Biotechnology Industry Organization

July 13, 2015

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

Re: Docket No. FDA–2011-D-0611: Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009; Draft Guidance for Industry

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Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the "Draft Guidance for Industry on Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (May 2015)" ("Q&A Draft Guidance").

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

The implementation of the *Biologics Price Competition and Innovation Act of 2009* (BPCIA) is of significant importance to BIO members, and we appreciate FDA's continued work to implement the Act. We also commend FDA's efforts, through mechanisms such as this Q&A Draft Guidance, to provide crucial insight into the Agency's current thinking on many important aspects of the law. BIO has previously commented on biosimilars issues and appreciates FDA's consideration of our comments.[1] We are pleased to provide

[1]BIO comments on FDA's Draft Guidance for Industry on Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, April 16, 2012, https://www.bio.org/sites/default/files/2012-04-16%20Scientific%20Considerations%20-%20FINAL.pdf

BIO comments on FDA's Draft Guidance for Industry on Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product, April 16, 2012, https://www.bio.org/sites/default/files/2012-04-16%20Biosimilars%20Quality%20Considerations%20-%20FINAL.pdf

BIO comments on FDA Draft Guidance for Industry on Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, April 16, 2012, https://www.bio.org/sites/default/files/2012-04-16%20Biosimilars%20Q&A%20-%20FINAL.pdf

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the following general comments on the Q&A Draft Guidance and also to provide recommendations on additional topics for consideration in future guidance. Specific, detailed comments are included in the chart at the end of this letter.

GENERAL COMMENTS:

One of our main concerns with respect to the Q&A Draft Guidance is the failure to articulate an Agency perspective on the reference product exclusivity provision of BCPIA that is consistent with the operation of the statute. As BIO has previously commented, we strongly urge the Agency to affirm in any final guidance that the BPCIA contains a presumption of statutory reference product exclusivity.[2] The Agency's use of permissive language in the Q&A Draft Guidance ("may" rather than "must") indicates that a sponsor has the option (rather than requirement) of including a request for reference product exclusivity in its initial 351(a) BLA submission; however, we urge the Agency to state definitively that any such request is optional and unnecessary, regardless of submission method or timing, as a new biologic product receives the statutory 12-year exclusivity by operation of statute.

Additionally, the Q&A Draft Guidance notes in the "Background" section that the BPCIA also includes, among other provisions, "[a] transition provision for biological products that have been or will be approved under section 505 of the FD&C Act (21 U.S.C. 355) before March 23, 2020 (see section 7002(e) of the Affordable Care Act)." Under these "transition provisions," biological products approved under applications submitted under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) will be "deemed" licensed under section 351 of the Public Health Service Act (PHS Act) as of March 23, 2020. There are a number of important questions relating to transition biologics that the Agency has yet to answer. For example, what are the scientific standards for approval of a biological product submitted under section 505(b)(2) of the FD&C Act to a reference product that, in 2020, will be deemed a biologic under section 351 of the PHS Act? Should the standards be those applicable to the review and approval of a biosimilar, since eventually the product will be a biosimilar? BIO will be providing the Agency with industry recommendations regarding the implementation of the transition provisions in the near future. Additionally, we request that the Agency provide industry with a list of "transition products" to ensure that both industry and the Agency are in agreement on the products to which the transition provisions are applicable.

Lastly, following the approval of the first biosimilar approved for marketing in the United States earlier this year, BIO notes that there are a number of key issues regarding

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[Footnote 1 continued] BIO Comments on Draft Guidance for Industry: Reference Product Exclusivity for Biological Products filed Under Section 351(a) of the PHS Act, October 6, 2014, https://www.bio.org/sites/default/files/BIO%20Comment%20Letter%20Biological%20Product%20Reference%20Product%20Exclusivity%2010%2006%202014.pdf

[2] BIO Comments on Draft Guidance for Industry: Reference Product Exclusivity for Biological Products filed Under Section 351(a) of the PHS Act.

biosimilars about which the Agency has yet to provide guidance. We strongly encourage the Agency to release, for example, its long-awaited draft guidance documents regarding biosimilar naming, labeling, and interchangeability as soon as possible.

