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April 16th, 2012

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

Re: Docket No. FDA–2011-D-0602: Draft Guidance for Industry on Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the "Draft Guidance for Industry on Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product" (the Draft Guidance).

BIO represents more than 1,100 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, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

PART 1: GENERAL COMMENTS:

BIO commends FDA for the issuance of this science-based draft guidance on quality considerations for demonstrating biosimilarity to a reference product. The document addresses many relevant issues associated with the topic and we believe it will assist manufacturers that are developing biosimilar products and help ensure that patients will receive high quality biosimilar products.

Manufacturing and quality aspects are critical components of a biosimilarity assessment. Each of these aspects needs to be assessed in relation to what knowledge lies in the public domain concerning the reference product, such as the formulation excipients, manufacturing equipment, raw materials used in the manufacturing process for the active ingredient, manufacturing process, the container closure system and the cold chain distribution system. A difference from the innovator product with respect to any one of these can potentially have a significant impact upon safety or efficacy of the biosimilar product.

It is neither expected nor required that a biosimilar applicant be able to demonstrate that all quality or physico-chemical attributes of the proposed biosimilar are identical to those of the reference product. The quality attributes of the products (both the active ingredients and the finished products) must be highly similar, however, and the biosimilar manufacturer must demonstrate that any differences between the products do not result in clinically meaningful differences. The results of the analytical comparison form the basis for determining the extent and nature of non-clinical and clinical testing needed to support a biosimilarity determination.

A. Comparability vs. Biosimilarity:

We appreciate FDA's comments made in the Draft Guidance regarding the difference between conducting a comparability assessment of an innovator product before and after a manufacturing change versus assessments required to establish biosimilarity. We agree that the two may share some common scientific principles regarding the approach to conducting the assessments, but there are significant differences in the knowledge of the innovator regarding the initial development and subsequent commercial manufacture of the innovator product and that available to a biosimilar manufacturer.

B. Quality Attributes that Shift over Time:

We also note that the Draft Guidance fails to address how quality comparisons between reference and biosimilar products should be conducted when quality attributes are unstable or may change over time (*e.g.*, size or charge variant purity). We encourage FDA to address this issue since it would be the responsibility of the biosimilar manufacturer to assess reference material of different dating periods to determine whether the biosimilar and the reference product have a highly similar degradation profile. BIO recommends that FDA publish guidance on the appropriate nature and extent of reference product sampling over time, and address whether quality comparisons need to be normalized for differences in product age to ensure valid assessments of biosimilarity.

C. Intentional Differences:

Differences between a proposed biosimilar's host cell type, primary structure, formulation, or immediate package and those of the reference product may significantly

affect the proposed biosimilar's safety, effectiveness, and immunogenicity profiles. These differences increase the risk of undetected, clinically significant differences between a proposed biosimilar and the reference product. They should not be permitted if they are reasonably avoidable. Further, a biosimilar applicant should always be required to demonstrate that any such difference (that is not reasonably avoidable) is not clinically meaningful. This demonstration may often necessitate substantial additional testing. If the possibility of clinically meaningful differences cannot be reasonably excluded, the proposed product should be submitted for approval under section 351(a) on the basis of a full application.

D. Clinical Trial Material:

The biosimilar material used in the principal clinical trial should be the same as the proposed to-be-marketed material. At a minimum, a clinical immunogenicity study evaluating the to-be-marketed biosimilar should always be required.

E. "Meaningful Finger-Print-Like Analysis":

The Agency discusses the use of a "meaningful fingerprint-like analysis algorithm" (lines 312-315) to gain additional insight into the similarity between a biosimilar product and the reference biological product. However, it is not clear what this term means. We request that the Agency provide greater clarity or explanation regarding whether these "additional product attributes" and their relationship to each other must correlate with clinical safety and efficacy, consistency in manufacture, or some other meaningful feature for establishing biosimilarity between the biosimilar product and the reference.

