May 19, 2017

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

Re: Docket No. FDA-2017-D-0154: Draft Guidance for Industry on Considerations in Demonstrating Interchangeability With a Reference Product (January 18, 2017)

Dear Sir/Madam:

The Biotechnology Innovation Organization ("BIO") welcomes the opportunity to submit comments on the Food and Drug Administration (FDA) draft guidance titled "Considerations in Demonstrating Interchangeability With a Reference Product" issued on January 18, 2017 ("Draft Guidance").[1]

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") remains of significant importance to BIO members. Thus, we greatly appreciate FDA's issuance of the long-awaited draft guidance on demonstrating interchangeability pursuant to section 351(k)(4) of the Public Health Service Act (PHSA) (42 U.S.C. 262(k)(4)).

I. Interchangeability Is an Additional and More Extensive Standard than Biosimilarity

As BIO has reiterated for some time, the licensure criteria for interchangeability are legally and scientifically distinct from the standards for establishing biosimilarity, and consequently demonstrating interchangeability requires an additional, more extensive showing.[2] This additional showing, one not required of a biosimilar applicant, is necessary in order to demonstrate FDA's determination of safety and effectiveness under conditions of use where the product will be dispensed at the pharmacy in substitution for the reference product without the intervention of the health care practitioner who prescribed the reference medication.[3] As such, FDA needs to clearly establish what additional criteria it is applying to demonstrate interchangeability to ensure the proposed interchangeable biological can be expected to have the

[1] 82 Fed. Reg. 5579 (Jan. 18, 2017).
[2] BIO Comment, Docket No. FDA-2010-N-0477, at 15 (Dec. 23, 2010) (BIO 2010 Comments).
[3] See 42 USC 262(i)(3).

"same clinical result in any given patient" and to ensure for products that are administered more than once that the "risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch." In many instances in this Draft Guidance, FDA cites the same criteria for biosimilarity as applying to interchangeability, and it is unclear what additional criteria are being applied for a demonstration of interchangeability.

Biosimilarity is a prerequisite showing for an interchangeability determination; it is a necessary means to interchangeability, not the end. Indeed, the plain language of the PHSA requires an additional, more extensive showing in order for a biological product to be determined to be interchangeable with the reference product. That is, interchangeability is an additional distinct standard than the threshold standard of biosimilarity. FDA's implementation of the interchangeability standard must not conflate the two. To do so would disregard the specific statutory mandate, potentially jeopardizing patients and, ultimately, the success of the carefully deliberated, abbreviated approval pathway created by Congress for biosimilar and interchangeable biological products.

As a legal matter, the different standards are clear from the plain language and structure of the statute. To support a demonstration of interchangeability, section 351(k)(4)(A) of the PHSA requires that a sponsor show that the proposed interchangeable product is: 1) "biosimilar to the reference product" and 2) "can be expected to produce the same clinical result as the reference product in any given patient."[4] In addition, as applied to those biological products expected to be administered more than once to an individual, section 351(k)(4)(B) requires the sponsor to show that the "risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch."

We do have concerns, however, that FDA is not carefully distinguishing between the biosimilarity showing and the more extensive interchangeability showing, which reflects FDA's determination that the product may be substituted without the intervention of the healthcare practitioner. For example, FDA identifies an additional analysis of the data developed in the biosimilarity exercise as the basis for making the "same clinical result in any given patient" showing.[5] While BIO recognizes that some biosimilar sponsors will develop a single data package intended to address the biosimilarity showing and the more extensive interchangeability showing, BIO urges FDA to clarify the guidance to make clear that the two standards will not be conflated.

These separate and additional legal standards codified in the PHSA align with the pressing scientific considerations and complexities presented for biological products. As FDA has long

[4] Emphasis added.

[5] See Draft Interchangeability Guidance at 3 ("The data and information to support a showing that the proposed interchangeable product can be expected to produce the same clinical result as the reference in all of the reference product's licensed conditions of use may vary depending on the nature of the proposed interchangeable product and may include, but need not be limited to, an evaluation of data and information generated to support a demonstration of a biological products biosimilarity…").

recognized, and reiterates in the Draft Guidance, the immunogenicity of biologic therapies may be increased by switching or alternating among products.[6]

Furthermore, as defined in the BPCIA, an FDA determination of interchangeability reflects an assessment that the interchangeable product may be substituted for the reference product without the intervention of the prescriber.[7] Thus, similar to how therapeutically equivalent generic drugs are treated under most State laws, interchangeable products may be subject to automatic substitution by a pharmacist when the criteria specified in those State pharmacy practice laws are satisfied. Given these realities, it is of paramount importance that healthcare providers and patients have maximum confidence that substitution of the interchangeable biological product is as safe and effective as maintaining current therapy on the reference product.