CONCLUSION:

BIO appreciates this opportunity to comment on the "Draft Guidance for Industry on Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (May 2015)." 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/

Scott Van Buren McGoohan, J.D.
Director, Science & Regulatory Affairs
Biotechnology Industry Organization

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
INTRODUCTION		
Lines 17-20 and 57-59	"This guidance provides answers to common questions from sponsors interested in developing proposed biosimilar products, biologics license application (BLA) holders, and other interested parties regarding FDA's interpretation of the Biologics Price Competition and Innovation Act of 2009 (BPCIA)." and "In addition, these Q&As respond to questions the Agency has received from prospective BLA and new drug application (NDA) applicants regarding the appropriate statutory authority under which certain products will be regulated."	The guidance seems to apply more broadly than to 351(k) applicants. For instance, Q.II.3 pertains to a marketing application for a proposed antibody-drug conjugate and does not mention 351(k) or "biosimilar," so it would be reasonable to interpret that this question and answer apples to all BLA and 351(k) applications. If the Agency intends this guidance, or any part thereof, to apply more broadly than to 351(k) applications, the Agency is requested to state, in each question and answer, whether the answer applies beyond 351(k) applications, such as to all BLAs or supplemental BLAs. If not, then the Agency is requested to clarify that the guidance should be read to only apply to 351(k) applications.
I. BIOSIMILARITY OR INTERCHANGEABILITY		
A. Q. I.10. – HOW LONG AND IN WHAT MANNER SHOULD SPONSORS RETAIN RESERVE SAMPLES OF THE BIOLOGICAL PRODUCTS USED IN COMPARATIVE CLINICAL PK AND/OR PD STUDIES INTENDED TO SUPPORT A 351(K) APPLICATION? [REVISED]		
Lines 161-166	"FDA recommends that the sponsor of a proposed biosimilar product retain reserve samples for at least 5 years following a comparative clinical PK and/or PD study of the reference product and the proposed biosimilar product (or other clinical study	The guidance should be clarified with respect to whether it would be sufficient to maintain samples from a representative lot of each product, or whether samples from every lot used in the study should be retained. The guidance states that FDA recommends retaining

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	in which PK or PD samples are collected with the primary objective of assessing PK similarity) that is intended to support a submission under section 351(k) of the PHS Act."	samples for a period of five years following the completion of the trial. BIO encourages FDA to clarify that the storage location can be located at the investigator site(s) or sponsor site(s), depending on the complexity of the study, as long as the storage location meets appropriate expectations. It is acknowledged that the scope of the sample retention requirements is stated as applying to comparative clinical PK and/or PD studies of reference products and proposed biosimilars (or other clinical studies in which PK or PD samples are collected with the primary objective of assessing PK similarity) that are intended to support submissions under section 351(k) of the PHS Act. It is understood from this that the Agency's expectation is that samples should only be retained in studies where the primary endpoint for the trial is intended to demonstrate PK similarity to the reference product, and/or between the differing sources of reference product. In situations where a pivotal safety and efficacy trial in patients is being performed with a PD primary endpoint, or with secondary PK/PD endpoints, it is assumed that retention samples are not required. Clarification on this point would be beneficial. Lastly, the Agency is requested to clarify whether these guidelines for retaining reserve samples also apply to the same types of studies (BE, or PK) conducted for a regular 351(a) application. Are reserve samples required for other biologics studies, other than biosimilars trials, and if so, do these same guidelines apply?

