February 4, 2017

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

Re: Docket No. FDA-2017-D-5767-0022: ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments to the Draft Guidance titled "ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin".

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial, and environmental biotechnology products.

BIO supports FDA's initiative to provide enhanced regulatory guidance on considerations for approval of generic and follow-on medicine products. In particular and as stated in the guidance,[1] we support FDA's recognition that when clinical studies are necessary for regulatory assessment of generic medicines and follow-on peptide products a 505(b)(2) application is the appropriate regulatory pathway for application submissions. However, BIO requests FDA provide greater scientific reasoning and specificity on its analysis for the sweeping determination within this guidance that an ANDA submission may be appropriate for the five specific peptides referenced in this Draft Guidance.[2]

BIO has made the following comments with respect to this Draft Guidance which are addressed in more detail below:

1) The Draft Guidance treats the regulatory assessment of these five polypeptides differently from biological products, which as communicated in previous comments is of concern to BIO.[3]
2) The Draft Guidance lacks support for the arguments that "sameness" of active ingredient for peptide products can be demonstrated without clinical comparative data.

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[1] *See* Draft Guidance line 8 ("If it is necessary to conduct clinical studies to establish the safety or effectiveness of a proposed synthetic peptide that seeks to rely, in part, on FDA's finding of safety or effectiveness for a previously approved product, submission of an application under the abbreviated pathway described in section 505(b)(2) of the FD&C Act would be necessary.").
[2] *See* id. at Lines 19-20.
[3] *See* BIO comments to Docket No. FDA–2011-D-0611 and Docket No. FDA-2015-D-4750 (May 13, 2016).

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3) The scope of the title does not align with the scientific support and potential approval for peptide products through an ANDA submission.
4) The Draft Guidance does not provide sufficient scientific justification for FDA's acceptance and identification thresholds that it has selected for peptide-related impurities.

1. The Draft Guidance treats these five polypeptides differently from biological products

BIO reiterates its concerns with FDA's interpretation of the definition of protein under the Biologics Price Competition and Innovation Act of 2009 and FDA's Draft Guidance entitled "Implementation of the 'Deemed to be a License' Provision of the Biologics Price Competition and Innovation Act of 2009," including the revocation of data exclusivity and pediatric exclusivity intellectual property protections granted for products approved under the Hatch-Waxman Act. BIO believes the standards applied for approval of biosimilars are equally applicable to follow-on products for the polypeptides covered by this Draft Guidance. We request FDA provide the scientific rationale for why such standards should not apply and, in the absence of such rationale, reconsider its position on the definition of biological product and the exclusivity protections per our previous comments.[4]

2. The Draft Guidance lacks scientific support for the arguments that "sameness" of active ingredient for peptide products can be demonstrated without clinical comparative data

Traditionally, section 505(b)(2) has been FDA's recommended pathway for regulatory assessment of follow-on polypeptides. This Draft Guidance sets new recommendations to permit ANDA applications for certain follow-on polypeptides but is lacking in scientific justification for such recommendations. BIO requests that FDA provide further rationale.

Initially, we note that it is unclear why the draft guidance focuses on five specific polypeptides but not others. We request that FDA provide clarity and scientific rationale for selection of the polypeptides covered by this Draft Guidance.

The Draft Guidance states that the "current state of technology for peptide synthesis and characterization" permits an ANDA applicant to now "demonstrate that the active ingredient in a proposed generic synthetic peptide drug product (proposed generic synthetic peptide) is the "same" as the active ingredient in a previously approved peptide of rDNA origin."[5] However, this position dramatically departs from FDA's previous position on follow-on polypeptides which support that rDNA polypeptide molecules cannot be fully characterized by analytical methods and, therefore, the ANDA

[4] *See* BIO comments to Docket No. FDA–2011-D-0611 and Docket No. FDA-2015-D-4750 (May 13, 2016).
[5] *See* Draft Guidance at lines 1, 22-25.

pathway is not appropriate since demonstrating active ingredient sameness is not possible.[6] BIO requests FDA provide rationale for changes in its interpretation.[7]

FDA acknowledges within this Draft Guidance that impurities may trigger immunogenic responses and these immunogenic responses may have "far reaching consequences."[8] It is also well known, as stated in the Draft Guidance,[9] that peptide-related impurities may generate immunogenicity or affect the safety or effectiveness of a peptide drug product. BIO is concerned that the Draft Guidance outlines an approach that relies on an impurity analysis to address residual uncertainty about active ingredient sameness. This approach may be appropriate for a 505(b)(2) analysis, but is not appropriate to satisfy ANDA statutory "sameness" requirements where therapeutic equivalence is a default. BIO agrees with the Draft Guidance statement that clinical data is still expected for follow-on products of rDNA origin and thus an ANDA would be inappropriate for these products.

