Biotechnology Industry Organization

August 12, 2014

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

Re: Docket No. FDA–2014-D-0234: Draft Guidance for Industry on Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product; Availability

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Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the "Draft Guidance for Industry on Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product."

BIO represents more than 1,000 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.

GENERAL COMMENTS:

BIO believes that clinical pharmacology studies are an essential part of the stepwise, "totality of evidence" approach to demonstrating biosimilarity between a proposed biosimilar product and its reference product, and as such, BIO greatly appreciates the Agency's work to publish the Draft Guidance. There are, however, several aspects of the Draft Guidance for which BIO requests additional information or clarification.

A. Proposed Outcomes of Analytical Characterization and Residual Uncertainty

In the Draft Guidance, FDA outlines four possible outcomes for the analytical comparison of a proposed biosimilar product with its reference product: (1) not similar; (2) similar; (3) highly similar; and (4) highly similar with fingerprint-like similarity. BIO does not find it clear from the Draft Guidance what type or scope of information is needed to differentiate a "similar" molecule from one that is considered "highly similar" or "highly similar with fingerprint-like similarity." Moreover, BIO believes it is unclear what, if any, implications the classification of "highly similar with fingerprint-like similarity" would have for biosimilar product development.

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BIO recommends that the Agency clarify and introduce limiting principles around the category of "similar: further information is needed" to comport with the statute, which requires data from "analytical studies that demonstrate that the biological product is ***highly similar*** to the reference product notwithstanding minor differences in clinically inactive components [emphasis added]."[1] The guidance introduces examples where a failure to demonstrate that a proposed biosimilar product is "highly similar" to its reference product at a given stage may be justified with additional data. BIO requests that the Agency convey limiting principles for such scenarios so that there is not the possibility that sequential analytical failures could ultimately be justified by virtue of the results of a clinical comparative safety/efficacy trial, which would expose human subjects to an experimental therapy that had not met the statutory analytical threshold of "highly similar." Finally, BIO requests that FDA elaborate on the potential regulatory implications of the "highly similar with fingerprint-like similarity" classification. Specific language is recommended in our line-by-line comments.

B. Analysis of Multiple PD Markers

The Agency introduces the concept of using multiple pharmacodynamic (PD) markers to address the absence of either a single meaningful, robust, and relevant PD biomarker or a PD endpoint that is closely associated with clinical outcome.[2,3,4] FDA seems to suggest that pooling or grouping multiple PD markers or endpoints can overcome these significant limitations. While this approach may have utility, it runs the risk of merely increasing the quantity of data without necessarily improving the quality and interpretability of the results. Such an approach is also concerning in that it may lead to a stacking of multiple uncertainties and erroneous conclusions drawn from disparate or clinically immaterial data. BIO recommends that FDA include additional principles to consider for determining how multiple markers may contribute meaningfully to the sensitivity of the PD comparison, as well as cautionary principles to aid in the determination of situations wherein additional markers may not add value.

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[1] Public Health Service Act § 351(k)(2)(A)(i)(I)(aa)

[2] Lines 133-136: "It is important to note that in some instances PD markers with the relevant characteristics listed above have not been identified, but the sponsor is encouraged to incorporate PD biomarkers that correlate well with drug exposure over a wide concentration range as these represent potentially orthogonal tests that may be supportive of clinical pharmacology similarity."

[3] Lines 304-305: "If the selected PD endpoint(s) are not closely related to clinical outcome, use of multiple complimentary PD assays may be most useful."

[4] Lines 508-513: "Use of a single, scientifically acceptable, established PD marker as described above, or a composite of more than one relevant PD markers, can reduce residual uncertainty with respect to clinically meaningful differences between products and add significantly to the overall demonstration of biosimilarity. Using broader panels of biomarkers (*e.g.*, by conducting a protein or mRNA microarray analysis) that capture multiple pharmacological effects of the product may be of additional value."

C. Clinical Pharmacology as the Full Assessment of Clinically Meaningful Differences

In several locations in Section IV of the Draft Guidance,[5] FDA refers to situations wherein clinical pharmacology studies may comprise the "full" or "complete" assessment of clinically meaningful differences. BIO believes this is a very important consideration for biosimilar development and recommends that the Agency address this topic in a more comprehensive manner in Section III B (Evaluation of Residual Uncertainty) or at the start of Section IV, so that the subsequent references do not appear as incomplete discussions of this topic.

