 2003	IRA Posting Date: Nov. 30, 2018; Official Date: Jan. 1, 2019
Insulin Glargine Injection	Insulin Glargine for Peak Identification (3.2 mg)	*USP 38-NF 33* May 1, 2015	IRA Posting Date: Sept. 30, 2016; Official Date: Nov. 1, 2016
Isophane Insulin Suspension	Insulin Pork (50 mg); Insulin (Beef) (50 mg); Endotoxin (10,000 USP Endotoxin Units)	*USP 15* Dec. 15, 1955	Revision Bulletin Posting Date: Mar. 29, 2019; Official Date: May 1, 2019 (Omission of USP Insulin Beef RS)

Table 3 – USP Chapters for Insulin

USP Chapter for Insulin	Reference Standard	Date of Admission of First Standard	Date of Most Recent Revision
<121> Insulin Assays	Insulin Glargine (15.06 mg); Insulin Lispro (5.73 mg); Insulin (Beef) (50 mg); Insulin Human (100 mg); Dextrose (500 mg) Insulin Pork (50 mg)	*USP 15* Sept. 1, 1970	Revision Bulletin Posting Date: Mar. 29, 2019; Official Date: May 1, 2019 (Omission of USP Insulin Beef RS)
<121.1> Physicochemical Analytical Procedures for Insulins	None	*USP 37-NF 32 S1* Aug. 1, 2014	*USP 39-NF 34 2S* Official Date: Mar. 21, 2016