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April 16, 2012

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

Re: Docket No. FDA–2011-D-0605: Draft Guidance for Industry on Scientific Considerations in Demonstrating Biosimilarity to a Reference Product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Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the "Draft Guidance for Industry on Scientific Considerations in Demonstrating Biosimilarity to a Reference Product" (the Draft Guidance).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.

Our comments below are grounded by the specific hands-on experience of BIO member companies, experience that is crucial to understanding biological products. These answers are also consistent with BIO's long-standing Principles on Biosimilars[1], which state that any pathway for the approval of biosimilars must protect patient safety and preserve incentives to innovate.

[1] BIO Principles on Biosimilars, http://www.bio.org/healthcare/followonbkg/Principles.asp

BIO appreciates that the issuance of this Draft Guidance, and the two other biosimilars guidances issued on the same day, is an important initial step in developing the regulatory framework for a biosimilars approval pathway. We request that FDA draft product-specific guidances in the future.

GENERAL COMMENTS

I. Complexities of Protein Products

BIO commends FDA for appropriately acknowledging the complexities of protein products in this Draft Guidance. As stated in the Draft Guidance, "unlike small molecule drugs, whose structure can be completely defined and entirely reproduced, proteins are typically more complex and are unlikely to be shown to be structurally identical to a reference product." BIO notes that the ability to characterize protein products has improved over the last decade; however, there are important differences among protein products that cannot be evaluated by analytical characterization and comparison alone.

II. U.S. Licensed Reference Product and other Comparators

The Draft Guidance proposes a number of regulatory and scientific factors to be considered in determining when and whether data comparing a prospective biosimilar to a non-U.S.-licensed comparator product may be useful in supporting a 351(k) application. BIO appreciates FDA's recognition of a number of the factors proposed in BIO's 2010 Comments[2], as they are reflected in the Draft Guidance. However, BIO believes that FDA should address this issue more clearly and specifically to assure that situations involving reference products and comparators are addressed in a manner that protects patient safety. BIO would also like to highlight several additional factors that we believe are critical:

- The Biologics Price Competition and Innovation Act (BPCIA) mandates that the biosimilar product be evaluated only against one reference product, which itself is licensed under 351(a);[3]

- Data from a foreign comparator product may only be used to support an application when both the foreign and domestic product are released by the same license holder/manufacturer;

- Introducing a second comparator product (in addition to the U.S.-licensed reference product) raises additional scientific questions and necessitates that a

[2] BIO Comments on the Food and Drug Administration Pathway for Biosimilar and Interchangeable Biological Products, December 23, 2010, http://www.bio.org/sites/default/files/20101223.pdf
[3] See BIO 2010 Comments at p. 19.

highly cautious approach be taken when accepting data from comparative studies using product that may differ from the U.S.-licensed reference product;[4]

- The fundamental support for a biosimilar must include at least one adequate and well-controlled clinical trial comparing the immunogenicity profiles of the proposed biosimilar and the U.S.-licensed reference product;

- Additional clarity is warranted to describe fully the type of bridging studies (and associated confidence intervals) that could support biosimilar approval, and the scientific bridge should generally include all of the bridging information listed in the "Draft Guidance for Industry on Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009" ("Q&A Draft Guidance") and the "Draft Guidance for Industry on Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product" ("Quality Draft Guidance");

- FDA should address scenarios where comparator data and bridging studies would not be sufficient to support licensure of a biosimilar or where additional bridging information would presumptively be required, *e.g.*, where the non-U.S. comparator product has a different strength, dosage form, or route of administration;

- Use of non-U.S. comparator data generally would not be appropriate for particularly complex biological products; and

- The confidential nature of manufacturing facility information must be recognized.

Please refer to BIO's comments to FDA's "Q&A Draft Guidance," where we highlight several additional factors that we believe are critical to consider in this regard.

III. Demonstrating Biosimilarity

Overall, BIO commends FDA for the scientifically rigorous approach taken by the Draft Guidance on scientific considerations for the demonstration of biosimilarity to a reference product. The document addresses many relevant issues associated with the topic, providing useful guidance to manufacturers of biosimilar products and helping to ensure that patients will receive high quality biosimilar products. However, BIO has a fundamental concern related to the use of the word “should” in the document. 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 are fundamental and expected to be performed, does not convey the criticality of certain

[4]See BIO 2010 Comments at p. 19.

studies that are necessary for performing a biosimilarity assessment. In many parts of the biosimilars Draft Guidances, the Agency uses phrases such as “is expected to,” “will need to,” “FDA recommends,” or “are fundamental components” to convey clearly the need for certain data and information. BIO recommends that the use of the word "should" be consistently avoided for fundamental requirements that are expected to be performed. These fundamental requirements are also flagged in our specific comments.

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 guidance. Therefore, it is important to be clear about the fundamental requirements, and what might be modified on a case-by-case basis.

BIO also recommends that FDA include more statistical specificities in its product specific guidance documents, when these guidances are developed, to ensure that all biosimilar applicants meet the same standards. More collaborative statistical research into methods of establishing biosimilarity (and, later, interchangeability) criteria is essential.

A. Stepwise, Totality-of-the-Evidence Approach

As stated in BIO's 2010 Comments, the impact of identified or unidentified structural differences should be evaluated in a stepwise manner starting with what is known about the mechanism of action and the development history of the reference product. However, BIO has a concern with the way this section of the Draft Guidance is written versus what is stated in the statute. As written, it appears as though the requirements for clinical data are a 'residual requirement,' and triggered only if there are gaps or insufficiencies in the analytical, pharmacokinetic/pharmacodynamic (PK/PD) data, and safety package. In contrast, the statute is set up such that clinical trials are required, and it takes an affirmative finding by the FDA in order to determine they are not necessary.

If there is a meaningful possibility that structural differences could impact potency, immunochemistry, immunogenicity, or PK, further studies will be essential to the evaluation of biosimilarity. Even if no structural differences have been detected, it will be important to confirm the biosimilarity of the biologic to the reference product using functional assays and appropriate non-clinical and clinical evaluations of the behavior of the biologic.

Biosimilarity should always be evaluated using sensitive *in vitro* and/or *in vivo* functional assays assessing all potential mechanisms of action for the biologic. However, such techniques may not be sensitive to all biologically relevant structural differences. For example, parameters that impact the PK of a biologic do not necessarily impact *in vitro* potency. Similarly, *in vitro* methods cannot reliably evaluate the relative immunogenic potential of a biologic. Thus, *in vivo* studies including non-clinical pharmacology (if biologically relevant for an individual product) and clinical evaluations are required.

The scope of such studies will depend on the findings of the analytical studies, the known limitations of analytical methods, or on other risk factors relating to the product itself and the state of knowledge about its structure and function.