We note that 'fingerprinting' has been used in other contexts to connote a strategy to derive an exact match or 'sameness.' It is critical to note that development of such a 'fingerprint' for recombinant DNA products presupposes that an applicant recognizes the necessary attributes to evaluate, designs the appropriate methods to fully interrogate the product and identifies compensatory measures for the limitations or 'test error' of its analytical methodology. Please clarify what is meant by "a meaningful fingerprint-like analysis algorithm" and what would be required to develop such an algorithm. We suggest that reference be made to the Kozlowski et al 2011 New England Journal article where this approach is mentioned in greater detail.[1]

F. Scientific and Technical Expectations Should Be Clearly Conveyed:

We have a fundamental concern related to the use of the word "should" in the Draft Guidance. We appreciate that the word "should" is used in guidance documents to mean that something is suggested or recommended, but not required. This allows for flexibility with respect to the necessity of certain requirements and is appropriate for making case-by-case decisions. However, the use of the word "should" where certain requirements

[1] Kozlowski et al, New England Journal of Medicine (NEJM 365;5 pp 385-388, August 4, 2011)

are fundamental and expected to be performed may not convey the necessary criticality of the data. In other parts of the draft guidances, the Agency uses phrases such as "is expected to", "will need to", "FDA recommends", or "are fundamental components" to convey clearer expectations for certain data and information. To give just one example, in line 321 the Agency states: "The type, nature, and extent of any differences between the proposed biosimilar product and the reference product, introduced by design or observed from comprehensive analytical characterization of multiple manufacturing lots, should be clearly described and discussed." We think this is a fundamental requirement for all biosimilar products, and that in this case the use of the phrase "is expected" instead of "should" is more appropriate, just as it is used in line 368 where the Agency states, "It is expected that the expression construct for a proposed biosimilar product will encode the same primary amino acid sequence as its reference product." In the chart in Part 3 of these comments, we provide other examples of the use of the word "should" for fundamental requirements that must be expected to be performed.

FDA is regarded as one of the leading regulatory agencies in the world, and other countries developing their own biosimilar guidance will consider the content and wording of FDA guidance documents for their own policies. Therefore, it is of global importance for the Agency to be clear about what are fundamental requirements, and what might be discussed on a case-by-case basis.

CONCLUSION:

BIO appreciates this opportunity to comment on the "Draft Guidance for Industry on Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product." Specific, detailed comments are included in the following charts. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Andrew J. Emmett
Managing Director, Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)

PART 2: SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. BACKGROUND		
Lines 124-127:	This provision states that "Greater knowledge due to advances in science and technology, and improvements in manufacturing processes, process controls, materials and product testing, as well as characterization tests and studies, facilitate the use of an abbreviated pathway for the approval of a protein product."	Please edit the statement to read: "Greater knowledge due to advances in science and technology, and improvements in manufacturing processes, process controls, materials and product testing, as well as characterization tests and studies, could facilitate the use of an abbreviated pathway for the approval of a protein product."
II. SCOPE		
Lines 159-162:	This provision states "This document is not intended to provide an overview of FDA's approach to determining interchangeability because FDA is continuing to consider the type of information sufficient to enable FDA to determine that a biological product is interchangeable with the reference product."	Please see BIO's comments to FDA's Draft Guidance "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009" (the Q&A Draft Guidance) for a more extensive discussion of interchangeability. We agree that interchangeability is a subject that will require its own guidance, which may be informed as analytics improve and/or experience with biosimilars grows. In particular, much discussion will be needed regarding the design of switching studies to assess product safety. As this statement is reflective of FDA's current scientific thinking on interchangeability, an interchangeability designation should not be given until analytics improve and there has been extensive post-marketing experience with the biosimilar. We also note that only the quality Draft Guidance specifies that it is not intended to address interchangeability. We request that FDA include similar statements in the other biosimilars guidances as

		appropriate.
III. DEFINITIONS		
Lines 197-200:	This provision reiterates the FDA proposed definition of a protein and synthetically derived peptide.	Please see BIO's comments in the Q&A Draft Guidance for a more detailed discussion of these definitions. Please add a cross-reference to the Q&A Final Guidance document to ensure harmonization of these definitions.
IV. GENERAL PRINCIPLES		
Lines 221-222:	"These analytical procedures have improved the ability to identify and characterize not only the desired product but also product-related substances and product- and process-related impurities." There is a lack of clarity about the duration of analytical similarity comparisons between biosimilar and reference products.	Please clarify the expected duration of analytical similarity comparisons, and at what time in the product development cycle they should be conducted.
Lines 239-241:	The Agency states that characterization should include consistency, as well as identity, purity, potency, etc…	It is not clear what is intended by the term "consistency". Please clarify whether this means batch-to-batch consistency of the biosimilar process and product, or consistency between the biosimilar and the reference product.
Lines 241-244:	This provision states that "the product-related impurities, product-related substances, and process-related impurities should be identified, characterized as appropriate, quantified, and compared to those of the reference product to the extent feasible and relevant, as part of an assessment of the	There may be significant differences in the assays used to assess process-related impurities such as host-cell proteins and DNA. An assessment of assays' performance on both the biosimilar and the reference product would be needed to determine whether the measurements (and differences) are relevant. Please clarify.