In brief, BIO urges FDA to implement the interchangeability standard in a way that fully captures the critical distinctions between the two standards of biosimilarity and interchangeability.

II. General Principles

A. "Can be Expected to Produce the Same Clinical Result as the Reference Product in Any Given Patient" Standard.

The Draft Guidance states FDA's expectation that "sponsors will submit data and information to support a showing that the proposed interchangeable product can be expected to produce the same clinical result as the reference product *in all of the reference product's licensed conditions of use*."[8] BIO fully agrees that the interchangeability standard must be demonstrated in all of the reference product's licensed conditions of use, though such demonstration can be satisfied through extrapolation with appropriate scientific justification

Moreover, although the Draft Guidance makes clear that a sponsor is permitted to seek licensure for fewer than all conditions of use for which the reference product is licensed, it goes on to recommend that "a sponsor seek licensure for all of the reference product's licensed conditions of use *when possible*."[9] The Draft Guidance does not, however, further discuss the "when possible" qualification. BIO agrees with FDA's recommendation that the expectation should be that licensure will be sought for all conditions of use, with an exception for where a reference product's condition of use is protected by regulatory exclusivity or an existing patent, but that the sponsor will nevertheless demonstrate interchangeability for the condition of use. Accordingly, BIO encourages FDA to strengthen this statement in a way that clarifies more affirmatively that (1) the sponsor of a proposed interchangeable product should generally seek licensure for all conditions of use; and (2) even if actual licensure of that product for one or more conditions of use is blocked by reference product exclusivity or is not sought because of patent protection, the sponsor should demonstrate interchangeability for that condition of use as well.

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[6] *See* Lines 586-588.
[7] *See* 42 U.S.C. § 262(i)(3).
[8] Lines 76-79 (emphasis added).
[9] Lines 116-119 (emphasis added).

B. "Automatic Substitution

Section 351(i) of the PHSA defines an interchangeable biological product as one that "may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product." Accordingly, BIO supports FDA's view, as articulated in the Draft Guidance, that "a proposed interchangeable product with a differently designed presentation than the reference product may raise uncertainty about whether the difference in presentations would impact the ability of end users, including patients or caregivers, to appropriately use the proposed product."[10] Given the public health implications of substitution, BIO supports the Draft Guidance's recommendation that sponsors develop "the proposed presentation to minimize differences between the proposed interchangeable product and the reference product."[11]

Last, BIO believes that confusion still exists among stakeholders regarding the distinct concepts of physician-mediated switching of biosimilar products and pharmacy-level substitution of interchangeable products. In particular, BIO notes that the Draft Guidance does not explicitly state that non-interchangeable biosimilar products should not be substituted at the pharmacy-level. Accordingly, BIO suggests that incorporating the following information from FDA's *Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations* ("Purple Book") into the Background section of the final guidance may be helpful in further educating stakeholders on these differences:

> Healthcare providers can prescribe biosimilar and interchangeable biological products just as they would prescribe other medications. The BPCI Act describes an interchangeable product as a product that may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product. In contrast, FDA expects that a biosimilar product will be specifically prescribed by the healthcare provider and cannot be substituted for a reference product at the pharmacy level.[12]

In addition, and as discussed in Section VII herein, BIO recommends that the labeling of biosimilars and interchangeable biological products also include template language to make this distinction clear.

[10] Lines 686-690.
[11] Lines 693-697.

