Biotechnology Innovation Organization

July 19, 2019

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

Re: Docket No. FDA-2019-D-2102-0001: Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the Draft Guidance titled Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations.

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BIO welcomes this well written Draft Guidance on the use of comparative analytical studies that are relevant to assessing whether the proposed product is biosimilar to a reference product for purposes of submission of a marketing application under section 351(k) of the PHS Act. Furthermore, we welcome the document's description of considerations for CMC information that is relevant to assessing whether the proposed product is biosimilar to the reference product. BIO is supportive of the Agency's decision to combine the comparative analytical assessment within the previously issued "Quality Considerations" draft guidance rather than as a standalone guidance.

BIO appreciates this opportunity to submit comments on the Draft Guidance titled Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations. We provide additional specific, detailed comments to improve the clarity of the Draft Guidance in the following chart.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/

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SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
II. BACKGROUND		
III. SCOPE		
IV. GENERAL PRINCIPLES		
Lines 276 and 278	The use of the word "these" is vague/confusing as it is unclear whether it points one sentence back, or collectively to all of the attributes described in the paragraph.	Recommended change: "Therefore, identification and determination of the relative levels of ~~**these**~~ **biologically relevant** variants should be included in the comparative analytical characterization studies."
Lines 304-307	It is appropriate for biosimilar sponsors to have the potential to perform independent testing where method performance is supportive of that strategy. Side by side comparisons are the basis of analytical similarity studies. A further explanation of cases where method performance supports independent testing would be beneficial. In addition, retesting should not be encouraged where it is not warranted.	Recommended change: "Proposed biosimilar product~~,~~ manufacturers should perform in-depth **comparative** chemical, physical, and bioactivity ~~**comparisons with side-by-side**~~ analyses of an appropriate number of lots of the proposed product and the reference product and, where available and appropriate, a comparison with a reference standard for suitable attributes (e.g., potency)."
Lines 317-319	While information on reference product lots may improve the accuracy of the characterized reference product range, it does not provide assurance of the *consistency* of the biosimilar's manufacturing process. Knowledge of sources of variability and critical parameters, and development of a robust integrated control strategy, provides assurance of process consistency.	Recommended change: "This information will be useful in justifying acceptance criteria~~ **to ensure product consistency, as well as to support**~~ **for** the comparative analytical assessment of the proposed product and the reference product."

SECTION	ISSUE	PROPOSED CHANGE
Line 319	The Draft Guidance states: "…acceptance criteria should be based on the totality of the analytical data and not simply on the observed range of product attributes of the reference product." This is helpful, but it is unclear what is meant by 'the totality of the analytical data'. It would be more useful if this was clarified as being 'on the basis of overall knowledge of attribute impact.'	Suggested edit: "acceptance criteria should be based on the totality of the analytical data **and knowledge of the attribute impact to the patient** and not simply on the observed range of product attributes of the reference product."
Lines 339-342	Use of the term "fingerprint-like" remains unclear. We note that the term was removed in the interchangeability guidance. In addition, there is an explanation in the sentence that more meaningfully conveys the recommendation.	Suggested edit: "It may be useful to compare differences in the quality attributes of the proposed product with those of the reference product using a meaningful ~~**fingerprint-like**~~ analysis algorithm[16] that covers a large number of additional product attributes and their combinations with high sensitivity using orthogonal methods."
Lines 366-368	The Draft Guidance states: "It is expected that the expression construct for a proposed product will encode the same primary amino acid sequence as its reference product" "Expected" is a somewhat vague term. Whereas heterogeneity is expected, the expression should target the same primary amino acid sequence.	Suggested edit: It is expected that the expression construct for a proposed product **should** ~~**will**~~ encode the same primary amino acid sequence as its reference product"
V. FACTORS FOR CONSIDERATION IN PERFORMING THE COMPARATIVE ANALYTICAL ASSESSMENT		
A. Expression System		
B. Manufacturing Process		

SECTION	ISSUE	PROPOSED CHANGE
Lines 393-397 **Footnote 19**	The text states that an application for a biological product submitted for licensure under 351(k) may not incorporate by reference drug substance, drug substance intermediate, or drug product information contained in a master file. While this may be the case, presumably someday there will be biosimilars filed via 351(k) for antibody drug conjugates, in which case a master file approach can be quite suitable for the linker payload. As written, this implies that it is not possible at all, however it is a possible scenario per 351(a) today.	Footnote 19 notes a master file for drug substance, drug substance intermediate, or drug product information for a biological product may be referenced to support an investigational new drug application (IND) for a proposed biosimilar product. BIO suggests the Agency update this footnote to include antibody-drug conjugates (ADCs) as another scenario where a master file may be referenced for an IND or a BLA because that is appropriate for ADCs. In addition, BIO suggests the following edit: "As a scientific matter, as with biological products originally licensed under section 351(a) of the PHS Act, an application for a biological product submitted for licensure under section 351(k) of the PHS Act may not incorporate by reference drug substance, drug substance intermediate, or drug product information contained in a Master File (MF) because a license holder is generally expected to have knowledge of and control over the manufacturing process for the biological product for which it has a license **unless exceptionally agreed with FDA.**"
C. Physicochemical Properties		
Lines 441-449	The Draft Guidance states: "Tests used to characterize the product do not necessarily need to be validated" Test should be validated if possible or at minimum qualified. A good assessment is partially based on the rigor of the assay criteria.	FDA should consider including additional criteria for test that should be validated if possible or at minimum qualified.
D. Functional Activities		
E. Target Binding		