	potential impact on the safety, purity, and potency of the product."	
Lines 281-283:	The body of knowledge that results from a comprehensive understanding of the analytical and functional attributes of the biosimilar product during design of the manufacturing process and the conduct of developmental studies is important to support both the demonstration of product quality and a suitable control system over the lifecycle of the product.	Please modify to include control system: The body of knowledge that emerges will serve to support a demonstration of product quality and the effectiveness of a suitably comprehensive control system during development, at approval, and over the post-approval life of the product.
Lines 285-289:	The evaluation of multiple lots of reference drug product will not necessarily provide comparable information regarding multiple lots of drug substance, and this limitation should be addressed with regard to justification of acceptance criteria.	Acceptance criteria for Drug Product (DP) and Drug Substance (DS) will not necessarily be the same, especially if the DS properties must be inferred by "back-engineering" of the reference DP (or foreign comparator if allowed). The process of trying to isolate or de-formulate the DS must be carefully assessed and the results of this should be weighted accordingly. Some more explicit guidance around isolating the DS from the DP should be provided (similar to European Medicines Agency (EMA) guidance).[2]
Lines 298:	It is unclear from the text to which types of glycoproteins the tetraantennary and lactosamine structures apply.	Please either remove reference to these structures from the Draft Guidance or provide more class-specific information. For example, for some fusion glycoproteins, the content and distribution of tetraantennary and N-acetyl lactosamine repeats can affect in vivo potency; the collective contributions of these structures on potency should be thoroughly evaluated.
Lines 313-315:	This provision states that "It may be useful to compare differences in the quality attributes of	Please see our general comments above (p. 3) requesting clarification on the term "meaningful fingerprint analysis."

[2]European Medicines Agency, *Similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues*, February 2006, http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003953.pdf

	the proposed protein product with those of the reference product using a meaningful fingerprint-like analysis algorithm that covers a large number of additional product attributes and their combinations with high sensitivity using orthogonal methods."	
Lines 344-356:	There is a lack of clarity on what bridging studies are needed when a biosimilar applicant seeks to rely on comparative data from nonclinical/clinical studies involving a non-U.S licensed comparator product.	We request more clarity on how bridging studies should be performed. Please see BIO's comments on the Q&A Draft Guidance for a more detailed discussion of non-U.S. comparator product data.
Lines 349-353:	It should be mentioned that multiple lots have to be used in establishing the "scientific bridge" mentioned here. Also the quality of the excipients may have an impact on the degradation profile of the product sourced from different regions and thus should be part of the investigation.	Please edit the statement to read: The scientific bridge between the non-U.S.-licensed product and the U.S.-licensed reference product is likely to include comparative physico-chemical characterization, bioassays/functional assays, and comparative clinical and/or nonclinical PK and/or PD data, as appropriate, and data to address any potential differences in formulation or primary packaging (*e.g.*, comparative stability and forced degradation studies using multiple lots from material sourced from the US licensed reference product as well as the non-US licensed comparator product.)
V. FACTORS FOR CONSIDERATION IN ASSESSING WHETHER PRODUCTS ARE HIGHLY SIMILAR		
Lines 374-375:	The text refers to impurities, but describes both impurities and contaminants.	Please include "contaminants" in this sentence: "Differences between the chosen expression system of the proposed biosimilar product and that of the reference product should be carefully considered because the type of expression system and host cell will significantly affect the types of process- and product-related substances, ~~and,~~ impurities, and contaminants (including potential

