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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
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SUPPLEMENT TO CITIZEN PETITION
Docket No. FDA-2015-P-2000

AbbVie Inc. (AbbVie) hereby supplements our June 2, 2015, Citizen Petition regarding biosimilar labeling (Petition). As explained in the Petition, the approach to biosimilar labeling reflected in FDA's March 6, 2015, approval of Zarxio® (filgrastim-sndz), and FDA's April 2015 guidance entitled "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product" (Final Scientific Guidance), is inconsistent with the Biologics Price Competition and Innovation Act of 2009 (BPCIA) and results in biosimilar labeling that omits material information contrary to sections 502(a) and 201(n) of the Federal Food, Drug, and Cosmetic Act (FDCA). The Petition asks FDA to ensure that biosimilar labeling includes the information necessary for informed prescribing to protect and promote the public health, as required by those statutory provisions.

Specifically, the Petition requests that FDA ensure that biosimilar labeling contain:

(a) A clear statement that the product is a biosimilar, that the biosimilar is licensed for fewer than all the reference product's conditions of use (if applicable), and that the biosimilar's licensed conditions of use were based on extrapolation (if applicable);

(b) A clear statement that FDA has not determined that the biosimilar product is interchangeable with the reference product (if applicable); and

(c) A concise description of the pertinent data developed to support licensure of the biosimilar, along with information adequate to enable prescribers to distinguish data derived from studies of the biosimilar from data derived from studies of the reference product.

This supplement provides additional relevant information and addresses events that arose after the Petition was filed. First, contrary to statements that FDA has made to the Senate Committee on Health, Education, Labor, and Pensions (HELP Committee), including some of the information described above in "The Purple Book" cannot cure the material omissions from labeling that result from FDA's current approach to labeling of biosimilar products (Section I). Second, FDA and the Department of Justice (DOJ) recently acknowledged in litigation that it is materially misleading for a prescription drug's labeling to fail to specify when studies pertain to other, non-identical products (Section II). Third, as discussed below in Section III, a diverse group of stakeholders have joined in requesting that FDA ensure that biosimilar labeling include the information set out above.

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I. Senate HELP Committee Correspondence

As noted in the Petition, the Chairman of the Senate HELP Committee, on behalf of himself and eight other Members, sent a letter to the Acting Commissioner on April 30, 2015, regarding FDA's approach to implementing the BPCIA.[1] Among other things, the letter objected that

> [T]he first approved labeling for a biosimilar product—which was approved as biosimilar to, but not interchangeable with, its reference product—contains no statement regarding the product's interchangeability status. Indeed, the label does not even include the word "biosimilar," which could further increase consumer confusion about how this product relates to the reference biologic. And, earlier this week, FDA issued a final version of the 2012 guidance document in which it deleted, without explanation, all discussion of what the labeling should say about a product's interchangeability status. Given FDA's earlier statement in draft guidance that information regarding interchangeability status is "necessary" for health professionals to make prescribing decisions, we are concerned that FDA has made its policy on this issue more uncertain, even while approving the first biosimilar product.[2]

In light of those concerns, the Senators requested that FDA explain the circumstances under which, in FDA's view, it is "necessary for a biosimilar product to disclose in its labeling that it has not been found interchangeable with its reference product (or other products found biosimilar to the same reference product)."[3]

In its June 22, 2015, response, FDA conceded that "health care professionals should have product labeling that includes the essential scientific information necessary to make informed prescribing decisions for their patients."[4] FDA also implicitly recognized, as the Agency had stated in the February 2012 draft guidance,[5] that information "regarding biosimilarity or interchangeability" is needed for informed prescribing decisions.[6] Inexplicably, however, FDA told the HELP Committee that crucial interchangeability information did not need to be included in biosimilar labeling because prescribers could obtain the omitted information from another source:

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[1] Petition at 15 & n.90.

[2] Ltr. to S. Ostroff from L. Alexander et al. (Apr. 30, 2015), http://1.usa.gov/1cC5Hi2.

[3] Id.