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Lines 174-176	"A minimum of 10 dosage units each of the proposed biosimilar, reference product and, if applicable, comparator product, depending on the amount of product within each unit."	The Agency is requested to clarify whether 10 samples would always be required. Specifically, could a smaller number of containers (perhaps a single container) be sufficient where this provides sufficient material to allow a comprehensive analytical assessment by state of the art methods. It is also unclear whether the samples in a single-site trial are expected to be obtained at the study site, or whether these could be reserved from the supplies provided by the sponsor to facilitate the trial. It is suggested that either option should be acceptable.
Lines 179-183	"For multi-site studies, 3 or more dosage units each of the proposed biosimilar, reference product, and, if applicable, comparator product, at the site where the highest number of patients enrolled, and 1 or more dosage units from the next highest enrolling sites until the minimum recommended total number of retained samples is met."	With respect to sampling in multi-site trials, and depending on the Agency's clarifications on the above points, the suggestion to retain 3 samples of each product from the highest enrolling site then 1 each from each of the next highest enrolling sites may be practically challenging to achieve. In particular, the identity of the highest enrolling sites may not be known until some point during the conduct of the trial, making it practically challenging to put in place the logistics to obtain the samples. In addition, in order to ensure that 3 or 1 sample(s) of each product are obtained from each of these sites, it would be necessary to be unblinded to the identity of the lots being sent to each site, and depending on the size and design of the trial, and the outcome of the randomization, it may not be guaranteed that each of the sites will receive all products being used in the trial. This would particularly be the case where a trial is being conducted in multiple regions, using the reference product available in each region.
B. Q. I.16 - How can a proposed biosimilar product applicant fulfill the requirements for pediatric assessments under the Pediatric Research Equity Act (PREA)? [New]		

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Lines 271-273	"…the term "extrapolation" generally refers to extrapolation from the reference product to the proposed biosimilar product under the BPCI Act…"	The Agency is requested to clarify whether studies based upon a comparator product, rather than a reference product, would be sufficient to satisfy pediatric assessments under PREA, or whether additional studies on the reference product would also be required in order to satisfy such PREA requirements.
C. Q. I.19 - IF A NON-U.S.-LICENSED PRODUCT IS PROPOSED FOR IMPORTATION AND USE IN THE U.S. IN A CLINICAL INVESTIGATION INTENDED TO SUPPORT A PROPOSED BIOSIMILAR DEVELOPMENT PROGRAM (E.G., A BRIDGING CLINICAL PK AND/OR PD STUDY) IS A SEPARATE IND REQUIRED FOR THE NON-U.S.-LICENSED PRODUCT? [NEW]		
Lines 396-399 and 409-411	"No, a sponsor may submit a single IND for its proposed biosimilar developed program and may submit information supporting the proposed clinical investigation with the non-U.S.-licensed comparator product under the same IND." and "A non-U.S.-licensed comparator product is considered an investigational new drug in the United States, and thus would require an IND for importation and use in the United States (see 21 CFR 312.110(a))."	These two statements can be read in such a way as to contradict one another. BIO requests that FDA clarify that a non-U.S.-licensed comparator product is considered an investigational new drug in the United States, and thus would require an IND for importation and use in the United States, but such requirement would be fulfilled by the submission of a single IND for a sponsor's proposed biosimilar development program which includes information supporting the proposed clinical investigation with the non-U.S.-licensed comparator product.

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II. EXCLUSIVITY		
D. Q. III.1. - CAN AN APPLICANT INCLUDE IN ITS 351(A) BLA SUBMISSION A REQUEST FOR REFERENCE PRODUCT EXCLUSIVITY UNDER SECTION 351(K)(7) OF THE PHS ACT?		
Lines 523-526	"An applicant may include in its BLA submission a request for reference product exclusivity under section 351(k)(7) of the PHS Act, and FDA will consider the applicant's assertions regarding the eligibility of its proposed product for exclusivity."	With regard to exclusivity for new BLA submissions, the statute clearly provides 12 years of exclusivity, which must be presumed unless any of the exclusion criteria are met. FDA should make clear that the statute does not require a sponsor to "apply" to the FDA for the exclusivity period for the biologic product, and revise the answer to this question to reflect that although a request for confirmation of reference product exclusivity may be submitted, such request is not required, as a new biologic product receives the statutory 12-year exclusivity by operation of statute.