		adventitious agents) that may be present in the protein product."
Lines 430-432:	These lines state, "Tests used to characterize the product do not necessarily need to be validated for routine quality control purposes, but should be scientifically sound, fit for their intended use, and provide results that are reproducible and reliable."	The Draft Guidance should be clear that while analytical methods for comparative characterization of the product do not necessarily need to be validated for routine quality control (QC) purposes, those used for release and stability assessment would need to be validated prior to submission of a 351(k) application.
Lines 503-507:	This provision states that "Process-related impurities arising from cell substrates (*e.g.*, host cell DNA, host cell proteins), cell culture components (*e.g.*, antibiotics, media components), and downstream processing steps (*e.g.*, reagents, residual solvents, leachables, endotoxin, bioburden) should be evaluated. The potential impact of differences in the impurity profile upon safety should be addressed and supported by appropriate data."	Greater clarity on the practical scope for evaluating process-related impurities is needed because the innovator and biosimilar use different manufacturing processes, and detailed information on the innovator's manufacture with respect to process reagents, cell culture components is not available to the biosimilar manufacturer. Further, the relevance of certain testing (*e.g.*, bioburden) should be clarified and whether certain comparative testing can be omitted as long as product meets certain regulatory (21 CFR) or compendial requirements. For example, bioburden is cited as an example for comparison, but this does not seem to make sense as drug products are tested for sterility not bioburden; also, would it be necessary to compare that both products are sterile?
Lines 529-532:	This provision states that "An analytical similarity assessment should support the use of lots that demonstrate the biosimilarity of the proposed biosimilar product used in the principal clinical trial to the reference product and the proposed commercial product."	Greater clarity on the appropriate types of materials relevant to performing similarity comparison to reference product is needed, particularly in "early product development" (Lines 525-526). *E.g.*, can similarity include representative nonclinical lots, or only lots intended for clinical use?
Lines 580-582:	Differences in primary packaging could have a significant impact on product quality, as indicated in the previous sentence, and shelf life, but primary packaging is not included in the sentence.	Please modify to read: "Differences in formulation and primary packaging between he proposed biosimilar product and the reference product are among the factors that may affect whether subsequent clinical studies may take a

		selective and targeted approach. We also suggest including reference to *ICH Q8: Pharmaceutical Development*.
VI. RELEVANT GUIDANCES		
Lines 641:	We recommend adding "*Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics* (issued jointly by CDER and CBER, May 1999)" as this is relevant to Section H (p. 14, line 558 of the Draft Guidance).	Please add this Guidance to list.

PART 3: SCIENTIFIC AND TECHNICAL EXPECTATIONS:

As discussed in our general comments (p.3), the following provisions represent fundamental requirements for a biosimilarity assessment, and we are concerned that use of the word "should" implies that they do not necessarily need to be done. Where specified, please replace "should" with wording such as "is expected to" or "needs to", which more clearly convey the scientific and technical expectations.

SECTION	ISSUE	PROPOSED CHANGE
Lines 108-111:	The Draft Guidance should be clear that because a biosimilar manufacturer will likely have a different manufacturing process from the reference product and have no direct knowledge of the manufacturing process of the reference product, the comparative assessment for a biosimilar will always be more extensive than for a manufacturer making a change to its own process. Even under circumstances where a manufacturer made multiple changes to its own product (*e.g.*, different cell line, upstream or downstream processing steps, equipment and conditions, etc…) at the same time, the data needed to support comparability would not be the same as that needed to support biosimilarity. It would be useful to point that out more clearly by substituting "will require" for "may require".	Please edit the statement to read: "However, demonstrating that a proposed protein product is biosimilar to an FDA-licensed reference product manufactured by a different manufacturer will be more complex and will ~~may~~ require in most cases more extensive and comprehensive data than assessing the comparability of a product before and after a manufacturing process change made by the product's sponsor."
Lines 173-175:	This provision states that "this guidance describes considerations for additional CMC information that may be relevant to the	Please change "may be" to "is" to reinforce the importance of the CMC information to an assessment of biosimilarity.