[4] Ltr. from T. Kraus to L. Alexander et al., 2 (June 22, 2015) (attached as Exhibit A hereto).

[5] FDA, Draft Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, 20-21 (Feb. 2012).

[6] Exhibit A at 2.

> FDA created the "Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations," which provides this information. The Purple Book enables a user to see whether a biological product has been determined by FDA to be biosimilar to, or interchangeable with, a reference product . . . . Biosimilar and interchangeable biological products will be listed under the reference product to which biosimilarity or interchangeability was demonstrated. Zarxio is identified as a biosimilar product, but not an interchangeable product, in the Purple Book.[7]

In other words, FDA is defending a material omission in the package insert for Zarxio on the ground that the relevant information can be obtained from another, non-labeling source.

The proposition that The Purple Book could cure a material omission in the labeling for a biosimilar is indefensible. FDA regulations explicitly state that prescription drug labeling found "on or within the package" (in other words, the package insert) must contain all of the information that prescribers require to administer the drug to their patients safely and effectively.[8] For decades, FDA, industry, and the medical profession have all understood that package inserts must provide "full disclosure."[9] If information is necessary for prescribing decisions, it must appear in the package insert. That is a foundational principle of FDA law—and one that FDA fought long and hard to vindicate.

At one time, "full disclosure" labeling was not required for new drugs. The package insert requirement grew out of the 1951 amendments to section 503 of the FDCA, which addressed prescription drugs for the first time.[10] Originally, FDA could exempt specific classes of drugs from the package insert requirement if the Agency had concluded that the required directions for use were "commonly known."[11] Between 1953 and 1962, FDA determined that thirty categories of drugs had directions for use that were commonly known, including some that are relatively harmless (e.g., "Water for injection") and some that present serious risks (e.g., "Barbiturates").[12] The exemptions were predicated on the idea that the information needed to administer those drugs had been readily

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[7] Id. at 2-3.

[8] See 21 C.F.R. § 201.100(c)(1) (emphasis added).

[9] 44 Fed. Reg. 37434, 37438 (1979).

[10] See 17 Fed. Reg. 6818 (1952) ("The labeling of the drug (which may include brochures readily available to licensed practitioners) . . . ."); 26 Fed. Reg. 8389 (1961) ("Labeling on or within the package from which the drug is dispensed . . . .").

[11] See 21 C.F.R. § 201.160(a) (1979).

[12] Id. § 201.160(b); see 42 Fed. Reg. 27263, 27263 (1977) (explaining that no products had been added to this list since June 1962).

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available from the "scientific literature," obviating the need for separate package insert-type labeling setting forth dosing information and other use instructions.[13]

After 17 years, however, FDA squarely repudiated that notion, concluding that "full disclosure labeling is needed for the safe and effective use of all drugs."[14] The Agency's experience in the intervening years had confirmed that new information continues to emerge while products are used in clinical practice, requiring modifications to labeling, including to safety language and directions for use. Full disclosure in current labeling was therefore necessary in every case, to ensure that physicians "have the information they need to use drugs safely and effectively."[15] Over the objections of comments submitted on the proposed rule, FDA in 1979 therefore revoked the long-standing exemptions, to ensure that all products would be accompanied by current information necessary for informed prescribing. For FDA to now assert that The Purple Book on its website is adequate to provide information necessary for the safe and effective use of biosimilars is nothing short of breathtaking in view of this history and established law. Such a fundamental change to the means of providing prescribers information critical to the safe and effective use of biological products, we think, would require notice and comment rulemaking.[16]

The Agency's reliance on The Purple Book as an ancillary source of information for prescribers is also curiously irrational, where the primary source of information – the labeling – does not tell prescribers that the product is a biosimilar (and to therefore consult The Purple Book) in the first instance. Perhaps FDA believes that The Purple Book is sufficient because FDA publishes therapeutic equivalence ratings for generic drugs in The Orange Book,[17] and generic drug labeling does not include such ratings. But no analogy to the small-molecule context is appropriate here. Congress declared in section 505(j) of the FDCA that generic and branded drugs are the same and should have, with few exceptions, identical labeling. It follows that the information in The Orange Book simply is not necessary for informed prescribing. The information in The Orange Book is, in fact, used primarily by states, pharmacists, and payors to fulfill other functions. As described in the Petition, however, Congress took a diametrically different approach in the BPCIA. Congress recognized that biosimilars and reference products are not the same, should not be labeled the same, and should not be substituted unless FDA has found that the standards for interchangeability are met. Information regarding interchangeability is therefore information prescribers need to know, particularly as there develops a multi-source environment for biologics, populated by different reference products and multiple biosimilars.