III. Factors Impacting the Type and Amount of Data and Information Needed to Support a Demonstration of Interchangeability

A. "Fingerprint-like" Analytical Similarity

The Draft Guidance states that "a 'fingerprint-like characterization' may reduce residual uncertainty regarding interchangeability and inform the data and information needed to support a demonstration of interchangeability, which may lead to a more selective and targeted approach to clinical studies necessary to demonstrate interchangeability."[13]

BIO believes that the lack of clarity surrounding the meaning of the concept "fingerprint-like characterization," as well as its proposed relationship to demonstrating interchangeability, creates uncertainty for sponsors developing interchangeable biological products.[14] As BIO has noted in other contexts in which FDA has discussed "fingerprint-like similarity," that term is nowhere defined.[15] BIO urges FDA to clarify the meaning of the term "fingerprint-like characterization," and to provide examples of specific tools, analytical processes, and other ways to demonstrate "fingerprint-like" similarity between the proposed interchangeable product and the reference product. Moreover, BIO asks that FDA describe how it expects these analytic assessments to address residual uncertainty around immunogenicity concerns associated with switching or alternating between the reference and proposed interchangeable biological product. Finally, BIO encourages FDA to provide additional examples illustrating how the Agency intends to apply this concept to potentially reduce the scope and extent of the clinical data package. We would ask that the agency solicit additional scientific input on the issues associated with fingerprint-like characterizations for its consideration.

Last, BIO is also concerned that the Draft Guidance's statements regarding "fingerprint-like" similarity, and its potential role in reducing residual uncertainty, may lead to inaccurate perceptions of the quality, safety, and effectiveness of different interchangeable biological products, depending on how FDA characterizes analytical similarity of the products. Accordingly, BIO recommends that FDA clearly state that a biological product designated as interchangeable is neither superior nor inferior in terms of its quality, safety, or effectiveness than any other biological product regardless of whether there has been a demonstration of "fingerprint-like" similarity. Similarly, BIO also asks FDA to clarify that a demonstration of fingerprint-like similarity, does not mitigate the need for ongoing post-market surveillance and data collection.

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[13] Lines 186-189.

[14] *See* BIO Comment, Docket No. FDA-2014-D-0234, at 1 (Aug. 12, 2014) (commenting that "it is unclear what, if any, implications the classification of 'highly similar with fingerprint-like similarity' would have for biosimilar product development") (BIO 2014 Pharmacology Comments).

[15] *See* BIO Comment, Docket No. FDA-2011-D-0602, at 3 (Apr. 16, 2012) (BIO 2012 Quality Considerations Comments); *see also* BIO Comment, Docket No. FDA-2014-D-0234, at 1 (Aug. 12, 2014) (BIO 2014 Pharmacology Comments).

B. Biosimilar Product Postmarketing Data

As a preliminary matter, BIO notes that section 351(k)(4) of the PHSA provides that FDA's determination of interchangeability is based on "the information submitted in *the application* (or a supplement to such application)."[16] Thus, as a legal matter, BIO does not believe that an applicant is precluded from obtaining an interchangeability designation in an original 351(k) application. BIO agrees, however, with FDA's previous statement that "it would be difficult as a scientific matter for a prospective biosimilar applicant to establish interchangeability in an original 351(k) application given the statutory standard for interchangeability and the sequential nature of that assessment."[17]

For structurally complex biological products, the Draft Guidance suggests that "postmarketing data for the product as a licensed biosimilar, in addition to an appropriately designed switching study [], may provide additional data and information necessary to support a demonstration of interchangeability."[18] The Draft Guidance also states that "where there is residual uncertainty regarding interchangeability based on immunogenicity-related adverse events … a sponsor may need to first obtain licensure as a biosimilar product and collect postmarketing data before interchangeability can be demonstrated."[19] BIO agrees with FDA that postmarketing data collected from use of a licensed biosimilar under real-world conditions would be needed.

Moreover, BIO finds it difficult, as a scientific matter, to imagine a scenario where it would be appropriate at this time for FDA to approve a *complex* biological product, or one with known immunogenicity issues, especially when related to endogenous proteins, as interchangeable in an original 351(k) application. BIO believes such a conclusion is especially required for complex biological products with the potential for immunogenicity, with diverse indications spanning multiple therapeutic areas, and with multiple mechanisms of action.

Current analytical techniques do not have complete clinical predictive value, especially with respect to predicting immunogenicity. Rather, use of a biological product under real-world conditions may be needed to detect any rare immunogenic events that could be caused by switching or alternating. Additionally, such real-world data could be helpful to both FDA and product sponsors in identifying patient populations or use cases where switching presents the greatest concern. Accordingly, BIO concurs with the Draft Guidance's suggestion that "postmarketing data may describe the real-world use of the biosimilar product, including certain safety data related to patient experience with some switching scenarios. Such data may impact residual uncertainty about interchangeability, but do not obviate the need for clinical switching data..."[20]

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[16] Emphasis added.
[17] FDA, Draft Guidance, *Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*, at Lines 221-224 (May. 2015).
[18] Lines 251-257.
[19] Lines 294-297.
[20] Lines 282-286.

