DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Building #51
Silver Spring, MD 20993

JUL 12 2016

Perry C. Siatis, Vice President, Biotherapeutics and Legal
Neal Parker, Section Head, Legal Regulatory
AbbVie, Inc.
1 Waukegan Road
North Chicago, IL 60064

Meredith Miller
Chief Corporate Governance Officer
UAW Retiree Medical Benefits Trust
P.O. Box 14309
Detroit, MI 48214

William W. Chin, M.D.
Executive Vice President
Scientific and Regulatory Affairs
Pharmaceutical Research and Manufacturers of America
1201 Maryland Avenue, SW, Suite 900
Washington, DC 20024

Kay Holcombe
Senior Vice President for Health Policy
Biotechnology Industry Organization
950 F Street, NW, Suite 300
Washington, DC 20004

Re: Docket Nos. FDA-2015-P-2000, FDA-2015-P-4529, FDA-2015-P-5022

This letter responds to the three above-referenced citizen petitions, each of which requests that the Food and Drug Administration (FDA) take certain actions regarding the labeling of biosimilar products. FDA recently issued draft guidance on this topic entitled *Labeling for Biosimilar Products* and has received over thirty public comments in response as of the date of this letter. Given the subject matter overlap between the comments and the petitions, with the exception of certain requests and legal arguments addressed in Parts II.B and II.C of this response, FDA intends to consider the petitions' requests together with comments received on the draft guidance in connection with finalizing that guidance, and will not separately address the petitions' requests in a petition response.

Accordingly, FDA is denying these petitions and inviting the petitioners to submit any further comments to the docket associated with the draft guidance (FDA-2016-D-0643) in accordance with the procedures set forth in the Federal Register Notice announcing the availability of the

draft guidance.[1] FDA will add these three petitions and this response to the docket associated with the draft guidance. With the exception of the certain specific arguments and requests addressed below in Parts II.B and II.C of this response, FDA's denial of these petitions does not constitute a determination that FDA disagrees with any aspect of these petitions.

I. BACKGROUND

A. The Petitions

On June 2, 2015, AbbVie, Inc., submitted a citizen petition (FDA-2015-P-2000, the AbbVie petition) requesting that FDA require the labeling of biological products licensed under section 351(k) of the Public Health Service Act (PHS Act) to contain (1) a clear statement that the product is a biosimilar, that the biosimilar is licensed for fewer than all of the reference product's conditions of use (if applicable), and that the biosimilar's licensed conditions of use were based on extrapolation (if applicable); (2) a clear statement that FDA has not determined that the biosimilar product is interchangeable with the reference product (if applicable); and (3) 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. The petition further contends that FDA's application of what the petition characterizes as a "same labeling" approach to its approval of the first biosimilar issued a license by FDA, Zarxio (filgrastim-sndz), Biologics License Application (BLA) 125553, was unlawful.

On November 24, 2015, FDA received a citizen petition (FDA-2015-P-4529) from a group of institutional investors including the United Auto Workers (UAW) Retiree Medical Benefits Trust (the UAW petition) requesting that FDA require that all approved prescription drug labeling for biosimilar and interchangeable biological products follow the "same labeling" approach that (according to the petition) the agency applied to Zarxio (filgrastim-sndz), and to hold a Part 15 public hearing on this issue as well as any other related issues being debated by the FDA and connected to biosimilars.[2]

Finally, on December 22, 2015, the Pharmaceutical Research and Manufacturers of America (PhRMA) and the Biotechnology Industry Organization (BIO) submitted a citizen petition (FDA-2015-P-0776, the PhRMA/BIO petition) requesting that FDA require that the approved prescription drug labeling of biological products licensed under section 351(k) of the PHS Act (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 bases 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

[1] 81 FR 19,194 (April 4, 2016). The comment period has been extended to August 3, 2016. See 81 FR 36313 (June 6, 2016).

[2] The petition requested that the Part 15 hearing address (a) the implications of labeling rules for biosimilar innovation and investment in the United States, (b) the European experience with biosimilars, including 'same labeling,' 'patient tracking,' and patient safety; and (c) stakeholder views on how different approaches to labeling may affect prescribing, dispensing, and patient use of biosimilars and interchangeable biologic products. (UAW petition at 2.)

interchangeability with the reference product and include any such FDA finding. The petition also requests that FDA promptly issue a guidance document on biosimilar labeling with content consistent with the petition's other requests.

B. The Draft Guidance

FDA published a draft guidance entitled *Labeling for Biosimilar Products* on March 31, 2016 (the draft biosimilar labeling guidance)[3] outlining FDA's recommendations for biosimilar product labeling. As the draft guidance explains, a demonstration of biosimilarity means, among other things, that FDA has determined that there are no clinically meaningful differences between the proposed product and the reference product in terms of safety, purity and potency. Accordingly, the guidance recommends that biosimilar applicants incorporate relevant data and information from the reference product labeling, with appropriate product-specific modifications. The draft guidance, when finalized, will represent FDA's current thinking on the labeling for biosimilar products. FDA invited comment on the guidance and has received many comments from various stakeholders.