While the draft guidance suggests the sponsor provide data to demonstrate that each new impurity does not contain sequences that have an increased affinity for the Major Histocompatibility Complex (MHC) and does not contain impurities or contaminants that produce a greater or distinct stimulation of innate immune activity as compared to the reference listed drug (RLD),[10] the Draft Guidance does not provide details of how this could be accomplished without clinical comparison of the follow-on peptide with the reference listed drug. Given that synthetically producing a polypeptide is a different manufacturing process to the recombinant-derived RLD, differences in impurity profile is likely to be different impurities (peptide related or other impurities) from the RLD (*e.g.,* impurities that are unique to synthetic peptides such as D-isomer and β-alanine side chain). Thus, we are confused by FDA's statement in the Draft Guidance which states that a "new specified peptide-related impurity level of no more than 0.5 percent of the drug substance for purposes of filing an ANDA is consistent with the small amount of unspecified peptide-related impurities observed in finished peptide drug products due to batch-to-batch variability, which occurs regardless of whether the peptide is produced by a recombinant or synthetic process."[11] A new impurity that is not present in the RLD cannot be "consistent" with batch-to-batch variation of impurities of the RLD no matter at what level they are present. Furthermore, *in vitro* T-cell testing for MHC affinity cannot predictably substitute for *in vivo* immunogenicity potential, especially for polypeptides that are injected repetitively and therefore exposed to the immune system repetitively over time. It is also unclear how new impurities that differ from the RLD and may have an impact on clinical safety and efficacy could be considered to have the "same" active ingredient as the RLD. Given the nature of polypeptide products and the

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[6] *Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States: Hearing Before the Subcomm. on Health of the H. Comm. on Energy and Commerce*, 110th Cong., at 42 (2007) (statement of Janet Woodcock, M.D., Deputy Comm'r and Chief Med. Officer, FDA) (Woodcock Testimony), https://www.gpo.gov/fdsys/pkg/CHRG-110hhrg40500/pdf/CHRG-110hhrg40500.pdf. Dr. Woodcock explained that "[f]or purposes of this discussion, I will use the term protein products to refer to certain biological products licensed under the PHS Act and to certain protein and peptide products approved under the FD&C Act." Id. at 25 (emphasis in original).
[7] Id. at 21.
[8] *See* id., at 6 n.18.
[9] *See* id., at 3.
[10] *See* id., at 6.
[11] Id.

risk for immunogenicity upon repeated exposure of new impurities, we request FDA provide their scientific rationale for how and why these five polypeptides can demonstrate "sameness" of active ingredient under the ANDA pathway.

3. **The scope of the Draft Guidance title does not align with the scientific support and potential approval scientific considerations for peptide products through an ANDA submission**

   BIO requests that the overall intended scope of the Draft Guidance be clarified, especially with respect to the Title and Introduction of the Draft Guidance which are broad in scope in comparison to the scientific rationale which is limited, almost exclusively, to peptide-related impurities. There are several other important scientific considerations beyond peptide-related impurities which are necessary to determine whether an ANDA is appropriate, including considerations regarding non-peptide related impurities (*e.g.,* resins, small-molecule carry-overs, process-related impurities, and leachables), demonstration of bioequivalence, stability testing, formulation differences, and baseline ANDA considerations such as route of administration, delivery device characteristics, dosage form, and strength. BIO requests that FDA either revise its stated scope to reflect that it focuses on peptide-related impurities or address these important considerations in the Draft Guidance.

4. **The Draft Guidance does not provide sufficient scientific justification for FDA's acceptance and identification thresholds that it has selected for peptide-related impurities**

   In the Draft Guidance, FDA recommends that the applicant identify in the ANDA each peptide-related impurity that is 0.10 percent of the drug substance or greater. FDA also recommends that for each new specified impurity that is no more than 0.5 percent of the drug substance that the applicant provide justification, including data, to show that any differences in impurity profiles between the proposed generic synthetic polypeptide and the RLD do not modify the physicochemical properties, biological activity, or immunogenicity risk of the product.

   FDA's selection of the threshold levels for peptide-related impurities of 0.5 and 0.1 percent of the drug substance are not scientifically supported. Given the criticality of scientifically justifying the impact of impurities in the safety and efficacy of polypeptide products, BIO requests that FDA provide its scientific rationale for the recommended acceptance and identification of these thresholds for peptide-related impurities. BIO also requests that FDA provide examples of the tools or methodologies that "now" permit analytical assessment and demonstration of "same" active ingredient for the rDNA derived polypeptides covered by this Draft Guidance.

BIO appreciates this opportunity to submit comments on the Draft Guidance on "ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin." We provide additional specific, detailed comments to improve the clarity of the Draft Guidance in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Sesquile Ramon, Ph.D.
Director, Science & Regulatory Affairs
Biotechnology Innovation Organization

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
II. BACKGROUND		
Lines 87-88	Impurities have the potential to generate significant safety and efficacy risks. However, the guidance suggest that impurities generally pose minimal safety or efficacy risks.	BIO requests deletion of the following statement: "These impurities generally pose minimal safety or efficacy risks and can be controlled."
III. SCIENTIFIC CONSIDERATIONS FOR ANDAS FOR PROPOSED GENERIC SYNTHETIC PEPTIDES		
Impurities		
Lines 137-140	A synthetically produced follow-on polypeptide is per se produced by a different method than a rDNA derived RLD. The different manufacturing method and more than likely different impurity profile may impact degradation and storage conditions for the product.	BIO requests deletion of the following statement: "Impurities that result from degradation during storage of the product, rather than from how the peptide is produced, would be expected to be the same where the RLD and proposed generic product have the same active ingredient, generally the same inactive ingredients, and the same labeled storage conditions."