June 3, 2016

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

Re: Draft Guidance for Industry: Labeling for Biosimilar Products (Docket No. FDA-2016-D-0643 (April 4, 2016))

The Biotechnology Innovation Organization ("BIO") welcomes the opportunity to submit comments on the Food and Drug Administration's ("FDA's") draft guidance entitled "Labeling for Biosimilar Products" issued on April 4, 2016 ("Draft Guidance").

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, 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.

Implementation of the Biologics Price Competition and Innovation Act ("BPCIA") is of significant importance to BIO members, and we greatly appreciate FDA's issuance of the long-awaited draft guidance on labeling of biological products licensed under section 351(k) of the Public Health Service Act (42 U.S.C. 262(k)). BIO is pleased to see the Agency's recognition that a clear statement of biosimilarity provides essential information to inform the safe prescribing and use of biosimilar biological products. However, the proposed biosimilarity statement fails to convey critical information as to whether or not FDA has made a determination of interchangeability with the reference product. The failure to include such information risks creating confusion among prescribers, payers and other stakeholders regarding whether the biosimilar product has been determined to be interchangeable with the reference product.

Furthermore, we have significant concerns about a fundamental premise of FDA's draft recommendations and some of the proposals that ostensibly flow from that premise. In finalizing the Draft Guidance, and in assisting applicants in developing draft labeling for biosimilar products, we strongly urge the agency to consider our comments and to implement the suggested changes.

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I. One Premise of FDA's Labeling Approach is Flawed, and Would Omit Information Essential to Safe and Appropriate Prescribing Decisions

FDA's approach to labeling appears to be grounded in the notion that providing clear and complete information about a biosimilar product is unnecessary and would somehow be misinterpreted by educated prescribers. The guidance emphasizes, therefore, that as a general principle, the labeling of a biosimilar product should not include information about the biosimilar, but instead rely on the data and information pertaining to the reference product. FDA takes the position that including the specific information about the specific biosimilar to which the specific labeling pertains would confuse healthcare providers and potentially impede their ability to safely and effectively prescribe the biosimilar product.

Specifically, FDA opines that "[d]ata from clinical studies designed to support a demonstration of biosimilarity are not likely to be relevant to a health care practitioner's considerations regarding safe and effective use of the biosimilar product and potentially may cause confusion, resulting in an inaccurate understanding of the risk-benefit profile of the product."[1]

To the contrary, BIO and its members believe that complete and transparent prescribing information is essential for the accurate prescribing and dispensing of biosimilar and interchangeable biological products. As BIO has long advocated, the labeling for a biosimilar should flow from the fundamental premise that due to the scientific complexities of biologics, biosimilars are neither expected nor required to be structurally identical to the reference product. [2] In this regard, more information is preferable to less. Providing limited information about the biosimilar product in the labeling for that biosimilar product leaves questions unanswered for healthcare providers in need of information to prescribe safely and effectively for an individual patient, as well as for formulary and other decision makers who rely on the label to determine how the biosimilar will be used. This is particularly the case when multiple biosimilars are approved for the same reference product and each has been approved based upon its own unique biosimilarity data.

The prescribing physician needs to have access to all relevant information, including the relevant nonclinical and clinical data supporting the finding of biosimilarity, and the resulting labeling should be transparent to allow the prescriber to identify whether the described studies were conducted with the biosimilar or reference product. Since each biosimilar is a different and unique "biosimilar" of the reference product, labeling for biosimilars should include essential scientific information specific to the biosimilar product (such as the relevant nonclinical and clinical data supporting a finding of biosimilarity); be informative and accurate; avoid misleading information; have adequate directions for use; and address safety, warnings, and

[1] FDA, Draft Guidance for Industry: Labeling for Biosimilar Products, p. 4 (March 2016).

[2] BIO Comments on FDA Approval Pathway for Biosimilar and Interchangeable Biologics (Docket No. FDA-2010-N-0477), p. 18 (Dec. 2010).

precautions. Specific information would ensure prescribing decisions are made based on scientific and clinical data, rather than erroneous assumptions or guesswork.

In summary, BIO believes that clear and complete labeling is the vehicle for ensuring that healthcare providers and patients are informed of any important distinctions between the licensed uses and characteristics of the reference product and the biosimilar versions of that product from which a prescriber may choose. Moreover, should FDA nevertheless decline to include biosimilar-specific data in biosimilar labeling, it should revise the guidance document to eliminate any suggestion that biosimilar data in all cases is necessarily somehow "confusing" or "irrelevant."