Also, the Draft Guidance is currently silent on the considerations for indication extrapolation as it relates to the situation where a pharmacokinetic (PK) and/or PD study completes the clinical assessment of clinically meaningful differences. BIO recommends that the Agency address this topic by reference to the considerations for extrapolation already described in prior Draft Guidance.[6,7]

The Agency also raises the situation wherein supplemental evaluation of safety and immunogenicity would be required either pre-approval or post-approval. BIO acknowledges that immunogenicity may be a rare safety event, and as such, post-approval pharmacovigilance (PV) monitoring should be required. BIO does not agree, however, that full evaluation of safety and immunogenicity should be deferred until after approval, rather full evaluation of safety and immunogenicity should still be necessary before approval. BIO requests, therefore, that FDA elaborate on the role of post-approval safety and/or immunogenicity studies in these instances, the types of conditions that would justify post- rather than pre-approval studies to address safety/immunogenicity, and FDA's view of how application of this construct aligns with the statutory requirement to demonstrate safety.

D. Class-Specific Guidance

As written, the Draft Guidance applies to a broad range of potential biosimilar products (*e.g.*, growth factors, monoclonal antibodies, fusion proteins, *etc.*), some of which require additional consideration of specific issues that cannot be readily generalized or extrapolated to other classes of products. The Draft Guidance aims to include broad, generalized guidance on appropriate clinical pharmacology studies for biosimilar development, but BIO believes that, in generalizing concepts across product classes, the Draft Guidance is in some places confusing and offers seemingly conflicting guidance.

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[5] Lines 411-413, Lines 451-455, and Lines 488-490

[6] FDA Draft Guidance on *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (2012), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

[7] FDA Draft Guidance on *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009* (2012), http://www.fda.gov/downloads/Drugs/Guidances/UCM273001.pdf

BIO believes this illustrates the need for product class-specific guidance on development issues for biosimilars, which, for some product classes, may include additional considerations for clinical pharmacology data to support the demonstration of biosimilarity to a reference product, among other topics.

The European Medicines Agency (EMA) has adopted the approach of issuing biosimilar guidance for specific product classes.[8] Through this approach, the EMA has encouraged open scientific debate about key biosimilarity issues and has released product class-specific guidance documents that aim to provide transparency and clarity to both biosimilar and innovator Sponsors. BIO encourages FDA to consider this approach and to develop vertical guidance for specific classes of products.

CONCLUSION:

BIO appreciates this opportunity to comment on the "Draft Guidance for Industry on Clinical Pharmacology Data to Support a Demonstration of 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/

Andrew W. Womack, Ph.D.
Director, Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)

[8] European Medicines Agency (EMA) Product-specific biosimilar guidelines, available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp#Productspecificbiosimilarguidelines

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SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
II. THE ROLE OF CLINICAL PHARMACOLOGY STUDIES IN THE DEMONSTRATION OF BIOSIMILARITY		
Lines 71-73	BIO believes this statement should be strengthened to reflect that pharmacology data is essential for a demonstration of biosimilarity and, therefore, extrapolation.	BIO requests that FDA revise to read: "Clinical pharmacology data ~~may be~~ is an ~~important~~ essential component of the scientific justification supporting extrapolation of clinical data to one or more additional conditions of use."
Lines 75-77:	BIO believes it is important to state that, in the absence of suitable PD markers, other components of the overall development program may assume an increased relevance for addressing residual uncertainty.	BIO recommends that FDA revise to read: "…overall program for biosimilar product development. In the case where there are no suitable PD markers amenable to clinically relevant pharmacometric analysis, other components of the overall development program may assume an increased relevance for addressing residual uncertainties."
III. CRITICAL CONSIDERATIONS IN THE USE OF CLINICAL PHARMACOLOGY STUDIES TO SUPPORT BIOSIMILARITY		
A. EXPOSURE AND RESPONSE ASSESSMENT TO SUPPORT A DEMONSTRATION OF BIOSIMILARITY		
Line 122:	BIO believes that, when considering the response of a PD marker to dosing, it is also important to assess the duration of response and the return of the PD marker to baseline effect upon discontinuation of dosing.	BIO recommends that FDA revise to read: " • The time of onset of the PD marker relative to dosing, the duration of response, and if feasible and relevant, the return of the PD marker to baseline effect upon discontinuation of dosing"
Lines 122-128:	BIO believes that, when considering the value in including a panel of PD markers, a	BIO recommends FDA revise to read:

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	key criterion to consider is the ability of the panel to further reduce uncertainty relative to individual markers.	" • The relationship between changes in the PD marker and clinical outcomes • The ability of a panel of PD markers to further reduce residual uncertainty, relative to individual markers, according to the preceding criteria"
Lines 130-133:	BIO believes that it is unclear whether all five of the criteria listed in lines 122-128 must be addressed in order to refine the scope of a clinical trials program and that there may be valid scientific reasons for retaining flexibility to refine a clinical program based on PD markers that meet a subset of the criteria (*e.g.*, that the marker is sensitive and an established surrogate marker).	BIO recommends FDA revise to read: "If ~~these criteria are addressed~~ a number of these criteria are met (based on discussions with the Agency), through the submission of…"
B. EVALUATION OF RESIDUAL UNCERTAINTY		
Lines 146-155:	BIO believes that the Agency should offer additional elaboration about circumstances wherein PK and PD data are sufficient to completely assess clinically meaningful differences between products.	BIO recommends FDA revise to read: "…whether or not the study can address these uncertainties. In certain circumstances, human PK and PD data may be sufficient to completely assess clinically meaningful differences between products. In such instances, safety and immunogenicity data from these studies may need to be supplemented by additional evaluations either preapproval or postapproval. Extrapolation of indications from the conditions of use and populations used in the clinical pharmacology studies should be justified scientifically."
C. ASSUMPTIONS ABOUT ANALYTICAL QUALITY AND SIMILARITY		

SECTION	ISSUE	PROPOSED CHANGE
Lines 181-183:	BIO believes it would be valuable to mention the limits of technology to detect measurable analytical similarity between a proposed biosimilar and its reference product.	BIO recommends FDA revise to read: "…methods. Such a strategy can further quantify the overall measurable analytical similarity (acknowledging that some attributes may not be measurable, even with state-of-the-art technology) between two products and may provide a basis for a more selective and targeted approach to subsequent animal and/or clinical studies."
Lines 194-203:	BIO believes the Agency should offer further clarification of appropriate additional studies for determining whether a proposed biosimilar product is, indeed, "highly similar" to its reference product.	BIO recommends FDA revise to read: "…similar to the reference product. Additional data should include sensitive analytical, functional, or pharmacological studies that are proximate to analytical studies in the step-wise development exercise and are capable of addressing whether observed structural differences may be clinically meaningful. If, after completing such additional studies, the evidence continues to suggest that the differences may be clinically meaningful, the product may no longer be considered eligible to be "highly similar." In such a case it would not be appropriate to further extend the scope of "additional studies" to the next stages of development (*e.g.*, clinical efficacy or safety studies)."
Lines 206-210:	BIO believes that the Agency should offer further clarification of what is meant by a "selected and targeted approach."	BIO recommends FDA revise to read: "…demonstration of biosimilarity. Clinical studies that are part of a selected and targeted development program should nonetheless be designed and powered to address any residual uncertainties and to provide a sensitive test of 'no clinically meaningful differences.'"
D. INTEGRITY OF THE BIOANALYTICAL METHODS USED IN PK AND PD STUDIES		

SECTION	ISSUE	PROPOSED CHANGE
Lines 304-305:	BIO believes it would be valuable to clarify how the utility of multiple PD assays should be evaluated in this context.	BIO requests that FDA revise to read: "…multiple complimentary PD assays may be most useful. In this context, the utility of multiple PD assays (where relevant) should be evaluated based on their capabilities to improve sensitivity or specificity, relative to individual PD markers or PK endpoints. Because the PD assay is…"
E. SAFETY AND IMMUNOGENICITY		
Lines 315-316:	BIO believes that consideration of binding antibodies should be included in the discussion of immunogenicity.	BIO recommends that FDA revise to read: "…product that may result in immune-mediated toxicity and/or lack of effectiveness. In addition, binding antibodies may also impact PK or PD endpoints by virtue of either suppressing or enhancing the rate of elimination of the biologic. Even though this effect may not result in toxicity or lack of effectiveness, this possibility should be considered and clinical pharmacology studies should assess the impact of binding antibodies. Safety and…"
Lines 315-319:	BIO believes it should be explicitly stated that single dose studies are generally not adequate for safety and immunogenicity evaluations.	BIO requests that FDA revise to read: "…supplemented by additional evaluations either preapproval or postapproval, as single dose studies are generally not adequate for safety and immunogenicity evaluations. However, as part…"
Line 319:	BIO believes it should be explicitly stated that safety and immunogenicity evaluations should be performed in a "sensitive" patient population that allows appropriate assessment (*i.e.*, an assessment in the early breast cancer population may be more informative than	BIO requests that FDA revise to read: "…supplemented by additional evaluations either preapproval or postapproval. Full safety and immunogenicity evaluations should be performed in a "sensitive" patient population that allows appropriate assessment. However, as part…"