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[13] 17 Fed. Reg. at 6818.

[14] 42 Fed. Reg. at 27264 (emphasis added); see 44 Fed. Reg. 20657 (1979) (final rule).

[15] Id.

[16] See generally 5 U.S.C. § 553. Even if notice and comment were not required, public input in the development of The Purple Book should be provided for pursuant to the Agency's Good Guidance Practices, 21 C.F.R. § 10.115.

[17] Office of Generic Drugs, Approved Drug Products With Therapeutic Equivalence Evaluations (35th ed. 2015), http://1.usa.gov/1ypXL8s.

Finally, even if essential prescribing information could lawfully be supplied through an ancillary government publication, which it cannot, The Purple Book would not be the answer. To begin with, it does not provide all of the information that FDA has described as critical to support informed prescribing decisions.[18] Among other things, it does not identify the indications and routes of administration for which the biological product has been found biosimilar to its reference product, information that the Agency called out as "necessary" in 2012. Further, if for no other reason than format, The Purple Book is not capable of providing the information that prescribers will require in a true multi-source environment. Eventually prescribers will be able to choose among reference products and multiple corresponding biosimilars, each of which may be licensed for a different subset of the reference product's indications and conditions of use, and only some of which may be designated interchangeable. The eight-column spreadsheet currently published as The Purple Book is incapable of portraying what could be a highly complicated landscape of products with varying scopes of biosimilarity and interchangeability. The only way to convey that nuanced information to prescribers is through product-specific disclosures in the labeling of each biosimilar.

II. ***Amarin Pharma, Inc. v. FDA***

We also wish to highlight statements as made by FDA and the Department of Justice (DOJ) in Amarin Pharma, Inc. v. FDA, No. 15-3588 (S.D.N.Y.). In a letter dated June 5, 2015, which was filed with the court on June 8, 2015, the Director of the Center for Drug Evaluation and Research discussed the permissible marketing of the new drug Vascepa® (isocapent ethyl). In relevant part, the letter states:

> [A] communication should not state or imply that studies conducted using products other than Vascepa were studies of Vascepa itself . . . . Rather, to ensure that your communications are not false or misleading, we recommend that they expressly disclose when studies were conducted using products other than Vascepa (in particular when those other products contain active ingredients that are different from the icosapent ethyl—an ester of EPA—that is contained in Vascepa) and that the results of the studies may not be applicable to Vascepa.[19]

Similarly, in a brief filed with the court on June 23, 2015, DOJ (on FDA's behalf) asserted that it would be "misleading for Amarin to suggest or imply . . . that studies using products other than Vascepa were studies of Vascepa itself."[20]

These statements underscore one of the critical shortcomings in FDA's current approach to biosimilar labeling. As explained in the Petition, a biosimilar and its reference product are – like Vascepa

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[18] See Petition § III.C.

[19] Ltr. from J. Woodcock to S. Ketchum, 8 (June 5, 2015), http://bit.ly/1FQ5TSK.

[20] FDA, Mem. of Law in Opp. to Pls. Mot. for Preliminary Injunction, 23 (June 23, 2015), ECF No. 51 in Amarin Pharma, Inc. v. FDA, No. 15-3588 (S.D.N.Y.).

and related products – similar, but not the same active ingredients or products.[21] But, the labeling that FDA approved for Zarxio relies entirely on studies involving a different product without acknowledging that the studies were not conducted with Zarxio. As both FDA and DOJ have now represented to a federal court, a failure to "expressly disclose when studies were conducted using [other] products" is misleading.