IV. Additional Evidence Needed to Demonstrate Interchangeability for Biological Products Expected to be Administered More Than Once to an Individual

A. Switching Studies

Section 351(k)(4)(B) of the PHSA sets forth an additional distinct requirement for licensure of a proposed interchangeable products expected to be "administered more than once to an individual." For such products, the statute requires that applicants further demonstrate that "the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch."[21] To satisfy this additional statutory requirement, the Draft Guidance states "that FDA expects that applications generally will include data from a switching study or studies in one or more appropriate conditions of use."[22] The Draft Guidance recommends that a switching study or studies "should evaluate changes in treatment that result in two or more alternating exposures (switch intervals) to the proposed interchangeable product and to the reference product."[23]

BIO supports the Draft Guidance's position that switching studies should be done to satisfy the "alternating or switching" standard set forth in section 351(k)(4)(B) of the PHSA. However, it is unclear to BIO whether the "two *or more*" language implies that there could be scenarios where additional switches might be needed.[24] Accordingly, we ask that FDA clarify what considerations determine the number of exposure periods a sponsor should include in a switching study. In addition, the Draft Guidance states that the last switch should be from originator to biosimilar with sufficiently long duration to allow for washout of originator.] BIO suggests that FDA further clarify considerations for determining what may constitute a "sufficiently long duration" and how best to ensure a sufficient washout period.

B. Use of a U.S.-Licensed Reference Product in a Switching Study or Studies

The Draft Guidance states that the "us[e] of a non-U.S.-licensed comparator product *generally* would not be appropriate in a switching study."[25] To support this position, FDA explains that use of the U.S.-licensed reference product is appropriate in switching studies because "with switching, multiple exposures to each product can prime the immune system to recognize subtle differences in structural features between products, and the overall immune response could be increased under these conditions."[26]

BIO strongly supports the Draft Guidance's general recommendation that the U.S.-licensed reference product be used in switching studies, as well as the rationale provided by the Agency to support this position. BIO further requests, however, that FDA clarify the circumstances in which the Agency may consider the use of a non-U.S.-licensed comparator product to be

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[21] 42 U.S.C. § 262(k)(4)(B).
[22] Lines 126-127.
[23] Lines 325-327.
[24] Lines 325-327 (emphasis added).
[25] Lines 578-79 (emphasis added).
[26] Lines 586-588.

scientifically justified and to outline more clearly what the Agency's expectations are for scientific justification of use of a non-US-licensed comparator[27]

C. Study Endpoints

The Draft Guidance states that "[t]he primary endpoint in a switching study or studies should assess the impact of switching or alternating between use of the proposed interchangeable product and the reference product on clinical pharmacokinetics and pharmacodynamics (if available), because these assessments are generally most likely to be sensitive to changes in immunogenicity and/or exposure that may arise as a result of alternating or switching."[28]

BIO recognizes that PK and PD assessments can be expected in many circumstances to provide sensitive endpoints useful in evaluating immunogenicity differences between a proposed interchangeable product and the reference product due to switching or alternating. However, BIO notes that, as a scientific matter, PK assessments may not be sensitive to all differences in immunogenicity responses. In particular, structural differences between an interchangeable product and the reference product can drive immunogenicity responses that may not, or may not detectably, affect PK. Indeed, FDA's own guidance document on immunogenicity assessments for therapeutic protein products does not solely rely on PK assessments to address immunogenicity concerns. Rather in assessing immunogenicity responses in a therapeutic protein product, FDA seeks comprehensive assessments of the immunogenicity response.[29] Recognizing that immunogenicity differences between a proposed interchangeable product and the reference product due to switching or alternating require careful evaluation, BIO believes that FDA should clarify the contours of a comprehensive assessment of immunogenicity, including the need to consider alternative approaches when scientifically justified. As part of that clarification, BIO asks FDA to more clearly describe the use of appropriately validated PD markers or efficacy endpoints and the study design and sampling needed for a direct and thorough assessment of immunogenicity.

