VIA ELECTRONIC SUBMISSION

May 31, 2019

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

Re: Docket No. FDA-2019-N-1132 for "The Future of Insulin Biosimilars: Increasing Access and Facilitating the Efficient Development of Insulin Biosimilar and Interchangeable Products; Public Hearing; Request for Comments

Dear Sir/Madam,

The United States Pharmacopeia (USP) appreciates the opportunity to comment on "The Future of Insulin Biosimilars: Increasing Access and Facilitating the Efficient Development of Insulin Biosimilar and Interchangeable Products" (Part 15 hearing and invitation to comment). We incorporate by reference our prior submissions to FDA dockets related to this topic.[1]

Quality Insulin is Essential to Patient Safety

USP's transparent and public quality standards are foundational to ensure the quality of drug and biological products, including insulin. Therefore, adherence to them is essential. USP's public quality standards contribute across the life cycle of insulin and other biologic medicines. These standards are available to biologics manufacturers worldwide, regulators for ensuring product quality regardless of whether manufactured in the United States or overseas, healthcare practitioners, healthcare plans and others. They foster the efficient development of products, help maintain the quality of currently approved or licensed products, and facilitate access to safe and reliable insulins for the many patients in the United States who need them. Standards also foster regulatory certainty around quality, so anyone can rely on core quality attributes, as publicly set forth in USP standards. USP public quality standards help ensure trust in biologic medicines, including insulin.

The regulatory status of insulin products will be deemed to be licensed biological products pursuant to the Biologics Price Competition and Innovation Act of 2009 (BPCI Act) as of March 23, 2020. While insulin will transition under this regulatory paradigm, the imperative for quality medicine continues, and trusted public standards are foundational to meeting this need.

[1] See USP comments on the "Nonproprietary Naming of Biological Products" draft guidance (Docket No. FDA-2013-D-1543) submitted Oct. 26, 2015; USP comments on FDA's proposed rule "Designation of Official Names and Proper Names for Certain Biological Products" (Docket No. FDA-2015-N-0648) submitted Nov. 12, 2015; USP comments on the "Nonproprietary Naming of Biological Products" final guidance (Docket No. FDA-2013-D1543) submitted Feb. 13, 2017, and "Nonproprietary Naming of Biological Products: Update" draft guidance (Docket No. FDA-2013-D-1543) submitted May 3, 2019.

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USP has worked closely with FDA, industry, and other stakeholders to develop public standards that help ensure product quality and support regulatory predictability as science evolves, regardless of the source of insulin (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 revised and updated to accommodate subsequent technological advances, and regulatory changes associated with insulin and its many forms (see Appendix below).

In addition, cross-cutting standards known as USP general chapters, such as testing for endotoxins (toxic substances), may be applicable to an extensive range of products or targeted to product families or classes, and are created to address common quality matters. These standards can add flexibility by offering choices of analytical approaches. They can establish baselines for analytical performance associated with technologies and methodologies used by multiple manufacturers, and help manufacturers bridge and transition between methods. Importantly, for biologic medicines, USP general chapters provide valuable information to manufacturers to support early development of new products. For nearly a century, these standards have helped to ensure the quality for insulin.

Quality standards also help Americans traveling within the United States or living abroad by helping to ensure that insulin purchased anywhere in the world meets quality standards. For a product such as insulin, where daily dosing and careful titration and long-term disease management is necessary for patient safety, this is particularly important, as patient representatives at the Part 15 hearing conveyed. To have standards that patients, their health care providers, as well as products sponsors, regulators, and health systems can depend upon is invaluable.

Transition Biological Products

The regulatory changes required by the BPCI Act must be implemented in a manner that is clear, transparent and minimally disruptive to patients. The updated draft guidance, “Nonproprietary Naming of Biological Products,”[2] indicates that the transition biological products will not have their nonproprietary names revised to match the naming convention being imposed on current and newly licensed biological products, and consequently no suffixes will be added. As such, the quality standards for insulin products will continue to be applicable for the articles listed in the Appendix below. USP standards should be applicable to the quality of both drug and biological products, irrespective of regulatory pathway.[3]

[2] FDA draft guidance, “Nonproprietary Naming of Biological Products: Update”, at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/nonproprietary-naming-biological-products-update-guidance-industry (March 2019).

[3] Quality standards should apply to all biological products, including originator, biosimilar, and interchangeable products.

See table below:

Biological Product Type	Nonproprietary Name
New originator biological products	Core name plus FDA-designated suffix
New biosimilar and interchangeable products	Core name plus FDA-designated suffix
Existing originator biological products that do not have an FDA-designated suffix	FDA-designated suffix will not be added to core name
Transition biological products	FDA-designated suffix will not be added to core name

Global Considerations

Robust biosimilar markets exist in the European Union (EU) and elsewhere, where adherence to public quality standards is integral to the regulatory ecosystem. While many factors have contributed to the success of the biosimilar market in Europe, public standards for the quality of biological products have played an important role in facilitating product development, ensuring regulatory predictability, and enhancing patient and provider trust.

Additional global considerations also place a need for harmonized approaches on product names. Healthcare providers and patients in the United States are accustomed to prescribing and using products, respectively, from different manufacturers which share the same nonproprietary name, and which meet the same quality standards applied throughout their life cycle. USP coordinates with other standards-setting organizations worldwide and important public health groups such as the World Health Organization (WHO) to optimize the availability of useful public standards around the world.