We also note that the guidance document leaves open the possibility of establishing biosimilarity based on human PK/PD and immunogenicity. Human PK and PD data may not always be sufficient to demonstrate biosimilarity, as they are not always sufficient to predict clinical efficacy and safety. We believe that, in general, clinical trials evaluating safety and effectiveness will be necessary, and equivalent efficacy between the biosimilar and the reference product likely will need to be demonstrated in a minimum of one adequately powered, randomized, and controlled confirmatory trial. If such clinical trials are not conducted, there must be an expectation that sufficient evidence to support patient safety will be provided at the intended market dose. If a PD marker is to be used to demonstrate equivalent efficacy, it must be measured with accuracy and precision, and it must be directly related to the mechanism of action and be clinically relevant (*i.e.*, the PD markers must reflect relevant activities).

Because no class specific guidances yet exist, BIO suggests that standards for a "totality-of-the-evidence" approach be clarified and maintained, and requests that FDA include a schematic or flow chart of the step-wise approach.

B. Functional Assays

The Draft Guidance does not address the scientific issues associated with optimization of the assay methodology for assessment of immunogenicity of the biosimilar product; importantly, it cannot be assumed that an assay methodology that has been optimized for the biosimilar product is optimal for assessment of the reference product. We look forward to continuing to engage with FDA on these issues.

C. Animal Data

Overall, BIO supports the Draft Guidance's recommendations concerning animal data and animal toxicity studies. However, the Draft Guidance suggests that FDA will require animal toxicity or safety data in only some cases. Permitting the testing (or marketed use) in humans of a biologic that has never been subject to animal toxicity testing may raise safety concerns. Animal toxicity or safety testing may detect differences between products that were not detected through analytical testing, including differences with respect to inactive ingredients, contaminants, and the presence of aggregates. Thus, some toxicity testing in a representative animal species should generally be expected.

BIO acknowledges that such factors would not justify the use of higher species such as non-human primates, and BIO agrees that large scale comparative nonclinical animal toxicity or safety studies are unlikely to be valuable. Furthermore, to reduce non-human primate use, it would be helpful for FDA to address whether and when the animal toxicity

studies can be designed with one dose level, one gender, and no recovery animals or control animals.

With biosimilars that have no relevant cross-reactivity in a non-human species, the biosimilar should still be assessed in an *in vivo* nonclinical animal toxicity or safety study that will support that the biosimilar can be safely administered to humans. BIO recommends that FDA state that an *in vivo* nonclinical toxicology study in a single species (*e.g.*, rodent) is the minimum nonclinical *in vivo* study prior to human dosing with a biosimilar. This approach is analogous with the International Conference on Harmonization (ICH) S6 guidance on "Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals," which indicates that for monoclonal antibodies and other related antibody products directed at foreign targets (*e.g.*, bacterial, viral, tumor specific), a short-term safety study in one species (*e.g.*, rodent) can be considered, with no additional toxicity studies. This approach is also consistent with the reasonable expectations of individuals enrolled as study subjects, as the vast majority of pharmaceuticals are studied in non-human animals before introduction into humans.

At a minimum, BIO recommends that if no nonclinical animal toxicity or safety studies are conducted with the biosimilar, patients enrolled in clinical studies should be informed via informed consents. For an approved biosimilar, the package insert should state that no non-clinical animal toxicity or safety studies have been conducted with the biosimilar.

D. Clinical Studies

i. Immunogenicity

As stated in BIO's 2010 Comments, immune-mediated responses may be affected by multiple factors, including the drug substance itself, its molecular size, its solubility, and its properties (as well as subtle changes that may affect these properties and which may not be detectable by analytical methods), the carriers used in the formulation of the finished drug product, use of concomitant medications, and factors that depend upon the patient (including age and underlying disease state). Such immune responses may be mild and benign, or may be severe and even fatal, and there is potential for a biosimilar to exhibit immunogenicity problems that do not occur with the reference product. Therefore, immunogenicity studies comparing the proposed biosimilar with the U.S. licensed reference product should always be conducted and should be of sufficient duration to assess the effects of immunogenicity on PK, biodistribution, safety, and efficacy. Testing should take into consideration the nature (*e.g.*, cross-reactivity, target epitopes, titer range, neutralizing activity, and/or isotope) and severity (*e.g.*, effects on PK and side effects) of immune responses. Differences with regard to these characteristics may result in clinically meaningful differences between the biosimilar and reference products. In many cases, some portion of the immunogenicity assessment may need to extend into the post-marketing period, for example where clinically meaningful or even serious antibody development has been encountered with the reference biologic

or the drug class. Further, a minimum of one year follow up for chronically administered agents prior to approval should generally be expected.

The antibody testing strategy, including the selection, assessment, and characterization of assays need to be justified by the Sponsor, and assays need to be validated for their intended purpose. Generally, the proposed biosimilar should be used as a reagent. Possible interference of circulating antigen with the antibody assay(s) should be taken into account. Detected antibodies need to be further characterized and their potential clinical implications regarding safety and efficacy evaluated. Special attention should be paid to the possibility that the immune response affects the endogenous protein's biological functioning.

ii. Clinical Study Designs (non-inferiority vs. superiority)

BIO understands that FDA has stated that, in some instances, a non-inferiority design for clinical trials assessing safety, effectiveness, and immunogenicity would be appropriate. Applicants should provide robust justification to support their selection of either an equivalence or a non-inferiority design. An applicant should be expected to demonstrate that a proposed biosimilar with less immunogenicity than that of the reference product, for example, does not have a different efficacy profile than that of the reference product. Lower immunogenicity or enhanced potency could be a sign of other—as yet undetected—clinically meaningful differences between the products that an applicant should rule out. In addition, a proposed biosimilar with a "superior" clinical outcome has a meaningfully different clinical profile and thus should be licensed on the basis of a full application under section 351(a) of the Public Health Service Act. Circumstances when a non-inferiority design would be appropriate will be rare.

Whether a non-inferiority or equivalence trial is chosen, the statistical boundary or boundaries must be clinically justified and declared prior to the initiation of the study. The acceptance margin for higher immunogenicity should be the same as it would have been had an equivalence trial been conducted and appropriate statistical methods should be utilized to ensure that the study is of adequate size to be likely to meet its stated objective.

iii. Patient Population(s)

When selecting the study population, an applicant should consider whether a population has characteristics consistent with those of the population studied to support licensure of the reference product. However, this population may not always be a population that is adequately sensitive to detect differences between the proposed biosimilar and the reference product, and a study in more than one population, or more than one study, may therefore be necessary. A biosimilar applicant should always be expected to justify the population(s) used during clinical development. In addition, a biosimilar's labeling should note which populations were studied.

iv. Extrapolation

BIO urges a cautious approach regarding any extrapolation across patient populations. It is widely recognized that limitations on the abilities of analytic and preclinical testing to exclude differences between an innovator biologic and candidate biosimilar will, in many cases, necessitate clinical studies. In such cases, it is important that caution be exercised in relying on clinical data showing no meaningful differences in one indication to determine that there is no meaningful difference in another, *i.e.*, extrapolating across indications.