III. Stakeholder Support For Distinct Labeling

In the Petition, AbbVie described stakeholder support for our requested actions. As we described in the Petition, according to a recent survey by the Alliance for Safe Biologic Medicines (ASBM), the information that we are asking FDA to require in biosimilar labeling is material to prescribers.[22] The Petition also described a policy statement from the Institute for Patient Access (IfPA) calling for more transparent biosimilar labeling,[23] and a letter to the Acting Commissioner of Food and Drugs signed by eight groups of biological product prescribers criticizing FDA's approach to biosimilar labeling.[24] The Petition also explained that public comments and testimony overwhelmingly supported more transparent biosimilar labeling.[25]

Stakeholder support for more transparent biosimilar labeling continues to grow. AbbVie's position is supported by three recent letters to the Acting Commissioner, an important conference on Capitol Hill, additional survey evidence, and a recent statement from the biosimilar industry.

First, on April 23, 2015, leading pharmacists—including the former presidents of the American Pharmacist Association and the American Society of Health System Pharmacists—sent a letter to the Acting Commissioner asserting that the approved labeling for Zarxio failed to "reflect[] FDA's commitment to patient safety, scientific accuracy, clarity, and transparency."[26] Their letter objected that the labeling for Zarxio failed to "state that it is a biosimilar, or to what product it is similar." It objected, further, that the labeling for Zarxio failed to state whether "FDA has determined the medicine to have met the standard for substitutability." Finally, the pharmacists objected to the failure of the labeling for Zarxio to provide the "clinical or analytical data used to demonstrate similarity to the reference product."[27] The pharmacists concluded that, without this information, "[n]either we, nor our

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[21] See, e.g., Petition at 3-6; see also 21 U.S.C. § 355c(m)(1)-(2) (defining a non-interchangeable biosimilar to be a "new active ingredient").

[22] See Petition at 7-8, 12 & nn. 42 & 69.

[23] See id. at 8 & n.44.

[24] See id. at 8-9, 10, 15 & n.45, 53, 91.

[25] See id. at 19-22 & n.113-136.

[26] Ltr. from P. Schneider, et al. to S. Ostroff, 1 (Apr. 23, 2015), http://bit.ly/1He8ZD2.

[27] Id.

patients, nor their physicians would be able to make informed treatment decisions" based on the labeling alone.[28]

Second, on May 19, 2015, a panel of physicians, advocates, and legislators convened on Capitol Hill under the auspices of the Alliance for Patient Access to discuss biosimilar-related policy issues, including labeling. According to an accompanying Institute for Patient Access policy paper:

> With a few modifications, prescribing information for biosimilars can be more useful for physicians. The prescribing information must clearly state that the product is a biosimilar and indicate whether or not it is therapeutically interchangeable with the original biologic. It must also include safety and effectiveness data obtained specifically with the biosimilar. If information generated from the original biologic is included, it should be clearly stated in the document. This approach would ensure transparency. Moreover, biosimilar prescribing information should specify the patient groups and disease states in which the medication has been tested. These inclusions would give physicians access to the most accurate and pertinent information about the original biologic or the biosimilar their patients receive.[29]

The panelists discussed the importance of assuring that prescribers receive "clear, accurate information about biosimilars to give them confidence in the new drugs," and "the challenges that patients face with drug substitution—and how those challenges are magnified if naming and labeling don't provide clear data or substitutions aren't disclosed in a timely manner."[30]

Third, on June 9, 2015, the Patients for Biologics Safety and Access (PBSA), a national coalition representing more than 20 patient advocacy organizations, sent a letter to the Acting Commissioner raising some of the same concerns set out in the Petition. According to the letter, the Final Scientific Guidance "appear[s] to diminish transparency and patient safety protections" related to biosimilars because it, contrary to the draft guidance, does not provide for the "labeling of biosimilars to identify the product as a biosimilar and to indicate whether or not the biosimilar is interchangeable with the reference product."[31] The PBSA objected to this change, which it said "violates a basic principle of transparency and denies patients important information about their health care."[32]

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[28] Id. at 2.