	assessment of biosimilarity between two protein products."	"This guidance describes considerations for some of the additional CMC information that ~~may be~~ are relevant to the assessment of biosimilarity between two protein products."
Lines 226-244:	The assessment of the analytical similarity of a biosimilar product to the reference product and the robustness of these methods are fundamental requirements for a biosimilarity assessment, and use of the word "should" implies that it does not necessarily need to be done. Please replace should with "is expected to" or "needs to".	Please edit text to read: "In addition to a complete CMC data submission as required under section 351(a) of the PHS Act, the applicant as a scientific matter is expected to thoroughly ~~should~~ assess the analytical similarity to the reference product. The rationale for the analytical similarity assessment needs to ~~should~~ be clearly described with consideration for the known quality attributes and performance characteristics of the specific reference product. Extensive, robust comparative physicochemical and functional studies (these may include bioassays, biological assays, binding assays, and enzyme kinetics) are expected to be performed to evaluate whether the proposed biosimilar product and the reference product are highly similar. A meaningful assessment as to whether the proposed biosimilar product is highly similar to the reference product depends on, among other things, the capabilities of available state-of-the-art analytical assays to assess, for example, the molecular weight of the protein, complexity of the protein (higher order structure and post-translational modifications), degree of heterogeneity, functional properties, impurity profiles, and degradation profiles denoting stability. The capabilities of the methods used in the analytical assessment, as well as their limitations are expected to be described by the applicant. Physicochemical and functional characterization studies ~~should~~ need to be ~~sufficient~~ comprehensive in order to establish relevant quality attributes including those that define a product's identity, quantity, purity, potency, and consistency. The product-related impurities, product-related substances, and process-related impurities are expected to be identified, characterized as appropriate, quantified, and compared to those of the reference product to the extent feasible and relevant,

		as part of an assessment of the potential impact on the safety, purity, and potency of the product."
Lines 283-287:	Side-by-side analysis of the intended biosimilar product and the reference product clearly is a fundamental requirement to establish biosimilarity and use of the word "should" implies that it does not necessarily need to be done.	Please replace "should" with "are expected to": "Manufacturers ~~should~~ are expected to perform in-depth chemical, physical, and bioactivity comparisons with side-by-side analyses of an appropriate number of lots of the proposed biosimilar product and the reference product and, where available and appropriate, a comparison with the reference standard for specific suitable attributes (e.g., potency)." Additionally, please clarify whether on-going assessment of biosimilarity to the reference product will be expected to ensure that process and quality drift is not occurring, or whether the biosimilar manufacturer will only be required to show comparability of its own product at approval and thereafter (as innovators must do now).
Lines 290-291:	We believe that identification of the specific lots of reference product with expiration dates and timeframes of actual use is necessary.	Please replace "of value" with: "necessary" in the sentence: Identification of the specific lots of the reference product used in the biosimilar studies together with expiration dates and timeframes of actual use would also be ~~of value~~ necessary.
Lines 295-297:	Potential interactions between certain product attributes that define a product's safety, purity, and potency profile must be assessed in order to ensure that the biosimilar product has a similar safety and efficacy profile to the reference biologic product, but use of the word "should" implies that this does not necessarily need to be done.	Please replace "should" with "needs to": For example, some product attributes act in combination to define a product's safety, purity, and potency profile and therefore their potential interaction ~~should~~ needs to be considered when evaluating similarity and setting specifications.

Lines 321-323:	Differences between the proposed biosimilar product and the reference product must be described and discussed, but use of the word "should" implies that it does not necessarily need to be done.	Please replace "should" with "are expected to be": "The type, nature, and extent of any differences between the proposed biosimilar product and the reference product, introduced by design or observed from comprehensive analytical characterization of multiple manufacturing lots, ~~should be~~ are expected to be clearly described and discussed." The discussion is expected to include identification and comparison of relevant quality attributes from product characterization, as this is an important factor in assessing whether the proposed biosimilar product is highly similar to the reference product. The potential effect of the differences on safety, purity, and potency is expected to be addressed and supported by appropriate data.
Lines 347-349:	Providing adequate data or information to justify scientifically the relevance of comparative data from a non U.S.-licensed reference product is required to establish the relevance of these comparative data to an assessment of biosimilarity, but use of the word "should" implies that it does not necessarily need to be done.	Please replace "should" with "is expected to": "In such a case, the sponsor ~~should~~ is expected to provide adequate data or information to scientifically justify the relevance of this comparative data to an assessment of biosimilarity and to establish an acceptable bridge to the U.S.-licensed reference product."
Lines 369-371:	The text states that "minor modifications, such as N or C terminal truncations that will not have an effect on safety purity or potency, may be justified by the applicant".	Additionally, please replace "will" with "have been demonstrated not to": "However, minor modifications, such as N or C terminal truncations that ~~will~~ have been demonstrated not to ~~not~~ have an effect on safety, purity, or potency, may be justified by the applicant.