Extrapolation of clinical data demonstrating that the proposed product is biosimilar to the reference product with regard to one indication to support the licensure of another indication may be acceptable if the mechanism(s) (and sites) of action for both indications are very well understood and are the same; if there are no significant differences between the PK and bio-distribution of the product in the indication and patient population(s) studied clinically and the new indication and patient population(s); and if the study in original indication is highly sensitive to potential differences that might emerge in the new indication. That said, many biologics have several potential mechanisms of action (MOA) and the importance of potential mechanisms may be unknown. Additionally, it is common that, in a new indication, the drug may be sensitive to differences that may not have been observed in the studied indication (due to differences with regard to, *e.g.*, concomitant medications, levels of immunocompetence, underlying disease, or patient factors such as age, tissue penetrated, dose, dosing regimen and/or route of administration. In such cases, extrapolation would be risky. A biosimilar applicant should always be expected to provide a robust scientific explanation of why indication- or patient-specific factors do not preclude data extrapolation.

With regard to extrapolation of one comparative assessment to other indications for which the reference product has previously been approved, PK/PD and immunogenicity must be considered for all indications.

The Draft Guidance states that when a Sponsor seeks to extrapolate across indications, it must consider studying the "most sensitive" population to detect differences in safety, effectiveness, and immune response. BIO suggests that "most sensitive" should be defined as the population/indication that can detect with the highest sensitivity and specificity (and thus with the highest positive and negative predictive values) clinically meaningful differences between a proposed biosimilar and the reference product, both in terms of safety (including immunogenicity) and efficacy. When it is not possible to identify a single most sensitive indication or patient population, testing in more than one sensitive indication and/or patient population will be necessary. For example, one patient population may be most sensitive to differences in immune responses whereas a different population may be most sensitive to efficacy differences. In that case, both patient populations should be studied clinically. In addition, an applicant should generally be expected to evaluate immunogenicity in a patient population sensitive to differences in immunogenicity even if the applicant is not seeking licensure for that indication.

BIO also questions how best to define criteria for recognizing the most sensitive endpoints. This is very challenging, especially when indication extrapolation is sought for different therapeutic areas. For example, how would one affirm that measuring a variable in one disease applies to other organ systems? Specific criteria will depend on the protein class, and the biosimilar Sponsor must justify the criteria to be used, on a case-by-case basis. We request that this Draft Guidance—or future product class or product specific guidance—address this issue.

v. Endpoints

In the Draft Guidance, FDA refers to "clinically relevant" and "sensitive" endpoints and further proposes that they be "scientifically justified." By way of illustration, examples are provided for PD measures, such as "international normalized ratio" as a scientifically justified endpoint.

We note that advances in medicine and science may result in newer/better outcome measures to use for trials, but recommend that the primary efficacy outcome measure used in the reference product's trial should be used in the biosimilar trial (as a secondary outcome, if necessary).

vi. Intentional Differences in Primary Structure and/or Formulation

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) with a full application.

IV. Post-Market Safety Monitoring Considerations

A. Pharmacovigilance

BIO agrees with FDA's assessment that "robust post-marketing safety monitoring is an important component in ensuring the safety and effectiveness of biological products, including biosimilar therapeutic protein products." Post-marketing data collection and evaluation are essential to assure product safety and effectiveness, especially because

some serious rare adverse events will not be seen in clinical trials. As BIO noted in our 2010 Comments, pharmacovigilance activities must be guided by the fact that biologics:

- are complex and challenging to characterize
- are more likely than small molecules to be affected by manufacturing, formulation, stock-keeping unit (SKU), primary container closure, and delivery system characteristics
- can produce a highly individualized response in patients associated with, or independent of, protein structural and other product characteristics
- have product properties that can sometimes result in unique immunogenic responses in patients
- are similar, not identical
- require a carefully designed pharmacovigilance effort for a product to graduate from being a biosimilar to being interchangeable, including the application of each of the above principles to multiple potential indications

The Draft Guidance states that "postmarketing safety monitoring should first take into consideration any particular safety or effectiveness concerns associated with the use of the reference product and its class, as well as the proposed product in its development and clinical use (if marketed outside the United States)." BIO agrees. We note also that pharmacovigilance standards should be equally rigorous for the reference product, biosimilar, and interchangeable biosimilar. Specific requirements may vary based on what is known about the reference product and product class at the time of approval of the biosimilar and/or interchangeable biosimilar, but because a biosimilar must have safety and efficacy profiles highly similar to those of the reference product, equally rigorous post-marketing monitoring should be required. Patient exposure in the development program, extrapolation of indications, and uncertainties that remain about differences between the products (including differences in immunogenicity) should also factor into post-market pharmacovigilance. Additional pharmacovigilance monitoring could take the form of an observational study or registry monitoring the biosimilar product for a certain period of time; this would also allow traceability to the patient level.

Pharmacovigilance programs should be able to distinguish between adverse events associated with the reference product, biosimilar, and interchangeable biosimilars. BIO appreciates FDA's statement that, "postmarketing safety monitoring for a proposed product should also have adequate mechanisms in place to differentiate between the adverse events associated with the proposed product and those associated with the reference product, including the identification of adverse events associated with the proposed product that have not been previously associated with the reference product." We encourage FDA to clarify how pharmacovigilance systems can achieve that goal. For example, BIO supports the use of a unique non-proprietary name for tracking purposes,

as discussed below, and we also suggest that the prescribing physician should note in the medical records of the patient the trade name of any prescribed biological products as well as the lot number.

BIO also supports enactment of the Biosimilars User Fee Act (BsUFA), which would provide FDA with additional resources and staff capacity to establish a life-cycle approach to biosimilar product evaluation and support the Agency's post-market pharmacovigilance activities.

B. Distinguishable Non-Proprietary Names for Biosimilar Products

Identification of the exact product received by the patient is essential to recognizing safety issues quickly and limiting risk to patients. Therefore, a unique brand and distinguishable nonproprietary name are essential. Biosimilars are "similar" but not "identical" to the reference product. Assignment of the same nonproprietary name to a biological medicine and any biosimilar versions may be taken to imply that these products are pharmacologically interchangeable when they are not. BIO takes the position that, in order to accommodate the subsequent advent of new biosimilars, each biological medicine should have a distinct non-proprietary name to permit tracing an adverse event to the product administered.

A standardized naming system for the nonproprietary name with distinguishing prefix and suffix should be considered. While a distinct international nonproprietary name (INN) could consist of the same stem name as the innovator, plus a unique suffix (such as "-alpha" or "-beta" or the manufacturer's name), distinguishing by prefix also provides traceability. Due to the potential for reporting errors, both proprietary and non-proprietary names should be collected on adverse experience reports.

BIO requests that FDA issue guidance on the topic of biosimilar naming. We ask that FDA be proactive about defining what the Agency means by "adequate mechanisms in place to differentiate between the adverse events associated with the proposed product and those associated with the reference product, including the identification of adverse events associated with the proposed product that have not been previously associated with the reference product." Unless the Agency takes the lead on defining uniform naming requirements that could distinguish among innovator biologics, biosimilars, and interchangeable biologics, there may be multiple approaches taken by Sponsors, resulting in confusion among health care providers and patients. We also encourage FDA to work with other health authorities to harmonize distinct non-proprietary naming requirements globally.