D. Extrapolation

The Draft Guidance states that if a sponsor submits data and information sufficient to demonstrate interchangeability in an appropriate condition of use, the sponsor "may seek licensure of the proposed product as an interchangeable product for one or more additional conditions of use for which the reference product is licensed."[30] To merit extrapolation, the Draft Guidance states that a sponsor "would need to provide sufficient scientific justification for

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[27] BIO notes that the Draft Guidance describes the use of a non-U.S.-licensed comparator product as "generally" not appropriate.

[28] Lines 358-362.

[29] FDA generally seeks one year of immunogenicity assessment with rigorous immunogenicity sampling—particularly at initiation and early use of a chronic use product and where use results in an adverse event. See FDA, Guidance for Industry, Immunogenicity Assessment for Therapeutic Protein Products, at 6-7 (2014). "Repeat sampling should generally occur over periods of sufficient duration to determine whether these [immunogenicity] responses are persistent, neutralizing, and associated with clinical sequelae." Id. In FDA's biosimilarity guidance, FDA asks sponsors to examine ADA titers, neutralizing activity of ADAs, and the relationship of the immunogenicity response to product function and clinical sequelae. FDA, Guidance for Industry, Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, 17 (2015).

[30] Lines 521-525.

extrapolating data to support a determination of interchangeability for each condition of use for which the reference product is licensed and for which licensure as an interchangeable product is sought."[31] The Draft Guidance proceeds to provide a list of issues that a sponsor should address in its scientific justification for extrapolation.[32]

As a general matter, BIO believes that, as part of the interchangeability determination, an appropriately stringent scientific justification in certain circumstances may permit extrapolation from one to other conditions of use not studied clinically. However, BIO encourages FDA to acknowledge that the scientific justification for extrapolation must be condition-of-use-specific and that the requisite evidentiary showing will vary significantly across conditions of use, including depending on the product's mechanism of action (MOA), disease pathophysiology, site of drug action, concomitant medications and immune status. As such, BIO strongly encourages FDA to articulate with greater specificity examples of the circumstances under which extrapolation may and may not be scientifically justified for purposes of demonstrating interchangeability.

As to the list of considerations provided in the Draft Guidance, BIO notes that they are essentially identical to the factors FDA previously recommended for indication extrapolation in the context of biosimilarity.[33] BIO thus requests that FDA clarify how the evidentiary burden proposed to justify extrapolation scientifically in the context of interchangeability will be different in either scope and extent from the burden for indication extrapolation to demonstrate biosimilarity. As noted at the outset, the statute is very clear that the standard of interchangeability is distinct and more extensive from that of biosimilarity.

Additionally, the Draft Guidance states that "[a]dvanced structural and functional characterization may also provide additional support for the justification for extrapolation."[34] It is unclear to BIO whether FDA is suggesting that the degree of analytical similarity between a proposed product and the reference product is a relevant factor to the scientific justification for extrapolation. Accordingly, BIO requests that FDA clarify how the Agency intends to apply this language.

V. Postmarketing Safety Monitoring Considerations

The Draft Guidance states that "[r]obust postmarketing safety monitoring is an important component in ensuring the safety and effectiveness of biological products, including biosimilar and interchangeable products."[35] BIO agrees that robust post-marketing pharmacovigilance is vital for all biological products, regardless of whether they are an originator, biosimilar, or an interchangeable product. As BIO has noted previously "[r]obust 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 a clinical trials."[36]

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[31] Lines 525-528.
[32] Llines 528-547.
[33] FDA, Final Guidance, *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*, at 21(Apr. 2015) (Scientific Considerations Guidance).
[34] Lines 550-552.
[35] Lines 870-871.
[36] BIO Comment, Docket No. FDA-2010-N-0477, at 17 (Dec. 23, 2010) (BIO 2010 Comments).

VI. Issues Omitted from Draft Guidance that FDA Needs to Address

A. Labeling of Interchangeable Biological Products

FDA's draft guidance on labeling for biosimilar products recommends the inclusion of a "biosimilarity statement" that identifies the product as a biosimilar and describes what is meant by biosimilarity.[37] Noticeably absent from the draft labeling guidance, however, was any discussion of labeling of interchangeable biological products. Instead, the Agency pledged that "[a]ny specific recommendations for labeling for interchangeable biological products, including any interchangeability statement similar to the biosimilarity statement described in this guidance, will be provided in future guidance."[38] BIO believes that FDA should address this important topic in its guidance on interchangeability.