Lines 401-403:	The physicochemical assessment of the proposed biosimilar product and the reference product must consider all relevant characteristics of the protein product, but use of the word "should" implies that it does not necessarily need to be done.	Please replace "should" with "needs to": "Physicochemical assessment of the proposed biosimilar product and the reference product ~~should~~ needs to consider all relevant characteristics of the protein product (e.g., the primary, secondary, tertiary, and quaternary structure, post-translational modifications, and functional activity(ies))."
Lines 437-439:	The methods used to detect post-translational modifications must be of appropriate sensitivity and specificity to provide meaningful information, but use of the word "should" implies that it does not necessarily need to be done.	Please replace "should" with "are expected to": "Tests chosen to detect and characterize these post-translational protein modifications ~~should~~ are expected to be of appropriate sensitivity and specificity to provide meaningful information as to whether the proposed biosimilar product and the reference product are highly similar."
Lines 449-452:	When a clinically relevant mechanism of action is known for the reference product, a functional assay must reflect the mechanism of action to the extent possible, but use of the word "should" implies that it does not necessarily need to be done.	Please replace "should" with "are expected to": "If the clinically relevant mechanism(s) of action are known for the reference product or can reasonably be determined, one or more of the functional assays ~~should~~ are expected to reflect these mechanisms of action and quantitative comparisons with the reference to the extent possible."
Lines 456-462:	If the reference product exhibits multiple functional activities, relevant assays need to be designed to evaluate the range of activities, but use of the word "should" implies that it does not necessarily need to be done.	Please replace "should" with "are expected to" and "need to": "If a reference product exhibits multiple functional activities, manufacturers ~~should~~ are expected to perform a set of relevant assays designed to evaluate the range of activities, including the potential for differences between biosimilar and reference. For example, with proteins that possess multiple functional domains that express enzymatic and receptor-mediated activities, manufacturers ~~should~~ need to evaluate both activities. For products where a single functional activity can be measured by more than

		one, but related, parameter (e.g., enzyme kinetics or interactions with blood clotting factors), comparative characterization of each parameter between products ~~should~~ is expected to be used to provide additional valuable information."
Lines 481-484:	If binding to a receptor is an inherent activity attributed to the reference biologic product, comparative analytical methods must be performed to assess this properly, but that use of the word "should" implies that it does not necessarily need to be done.	Please replace "should" with "are expected to": "When binding or immunochemical properties are part of the activity attributed to the protein product, analytical tests ~~should~~ are expected to be performed to characterize the product in terms of these specific properties (e.g., if binding to a receptor is inherent in protein function, this property ~~should~~ is expected to be measured and used in comparative studies, see ICH Q6B for additional details)."
Lines 492-493:	Characterization of impurities is a fundamental requirement of a biosimilarity assessment to ensure patient safety, but use of the word "should" implies that it does not necessarily need to be done.	Please replace "should" with "is expected to": "The applicant ~~should~~ is expected to characterize, identify, and quantify impurities (product- and process-related as defined in ICH Q6B) in the proposed biosimilar product and the reference product."
Lines 496-499:	The presence of different impurities or higher levels of impurities in a biosimilar product due to different manufacturing processes is a safety issue and the guidance should be clear about the need for additional pharmacologic/toxicological studies to address these differences.	Please replace "may" with "will": "However, if the manufacturing process used to produce the proposed biosimilar product introduces different impurities or higher levels of impurities than those present in the reference product, additional pharmacological/toxicological or other studies ~~may~~ will be necessary."
Lines 503-512:	Characterization of process related impurities is a fundamental requirement of a biosimilarity assessment to ensure patient safety, and use of the word "should" implies	Please replace "should" with " expected to" or "need to": "Process-related impurities arising from cell substrates (e.g., host cell DNA, host cell proteins), cell culture components (e.g.,