C. Labeling

In section VIII, "Postmarketing Safety Monitoring Considerations," FDA states that labeling submitted to the Agency for a proposed product should include a clear statement showing that:

- The product is approved as biosimilar to a reference product (for stated indication(s) and route of administration(s).

- This product (has or has not) been determined to be interchangeable with the reference product.[5]

BIO supports FDA's proposed labeling statements, as a means of clearly and factually stating what a biosimilar has been approved for, and how it differs from a reference product. Likewise, in BIO's 2010 Comments, we stated that the labeling requirements for biosimilars should flow from the fundamental premise that they are similar, but not the same, as the reference product.

BIO requests that FDA clarify whether these statements in the Draft Scientific Guidance are intended as model language for use in biosimilar labeling, *i.e.*, whether the two bullet points in lines 824-827 are intended to be boilerplate statements to be included in each product package insert, or whether this language is set forth as an example. It would also be helpful for FDA to further clarify whether, for example, labeling for a biosimilar is expected to state, literally, "This product is approved as biosimilar to a reference product . . . " or rather to state specifically the name of the biosimilar and the name of the reference product. It would also be useful for FDA to provide details regarding the portion(s) of the labeling within which this statement would be included.

Further, BIO encourages FDA to address in separate guidance the other components of biosimilar labeling, *i.e.*, what would be included in the highlights section, the clinical studies section, and the warnings section. As discussed in BIO's 2010 Comments, each of these sections should clearly reflect the differences between a biosimilar and the reference product, including: a warning regarding the risks of substituting or alternating innovator and biosimilar products that have not been approved as interchangeable; the nature of the clinical studies that were conducted for approval; and any observed differences in incidence or type of adverse event compared to the reference product.

Labeling for biosimilars should contain essential scientific information specific to the biosimilar product; be informative and accurate; avoid misleading and false claims; have adequate directions for use; and address safety, warnings, and precautions. As treatment options are usually discussed between the prescribing physician and the patient, the prescribing physician also needs to have access to all relevant information in a transparent way. We recommend that FDA require the label to explicitly identify the essential clinical data that served as the basis of the licensure decision (*i.e.*, clinical data

[5] Draft Scientific Guidance, p. 21.

compared to the reference product) and what, if any, indications have been granted based on data extrapolation.

V. Consultation with FDA

In the early years of the development of the U.S. biosimilars market, there is expected to be significant variability in the types of biosimilars development programs pursued by Sponsors. Because there will be no "one-size-fits all" approach to biosimilars development, and it is to be stepwise based on prior evidence, we agree with FDA's encouragement to Sponsors to meet with FDA early in the development process, in order to identify in advance all of the necessary components of a development program, and also to continue to meet with FDA to assess the program as it progresses. In fact, the biosimilars user fee program is structured with a "biosimilars product development fee" to ensure that FDA is adequately resourced for these types of early consultations. BIO believes that this type of consultation during development is appropriate, and we encourage robust, interactive communication between FDA and the Sponsor for both biosimilar and innovator programs.

CONCLUSION

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

Sincerely,

/S/

Kelly Lai
Director, Science & Regulatory Affairs
Biotechnology Industry Organization (BIO)

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. COMPLEXITIES OF PROTEIN PRODUCTS		
Line 132:	Consideration of protein complexity and related scientific issues is fundamental in the design of a development program to establish biosimilarity, but use of the word "should" implies that it does not necessarily need to be done.	Please edit the statement to read: "A sponsor ~~should~~ is expected to consider the complexities of protein products and related scientific issues when it designs a development program to support a demonstration of biosimilarity."
Lines 144-152:	Product-related impurities, such as precursors, fragments, aggregates and degradation products, may also play a role in triggering an immunogenic reaction in human subjects. Even though modifications to the amino acid sequence and protein modifications (focus on post-translational modifications) and higher order structure are addressed in the paragraph (lines 144-150), product-related impurities are different from these and should also be addressed herein.	Please revise the statement to read: "Additionally, process- and product-related impurities may increase the likelihood and/or the severity of an immune response to a protein product, and certain excipients may limit the ability to characterize the drug substance."
Lines 160-162:	FDA states, "Despite such significant improvements in analytical techniques, however, current analytical methodology may not be able to detect all relevant structural and functional differences between two proteins."	BIO suggests that FDA consider reinforcing this statement as an important one based on the current state-of-the-art.

Lines 169-171:	Post-translational modifications may affect both the safety and efficacy of any given biotherapeutic/biosimilar.	Please edit the statement to read: "For example, differences in biological systems used to manufacture a protein product may cause different post-translational modifications, which in turn may affect safety and/or effectiveness of the product."
Lines 181-192:	FDA states, "Demonstrating that a proposed product is biosimilar to a reference product typically will be more complex than assessing the comparability of a product before and after manufacturing changes made by the same manufacturer ... a manufacturer's post-manufacturing change product is comparable to the pre-manufacturing change product."	BIO suggests considering reinforcing/commending this as an important clarification of the distinction between a comparability and a similarity exercise.
II. U.S.-LICENSED REFERENCE PRODUCT AND OTHER COMPARATORS		
Please see BIO's comments in the Q&A document for a more detailed discussion of this topic. We also suggest the following edits to clarify the use of bridging data.		
Lines 197-212:	A Sponsor should always be required to provide information to demonstrate biosimilarity based on data directly comparing the proposed product with the reference product. Thus, the term "in general" does not meet the requirements for an adequate comparability exercise.	BIO recommends providing more specific guidance in both documents regarding when a non-U.S. licensed comparator product could be used. BIO also suggests editing the statement to read: ~~"In general, a~~A sponsor needs to provide information to demonstrate biosimilarity based on data directly comparing the proposed product with the reference product."

Lines 208-209:	FDA states, "In such a case, the sponsor should 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." An acceptable bridge study showing comparability assessments to the U.S.-licensed reference product should include both "the biosimilar product to the U.S.-licensed reference product" and the "non-U.S.-licensed comparator product to the U.S.-licensed reference product."	Please amend the sentence to read: "In such a case, the sponsor should 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 for both the non-U.S.-licensed comparator product and the proposed product."
Lines 209-212:	FDA states, "Sponsors are encouraged to discuss with FDA during the development program the adequacy of the scientific justification and bridge to the U.S.-licensed reference product; a final decision about such adequacy will be made by FDA during review of the 351(k) application."	It is unclear when, why, and how bridging studies may be needed and what studies could potentially bridge to a non-U.S. licensed comparator product. Please see BIO's comments to the Q&A Draft Guidance for further details.
III. APPROACHES TO DEVELOPING AND ASSESSING EVIDENCE TO DEMONSTRATE BIOSIMILARITY		
Line 228:	Section A. Using a Stepwise Approach to Demonstrate Biosimilarity	For the stepwise approach to demonstrate biosimilarity, there should be quantitative rules to determine difference at each step.
Line 241:	Extensive comparative structural and functional characterization is the starting point for design of a biosimilarity program, but use of the word "should" implies that this	Please edit statement to read: "The stepwise approach ~~should~~ is expected to start with extensive structural and functional characterization of both the proposed

