December 22, 2015

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

CITIZEN PETITION

The Pharmaceutical Research and Manufacturers of America ("PhRMA") and the Biotechnology Industry Organization ("BIO") (collectively, "Petitioners") respectfully submit this petition under section 351 of the Public Health Service Act ("PHSA"), as amended by the Biologics Price Competition and Innovation Act of 2009 ("BPCIA"), 21 C.F.R. § 10.30, and 21 C.F.R. Part 201 to request the Commissioner of Food and Drugs to take the actions described in Section A with respect to the labeling of biosimilar biological products.

A. Actions Requested

Petitioners request that the Food and Drug Administration ("FDA") require that the approved prescription drug labeling for biosimilar biological products licensed under section 351(k) of the PHSA:

1. State that the product has been approved as a biosimilar for stated indications and routes of administration and identify the reference product;

2. Describe the basis of approval for each indication by identifying the relevant data for the reference product and biosimilar that support a finding of biosimilarity; and

3. State whether or not FDA has made a determination of interchangeability with the reference product and include any such FDA finding.

Petitioners also request that FDA promptly issue a guidance document on biosimilar labeling with content that is consistent with this petition.

B. Statement of Grounds

I. Background

PhRMA is a voluntary, nonprofit association that represents the country's leading innovative biopharmaceutical research companies, which are devoted to discovering and developing medicines that enable patients to live longer, healthier, and more productive lives. PhRMA companies are leading the way in the search for new cures, with members investing an

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estimated $51 billion in 2014 in the discovery and development of new medicines. Importantly, many PhRMA members are now researching and developing biosimilar products for use in the United States.

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. Many BIO member companies are researching and developing biosimilar products for use in the United States.

Petitioners supported the enactment of the BPCIA and have actively participated in FDA's ongoing efforts to implement the statute. Petitioners' consideration of issues regarding FDA's approach to biosimilar labeling is guided by their support for:

- **Science-based** implementation of the BPCIA and regulatory decision-making;
- **Patient safety** through effective identification of biologics and robust pharmacovigilance;
- **Healthcare provider and patient choice** in prescribing;
- **Regulatory transparency** that enables stakeholders to understand the basis for regulatory decisions; and
- **Long-term stability of the biosimilar user fee program** through financial transparency, efficiency, and accountability.

As explained below, Petitioners believe that, in order to facilitate patient-centric prescribing and choice, biosimilar labeling should provide appropriate regulatory transparency, including a statement of biosimilarity, a description of the nonclinical and clinical data supporting the biosimilar's approval, a description of the basis of approval for each indication, and a statement regarding whether or not FDA has made a determination of interchangeability with the reference product and the result of that finding. Petitioners believe that the requested approach will facilitate informed prescribing, protect against inadvertent substitution, and promote consistency with domestic and international precedents.

Petitioners also request that FDA's forthcoming draft guidance on biosimilar labeling reflect these principles. Further, we request that FDA develop promptly its biosimilar labeling policy through the public guidance process. This approach will ensure that stakeholders receive notice and an opportunity to comment on FDA's policies on this important topic before they are applied.

II. FDA Should Adopt an Approach to Biosimilar Labeling that Provides Regulatory Transparency to Facilitate Informed Choices by Healthcare Professionals and Patients.

Petitioners request that FDA require biosimilar labeling to include the elements described below in order to provide healthcare professionals (and through them patients) with adequate regulatory transparency and to facilitate informed prescribing choices for patients. Each of these elements would appropriately reflect the differences between biosimilars and generic drugs. Although an abbreviated new drug application must show that the generic and reference drug have the "same" active ingredient,[1] sameness cannot be demonstrated for biosimilars in the current state of science. Further, biosimilars and their reference products might differ with respect to immunogenicity. For these reasons, BPCIA requires the applicant to show that its proposed product is "highly similar to the reference product notwithstanding minor differences in clinically inactive components" and has "no clinically meaningful differences" in safety, purity, and potency from the reference product.[2] In light of these scientific and statutory differences from generic drugs, biosimilar labeling should follow a different model than generic drug labeling, as set forth below.

