February 2, 2018

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

Regarding: Docket No. FDA-2017-D-5767 for "ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin"
Electronically filed.

Dear Sir/Madam:

The United States PharmacopeiaI Convention (USP) appreciates the opportunity to provide comments on the Food and Drug Administration's (FDA) Draft Guidance "ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin". We commend FDA in developing its policy on applications for follow-on synthetic peptide drug products, while recognizing the scientific challenges as well as the need for continued dialog.

USP[1] is a nongovernment, nonprofit organization with a mission to improve global health through public standards and related programs. We offer a trusted source of science-based information and set public standards for the identity, strength, quality, purity, packaging, and labeling of medicines, working with independent scientific experts who volunteer their time and expertise to the standard setting process. USP standards are published in the *United States Pharmacopeia-National Formulary*, an official compendium of the United States. USP's longstanding collaboration with FDA has worked continuously to benefit public health through accessible quality medicines.

USP and Peptides

USP's longstanding history of standards development for peptide drugs began with naturally derived products, like hormones, and as the manufacturing process for these evolved into using recombinant means, so did the associated USP standards. Recent technological developments permit peptide drugs

[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.

to now be chemically synthesized—as a result, USP's Peptides and Insulins Expert Committee has been working with regulators and stakeholders on the scientific and regulatory considerations associated with synthetic peptides. USP is committed to continue convening discussion forums to further the dialogue on therapeutic peptides.

At the fourth USP Workshop on Synthetic Therapeutic Peptides[2] held November 5-6, 2017, this Draft Guidance was discussed with participation from FDA, industry and other stakeholders. More discussions followed at the USP Peptides and Insulins Expert Committee meeting held November 8-9, 2017. The committee considered the implications for structure elucidation, manufacturability, comparability, immunogenicity, and compendial science and standards—informed by the discussions, we respectfully provide the comments below regarding certain requirements in the Draft Guidance.

Comments on the Draft Guidance

USP appreciates and is supportive of FDA's efforts to provide detailed regulatory expectations and requirements for the transition from recombinant to synthetic forms for the five peptide drug products.

1. The USP flexible approach to monographs allows for multiple tests for impurities to be included in a monograph so that substances obtained from different routes of synthesis or different processes (e.g. recombinant vs. synthetic) are addressed in a single monograph. USP supports addition of new impurity methods and limits for new routes of synthesis in collaboration with FDA and manufacturers.

2. The Draft Guidance proposes a requirement to identify and characterize all new, peptide-related impurities present at levels between 0.10% and 0.5% in the synthetic forms of the specified Reference Listed Drugs appears to be beyond the current state of the art. While the identification of impurities at a level of 0.10% may often be feasible; in some cases, attempts to identify such impurities by modern methods, such as UHPLC-HRMS, may be very difficult or impossible. In addition, peptide-related impurities may co-elute with the product.

3. Some of these impurities will be difficult to identify, quantify, and then synthesize in a stable form for the additional immunogenicity studies advised by the Draft Guidance. A risk-based evaluation of potential toxicity and immunogenicity of these impurities should be performed, and should take into account expected impurities that would be different from the recombinant form (where immunogenicity concerns are already understood), route of administration, etc. as also described in USP Chapter <1106> and FDA Guidances. As there is no accepted threshold for an adverse immunogenic potential, the daily exposure expected at these proposed levels should be considered in relation to other officially recognized limits.

[2] https://www.usp.org/sites/default/files/usp/document/workshops/2017-november-6-7-peptides-ws-agenda.pdf

Thank you for FDA's leadership on this issue and for considering our comments. USP shares FDA's goal of accessibility to high quality, safe, effective and affordable medicines and we look forward to continuing our partnership with FDA, industry and other stakeholders towards this shared vision. We would welcome the opportunity to discuss these comments further. 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,

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Executive Vice President and Chief Science Officer
United States Pharmacopeia