	does not necessarily need to be done.	product and the reference product, which serves as the foundation of a biosimilar development program (sections VII.A and VII.B)."
Lines 251-253:	FDA mentions throughout the Draft Guidance the concept of "fingerprint-like" characterization. Please provide a reference that gives more detail on the meaning of this term. We request clarity regarding whether the "additional product attributes" and their relationship to each other must correlate with clinical safety and efficacy, consistency in manufacturing, or some other meaningful feature for establishing biosimilarity between the biosimilar product and the reference product.	BIO requests that the Agency clarify its thinking on fingerprint-like analysis and characterization by adding references or through subsequent guidance development. For a more detailed discussion on this topic, please see BIO's comments to the Quality Draft Guidance.
Line 259:	Use of relevant and validated PD markers for clinical outcome is necessary to provide clinically meaningful data which may allow for a selective and targeted approach to animal and/or clinical studies.	BIO suggests changing the term "relevant" to "validated". Please edit the statement to read: "A sufficient understanding of the mechanism of action (MOA) of the drug substance and clinical relevance of any observed structural differences, clinical knowledge of the reference product and its class indicating that the overall safety risks are low, and the availability of a clinically relevant and validated PD measure may provide further scientific justification for a selective and targeted approach to animal and/or clinical studies."
Lines 256-261:	Data and information that "may provide further scientific justification for a selective and targeted approach to animal and/or clinical studies," includes "clinical relevance	BIO suggests rephrasing this section to assure that proprietary data in the reference product BLA is protected.

	of any observed structural differences." How will FDA assess this information, where the impact of structural differences stems from proprietary reference product data, *e.g.*, from data pertaining to manufacturing changes in the reference product? Every effort should be made to avoid reliance on proprietary data from the reference product to "influence" the assessment of the proposed biological product.	
Lines 295-298:	The Agency's attempt to define what it considers to be clinically meaningful differences—in terms of "difference in the expected range of safety, purity, and potency," and differences that would not rise to the level of clinical significance in terms of "slight differences in rates of occurrence of adverse events between the two products"—lacks clarity on this important issue for establishing biosimilarity. As patient exposure during the clinical development of a biosimilar will be limited, it will be difficult to assess 'slight' differences. In general, one would need about 300 patients exposed to detect an adverse event which occurs in approximately 1% of patients (and this number increases significantly if there is a significant background incidence in the general population). Although we agree that, in general, the biosimilar pathway is designed not to	We request that the Agency provide more clarity on this topic through subsequent guidance development.

	replicate the safety and efficacy data of the reference product, we stress that for patient safety, the Agency should insist on having a sufficiently large patient population that is exposed to the biosimilar, either in the pre-approval phase or in the post-marketing phase.	
IV. DEMONSTRATING BIOSIMILARITY		
Lines 304-306:	It would be informative to know what kind of protein products, in addition to well-characterized protein products, might be developed as biosimilars.	Please edit the text to read: "Although this guidance focuses on proposed biosimilar therapeutic protein products, the scientific principles discussed may also apply to other types of proposed biosimilar biological products, such as…"
Lines 313-391:	This section mentions the structural analysis and functional analysis of a product, but does not mention process-related impurities and stability.	Please add the assessment of process-related impurities and stability.
Lines 322-323:	FDA states, "In general, FDA expects that the expression construct for a proposed product will encode the same primary amino acid sequence as the reference product." BIO requests clarification that the proposed biosimilar product must have the same primary amino acid sequence (this is true irrespective of the fact that, as the Agency acknowledges, low levels of DNA mutation and amino acid incorporation, as well as post-translational modifications, may occur).	We recommend that "In general, FDA expects…" be changed to "In general, FDA requires…" For the statement in lines 322-323, please remove "In general" such that the sentence now reads as follows: "~~In general,~~ FDA expects that the expression construct for a proposed product will encode the same primary amino acid sequence as the reference product."

	The concept of some modifications being allowable (*e.g.*, C- or N-terminal truncations) should be separated from the primary amino acid sequence requirement. Even these allowances must be accepted only on a case-by-case basis, and must be justified by appropriate analytical and possibly clinical data.	
Lines 333-334:	Use of appropriate analytical methodology with adequate sensitivity and specificity is a fundamental requirement for a comparative structural comparison of a biosimilar and reference biological product, but use of the word "should" implies that it does not necessarily need to be done.	Please edit the statement to read: "Sponsors ~~should~~ need to use an appropriate analytical methodology with adequate sensitivity and specificity for structural characterization of the proteins. Generally, such tests include the following comparisons of the drug substances of the proposed product and reference product."
Lines 333-335:	If the drug substance for the reference and the proposed biosimilar are used during the structural analyses, rather than the drug product, this should be done with great care.	Please clarify that the drug substance purified from a formulated reference biologic must be appropriately tested to demonstrate that product heterogeneity and relevant attributes of the active moiety are not affected by the isolation process.
Lines 345-350:	Lot-to-lot variability of the biosimilar product and the reference biological product needs to be assessed through extensive structural characterization of multiple representative lots, but use of the word "should" implies that it does not necessarily need to be done.	Please edit the text to read: "Sponsors are expected to conduct extensive structural characterization in multiple representative lots of the proposed product and the reference product to understand the lot-to-lot variability of both drug substances in the manufacturing processes. Lots used for the analysis should support the biosimilarity of both the clinical material used in confirmatory clinical trials and the to-be marketed product. Sponsors need to justify the selection of the representative lots, including the number of lots."

Lines 371-374:	Current science does not support the notion that functional assays "provide additional evidence that the biologic activity and potency of the proposed product are highly similar to those of the reference product and/or to demonstrate that there are no clinically meaningful differences." Clinically meaningful differences must come from data gathered through adequately designed efficacy and safety/immunogenicity trials.	Please revise statement to read: "Sponsors can use functional assays to provide additional evidence that the biologic activity and potency of the proposed product are highly similar to those of the reference product ~~and/or to demonstrate that there are no clinically meaningful differences~~."
Lines 378-381:	Given the important role functional assays provide in supporting a demonstration of biosimilarity, use of the word "should" does not convey the appropriate emphasis on the need for "comparative" functional assays.	Please edit the text to read: "~~To be useful, these assays should~~ As a scientific matter, functional assays generally are expected to be comparative, so they can provide evidence of similarity, or reveal differences, in the performance of the proposed product compared to the reference product, especially differences resulting from structural variations that cannot be detected using current analytical methods."
Lines 390-391:	Use of appropriate lots for the structural evaluation of a biosimilar product is a fundamental requirement to establish biosimilarity, but use of the word "should" implies that it does not necessarily need to be done.	Please edit the text to read: "As for the structural evaluation, appropriate lots ~~should~~ need to be used in the analysis."
Lines 391-392:	As noted in our comments on lines 333-335, if during the structural analyses drug substance for both the reference and the proposed biotherapeutic are used rather than the drug product, then the drug substance purified from a formulated reference biologic	Please clarify.