SECTION	ISSUE	PROPOSED CHANGE
F. Impurities		
Lines 519 -521	The Draft Guidance states: "The chosen analytical procedures should be adequate to detect, identify, and accurately quantify biologically significant levels of impurities." It is unclear what the term "biologically significant" levels of impurities imply including how it is determined that a level is significant.	BIO suggested edit: "The chosen analytical procedures should be adequate to detect, identify, and accurately quantify **appropriately low** biologically significant levels of impurities **in accordance with ICH guidelines"**
G. Reference Product and Reference Standards		
General	This section focuses on Reference Standards (materials) mixed with Reference Products which makes the section hard to read and is somewhat confusing.	In order to improve clarity of the document BIO suggests FDA split this section in two. One section on Reference Materials, and another on Reference Product. In addition, the following lines do not belong to Reference Materials: 543-545; 549-554, 582-586, 600-602, 604-608. These lines can be separated out into a 'Reference Product' section or distributed to appropriate other sections.
Lines 564-565 and 572-575	Information is inconsistent between the two locations regarding what type of lot may be qualified as a reference standard representative of the proposed product. Recommend amending the sentence at line 572 to align with lines 564-568 which allows use of either an early development lot or a lot used in clinical studies as long as it is representative of the proposed product.	Recommended change: "Once clinical lots, **or lots that have been demonstrated to be representative,** of the proposed product have been manufactured, it is expected that one of these lots will be properly qualified (including bridging to previous reference standards) for use as a reference standard for release and stability, as well as comparative analytical testing."
Lines 570-572	The comparator product could be a biosimilar with use of this language.	BIO suggested edit:

SECTION	ISSUE	PROPOSED CHANGE
		"For the development of a proposed product, a reference product lot or a lot of a non-U.S.- licensed **reference** ~~**comparator**~~ product (see section VI.A.4 of this guidance) is typically qualified as an initial reference standard."
Lines 590-591	To enable comparison of assay results reported relative to reference standard over the lifetime of the product, it may be necessary to provide a correction factor for a reference standard, specifically in situations where there are both Fab- and Fc-mediated biological activities. It is important to maintain a consistency with historical data to assure any changes throughout the entirety of the product lifecycle can be appropriately identified.	Recommended change: "A sponsor generally should not use a correction factor to account for any differences in, for example, potency or biological activity between reference standards**, during evaluation of analytical similarity.**"
Lines 593-602	We support the Agency's approach to allow the potential to store the reference product and non-U.S.-licensed comparator product lots under conditions that maintain stability long term, if feasible.	
H. Finished Drug Product		
Lines 635-646	This section lacks considerations related to physical stability, sub-visible particles, viscosity among others. For example, many proteins form aggregates or fibrils under various conditions. Such particles may contain proteins with modified tertiary structure. Many factors such as pH, temperature, time, shear, metal ions, impurities (peptide related as well as non-peptide related) are known to affect particle formation and therefore formulation and manufacturing conditions including scale may	BIO suggest the Agency consider addition additional information on considerations related to physical stability, sub-visible particles, viscosity among others.

SECTION	ISSUE	PROPOSED CHANGE
	increase the propensity for particle formations. Particle formation should be assessed in full scale batches and followed during storage	
I. Stability		
Line 641-643	It does not seem necessary that stress conditions other than those relevant to the product should be required testing. Suggest rewording to "relevant" stress conditions.	Recommended change: "These comparative studies should be conducted under ~~**multiple**~~ **relevant** stress conditions (e.g., high temperature, freeze thaw, light exposure, and agitation) that can cause incremental product degradation over a defined time period."
VI. COMPARATIVE ANALYTICAL ASSESSMENT		
A. Considerations for Reference and Biosimilar Products		
Lines 689-697	We appreciate the clear considerations outlined in the Draft Guidance on how sponsors should approach changes made to the biosimilar product during development.	
Lines 781-786	It is unlikely that detailed information about the impact of the reference product attributes' impact on clinical performance is available.	FDA should include more guidance on how this can be determined in the absence of publicly available information. For example, Sponsors should consider publicly available information, as well as the Sponsor's own characterization of the reference product, in determining the potential impact of an attribute on clinical performance.