A. Statement of Biosimilarity.

Petitioners request that FDA require biosimilar labeling to state that the product has been approved as a biosimilar for the stated indications and routes of administration and identify the reference product. As Petitioners have each previously commented to FDA, including this information is critical for doctors to safely and effectively treat their patients.[3] Indeed, FDA recognized that this information is "necessary for a health professional to make prescribing decisions" in its 2012 draft guidance entitled "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product" ("Draft Guidance").[4] Further, in a prescriber survey, 90 percent of surveyed prescribers responded that it was important for biosimilar labeling to clearly indicate that the product is a biosimilar.[5] Because FDA's regulations provide that a medicine's prescribing information must contain "a summary of the essential scientific information needed for the safe and effective use of the drug," biosimilar labeling should include the described statement of biosimilarity.[6] Including a statement of

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[1] *See* Federal Food, Drug, and Cosmetic Act ("FDCA") § 505(j)(4)(C) (requiring FDA to approve an abbreviated new drug application unless, among other things, "information submitted with the application is insufficient to show that the active ingredient is the same as that of the listed drug"); *see also id.* § 505(j)(2)(A)(ii)(I) (requiring an abbreviated new drug application to show that "the active ingredient of the new drug is the same as that of the listed drug").

[2] PHSA § 351(i)(2); *see also id.* § 351(k)(3)(A)(i).

[3] PhRMA Comment, Docket No. FDA-2011-D-0605, at 18-19 (Apr. 16, 2012); BIO Comment, Docket No. FDA-2011-D-0605, at 12-13 (Apr. 16, 2012).

[4] 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 (Apr. 2015). In a letter to Senator Alexander, FDA stated: "FDA did not address labeling issues in [the final guidance] because it was considered outside the scope of that guidance. Instead, FDA expects to issue draft guidance on labeling for biosimilar products in 2015." Letter from Thomas A. Kraus, Associate Commissioner for Legislation, FDA, to Hon. Lamar Alexander, Chairman, Committee on Health, Education, Labor & Pensions, U.S. Senate (June 22, 2015) (Exhibit A).

[5] Kevin Olson, ASBM Labeling Survey (Feb. 2015), http://safebiologics.org/resources/wp-content/uploads/2015/03/February-2015-Labeling-Report.pdf ("ASBM Labeling Survey"), Slide 9 (Exhibit B).

[6] 21 C.F.R. § 201.56(a)(1).

biosimilarity in the labeling also accords with the principles underlying FDA's Transparency Initiative[7] and with the approach adopted by health authorities in the European Union and Canada.[8]

B. Description of Data Supporting Approval.

Petitioners request that FDA require biosimilar labeling to describe the basis of approval for each indication by identifying the relevant data for the reference product and biosimilar that support a finding of biosimilarity and including a description of the basis of approval for each indication. Specifically, biosimilar labeling should include the relevant nonclinical and clinical data supporting the finding of biosimilarity and identify whether the described studies were conducted with the biosimilar or reference product. This approach will ensure that healthcare providers are fully informed when evaluating prescribing options and will avoid misimpressions about the product studied in each trial. A prescriber survey demonstrated that 82 percent and 83 percent of responding physicians deemed it important for biosimilar labeling to describe, respectively, the analytical data and clinical biosimilarity data, if any, submitted to FDA.[9] Seventy-nine percent thought it is important for the labeling to distinguish data generated by the biosimilar and reference product sponsors.[10] Finally, 80 percent of the practicing physicians surveyed deemed it important for biosimilar labeling to clarify which indications were studied by the biosimilar sponsor.[11]

The requested approach accords with FDA's goal, in connection with its Transparency Initiative, to "make information about agency . . . decision-making more transparent, useful, and understandable to the public."[12] As the primary vehicle for communicating essential scientific information to healthcare providers, the prescribing information is the obvious mechanism for informing prescribers about the basis for FDA's approval of a biosimilar for each indication, and it is also the one to which physicians are most likely to turn.

A description of the nonclinical and clinical data supporting approval of a biosimilar is relevant, because FDA may approve different biosimilars on the basis of different information. For example, it may be relevant whether a given biosimilar was approved for the indication for which a physician is prescribing a product based in part on clinical data for the biosimilar in that indication or, instead, was approved without clinical data in that indication for the biosimilar. Indeed, in an analogous situation, FDA has previously approved a section 505(b)(2) application in which the approved labeling contained both the innovator's clinical trial

[7] *See* 74 Fed. Reg. 26712, 26713 (June 3, 2009). The Transparency Initiative is aimed at "making useful and understandable information about FDA activities and decisionmaking more readily available to the public in a timely manner[.]" *Id.*

[8] *See, e.g.*, Health Canada Remsima Product Monograph (Feb. 2015), at 3 ("REMSIMA™ (infliximab) is a subsequent entry biologic product") (Exhibit C); European Medicines Agency, Summary of Product Characteristics for Remsima (last revised Apr. 2015) § 5.1 ("Remsima is a biosimilar medicinal product. Detailed information is available on the website of the European Medicines Agency http://www.ema.europa.eu.") (Exhibit D).

[9] ASBM Labeling Survey, Slides 11, 12.