	must be appropriately tested to demonstrate that product heterogeneity and relevant attributes of the active moiety are not affected by the isolation process.	
Section C	The Terminology section states that "Product" may refer to "intermediates, drug substance and/or drug product, as appropriate," but does not clarify that with few exceptions, the drug product as intended for commercial use should be used as the comparator for non-clinical *in vivo* studies and for clinical trials. If the drug substance is used, this should be clearly justified by the Sponsor.	Please clarify.
Lines 401-404, 417-419:	No matter how thorough the characterizations of structural and functional attributes of the proposed product, there would be uncertainties about safety that would argue for animal toxicity testing prior to initiation of human clinical studies.	BIO recommends revising the text in lines 401-404 to the following, and requests that the FDA provide more detailed criteria as to when animal toxicity data might not be required: "As a scientific matter, animal toxicity data are considered useful."
Lines 404-406:	FDA states, "Animal toxicity studies are generally not useful if there is no animal species that can provide pharmacologically relevant data for the protein product (*i.e.*, no species in which the biologic activity of the protein product mimics the human response)."	BIO recommends that FDA clarify its statements regarding animal toxicity studies, because lines 405-406 say that in some instances such data can be useful, while lines 395-397 say that a toxicity assessment is required. In addition, we note that per ICH S6(R1), tissue cross-reactivity studies are not recommended for assessing comparability of the test article as a result of process changes. This suggests tissue cross-reactivity studies would likewise not be useful for biosimilar comparability. Please consider addressing this issue in the draft guidance.

Lines 435-438:	The phrase "…and animal toxicity studies" at the end of this sentence is unclear and seems unnecessary. If, for a particular proposed product, it has already been determined that animal toxicology studies are not warranted based on the considerations described in this section, then there would be no need for nonclinical safety pharmacology, reproductive and developmental toxicity, and carcinogenicity studies.	Please edit the text to read: "...and general ~~animal~~ toxicity studies."
Lines 438-439:	The text mentions "specific safety concerns based on the clinical use of the reference product" that may lead to a requirement for additional animal studies to be conducted with the proposed product.	Please provide examples of the type of safety concerns that may lead to the need for additional animal studies.
Lines 459-461:	FDA states, "Additionally, significant differences in the immune response profile in inbred strains of mice, for example, may indicate that the proposed product and the reference product differ in one or more product attributes not captured by other analytical methods."	BIO agrees with FDA that "Animal immunogenicity assessments generally do not predict potential immunogenic responses to protein products in human." The relevance of such studies is, at best, scientifically debatable and, thus, they are not part of comparability or other product development protocols. This raises the question of why FDA includes this section in the Draft Guidance. Further, the section is ambiguous with regard to its intent and, in particular, includes an example – the use of inbred strains of mice – that is particularly confusing. We urge FDA to delete this section from the Guidance, or to include only the first sentence of the section (referenced above). At a minimum, if the Agency believes it essential to include a section on animal immunogenicity studies, we request clarification of the Agency's intent. Does the Agency envision requiring such studies as a way to understand potential impact of a biosimilar on human immunogenicity? Under what circumstances – *i.e.*, based on what other data – could such studies be

		required? What unanswered questions does the Agency believe could be answered by such studies, under the Agency's stepwise approach? If the rationale for inclusion of this section cannot be explained further, and if the Agency cannot be more specific regarding the usefulness of such studies and the circumstances under which they might be required, we request that the section be deleted.
Lines 483-531:	The European Medicines Agency's guideline on "similar biological medicinal products containing monoclonal antibodies dedicates a sub-section to "Multidose PK and endpoints."	Please provide FDA's views on multi-dose PK and endpoints.
Lines 483-531:	In general, the data requirements here are presented in a confusing manner. There should be internal consistency and order.	Please clarify. We suggest separating the text into PK requirements, PD requirements, and joint PK/PD assessments, and then stating PK/PD requirements.
Lines 485-849, 491-495:	The message conveyed in lines 485-489 and in lines 491-495 seems redundant.	BIO suggests merging and condensing these two sections.
Lines 487-489:	FDA states, "We have determined that both PK and PD studies (where there is a relevant PD measure) generally will be expected to establish biosimilarity, unless a Sponsor can scientifically justify that an element is unnecessary."	Human PK and PD studies should be required, and if an exception is to be considered, there should be clear guidance on the criteria for granting such an exception.
Lines 492:	Does FDA intend that the PK results should meet the typical bioequivalence criteria of 80-125%?	Please clarify.

Lines 508-509:	FDA states, "…as well as the current knowledge of the intra-subject and inter-subject variability of human PK and PD for the reference product."	For biologics with long half-lives, crossover PK/PD studies are not feasible. In these cases, total variability for the reference product should be considered. Please edit the statement so that it reads: "…as well as the current knowledge of the intra-subject, ~~and~~ inter-subject and total variability of human PK and PD for the reference product.
Lines 548:	Although the immunogenicity assessment begins with the chemistry, manufacturing and controls (CMC) comparability exercise, and non-clinical studies provide complementary information, in the vast majority of cases, both CMC and non-clinical studies do not predict immunogenicity in humans. Hence, there remains a need for immunogenicity studies during the clinical phase. As mentioned in the Draft Guidance, "at least one clinical study that includes a comparison of the immunogenicity of the proposed product to that of the reference product will generally be expected." The exact wording used in the Draft Guidance: "The extent and timing (*e.g.*, premarket testing versus pre- and postmarketing testing) of a clinical immunogenicity program will vary depending on a range of factors..." implies that pre-market studies will not be waived, but complemented by post-marketing surveillance. BIO agrees. Because immunogenicity may appear late in the course of treatment, immunogenicity	Please describe additional post-marketing measures that may be useful; registries could be offered as an example here.

	assessments should be part of the post-market surveillance program proposed by the biosimilar Sponsor; also, and depending on the product class and the experience gathered with the reference product, some additional post-marketing measures aimed at identifying rare/unexpected immunogenicity events may be carried out, such as a Risk Evaluation Mitigation Strategy or Risk Management Plan (REMS/RMP) and post-approval safety studies (*e.g.*, registries).	
Lines 555-559:	The Draft Guidance indicates that, if the immune response is "rare," both pre- and post-marketing studies may be needed, and suggests that these studies should be comparative with endpoints and non-inferiority margins discussed with FDA.	Please: 1) clarify the definition of "rare;" 2) add an example to illustrate what would be considered a major or subtle difference in immune response; 3) provide guidance on detecting differences in immune responses between the two products when the immune response to the reference product is "rare"; and 4) provide guidance when immune response to the reference product is not "rare." An example of what a post-marketing study design might look like would also be useful.
Lines 562-564:	Section VII D.1, "Human Pharmacology Data," covers general considerations for PK and PD studies, but is vague as to specific study designs. However, sections VII D.2 "Clinical Immunogenicity Assessment" and VII D.3 "Clinical Safety and Efficacy Data," do specifically mention study designs, *i.e.*, "head-to-head" study or "comparative parallel design" in the case of immunogenicity, and "comparative clinical trials (using an equivalence or non-inferiority design)" in the case of Clinical Safety and Efficacy (lines	Please provide additional information on study designs for PK and PD studies.