[29] David Charles & Mary Ann Chapman, Informed Prescribing: Physicians Need Complete And Specific Prescribing Information For Biosimilar Medications, at 2 (May 2015), http://bit.ly/1KNCQCo.

[30] See IfPA, Capitol Hill Panel Explores Need for Transparency with Biosimilar Medicines (May 21, 2015), http://bit.ly/1K5Xnmy.

[31] Ltr. from PBSA to S. Ostroff, 1 (June 9, 2015), http://bit.ly/1S6M5jX.

[32] Id.

Fourth, on June 12, 2015, the Global Healthy Living Foundation (GHLF), which represents more than 80,000 chronically ill patients, sent a letter to the Acting Commissioner urging FDA to require "distinct labeling" for biosimilars as an important patient safeguard.[33] Specifically, the GHLF stated that biosimilar labeling should reflect the biosimilar's own clinical data, "which will enable prescribers to distinguish" between reference product and biosimilar data, thereby helping "physicians and consumers make informed decisions."[34] The GHLF also stated that biosimilar labeling should both disclose the product's interchangeability status and identify the indications approved based on extrapolation.[35]

Fifth, on July 1, 2015, the Coalition of State Rheumatology Organizations (CSRO) issued the results of a survey of roughly 3,000 rheumatologists located throughout the United States.[36] "The survey asked if the FDA should require a biosimilar to have a label that identifies the medication as a biosimilar and convey any important difference between it and the innovator biologic. Nearly 96 percent of respondents answered 'yes.'"[37]

Finally, on July 9, 2015, the Biosimilars Forum—an organization comprising "the majority of companies with the most significant U.S. biosimilars development portfolios"[38]—issued a statement endorsing the fundamental premise of the Petition:

> The lawmakers who passed the Biologics Price Competition and Innovation Act of 2009 (BPCIA) understood that biosimilars are not the same as generic drugs and should not be treated that way in policy making. This is also evident in the multi-tiered system of biologics and biosimilars, with interchangeable and non-interchangeable biosimilars, and the potential for multiple different reference biologics within a therapy as well as the possibility that multiple biosimilars to a single reference product may not share all indications.[39]

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[33] Ltr. from S. Ginsberg to S. Ostroff, 1 (June 12, 2015), http://bit.ly/1JSwhzt.

[34] Id.

[35] Id.

[36] CSRO, CSRO Releases Physician Biosimilars Survey Results (July 1, 2015), http://bit.ly/1RCa9QI.

[37] CSRO, Biologics and Biosimilars: Rheumatologist Perceptions about Standards and Oversight (June 29, 2015), http://bit.ly/1CGcTWC.

[38] Biosimilars Forum, About the Biosimilars Forum, http://bit.ly/1HtPpk9. The founding members of the Biosimilars Forum include Allergan, Amgen, Boehringer Ingelheim, Coherus BioSciences, EMD Serono, Hospira, Merck, Pfizer, Samsung, Sandoz, and Teva. Id.

[39] Biosimilars Forum, Biosimilars Forum Expresses Concern with CMS Proposed Rule on Biosimilar Payment and Coding (July 9, 2015), http://bit.ly/1CseJKq.

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That statement is consistent with the Petition, which also explains that biosimilars are not generic drugs and should not be treated that way in policy making.[40]

* * *

I certify that, to my best knowledge and belief: (a) I have not intentionally delayed submission of this document or its contents; and (b) the information upon which I have based the action requested herein first became known to me on or about April 23, 2015 (pharmacist letter); May 19, 2015 (Capitol Hill panel); June 8, 2015 (Amarin letter); June 9, 2015 (PBSA letter); June 12, 2015 (GHLF letter), June 22, 2015 (HELP letter); June 23, 2015 (Amarin brief); July 1, 2015 (CSRO survey); July 9, 2015 (Biosimilar Forum statement). 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: AbbVie, Inc. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully Submitted,

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[40] See, e.g., Petition at 1 ("Biosimilars are not generic drugs and should not be labeled like generic drugs.").