FDA has reviewed and approved the labeling of the two biosimilar products licensed in the United States, Zarxio (filgrastim-sndz) and Inflectra (infliximab-dyyb), BLA 125544. The Agency took these actions on a product-specific basis, and they should not be understood to reflect a broader policy on how biosimilar products should be labeled. FDA is continuing to develop its broader policy on this topic, including its positions on the issues raised in the petitions, in connection with reviewing comments submitted to the biosimilar labeling guidance docket and finalizing that guidance.

C. Applicable Statutory and Regulatory Standards

The Biologics Price Competition and Innovation Act of 2009 (BCPI Act), enacted as part of the Patient Protection and Affordable Care Act (Affordable Care Act) (Pub. L. 111-148) on March 23, 2010, created an abbreviated licensure pathway for biological products demonstrated to be biosimilar to or interchangeable with a reference product. Section 351(k) of the PHS 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 supplement for a proposed interchangeable product.

A prescription biological product, including a biosimilar product, is misbranded if its labeling is false or misleading in any particular (see section 502(a) of the Federal Food, Drug, & Cosmetic Act (FD&C Act); see also 21 CFR 201.56(a)(2)). Labeling can be misleading if it fails to reveal material facts as described at FD&C Act Section 201(n). A prescription biological product is also misbranded if its labeling does not include adequate information for use under which licensed practitioners can use the product safely and for the purposes for which it is intended (see

---

[3] Available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm493439.pdf. This draft guidance, when finalized, will represent FDA's current thinking on this topic.

FD&C Act section 502(f)(1); 21 CFR 201.100(c)(1) & (d)(1)). Likewise, the labeling of a prescription biological product must contain a summary of the essential scientific information needed for the safe and effective use of the product (21 CFR 201.56(a)(1)). The labeling of certain biological products, including all biosimilars, must also meet the content and format requirements of the physician labeling rule (PLR) as described in 21 CFR 201.56(d) and 201.57.

II. DISCUSSION

As discussed in more detail below, with the exception of requests and arguments addressed in sections II.B and II.C, FDA intends to consider the petitions' requests together with comments received on the draft biosimilar labeling guidance in connection with finalizing that guidance.

A. FDA Will Consider the Petitioners' Requests in Connection with Finalizing the Biosimilar Labeling Guidance

As described in section I.A, the AbbVie, PhRMA/BIO, and UAW petitions each request that FDA take certain actions regarding the labeling of biosimilar products. As described in section I.B, FDA recently issued draft guidance on this topic (the biosimilar labeling guidance) and has received many public comments in response. Given the subject matter overlap between the draft biosimilar labeling guidance, the comments to that draft guidance, and the petitions, with the exception of certain requests and legal arguments addressed in section II.B and II.C of this response, FDA intends to consider the petitions' requests together with comments received on the draft guidance in connection with finalizing that guidance, and will not separately address the petitions' requests in a petition response.

FDA's decision to address the petitions in this manner will permit FDA to more efficiently finalize the biosimilar labeling guidance and, in doing so, consider and address the issues raised in the petitions. FDA will give the petitions' requests and arguments careful and thorough consideration during this process. FDA further invites the petitioners to submit any further requests or comments regarding the content of biosimilar labeling to the docket associated with the draft guidance (FDA-2016-D-0643).

B. Request for Public Hearing in UAW Petition

The UAW petition requests that FDA hold a Part 15 public hearing to address, among other things, the petition's request that FDA employ a "same labeling" approach to biosimilar labeling. (UAW petition at 2.) FDA denies the request to hold such a hearing as doing so would be administratively burdensome and would unnecessarily delay development and publication of the final version of the biosimilar labeling guidance. FDA will carefully consider all comments submitted to the docket associated with the draft biosimilar labeling guidance.

C. Legal Arguments in AbbVie Petition

In its petition, AbbVie argues that FDA's application of a "same labeling" approach to its approval of the first biosimilar, Zarxio (filgrastim-sndz), was unlawful. In particular, AbbVie argues that Congress' omission of a "same labeling" requirement for biosimilars in the BPCIA

was intended to foreclose this approach for biosimilar labeling. (AbbVie petition at 5.) AbbVie also argues that a non-interchangeable biologic is a "different therapeutic agent," and a same-labeling approach therefore is unlawful, because the BPCIA amended the FD&C Act to state that a non-interchangeable biological product is "a new active ingredient" for purposes of the Pediatric Research Equity Act (PREA). (AbbVie petition at 6.) Finally, AbbVie argues that a "same labeling" approach would create "serious misbranding issues" under the FD&C Act and FDA's regulations by making biosimilar labeling false or misleading. (AbbVie petition at 7-18.)