	646-648).	
Lines 578:	The "most sensitive" study population may be influenced not only by the disease state, but also by concomitant medications (for example rheumatoid arthritis patients may be more or less sensitive, depending on their exact concomitant medication regime).	The text should indicate how the most sensitive study population should be selected from approved indications.
Lines 604-605:	FDA states, "Binding antibody: titer, specificity, relevant isotype distribution, time course of development, persistence, disappearance, and association with clinical sequelae."	BIO requests clarification regarding isotope distribution for clinical immunogenicity studies. Would isotope distribution be required for all clinical studies demonstrating immunogenicity, or would this be decided on a case-by-case basis (and required to be scientifically justified by the Sponsor)? We request clarification of the frequency of anti-drug antibody (ADA) testing in order to determine time course of development, persistence and disappearance. Please add: "Anti-drug antibody samples should be drawn every three months at a minimum."
Lines 610-612:	"The sponsor should develop assays capable of sensitively detecting immune responses, even in the presence of circulating drug product (proposed product and reference product)." If a single product (*i.e.*, innovator product) is used to develop the immunogenicity assay, and there are differences between the products, there is no guarantee that an unusual antibody to the other product (*i.e.*, the biosimilar) will be picked up. However, it	Please add: Assays should sensitively and reliably detect all classes of antibodies… The does not explicitly state that assays should be state-of-the-art rather than a match for the innovator original assay. BIO recommends that this be explicitly stated, and that it is noted that the incidence of detected immunogenicity may differ from the original innovator data using state-of-the-art assays. BIO recommends that the biosimilar be used as reagent when an applicant develops immunogenicity assays. The Draft Guidance also states that the same assay should be used to evaluate both products evaluated. This should be clarified to say that

	should be picked up in an assay based on the biosimilar. Cross-validating a positive clinical sample identified in each specific assay (per subject) would ensure that the antibodies detected were not unique to one product or the other.	the same type of assay should be developed for each product, and then cross-validation should occur for positive samples.
Lines 612:	FDA states, "The proposed product and reference product should be assessed in the same assay with the same patient sera whenever possible." To remove ambiguity and to be consistent with surrounding text, this sentence needs more clarity.	Please clarify. For example, change to "As a scientific matter, the proposed product and reference product need to be assessed in similar ADA assays (*i.e.*, assays with the same format and comparable performance parameters but based upon the use of proposed and reference products) to be run in parallel using patient sera from a head to head clinical trial whenever possible. In general, the assay should use the proposed biosimilar as a reagent."
Lines 620-623:	FDA states, "As a scientific matter, comparative safety and effectiveness data will be necessary to support a demonstration of biosimilarity if there are residual uncertainties about the biosimilarity of the two products based on structural and functional characterization, animal testing, human PK and PD data, and clinical immunogenicity assessment." As noted previously in our general comments, there is a question about the way this text is written versus what is in the statute. As this Draft Guidance is written, it appears as though the requirements for clinical data are a 'residual requirement,' which is triggered only if there are gaps or insufficiencies in the analytical, PK/PD, and safety package. In contrast, the statute is set	We request more clarity and alignment with the statute**.** The conclusion could be drawn that if no "residual uncertainties" persist, then comparative safety and effectiveness data are unnecessary. Please provide clarity on how it will be determined whether residual uncertainties still exist, and please provide standards for how it will be determined at each step if sufficient data has been provided such that residual uncertainty no longer exists. We suggest editing the statement to read: "As a scientific matter, comparative safety and effectiveness data will be necessary to support a demonstration of biosimilarity ~~if there are residual uncertainties about the biosimilarity of the two produces based on structural and functional characterization, animal testing, human PK and PD data, and clinical immunogenicity assessment~~."

	up such that clinical trials are required, and it takes an affirmative finding by FDA in order to determine they are not necessary.	
Lines 624-625:	FDA states, "some or all of these comparisons ..."	BIO is concerned that this language implies that a company may be able to justify not providing any clinical data. Please revise this statement to read: "A sponsor may provide a scientific justification if it believes some ~~or all~~ of these comparisons on clinical safety and effectiveness are not necessary."
Lines 652-656:	FDA states, "…warrant more comparative clinical safety and effectiveness data. Alternatively, if the reference product has a long, relatively safe marketing history and there have been multiple versions of the reference product on the market with no apparent differences in clinical safety and effectiveness profiles, there may be a basis for a selective and targeted approach to the clinical program." Despite an innovator's product history that shows an acceptable safety and potency profile of a biologic over multiple process versions, this alone should not be the basis for a selective and targeted approach to the clinical program.	This suggests that a safe reference product means a safe biosimilar. This is not necessarily the case. BIO asks that FDA reiterate the importance of data from clinical trials. Although there will be extensive clinical experience with the innovator biologic when a biosimilar is approved, it should not be assumed that the safety record of the biosimilar will mirror experience with the innovator biologic. As biological molecules are complicated, immunogenicity may not be predictable on the basis of preclinical data. Please edit the statement to read: "Alternatively, if the reference product has a long, relatively safe marketing history and there have been multiple versions of the reference product on the market with no apparent differences in clinical safety and effectiveness profiles, ~~there may be a basis~~ this may be one factor supporting ~~for~~ a selective and targeted approach to the clinical program."
Lines 674-675:	FDA states, "…cases in which a different	Please provide examples where the superiority boundary would be

	upper and lower bound may be appropriate" It is unclear when a different upper and lower bound might be appropriate.	different from the inferiority boundary. Different allowable Type 1 errors could also be considered. Please amend statement to read: "…cases in which a different upper and lower bound**,** or different Type 1 errors, may be appropriate."
Lines 677-679:	An "equivalence trial" instead of a "non-inferiority trial" is recommended to determine whether the proposed product has superior efficacy advantage, as this would generally allow for a smaller sample size than the reference product. However, in this case the product cannot be considered a "biosimilar." A two-sided test should be the standard, and one-sided tests should be allowed when clinically justified.	Please edit statement to read: When scientifically justified, ~~In some cases,~~ a one-sided test – non-inferiority design – may be appropriate for comparing safety and effectiveness. ~~advantageous as it would generally allow for a smaller sample size an~~ However, the standard must remain the equivalence (two-sided) design.
Lines 679:	FDA states, "well-established that doses of the reference product higher than are recommended in its labelling..."	Please clarify what "well-established" means in practice. Does this mean that a Sponsor has done work past Phase III and submitted it for review? Furthermore, if the reference is to the Sponsor supplying two-dose Phase III studies (along with a placebo), and FDA has allowed only the lower dose on the label, then the establishment of safety would be in the original Sponsor's dossier and public knowledge. Why limit the drug to the lower dose only?
Lines 680-684:	FDA states, "For example, if it is well established that doses of the reference product higher than are recommended in its labeling do not create safety concerns, a one-sided test may be sufficient for comparing the efficacy of certain protein products (*e.g.*, those	This statement is inconsistent with line 664 which states that a product with superior efficacy should be submitted under 351(a). It is also unclear how information about a reference product's safety at higher doses could inform a potential difference (superiority) in efficacy in a way that would not potentially be clinically meaningful.