II. Statement of Biosimilarity Should Identify Whether or Not FDA Has Made a Determination of Interchangeability and Any Such Finding

BIO is pleased to see that FDA's proposed biosimilar labeling information includes a clear and prominent statement identifying the product as a biosimilar ("biosimilarity statement"). Notably, however, BIO and its members believe that the proposed biosimilarity statement falls far short of the complete and accurate information needed to ensure appropriate prescribing and use of such product. Absent from FDA's proposed biosimilarity statement is any information to convey whether FDA has made a determination of interchangeability with the reference product. To the contrary, FDA proposed biosimilarity statement reads only:

> "[BIOSIMILAR PRODUCT'S PROPRIETARY NAME (biosimilar product's proper name)] is biosimilar* to [REFERENCE PRODUCT'S PROPRIETARY NAME (reference product's proper name)] for the indications listed. (1)
> …
> *Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product."

In other words, FDA's proposal excerpts the statutory language describing biosimilarity, and omits the statutory language relevant to the additional and appropriately rigorous standard of interchangeability. Given that FDA's labeling approach is largely that used for generic drugs – i.e., a replication of the reference product label – BIO believes that the proposed biosimilarity statement could result in prescribers, payers and other stakeholders erroneously concluding that the biosimilar can be used like a generic and substituted for the reference product, even when FDA has not determined the biosimilar to be interchangeable with the reference product.

The provisions of the BPCIA are clear that the approval criteria for biosimilarity are readily distinct from the standards for establishing interchangeability. Eligibility for approval as a biosimilar is necessary but not sufficient for FDA approval as an interchangeable biologic. In addition to satisfying the approval standards for biosimiliarity, an interchangeability determination requires a demonstration that the product can be "expected to produce the same

clinical result as the reference product in any given patient."[3] These key components of the interchangeability standard illustrate that FDA's proposed biosimilarity statement is incomplete.

The "same clinical result in any given patient" requirement of interchangeability is more rigorous than the "highly similar" and "no clinically meaningful difference" standard for biosimilarity. Yet, when the "highly similar" description of biosimilarity is provided in isolation, as FDA has proposed to do, the reader of the product labeling may infer that the term "biosimilar" is tantamount to "same." This is further compounded by the critical distinction between the more general "no clinically meaningful differences" standard of biosimilarity and the more exacting standard of "same clinical result . . . in any given patient." Moreover, if the biosimilar is a repeat-use product, then the BPCIA requires that the sponsor of an interchangeable product also demonstrate that the "risk in terms of safety or diminished efficacy of alternating tor switching between use of the [biosimilar] biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch."[4]

BIO is concerned that the detailed recitation in the product labeling about what it means to have been approved as a biosimilar without any companion information about whether the product has been determined to be interchangeable with the reference product provides only half of the picture. Because prescribers are familiar with the generic drug paradigm – a paradigm that is distinct from that applicable to biosimilars – they may inappropriately conclude based on the incomplete information provided in the label that the product can be used interchangeably with the reference product. [5]

Notably, FDA itself previously had shared BIO's concern about this risk. In its 2012 draft guidance entitled "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product," FDA recognized that information pertaining to a biosimilar's interchangeability status is "necessary for a health professional to make prescribing decisions."[6] BIO is disappointed that the FDA seems to now have chosen to disregard its prior concerns and the reasonable solution that the Agency had proposed previously.

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[3] 42 U.S.C. § 262(k)(4)(A)(ii) (emphasis added).

[4] 42 U.S.C. § 262(k)(4). Section 351(k) of the Public Health Service Act (42 U.S.C. 262(k)), added by the BPCI Act, sets forth the requirements for an application for a proposed biosimilar product and an application or a supplement for a proposed interchangeable product.

[5] The inclusion in the labeling of information pertaining to interchangeability status will help to mitigate the risk of inadvertent substitution. As FDA has noted previously, inadvertent substitution of non-interchangeable products may create risks for patient health. See, e.g., 80 Fed. Reg. 52224, 52226 (Aug. 28, 2015) (observing, in part, that "[i]nadvertent switching between biological products that have not been shown to be interchangeable may affect immune response.").

[6] FDA, Draft Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, Lines 821-827 (Feb. 2012). FDA later finalized this guidance without the content on labeling. FDA, Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (April 2015).

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BIO and its members urge FDA to reconsider its current proposal, and to revert to its original position that the labeling of a biosimilar should include a clear statement as to whether or not FDA has made a determination of interchangeability with the reference product and to include any such FDA finding. There are several different forms that an interchangeability disclosure could take, and BIO is not wedded to any particular one so long as the information provided is clear and accurate. However, no matter what form the interchangeability disclosure takes, BIO believes that, in addition to including the definition of "biosimilar," FDA should also include the definition of "interchangeable" in any such statement in order to provide a full understanding of the differences between the two regulatory standards.

