JAN 17 2017

Perry Siatis
Vice President, Biotherapeutics and Legal
AbbVie, Inc.
1 Waukegan Road
North Chicago, IL 60064

Re: Docket No. FDA-2015-P-4935

Dear Mr. Siatis:

This letter responds to the citizen petition that you submitted to the Food and Drug Administration (FDA or the Agency) on December 17, 2015 on behalf of AbbVie, Inc. (AbbVie). In the Petition, you ask FDA to "ensure that applicants seeking interchangeability determinations meet the 'Safety Standards for Determining Interchangeability' set forth in [Public Health Service Act (PHS Act)] PHSA section 351(k)(4) with respect to *each* condition of use for which the reference product is licensed, regardless of whether the applicant intends to label its product for every such condition of use."[1] AbbVie further requests that FDA "clarify that the statutory standards for establishing interchangeability differ in both kind and scope from the standard for establishing biosimilarity."[2] In addition, "AbbVie asks FDA to convene a Part 15 hearing to obtain public input on the topic," and "then issue guidance or regulations that address this important public health issue."[3]

We have carefully considered the information submitted in the Petition and the comments to this docket.[4] For the reasons stated below, the Petition is denied.

I. BACKGROUND

Section 351(k) of the PHS Act (42 U.S.C. 262(k)), added by the Biologics Price Competition and Innovation Act (BPCI Act), sets forth the requirements for an application for a proposed biosimilar product and an application or a supplement for a proposed interchangeable product. Section 351(k)(4) of the PHS Act further provides that upon review of an application submitted under section 351(k) or any supplement to such an application, FDA will determine the biological product to be interchangeable with the reference product if FDA determines that the information submitted in the application or the supplement is sufficient

[1] Petition at 1.
[2] Id.
[3] Id. at 2.
[4] Sandoz, a Novartis company, submitted a comment on March 23, 2016. The Generic Pharmaceutical Association GPhA and the Biosimilars Council submitted a comment on April 14, 2016.

to show that the biological product "is biosimilar to the reference product," and "can be expected to produce the same clinical result as the reference product in any given patient,"[5] and that "for a biological product that is administered more than once to an individual, 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."[6]

Section 351(i) of the PHS Act states that the terms *interchangeable* or *interchangeability*, in reference to a biological product that is shown to meet the standards described in section 351(k)(4) of the PHS Act, means that "the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product."[7]

II. SUMMARY OF THE PETITION

In the Petition, AbbVie asserts that FDA should "consider that interchangeability determinations for biological products are, like therapeutic equivalence ratings assigned to generic small molecule drugs, intended to facilitate pharmacy substitution of lower-cost follow-on products for their respective reference products without the intervention of the prescribers."[8] The Petition also contends that biological products differ from small molecule drugs in at least two respects relevant to interchangeability: that "biological products present significant risks of immunogenicity, affecting both patient safety and product efficacy," and that "one biological product cannot be the 'same' as another" because "proteins are typically more complex [than small molecule drugs] and unlikely to be shown to be structurally identical to the reference product."[9]

Based on these asserted differences and the descriptions of these differences in the Petition, AbbVie concludes that "FDA should not find a biosimilar biological product interchangeable with a reference product unless the agency has found the two products interchangeable for *every* condition of use for which the reference product is licensed, regardless of how the interchangeable biological product is labeled."[10] According to the Petition, state laws governing pharmacy substitution of biological products assume that "an interchangeable biological product is functionally the same as a generic drug — it is therapeutically equivalent for all uses" and "FDA therefore needs to ensure that biological products listed as substitutable are *in fact* interchangeable for all indications and conditions of use for which the reference product is labeled and might be prescribed."[11]

The Petition also contends, among other things, that the PHS Act requires that "any applicant seeking an interchangeability determination must demonstrate interchangeability for every approved reference product condition of use."[12] Further, AbbVie states that "because it is juxtaposed with 'the reference product,' the phrase 'any given patient' must be understood to mean all patients for whom the reference product is known, stated, or specified."[13] In support of its interpretation, the Petition also points to differences between the standards for biosimilarity in section 351(k)(2)(A) and interchangeability in section

[5] Section 351(k)(4)(A) of the PHS Act.
[6] Section 351(k)(4)(B) of the PHS Act.
[7] The terms interchangeable or interchangeability in this response have the same meaning as defined in section 351(i)(3) of the PHS Act.
[8] Petition at 2.
[9] Id. at 2 - 3.
[10] Id. at 3.
[11] Id. at 11.
[12] Id. at 14.
[13] Id.

351(k)(4)(A). Based on the differences between these two paragraphs, as analyzed in the Petition, AbbVie asserts that "Sections (k)(4)(A) and (k)(2)(A) must be harmonized, and the most logical harmonized reading is that a biosimilarity license permits a demonstration in only one condition of use, while an interchangeability determination requires that every condition of use be addressed."[14] According to the Petition, this interpretation is consistent with the legislative history of the BPCI Act.[15]

The Petition also asserts that "[t]he requirement to take into consideration all conditions of use approved for the reference product in making interchangeability determinations means that FDA will need to consider the impact of changes made to either the reference product or the interchangeable biological product after an interchangeability determination has issued."[16] AbbVie contends that "a previously issued interchangeability determination should not be disturbed absent significant scientific questions regarding the continuing validity of the determination following a product change," which, according to the Petition, "should be a rare occurrence."[17] The Petition states that "a previously issued interchangeability determination for a biological product should not be altered unless a manufacturing change or a new condition of use raises significant scientific questions (that were not answered satisfactorily) about the continuing validity of the determination."[18] In addition, the Petition makes certain assertions with respect to differences between the standards for demonstrating biosimilarity and for demonstrating interchangeability.[19]

III. DISCUSSION

The Petition asks FDA to take three actions: (1) to "ensure that applicants seeking interchangeability determinations under the BPCIA meet the 'Safety Standards for Determining Interchangeability' set forth in PHSA section 351(k)(4) with respect to *each* condition of use for which the reference product is licensed, regardless of whether the applicant intends to label its product for every such condition of use";[20] (2) "to clarify that the statutory standards for establishing interchangeability differ in both kind and scope from the standard for establishing biosimilarity"; and (3) "to convene a Part 15 hearing to obtain public input on the topic . . . and then issue guidance or regulations that address this important public health issue."[21]

On January 17, 2017, FDA published the draft guidance *Considerations in Demonstrating Interchangeability with a Reference Product.* We encourage AbbVie to participate in FDA's guidance development process by reviewing the guidance and submitting any comments to the public docket number FDA-2017-D-0154 on http://regulations.gov. FDA intends to consider issues related to interchangeability in the context of the public docket opened for comment on the draft guidance. Further, at this time, FDA does not intend to hold a public hearing or public meeting concerning the draft guidance. The Agency does not believe that such a hearing is necessary at this time given the other mechanisms at stakeholders' disposal to interact with FDA on this issue, including submission of comments on the recently published draft guidance.

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[14] Id. at 13.
[15] Id. at 14-15.
[16] Id. at 15.
[17] Id.
[18] Id..
[19] Id. at 15-18.
[20] Petition at 1.
[21] Id. at 2.

IV. CONCLUSION

For the reasons described in this response, the Petition is denied.

Sincerely,

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