[10] *Id.*, Slide 16.

[11] *Id.*, Slide 18.

[12] FDA, FDA Transparency Initiative, http://www.fda.gov/AboutFDA/Transparency/TransparencytoRegulatedIndustry/PhaseIIITransparencyReport/FDATransparencyInitiative/default.htm (last visited Dec. 15, 2015).

results as well as some of the follow-on sponsor's clinical data. Petitioners' proposed approach would be consistent with FDA's approach to the labeling of Omnitrope® (somatropin [rDNA origin] for injection), a follow-on protein product approved under a section 505(b)(2) application. The application for Omnitrope referenced Pfizer's listed drug Genotropin® (somatropin [rDNA origin] for injection). The Omnitrope labeling distinguishes the reference product, referring to Genotropin as "*another* somatropin product."[13] A comparable approach is appropriate for biosimilars given their similarities to follow-on protein products approved under the Federal Food, Drug, and Cosmetic Act ("FDCA"). Section 505(b)(2) of the FDCA, like section 351(k) of the PHSA, does not contain a "same labeling" requirement. Moreover, Omnitrope and other somatropin products are subject to the BPCIA's transition provisions.[14] This means that such follow-on products will eventually be subject to approval under section 351(k), suggesting the approach for biosimilar labeling should accord with that applied to Omnitrope.

C. Statement on Interchangeability.

Petitioners request that FDA require biosimilar labeling to state whether or not FDA has made a determination of interchangeability with the reference product and to include any such FDA finding. As with the recommended labeling statement on biosimilarity, FDA previously recognized that this information is "necessary for a health professional to make prescribing decisions" in the Draft Guidance,[15] and Petitioners have previously supported the inclusion of this statement in biosimilar labeling.[16] Further, 79 percent of the surveyed physicians described above indicated that they view as important a statement of interchangeability status in biosimilar labeling.[17]

The inclusion of this statement in biosimilar labeling also will guard against inadvertent substitution. As the agency has previously noted, inadvertent substitution of non-interchangeable products may create risks for patient health.[18] In contrast, applying the same

[13] Omnitrope Prescribing Information, Sections 2.2, 6.2, 8.1, 14 (Oct. 2014) (emphasis added). The 2006 Omnitrope package insert referred to Genotropin as "another somatropin" and also as "somatropin." Omnitrope Prescribing Information, at 2-3, 5-7, 11 (May 2006).

[14] Pub. L. No. 111-148 § 7002(e), 124 Stat. 119, 817 (2010).

[15] *See supra* note 4.

[16] PhRMA Comment, Docket No. FDA-2011-D-0605, at 18-19 (Apr. 16, 2012); BIO Comment, Docket No. FDA-2011-D-0605, at 12-13 (Apr. 16, 2012).

[17] ASBM Labeling Survey, Slide 19.

[18] *See* 80 Fed. Reg. 52224, 52226 (Aug. 28, 2015) ("Inadvertent switching between biological products that have not been shown to be interchangeable may affect immune response. For example, in some instances, immune response to therapeutic proteins may pose safety and efficacy issues. For example, immune responses can lead to significant clinical consequences, such as pure red cell aplasia; inhibition of the efficacy of therapeutics; and reactions, including serum sickness and anaphylaxis. Individual patients can vary in their immune responses to protein products, and these differences can be caused by the same genetic components that have an impact on sensitivity to small changes in structure. Thus, switching or alternating of biological products not determined by FDA to be interchangeable may raise unique safety concerns related to immunogenicity.") (internal citations omitted); 75 Fed. Reg. 61497, 61499 (Oct. 5, 2010) (explaining that, "[i]n the interest of patient safety and for the purpose of pharmacovigilance, the agency must be able to distinguish between a reference product, a related biological product that has not been demonstrated to be biosimilar, a biosimilar product, and an interchangeable product" and seeking comments as to "[w]hat safeguards [it] should…consider to assist the healthcare community when prescribing, administering, and dispensing biological products to prevent unsafe substitution of biological products?"); *see also* Steven Kozlowski, M.D., Janet Woodcock, M.D., Karen Midthun, M.D., and Rachel Behrman Sherman, M.D., M.P.H., *Developing the Nation's Biosimilars Program*, 365 New Eng. J. Med. 385, 388 (2011), *available at* http://www.nejm.org/doi/pdf/10.1056/NEJMp1107285 ("The agency will also develop

labeling approach to these biosimilars could confuse prescribers about whether the biosimilar and reference product are substitutable. In these cases, FDA will not have determined whether the biosimilar "can be expected to produce the same clinical result as the reference product in any given patient" and 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."[19] Application of the same labeling approach to biosimilars nevertheless could suggest to prescribers that a conclusion of substitutability is warranted. A clear statement about whether FDA has determined that the biosimilar is interchangeable with the reference product will help address these concerns.