As BIO has explained previously, complete and transparent product information is essential for the accurate prescribing and dispensing of biosimilar and interchangeable biological products.[39] Such information, of necessity, includes whether FDA has made a determination that the biological product is interchangeable with the reference product, and what such a determination means.[40] Indeed, FDA itself has acknowledged previously that information pertaining to a biological product's interchangeability status is necessary for a health professional to make prescribing decisions.[41]

BIO strongly urges FDA to include in the labeling for biosimilars and interchangeable biological products a statement that identifies whether the product has been determined to be interchangeable and a brief description of what such a determination means. We believe that such a statement is critical and that it needs to clearly provide the following information. First, when FDA makes a determination of interchangeability, a statement in the labeling should indicate the reference product and state that a determination of interchangeability: (1) reflects FDA's determination that the substitution of that product for the reference product without the intervention of the prescriber poses no additional safety or efficacy risks to the patient than posed by the reference product; and (2) applies only to that interchangeable biological product and the reference product (i.e., not between that interchangeable product and other biological products determined to be interchangeable with that same reference product).

B. Naming of Interchangeable Biological Products

In FDA's final guidance on naming biological products, the Agency commented that it was "continuing to consider the appropriate suffix format for interchangeable products."[42] BIO believes that the Agency's draft guidance on interchangeability fails to address this topic, and we

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[37] FDA, Draft Guidance, *Labeling for Biosimilar Products*, at 9 (Mar. 2016) (Labeling Guidance).
[38] FDA, Draft Guidance, *Labeling for Biosimilar Products*, at 12 (Mar. 2016) (Labeling Guidance).
[39] BIO Comment, Docket No. FDA-2016-D-0643, at 3 (Jun. 3, 2016) (BIO 2016 Labeling Comments).
[40] BIO Comment, Docket No. FDA-2016-D-0643, at 3-5 (Jun. 3, 2016) (BIO 2016 Labeling Comments).
[41] FDA, Draft Guidance, *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*, at Lines 821-827 (Feb. 2012) (Scientific Considerations Draft Guidance). Note, FDA later finalized this guidance without the content on labeling.
[42] FDA, Final Guidance, *Nonproprietary Naming of Biological Products*, at 1 (Jan. 2017) (Naming Guidance).

urge FDA to do so in the final guidance. In doing so, we further urge that FDA adopt the same naming convention that FDA is applying to all other biologics. Distinguishable suffixes are necessary to support the tracking of product-specific events. A determination of interchangeability does not obviate the need for effective pharmacovigilance practices and the ability to trace adverse events to an individual manufacturer. Moreover, as discussed in Section III.B, BIO notes that most interchangeable biological products are likely to be first licensed as biosimilar products, and, therefore, will already have a distinguishable suffix under FDA's proposed naming convention.

Finally, BIO also believes that such a uniform approach across all biologics, including biosimilar and interchangeable biological products is necessary to avoid inaccurate perceptions of the safety and effectiveness of biological products based on their licensure pathway. If FDA were to recommend that interchangeable biological products share the same suffix as their reference product, or have a different naming convention than biological products approved as biosimilars, this could lead to inaccurate perceptions of superior quality, safety, and effectiveness of interchangeable products as compared with biosimilars.

C. Applicability of Interchangeability Determination to Biosimilar and Reference Product Only

BIO also asks that FDA address the real-world possibility that multiple biological products designated as interchangeable with the same reference product may be marketed simultaneously. It is possible under some state pharmacy laws that, when a reference product is prescribed, a patient could receive a particular interchangeable biological upon one dispensing and a different interchangeable biological upon another dispensing. State pharmacies are accustomed to automatically substituting across generic drugs that have been determined by FDA to be A-rated (i.e., therapeutically equivalent) to the same reference product. Although FDA states in the *Orange Book* that all generic drugs that share such A-ratings are A-rated to each other, FDA needs to make clear that the same is not true for interchangeable biological products. Rather, the statutory and scientific considerations only permit FDA to designate a biological product as being interchangeable with a single reference product. FDA should therefore take steps to help ensure that only an interchangeable biological product and its reference product are subject to automatic pharmacy substitution. At a minimum, FDA should do this through product labeling that makes clear when a particular biological product has or has not been determined interchangeable with a specific reference product, as well as including a clarifying statement in the Purple Book. In addition, maintaining the nomenclature of distinguishable suffixes for all biological products, including interchangeable products, will also help to maintain this important distinction.