The United States is pursuing a different naming convention than the rest of the world for biological products by attaching suffixes to the non-proprietary name of the biologic product. The rest of the world continues to use international nonproprietary names (INN), as administered by WHO, consistently for all medicines, whether the product is a drug or biological product. We encourage FDA to consider experiences from EU and other highly regulated and successful markets for biological products, that use shared science-based regulatory mechanisms that include compendia, as appropriate. As a scientific and regulatory matter, the opportunity for harmonization with other regulatory authorities is clear, and we continue to encourage alignment globally in the interest of public health.

Conclusion

Thank you for the opportunity to comment on this important issue. USP will continue to partner with FDA, industry, healthcare practitioners and other stakeholders to develop and continuously evolve, science-based public quality that are available and transparent for stakeholders everywhere to help ensure the quality of insulin. We look forward to continuing our long-standing work with FDA to help ensure trust in biologic medicines for patients.

For more information, please contact Elizabeth Miller, 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)	April 1, 2002 (Official Date in USP-NF) History is that it was transferred from NF May 1, 1978. First published in USP 19	March 2019 – May 2019 revision bulletin
Insulin Human	Endotoxin (10,000 USP Endotoxin Units) Insulin Human (100 mg) Insulin Pork (50 mg)	January 1, 1985 (Official)	2016 USP 39 NF34
Insulin Apsart	Insulin Aspart (7.62 mg)	May 1, 2018 (Official) Published in compendium January 6, 2014, but several revisions without becoming official until May 1, 2018	2017 USP40-NF35 2S
Insulin Lispro	Insulin Lispro (5.73 mg) Endotoxin (10,000 USP Endotoxin Units) Insulin Human (100 mg)	April 1, 2003 (Official)	Jan. 2019 Interim Revision Announcement
Insulin Glargine	Insulin Glargine (15.06 mg) Insulin Glargine for Peak Identification (3.2 mg) (Mixture of Insulin Glargine and 0A-Arg-Insulin Glargine)	May 1, 2015 (Official)	Nov. 2016 Interim Revision Announcement (IRA)

Table 2 – USP Insulin Drug Product Monographs

Insulin Drug Product Monograph	Reference Standard	Date of Admission of First Standard	Date of Most Recent Revision
Extended Insulin Zinc Suspension	Insulin (Beef) (50 mg) Endotoxin (10,000 USP Endotoxin Units) Insulin Pork (50 mg)	September 1, 1965 (first Official Date)	Mar. 2019 – May 2019 Revision Bulletin
Human Insulin Isophane Suspension And Human Insulin Injection	Insulin Human (100 mg) Endotoxin (10,000 USP Endotoxin Units)	August 1, 2007 (official)	Jan. 2019 Interim Revision Announcement (IRA)
Insulin Zinc Suspension	Insulin (Beef) (50 mg) Endotoxin (10,000 USP Endotoxin Units) Insulin Pork (50 mg)	May 1, 2019 (Official) October 1, 1960 (First official date)	Mar. 2019 – May 2019 Revision Bulletin Official May 1, 2019
Insulin Lispro Injection	Endotoxin (10,000 USP Endotoxin Units) Insulin Lispro (5.73 mg)	April 1, 2003	Jan. 2019 Interim Revision Announcement (IRA)
Insulin Injection	Insulin (Beef) (50 mg) Endotoxin (10,000 USP Endotoxin Units) Insulin Pork (50 mg)	April 1, 2002 (First official date- Insulin Injection monograph in 1930 in *USP XI*	Mar 2019-May 2019 Revision Bulletin Official May 1, 2019
Extended Insulin Zinc Suspension	Insulin (Beef) (50 mg) Endotoxin (10,000 USP Endotoxin Units) Insulin Pork (50 mg)	September 1, 1965 (First official date)	Mar. 2019 – May 2019 Revision Bulletin (omission of USP Insulin Beef RS)
Prompt Insulin Zinc Suspension	Insulin (Beef) (50 mg) Endotoxin (10,000 USP Endotoxin Units) Insulin Pork (50 mg)	September 1, 1965 (First official date)	Mar. 2019 – May 2019 Revision Bulletin
Insulin Aspart Injection	Insulin Aspart (7.62 mg)	First Official, August 1, 2014	January 1, 2019, IRA

Insulin Drug Product Monograph	Reference Standard	Date of Admission of First Standard	Date of Most Recent Revision
Isophane Insulin Human Suspension	Endotoxin (10,000 USP Endotoxin Units) Insulin Human (100 mg) Insulin Pork (50 mg)	First Official, May 15, 1995	Jan. 2019 Interim Revision Announcement (IRA)
Insulin Human Injection	Endotoxin (10,000 USP Endotoxin Units) Insulin Human (100 mg) Insulin Pork (50 mg)	January 1, 1985 (first official date)	2015 USP38-NF33 2S
Insulin Lispro Injection	Endotoxin (10,000 USP Endotoxin Units) Insulin Lispro (5.73 mg)	April 1, 2003 (first official date)	Jan. 2019 Interim Revision Announcement (IRA)
Insulin Glargine Injection	Insulin Glargine for Peak Identification (3.2 mg	May 1, 2015 (first official date)	Nov. 2016 Interim Revision Announcement (IRA)
Isophane Insulin Suspension	Insulin Pork (50 mg) Insulin (Beef) (50 mg) Endotoxin (10,000 USP Endotoxin Units)	December 15, 1955	March 2019 – May 2019 Revision Bulletin

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)	April 19, 2002 1970 (first official date)	March 2019 – May 2019 Bulletin Revision
<121.1> Physicochemical Analytical Procedures for Insulins	None	August 1, 2014	March 21, 2016