D. Labeling Changes

Finally, Petitioners believe that, from a patient and healthcare professional perspective, the approach to biosimilar labeling requested in this petition is most appropriate given that biosimilars are similar to, but not the same as, their reference products. After biosimilar approval, additional information about the biosimilar will accumulate through real world use. In addition, a reference product may gain approval for new indications for which a biosimilar will need to be separately approved by FDA. The labeling for reference products and biosimilars thus will need to evolve separately as a matter of public health. Indeed, to protect patients, it is essential that sponsors timely update their labeling to reflect new safety and effectiveness information about the biosimilar or reference product seen in postmarket experience.[20]

III. Petitioners Request that FDA Issue Guidance Reflecting the Above Approach to Biosimilar Labeling.

Because physician labeling is the central mechanism through which FDA and manufacturers communicate authoritative information for safe and effective prescribing of biologics, stakeholders need insight into FDA's biosimilars labeling policy. Petitioners therefore request that FDA promptly issue its planned draft guidance on this topic for public comment.[21] Release of a formal policy document on biosimilar labeling in accordance with good guidance practices will ensure that stakeholders receive notice and an opportunity to comment on FDA's policies on this important topic before they are applied. Petitioners further request that the forthcoming guidance on biosimilar labeling reflect the approaches described in this petition.

C. Environmental Impact

The actions requested in this petition are subject to categorical exclusion under 21 C.F.R. §§ 25.30(h) & 25.31.

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standards to ensure that products not deemed interchangeable are not inadvertently substituted for a reference product without the prescriber's consent.").

[19] PHSA § 351(k)(4).

[20] *E.g.* 21 C.F.R. § 201.56(a)(2) ("In accordance with §§ 314.70 and 601.12 of this chapter, the labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading").

[21] Center for Drug Evaluation and Research, FDA, Guidance Agenda: New & Revised Draft Guidances CDER is Planning to Publish During Calendar Year 2015 (listing "Labeling for Biosimilar Biological Products" as a planned guidance to be published during 2015).

D. Economic Impact

An economic impact statement will be submitted at the request of the Commissioner per 21 C.F.R. § 10.30(b).

E. Certifications

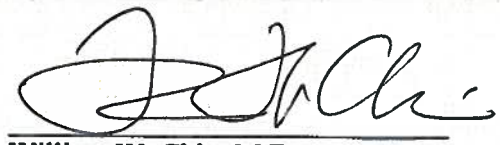
Pursuant to 21 C.F.R. § 10.30(b): The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Petitioners believe that this petition is not subject to section 505(q) of the FDCA, because Petitioners are not asking that FDA take any action that could delay approval of biosimilars.[22] Nonetheless, out of an abundance of caution, and in order to avoid delay if FDA concludes that section 505(q) is applicable, Petitioners are providing the certification required by section 505(q)(1)(H) of the FDCA.

Pursuant to section 505(q)(1)(H) of the FDCA: I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: March 6, 2015 (the date of the first biosimilar approval), April 30, 2015 (publication of final "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product" guidance), June 2, 2015 (posting of citizen petition in Docket No. FDA-2015-P-2000), and June 22, 2015 (date of FDA letter to Senator Alexander). If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: my employer, Pharmaceutical Research and Manufacturers of America (PhRMA signatories) or my employer, Biotechnology Industry Organization (BIO signatories). I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

[22] *See* FDCA § 505(q)(1)(A); FDA, Guidance for Industry: Citizen Petitions and Petitions for Stay of Action Subject to Section 505(q) of the Federal Food, Drug, and Cosmetic Act, at 8 (Nov. 2014) (noting that FDA "interpret[s] section 505(q) to apply only to petitions that request an action that could delay approval of a pending ANDA, 505(b)(2) application, or biosimilar application"). Instead, the actions requested relate to policy issues concerning biosimilar labeling that could be addressed before or after approval of individual biosimilar products.

Respectfully submitted,



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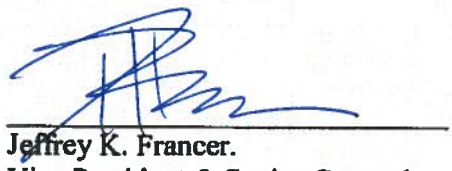

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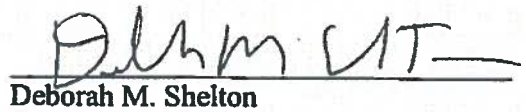

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