	that it does not necessarily need to be done.	antibiotics, media components), and downstream processing steps (e.g., reagents, residual solvents, leachables, endotoxin, bioburden) ~~should~~ need to be evaluated. The potential impact of differences in the impurity profile upon safety ~~should~~ is expected to be addressed and supported by appropriate data. In all cases, the chosen analytical procedures ~~should~~ need to be adequate to detect, identify, and accurately quantify biologically significant levels of impurities (see ICH Q2B). In particular, the results of the immunological methods used to detect host cell proteins depend on the assay reagents and the cell substrate used. Such assays ~~should~~ are expected to be validated using the product cell substrate and orthogonal methodologies to ensure accuracy and sensitivity. This ~~should~~ is expected to be done across both products to the extent relevant and feasible.
Lines 505-507:	The importance of differences in impurity profile between a biosimilar and a reference product on safety must be emphasized.	Please edit the statement to read: "As a scientific matter, the potential impact of differences in the impurity profile upon safety ~~should~~ needs to be addressed and supported by appropriate data."
Lines 514-517:	Safety of any biological product with regard to adventitious agents or endogenous viral contamination must be demonstrated, but use of the word "should" implies that it does not necessarily need to be done.	Please replace should with "needs to": "An analytical similarity assessment ~~should~~ is expected to support the use of lots that demonstrate the biosimilarity of the proposed biosimilar product used in the principal clinical trial to the reference product and the proposed commercial product."
Lines 529-532:	Providing support for the use of lots in the analytical similarity assessment is a fundamental requirement to establish biosimilarity, but use of the word "should" implies that it does not necessarily need to be done.	Please change "should" to "is expected to": "An analytical similarity assessment ~~should~~ is expected to support the use of lots that demonstrate the biosimilarity of the proposed biosimilar product used in the principal clinical trial to the reference product and the proposed commercial product."

Lines 537-542:	Providing information on the extraction procedure for obtaining reference product from the drug substance and ensuring the procedure does not alter the reference product quality is a fundamental requirement to establish biosimilarity, but use of the word "should" implies that it does not necessarily need to be done.	Please replace "should" with "is expected to" or "needs to": "If the drug substance has been extracted from the reference product in order to assess analytical similarity, the applicant ~~should~~ is expected to describe the extraction procedure and provide support that the procedure itself does not alter product quality. This undertaking would include consideration for alteration or loss of the desired products and impurities and relevant product-related substances, and ~~should~~ needs to include appropriate controls that ensure the relevant product characteristics of the reference product are not significantly altered by the extraction procedure."
Lines 560-562:	Performance of product characterization studies on the most downstream intermediate best suited for the analytical procedures is a fundamental requirement to establish biosimilarity, but use of the word "should" implies that it does not necessarily need to be done.	Please replace "should" with "is expected to" or "need to": "Product characterization studies ~~should~~ need to be performed on the most downstream intermediate best suited for the analytical procedures used. The attributes evaluated ~~should~~ are expected to be stable through any further processing steps."
Lines 573-575:	The acceptability of any differences between the proposed finished biosimilar product and the finished reference product must be evaluated, but use of the word "should" implies that it does not necessarily need to be done.	Please replace "should" with "is expected to": "The acceptability of the type, nature, and extent of any differences between the proposed finished biosimilar product and the finished reference product ~~should~~ is expected to be evaluated and supported by appropriate data and rationale."
Lines 586-595:	A comparative assessment of the stability profile of the biosimilar product and the reference biological product is a fundamental requirement to establish biosimilarity, but use of the word "should"	Please replace "should" with "is expected to" or "need to": "An appropriate physicochemical and functional comparison of the stability of the proposed biosimilar product with that of the reference product ~~should~~ needs to be initiated. Accelerated and

	implies that it does not necessarily need to be done.	stress stability studies, or forced degradation studies, should be used to establish degradation profiles and provide direct comparison of the proposed biosimilar product with the reference product. These comparative studies ~~should~~ are expected to be conducted under multiple stress conditions (e.g., high temperature, freeze thaw, light exposure, and agitation) that can cause incremental product degradation over a defined time period. Results of these studies may reveal product differences that warrant additional evaluation and also identify conditions under which additional controls should be employed in manufacturing and storage (see ICH Q5C and Q1A(R) for guidance). Sufficient real time, real condition stability data ~~should~~ need to be provided to support the proposed dating period."
Lines 591-592:	This is a fundamental requirement for a biosimilarity assessment, but use of the word "should" implies that it does not necessarily need to be done.	Please change "should to "are expected to": "These comparative studies are expected to ~~should~~ be conducted under multiple stress conditions (e.g., high temperature, freeze thaw, light exposure, and agitation) that can cause incremental product degradation over a defined time period."