AbbVie's arguments that FDA applied a "same labeling" approach to the Zarxio (filgrastim-sndz) approved labeling lack merit. FDA does not believe that the "same labeling" requirement for abbreviated new drug applications described in section 505(j) of the FD&C Act applies to products licensed under section 351(k) of the PHS Act. Rather, FDA follows the applicable statutory and regulatory requirements to biosimilar labeling, which include the requirement that the prescription drug labeling described in 21 CFR 201.100(d) "contain a summary of the essential scientific information needed for the safe and effective use of the drug."[4] As described in the draft biosimilars labeling guidance, the agency's finding of safety and effectiveness for the reference product, as reflected in its FDA-approved prescribing information, may be relied upon to provide health care practitioners with the essential scientific information needed to facilitate prescribing decisions for the proposed biosimilar product's labeled conditions of use. Nevertheless, it may be appropriate to make certain product-specific modifications in the biosimilar's prescribing information. Further, FDA's current thinking is that the labeling of a biosimilar product should include a biosimilarity statement in the Highlights of Prescribing Information (Highlights) that explains that the product is biosimilar to its reference product.

FDA makes decisions about the appropriate content of drug labeling, including biosimilar labeling, on a product-by-product basis. Although the prescribing information for Zarxio (filgrastim-sndz) and Inflectra (infliximab-dyyb) closely resemble the prescribing information for their reference products in many key aspects, those similarities reflect the relevance of certain information in the reference product labeling to the biosimilar product, as well as the further consideration that biosimilar product labeling that is consistent with the reference product labeling to the extent appropriate should more clearly convey FDA's conclusion that the two products are highly similar and that there are no clinically meaningful differences between the products. Such similarities do not mean that FDA applied a "same labeling" approach.[5] Further,

---

[4] 21 CFR 201.56(a)(1).

[5] We note that AbbVie points to meeting minutes and correspondence made available in the action package for Zarxio (filgrastim-sndz) and the transcript of a press briefing to argue that FDA applied a "same labeling" approach to the Zarxio labeling. See AbbVie CP at 2-3. These statements describe an approach to ensuring that the presentation of information in the biosimilar product labeling is consistent with the format of the approved labeling of the reference product, and indicate FDA staff's view that the labeling of Zarxio should incorporate relevant data and information from the reference product labeling. See Ltr. from Ann T. Farrell, M.D., to John M. Pakulski, R.Ph, 6 (Feb. 6, 2015) ("We recommend that you incorporate relevant data and information from the reference product labeling, with appropriate product-specific modifications, in your draft proposed labeling. You may use this PLR format labeling as a template to facilitate a consistent approach to your draft proposed PLR format labeling. Submit to your BLA annotated labeling that describes the areas where your proposed labeling differs from the approved Neupogen labeling. Please also submit your proposed labeling in tracked changes where the areas that differ are noted."). These statements do not describe a "same labeling" approach or requirement.

contrary to AbbVie's argument, nothing in the PHS Act prohibits the labeling of a biosimilar product and a reference product from containing identical content where appropriate.[6]

AbbVie also argues that FDA violated the Administrative Procedure Act by issuing a draft guidance for industry, "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product" ("Scientific Considerations Guidance") that recommended certain statements in biosimilar labeling, then approving Zarxio with labeling that did not feature those statements, and subsequently finalizing the Scientific Considerations Guidance without these recommendations. (AbbVie petition at 18.) The crux of AbbVie's argument is that FDA arbitrarily and capriciously engaged in a "reverse course" on its biosimilar labeling policy without explanation. (AbbVie petition at 22.)[7]

FDA finalized the Scientific Considerations Guidance without addressing biosimilar labeling because we intended to issue separate draft guidance on this specific topic, which we did by issuing the draft biosimilar labeling guidance in March of this year. FDA has followed and will continue to follow its good guidance practices in developing, issuing, and finalizing this guidance,[8] giving the public the opportunity to review and comment upon the Agency's proposed recommendations. During that process, FDA has made, and will continue to make decisions regarding the labeling of specific biosimilar products on a product-by-product basis, but these decisions made pending finalization of the biosimilar labeling guidance should not be understood to reflect a broader policy on biosimilar labeling. Thus, contrary to AbbVie's assertions, FDA has neither adopted nor abandoned a policy on biosimilar labeling.

III. CONCLUSION

For the reasons explained above, the AbbVie, PhRMA/BIO, and UAW petitions are denied.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

Peter W. Marks, M.D., PhD
Director
Center for Biologics Evaluation and Research

[6] The BPCIA's silence on labeling should not be viewed as a rejection of one labeling approach over another. See, e.g., Jama v. Immigration & Customs Enforcement, 543 U.S. 335, 341 (2005) ("We do not lightly assume that Congress has omitted from its adopted text requirements that it nonetheless intends to apply . . . ."). Rather, this silence preserves FDA's discretion to apply the existing requirements that apply to biological product labeling (described above) in a manner consistent with the agency's scientific judgment.

[7] We note that FDA's guidance documents, such as the one at issue here, do not establish legally enforceable rights or responsibilities, and they do not legally bind the public or FDA. 21 CFR 10.115(d)(1). Instead, they set forth the agency's current thinking on matters such as policy, statutory or regulatory interpretation, and scientific issues. See 21 CFR 10.115(c)-(d).

[8] See 21 CFR 10.115(g) (setting forth procedures for developing and issuing guidance documents).