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	in the metastatic breast cancer population, which may not be sensitive due to the immune-compromised state of the patient).	
Lines 329-332:	BIO believes that even if there is not a known immune-mediated toxicity with the reference product, it is still important to develop a neutralizing antibody assay to monitor whether patients develop anti-drug antibodies.	BIO requests that FDA revise to read: "…clinical pharmacology studies.[9] ~~For example, when~~ Even if a reference product is not previously known to have the potential for immune-mediated toxicity, assays capable of detecting binding antibodies (and their neutralizing potential) should be developed in advance to analyze samples obtained from PK and PD studies, so that immunogenicity may be evaluated in real time. Generally, samples can be…"
IV. DEVELOPING CLINICAL PHARMACOLOGY DATA FOR SUPPORTING A DEMONSTRATION OF BIOSIMILARITY		
A. STUDY DESIGN		
Lines 365-367:	BIO recommends that the Agency clarify that the multiple dose PD study is a separate study and not part of the single dose cross-over study.	BIO recommends that FDA revise to read: "For PD similarity assessments, a separate parallel design study using multiple doses may be appropriate when the PD effect is delayed or otherwise not parallel to the single-dose drug PK profile."
D. DOSE SELECTION		
Lines 444-447:	BIO believes that another factor to consider when choosing alternative regimens is the drug's immunogenicity potential, especially if the reference product is known for its potential to generate neutralizing antibodies.	BIO recommends that FDA revise to read: "However, the appropriateness of an alternative dosing regimen will depend on certain factors, e.g., the lower dose is known to have the same effect as the approved dose, ~~or~~ if it is ethically acceptable to give lower doses notwithstanding differences in effect, or the drug's

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		immunogenicity potential, especially if the reference product is known for its potential to generate neutralizing antibodies."
Lines 451-455:	BIO believes that immunogenicity studies should not be precluded by a demonstration of clinical pharmacology similarity between a proposed biosimilar product and its reference product.	BIO recommends that FDA revise to read: "…instances this may complete the clinical evaluation, excluding immunogenicity, and in others it may support a more targeted…"
Line 455:	BIO believes it should be explicitly stated that both PK and PD assessments for the primary study endpoint should have adequate statistical power.	BIO requests that FDA revise to read: "…clinical development program. Both PK and PD assessments for the primary study endpoint should have adequate statistical power."
I. STATISTICAL COMPARISON OF PK AND PD RESULTS		
Lines 529-550:	BIO believes additional clarity on the PK parameters that will be subject to statistical comparison and considered in the context of determining biosimilarity would be helpful for Sponsors.	BIO requests that FDA confirm that additional measures beyond Area Under the Curve (AUC) and C_{max} (the latter only for non-IV administered products) will be taken into consideration — including $C_{min,ss}$ and C_{trough} — and explain how these measures will be evaluated in an overall analysis of biosimilarity.
Lines 541-544:	BIO believes it would be useful for FDA to address confounding variability in PD endpoints measured in the steepest part of the response curve.	BIO recommends that FDA revise to read: "…product. A typical bioequivalence approach with 90% CI of the geometric mean ratios on PD is often not appropriate for PD endpoints due to high variability, particularly in the steepest part of the response curve. In these circumstances, it may be more appropriate to use a modeling approach that utilizes the entire PK/PD curve as discussed below in Section V. There may be situations in which the results of the PK and/or PD study fall outside the…"

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Lines 544-550:	BIO strongly believes that the Agency should strengthen this statement.	BIO recommends that FDA revise to read: "~~There may be situations in which~~ If the results of a PK and/or PD study fall outside of the pre-defined limits, the sponsor should redesign its product and/or study design, as such candidates will be excluded from being approved under the 351(k) pathway. ~~Although such results may suggest existence of underlying differences between the proposed biosimilar product and the reference product that may preclude development under the 351(k) pathway, FDA encourages sponsors to analyze and explain such findings. If such differences do not translate into clinically meaningful differences and the safety, purity and potency of the product are not affected, it may be possible to continue development under the 351(k) pathway.~~"