III. OTHER RECOMMENDATIONS

In addition to BIO's concerns with the general principles espoused in the draft labeling guidance and the absence of an interchangeability statement, BIO has significant concerns with some of the specific recommendations, and also recommends clarification of others.[7]

a. Biosimilar Product Labeling Should Be Consistent With The Format of the Reference Product As It Relates to PLR and PLLR

FDA proposes that the biosimilar product conform to the requirements of the Physician Labeling Rule[8] (PLR) and Pregnancy and Lactation Labeling Final Rule[9] (PLLR), regardless of whether the reference product is required to meet the PLR and PLLR requirements at the time of licensure of the biosimilar product. BIO is concerned that requiring the biosimilar product labeling to conform to content and format requirements which do not apply to its reference product may result in confusion to prescribers and patients.

Moreover, updates to the PLR or PLLR format and content may require input of the reference product sponsor. Therefore, the guidance should provide that the biosimilar label be approved consistent with the same PLLR format and content labeling requirements as applicable currently to the reference product sponsor, and be updated when the reference product label is modified to conform to the new implementation requirements.

Suggested edits to the guidance relevant to this comment are provided in the chart attached to this letter.

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[7] In a joint petition submitted with PhRMA in December 2015, BIO set forth a detailed explication of what it and its members believe should be included in the content of labeling for a biosimilar product to ensure complete and accurate informed decision making by a healthcare provider on behalf of his or her individual patients. (BIO and PhRMA Citizen Petition to U.S. FDA, requesting the Commissioner of Food and Drugs take actions described in Section A with respect to the labeling of biosimilar biological products (Dec. 2015)). Rather than reiterating those positions here, BIO incorporates that Petition by reference.

[8] 21 CFR 201.56(c)(1) and 21 CFR 201.57

[9] 21 CFR 201.57(c)(9)(i)-(iii)

b. Nomenclature Terminology Should be Used Consistently

The Draft Guidance provides definitions for the terms "proper name" and "core name," but uses additional nomenclature to refer to the names by which products may be identified, including "proprietary name" and "product name." In order to provide greater clarity to sponsors of both biosimilar products and reference products alike, FDA should provide definitions for all of these terms, and ensure their consistent use throughout the guidance.

c. Future Draft Guidance for Labeling of Interchangeable Biological Products

BIO appreciates FDA's announcement that it will issue separate draft guidance for the labeling of interchangeable biological products. BIO, therefore, reserves comment on data and information to be included in the labeling for an interchangeable biological product until such time as that draft guidance issues.

d. Line-Specific Additional Comments

Finally, in addition to the more overarching comments discussed above, BIO offers line-specific comments in the following chart.

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Page/Section number	Comment and Rationale	Proposed change (if applicable)
Page 3/line 97	Edit for clarity; insert "biosimilar" between "appropriate" and "product-".	. . . relevant data and information for the reference product labeling, with appropriate biosimilar product specific modifications.
Page 3/line 100-Page 4/line 120	FDA's regulations at 21 CFR 201.57(c)(15) state that the *Clinical Studies* section of the drug label "must discuss those clinical studies that facilitate an understanding of how to use the drug safely and effectively. Ordinarily, this section will describe the studies that support effectiveness for the labeled indications(s), including discussion of study design, population, endpoints, and results, but must not include an encyclopedic listing of all, or even most, studies performed as part of the product's clinical development program." The clinical studies that a biosimilar sponsor submits to FDA as part of the totality of the evidence to show that a biological product is biosimilar to a reference products are the "studies that support effectiveness for the labelled indication(s)" and, therefore, must be discussed in the biosimilar product's label under this regulation. Moreover, FDA's Guidance for Industry, "Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" (January 2006) ("Clinical Studies Section Guidance"), at page 3, explains that "[t]he primary objectives of the CLINICAL STUDIES section is to summarize (1) the evidence supporting effectiveness in the subjects who were studied, (2) the critical design aspects of the studies, including the populations studied and endpoints measured, and (3) the important limitations of the available evidence." This last objective manifests itself in several ways in the typical drug label. For example, it is important in the	Information and data from a clinical study of a proposed biosimilar product should be described in its labeling ~~only~~ when necessary to inform safe and effective use by a health care practitioner. ~~As a general matter, it is FDA's view that biosimilar product labeling should not include a description of these data, given that~~ Although a clinical study supporting the licensure of the biosimilar product generally would not be designed to independently demonstrate the safety and efficacy of the product, but rather to support a demonstration that there are no clinically meaningful differences between the proposed biosimilar product and the reference product for the approved indications~~. Data~~, data from clinical studies designed to support a demonstration of biosimilarity ~~are not likely to be~~may be relevant to a health care practitioner's considerations regarding safe and effective use of the biosimilar product ~~and potentially may cause confusion, resulting in an inaccurate understanding of the risk-benefit profile of the product~~. For example, although the endpoints used in a clinical study intended to support a demonstration of no clinically meaningful differences may not be the same endpoints studied to support approval of the reference product ~~and~~, they may ~~not~~ inform prescribing decisions regarding safety and efficacy. Similarly, there may be rare instances where the subjects in such a study may be healthy volunteers or the condition of use studied may be one for which the