D. "Any Given Patient" Standard

Section 351(k)(4)(A)(ii) of the PHSA requires that a sponsor show that a proposed interchangeable product "can be expected to produce the *same clinical result* as the reference product ***in any given patient.***"[43] The "in any given patient" standard is a unique requirement of

[43] PHSA § 351(k)(4)(A) (emphasis added).

the interchangeability determination.[44] As BIO has previously stated, FDA should "focus on the need to rule out any reasonable potential for a different result in any individual patient" when implementing this statutory requirement. [45] We maintain that this is the most reasonable approach. However, should FDA be thinking about implementing the "any given patient" in some other way, BIO urges FDA to clarify its thinking and to identify what proposals included in the Draft Guidance otherwise satisfies the "any given patient" requirement.

While a population-level assessment of bioequivalence may be sufficient in most circumstances, BIO believes that there might be circumstances where there is a science-based rationale for conducting individual rather than population-level testing. In such circumstances, an alternative approach may be necessary to ensure that there is not a subset of patients in which the interchangeable fails to have the same clinical effect as it does in the broader patient population when that patient is switched from the reference product to the interchangeable.[46] Under these circumstances, FDA should consider a statistical approach to assessing bioavailability that gives full meaning to the "any given patient" interchangeability standard and helps to ensure that all patients will experience the same clinical result as the reference when switched or alternated between the reference and interchangeable without the intervention of the health care provider.

VII. Additional Questions Posed in Federal Register

In addition to seeking comments on the Draft Guidance, FDA also invited specific comments on the following topics:[47]

A. Topic #1: Post-approval Manufacturing Changes

Question Posed: With respect to interchangeable products, are there considerations in addition to comparability assessments that FDA should consider in regulating post-approval manufacturing changes of interchangeable products?

BIO believes that this topic poses significant issues that FDA should continue to examine and resolve. To this end, we believe that additional input is necessary from FDA, working with industry, to ensure clear and consistent guidance on this topic.

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[44] 42 U.S.C. § 262(k)(4)(A)(ii).

[45] BIO Comment, Docket No. FDA-2010-N-0477, at 15 (Dec. 23, 2010) (BIO 2010 Comments).

[46] FDA has proposed a statistical approach that considers individual responses to changes in therapy, namely individual bioequivalence (IBE). See FDA, Guidance for Industry, Statistical Approaches to Establishing Bioequivalence, 6-7 (2001). FDA should consider the merit of other possible statistical methods for assessing interchangeability proposed in the scientific literature. See, for example, Tothfalusi, Endrenyi, & Chow, *Statistical and Regulatory Considerations in Assessments of Interchangeability of Biological Drug Products*, Eur J. Health Econ. 15 (Suppl 1):S5–S11 (2014); Shein-Chung Chow, Fuyu Song & Meng Chen, *Some Thoughts on Drug Interchangeability*, J. Biopharm. Stat, 26:1, 178-186 (2015); Jianghao Li & Shein-Chung Chow, *Statistical Evaluation of the Scaled Criterion for Drug Interchangeability*, J. Biopharm. Stat 27:2, 282-292 (2017); Meng Chen & Shein-Chung Chow, *Assessing Bioequivalence and Drug Interchangeability*, J. Biopharm. Stat., 27:2, 272–281 (2017)

[47] 82 Fed. Reg. 5579, 5580 (Jan. 18, 2017).

B. Topic #2: New Conditions of Use (e.g., Indications) Licensed by the Reference Product After Approval of an Interchangeable Product

Question Posed: How, if at all, should the Agency consider conditions of use that are licensed for the reference product after an interchangeable product has been licensed?

BIO recommends that FDA direct sponsors of interchangeable products to submit a supplemental application that provides scientific justification for extrapolating the data from its original application to the new condition of use for which the reference product has been approved. The scientific justification for extrapolation would be the same in this setting as in the context of the initial application, and would be required to be provided within a specified time period after approval of the reference product for that additional indication. Absent appropriately robust scientific justification, clinical data demonstrating that the interchangeability standard has been satisfied for the additional indications would be necessary. Under this unlikely situation, an interchangeable biologic may not be considered interchangeable in all conditions of use approved for the reference product.

For this reason, we also believe that FDA should establish a formal mechanism by which it can reclassify an interchangeable product to a biosimilar should the need arise.

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Respectfully submitted,

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