	products that pharmacodynamically saturate the target at some level and are used at or near the maximal level of clinical effect)."	Line 684: FDA is inappropriately assuming that if the reference product shows a dose-response plateau, then the biosimilar product would automatically also plateau at the same level. This should be demonstrated as opposed to assumed (for example, different anti-tumor necrosis factors can show different plateaus).
Lines 685-686, 694, 733, 813:	Most of the humanized monoclonal antibodies report a low incidence of immunogenicity in humans. What immunogenicity rate in humans should be considered rare and would not require testing in a biosimilar clinical study evaluating immunogenicity? (Line 685-686, 694, 733, 813)	Please clarify.
Lines 709-721:	FDA refers to "clinically relevant" and "sensitive" endpoints and further proposes that they be "scientifically justified." By way of illustration, examples are provided for PD measures like international normalized ratio, or INR, as "scientifically justified" endpoints.	FDA should clarify that the Agency is referring to "validated endpoints" or (validated) "surrogate endpoints."
Lines 711-713:	The Draft Guidance suggests that different endpoints from those used by the reference compound can be used if they are scientifically justified. As noted in our general comments, advances in medicine and science may result in newer/better outcome measures to use for trials, but in order to allow for comparison of results from the biosimilar clinical trial and the reference product's essential trials, the primary efficacy outcome measure used in the reference	We suggest adding the following sentence immediately after the statement in lines 711-713: However, the primary efficacy outcome measure used for the essential trials of the reference product should also be included in the clinical trial for the proposed product.

	product's trial should be used in the biosimilar trial (as a secondary outcome, if necessary). Typically, the Sponsor will want to use the same endpoints as those used by the reference compound, to facilitate comparisons.	
Lines 717-756:	As written, it looks as though an immunogenicity trial may be performed in lieu of efficacy/safety trials. This is not scientifically justified because immunogenicity trials do not address non-immunogenicity related aspects of safety. Rather immunogenicity assessment should be part of an efficacy/safety trial. The only exceptions to this rule should be those outlined in the Draft Guidance, where a clinical PK, PD and/or PK/PD study(ies) can be sufficient under a well defined and justified set of conditions (section VII.D.1 and VII.D.4, lines 717-756).	Please clarify.
Lines 717-720:	Lines 717-720 and 732-756 deal with situations in which PD measures enhance the sensitivity of a study, and the suggested design of PK and PD studies. These situations should be put together with those outlined on Lines 527-531 to give the document more internal coherence.	Please merge with information in lines 527-531.
Lines 735-737:	For human PK and PD studies, the text states that Sponsors should provide a justification for the route of administration.	BIO suggests deleting route of administration from the referenced sentence. Please edit statement to read:

	Per the Q&A document, a prospective biosimilar applicant will not be able to obtain licensure under 351(k) with a different route of administration.	"In addition, sponsors should provide a scientific justification for the selection of study subjects (*e.g.*, health volunteers or patients), study does (*e.g.*, one dose or multiple doses, ~~route of administration~~, and sample size."
Lines 783-784:	Given the importance of immunogenicity and its potential to impact safety and/or efficacy, it should be listed as one of the considerations for justification of extrapolation of clinical data across indications.	We suggest that another bullet be added for immunogenicity assessment across different indications. The bullet could read: "Differences in immunogenicity rates and the immune status/competency in patients in different clinical settings within a therapeutic area as well as across therapeutic areas. An example would be the immune status difference in patients when comparing an oncologic indication versus a rheumatoid arthritis setting."
Lines 787-790:	The Draft Guidance states that when a Sponsor seeks to extrapolate across indications, it must consider studying the "most sensitive" population to detect differences in safety, effectiveness, and immune response. Immunogenicity criteria are much more complex than those for other types of adverse events, because immunogenicity depends on many factors, only some of which are known and fairly predictable. That is why finding the population/indication in which immunogenicity detection is most "sensitive" poses more challenges than for other types of adverse events. As mentioned in our general comments, there	Please clarify how to identify the "most sensitive" population. Efficacy should always be considered, because lack of efficacy can imply serious health risks for patients (*e.g.*, less efficacy in oncology indications). We suggest that "most sensitive" should be defined as the population/indication in which clinically meaningful differences in both safety (including immunogenicity) and efficacy can be detected with the highest sensitivity and specificity (and thus with the highest positive and negative predictive values). BIO notes that specific criteria will depend on the protein class, and, as mentioned in the FDA Draft Guidance, these will have to be agreed upon on a case-by-case basis.

	are no clear criteria/parameters on how to determine which is the "most sensitive condition" to include in the evaluation of the proposed biosimilar. Should such criteria address both safety and efficacy together or separately? What if one condition is the most sensitive in detecting effectiveness and a different condition is the most sensitive for detecting safety risks?	
V. POSTMARKETING SAFETY MONITORING CONSIDERATIONS		
Line 806-808:	The Draft Guidance should clearly state that pharmacovigilance programs for biosimilars should, at a minimum, be equivalent in rigor to that of the innovator reference product.	Please edit text to read: ~~The rigor of p~~Postmarketing safety monitoring should be at least as rigorous as for the reference biological product, taking into consideration any particular safety or effectiveness concerns associated with the use of the reference product and its class, as well as the proposed product in its development and clinical use (if marketed outside of the United States).
Lines 809-813:	We agree with the recommendation to ensure traceability of the product in medical practice in case adverse events are experienced. It is indeed important to be able to distinguish between the reference product and the biosimilar. At a minimum, prescribers should note the trade name and the batch number in the medical records of patients. Options to consider are different trade names, different international nonproprietary names (INN), batch numbers, or any other technical solution. At a minimum, manufacturers	We commend FDA for specifying the need to differentiate between the adverse events, but urge the Agency to be more specific about the obligation to do so. The prescribing physician should note in the medical records of the patient the trade name of any prescribed biological products as well as the batch number.

	should note the trade name and batch number.	
Lines 814-815:	FDA states, "Rare, but potentially serious, safety risks (*e.g.*, immunogenicity) may not be detected during preapproval clinical testing because the size of the population exposed likely will not be large enough to assess rare events." Rare and serious events include not only immunogenicity, but also to enhanced pharmacodynamic effects (*e.g,*. tuberculosis with anti-tumor necrosis factor (anti-TNF) therapies, or progressive multifocal leukoencephalopathy (PML) with anti-B cell monoclonal antibodies).	The naming convention is critical to the ability to monitor safety independent from the reference compound. A biosimilar and a biosimilar that is interchangeable should have different names from the reference compound. The Draft Guidance would permit rare adverse events to be examined in a post-marketing setting rather than prior to approval. Please define what qualifies as a "rare" AE. Please also edit the text to read: Rare, but potentially serious, safety risks (*e.g.*, immunogenicity, or events caused by enhanced pharmacodynamic effects) may not be detected during preapproval clinical testing because the size of the population exposed likely will not be large enough to assess rare events.