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	description of the study population to "identify important inclusion and exclusion criteria, the demographic characteristics of the studied population, baseline values of any clinically relevant variables important for understanding the treatment effect, and other characteristics of the population that have important implications for the extent to which results can be generalized" (Clinical Studies Section Guidance, page 7). In addition, the clinical studies section is to include the confidence interval and p-value, to allow an understanding of the uncertainty of the treatment effect (Clinical Studies Section Guidance, page 8). In a biosimilarity exercise, clinical studies are intended to address "the nature and extent of residual uncertainty about biosimilarity after conducting structural and functional characterization and, where relevant, animal studies" (Guidance for Industry, "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product" (April 2015) ("Scientific Considerations Guidance")).	reference product is not licensed if, with sufficient data, that population or condition of use is thought to be adequately sensitive to support designing a study to show a demonstration of no clinically meaningful differences. Hence, the patient population may be different than what was studied in the clinical trials that supported safety and effectiveness of the reference product. ~~Accordingly, FDA believes that~~ Including data from such studies in the prescribing information would ~~not~~ be useful for health care practitioners.
Page 4/lines 122-24	We suggest that this conclusory paragraph needs to be modified to conform to the edits suggested for page 3/line 100-page 4/line 120.	Therefore, based on a demonstration of biosimilarity, biosimilar product labeling should include a description of the clinical data that supported safety and efficacy of the reference product as described in the FDA-approved product labeling for the reference product, as well as a description of the clinical data of the biosimilar in any of its approved indications, as may be appropriate.
Page 4/lines 126-31	As stated above, the Draft Guidance states that FDA expects the biosimilar product to conform to the PLR and PLLR regardless of whether the reference product meets the PLR and PLLR requirements. This approach will lead to a dissonant PLLR labeling construct, and such differences could lead to confusion. Therefore, FDA should provide that the biosimilar label be approved consistent with the same	~~As required under 21 CFR 201.56(c)(1), b~~Biosimilar product labeling must meet the content and format requirements of the physician labeling rule (PLR) as described in 21 CFR 201.56(d) and 201.57~~, regardless of~~ when that is the format of the reference product labeling. ~~In addition~~Similarly, biosimilar product labeling must meet the content and format

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	PLLR format and content labeling requirements as applicable currently to the reference product sponsor, and be updated when the reference product label is modified to conform to the new implementation requirements. In those cases when the reference product label is not required to be updated, FDA should provide the reference product sponsor with the opportunity to update its label before the biosimilar is required to, and only require the biosimilar sponsor to update its label before the reference product sponsor does if the reference product sponsor declines to update its label in a timely way. In addition, in those cases when new labeling requirements are being implemented, the reference product sponsor should be given the opportunity to update the product label in accordance with the timeline associated with the new requirement.	requirements of the pregnancy and lactation labeling final rule (PLLR) as described in 21 CFR 201.57(c)(9)(i) through (iii)~~, regardless of whether~~ when the reference product must meet these requirements. Generally, implementation of the new PLLR format and content requirements should only be required when the reference product label is updated to meet these requirements. FDA will provide a reference product sponsor that is not required to update its label to conform to the PLR format with the opportunity to do so before the agency requires the biosimilar label to be updated to the PLR format.
Page 5/line 138	Edit for clarity; insert "biosimilar" between "appropriate" and "product-".	. . . from the reference product labeling, with appropriate biosimilar product specific modifications.
Page 5/line 153	Formulation differences, such as different excipients, would also inform safe and effective use of a biosimilar.	. . . product, which could include differences such as administration, formulation, preparation, storage, or safety . . .
Page 6/line 173-178	The biosimilar product name should also be used in the CLINICAL STUDIES section (in addition to the list of PI sections provided in the Draft Guidance). This use of the biosimilar product name should be limited to those studies conducted by the biosimilar product sponsor and used to demonstrate biosimilarity (as the reference product's proper name should be used when describing the studies conducted by the reference product sponsor).	

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BIO appreciates the opportunity to submit these comments, and we would be happy to provide further input or clarification of these comments, as needed.

Respectfully submitted,

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