Genentech
A Member of the Roche Group

August 27, 2015

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

Re: Docket No. FDA-2015-P-2000

Dear Sir or Madam:

Genentech, Inc. (Genentech) submits these comments generally supporting the above-referenced Citizen Petition of AbbVie Inc. (AbbVie) and its requests for enhanced transparency in biosimilar labeling (AbbVie Petition). Genentech agrees with AbbVie's position that the unique characteristics of biosimilars—especially their unique approval standard and immunogenicity risks in comparison with those of generic drugs—necessitate a distinct labeling approach; in particular, Genentech agrees that the "same" labeling approach for generic drugs is not fitting for biosimilars.

Specifically, Genentech recommends that FDA adopt a policy in which biosimilar labeling: (1) state that the product is a biosimilar to an identified reference product; (2) state whether or not FDA has determined that the biosimilar is interchangeable with the reference product; and (3) describe the design of the key studies on which the biosimilarity determination was based and transparently identify the studied drug when describing clinical studies of the reference product sponsor. In addition, Genentech recommends that biosimilar and reference product labeling be updated independently over the products' life cycles, to reflect product-specific postmarket pharmacovigilance data as well as differences due to manufacturing changes. We believe that the described approach will best reflect that a biosimilar is highly similar to—rather than the same as—the reference product and will assure that biosimilar labeling provides all necessary information to enable informed treatment decisions and ensure the safe and effective use of biosimilars.

Genentech also recommends that FDA timely issue its planned draft guidance on biosimilar labeling. The guidance process will permit meaningful public comment on the agency's revised biosimilar labeling policy. We share AbbVie's concern that FDA changed its views on biosimilar labeling from those described in 2012 draft guidance without providing an opportunity for stakeholders to comment on those changes in advance of approval actions. Genentech believes that the guidance process will permit meaningful public comment on the agency's new overarching policy on biosimilar labeling and urges FDA to begin this process as soon as possible. Given the public health significance of labeling in communicating critical information to physicians and in informing treatment decisions, clear guidance on the agency's policy for biosimilar labeling is crucial for manufacturers, physicians, and patients.

I. Background

A. The Unique Characteristics of Biosimilars Require a Different Approach to Labeling Than For Generic Drugs.

Biologics and chemically synthesized drugs are fundamentally different. Biological products have far more complex structures. They also are more heterogeneous and sensitive to small process changes, owing to their manufacture in living cells and the complexity of their manufacturing processes. As a result, biologics cannot be demonstrated to be the "same" as other biologics in the current state of science. In addition, by their nature, biologics have a much greater potential than small molecule drugs to elicit unwanted immune responses that may pose significant risks to patients.

In light of these important differences between biologics and small molecule drugs, Congress created different approval pathways for biosimilars and generic drugs. Generic drugs must be shown to be chemically the "same" as their reference listed drugs (RLDs) and bioequivalent to those RLDs.[1] Consistent with this demonstration of "sameness," the statute generally requires generic drugs to have the same labeling as their RLDs.[2] By contrast, a biosimilar is licensed based on a showing that the product is highly similar to, and has no clinically meaningful differences from, a licensed reference product.[3] This showing is made through a stepwise process involving structural and functional studies, animal studies, and clinical studies that may assess pharmacokinetics, pharmacodynamics, immunogenicity, safety, and/or effectiveness.[4] The statutory pathway for licensure of biosimilars lacks a same labeling requirement.

In light of these scientific and statutory differences, Genentech recommends that FDA refrain from applying the generic drug labeling model to biosimilars and adopt an approach to biosimilar labeling that is transparent and tailored to the unique features of biosimilars. Our proposed approach would reflect the scientific reality that a biosimilar is not the same as its reference product. It also is apt given that biosimilar development programs will be tailored to each individual biosimilar. For example, one biosimilar manufacturer may rely heavily on analytical studies for approval, whereas another may rely more heavily on clinical data.[5] Moreover, biosimilar applicants are unlikely to directly compare their biosimilars to

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[1] Federal Food, Drug and Cosmetic Act (FDCA) § 505(j)(2)(A)(ii)(I)-(II), 21 U.S.C. § 355(j)(2)(A)(ii)(I)-(II).

[2] FDCA § 505(j)(2)(A)(v) & (j)(4)(G), 21 U.S.C. § 355(j)(2)(A)(v) & (j)(4)(G).

[3] Public Health Service Act (PHSA) § 351(i)(2), 42 U.S.C. § 262(i)(2).

[4] PHSA § 351(k)(2)(A)(i), 42 U.S.C. § 262(k)(2)(A)(i); FDA, Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (April 2015) (Final Scientific Considerations Guidance).

[5] *See* Final Scientific Considerations Guidance at 7 ("The more comprehensive and robust the comparative structural and functional characterization . . . the more useful such characterization will be in determining what additional studies may be needed. For example, rigorous structural and functional comparisons that show minimal or no difference between the proposed product and the reference product will strengthen (continued...)

other biosimilars of the same reference product. In other words, just because Biosimilar A and Biosimilar B have both been proven biosimilar to Reference Product X, these biosimilars might not be proven biosimilar to one another. Instead, there could be clinically meaningful differences between Biosimilar A and Biosimilar B. Our proposed approach to biosimilar labeling is most consistent with these realities.

The suggested approach also best reflects that the biosimilar and reference product labeling will need to be updated separately throughout the products' life cycles. Individual biosimilars might be associated with different adverse events (e.g., immunogenic events) in the postmarket phase than the reference product or other biosimilars of the particular reference product. Moreover, both reference product and biosimilar manufacturers may make manufacturing process changes after initial biosimilar approval, causing the biosimilar and reference product to have different efficacy and safety profiles over time. Because each manufacturer should be responsible for updating its own labeling to reflect changes due to post-approval process changes and pharmacovigilance findings, a same labeling approach will be particularly inappropriate over the life cycle of biosimilars.

B. Scientific and Public Health Considerations Favor Transparent Biosimilar Labeling.

Transparent biosimilar labeling is critical to ensuring informed prescribing decisions and assuring the safe and effective use of biosimilars. As FDA has recognized, the prescribing information is the primary mechanism through which FDA and manufacturers communicate essential scientific information about a biologic to health care professionals.[6] The central role of the prescribing information will be effectively maintained only if product labeling continues to include clear, accurate, and complete information necessary for physicians to make educated prescribing decisions.

At present, healthcare professionals might be unaware of the differences between biosimilars and generic drugs, given that the first biosimilar has been approved only recently. Transparent biosimilar labeling is needed to allow physicians to develop a better understanding of this new class of products and promote acceptance of biosimilars. As described further below, transparent biosimilar labeling also will help avoid unintended substitution.

II. FDA Should Require Transparent Biosimilar Labeling That Includes the Disclosure of Relevant Information Related to the Biosimilar and to the Reference Product.

Genentech supports AbbVie's request for transparent biosimilar labeling that discloses important information about both the reference product and the biosimilar. Specifically, Genentech recommends that FDA require biosimilar labeling to: (1) identify the product as a biosimilar to an specified reference product, (2) clearly state whether or not the

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the scientific justification for a selective and targeted approach to animal and/or clinical testing to support a demonstration of biosimilarity.").

[6] 21 C.F.R. § 201.56(a)(1) ("The labeling must contain a summary of the essential scientific information needed for the safe and effective use of the drug").

biosimilar has been found interchangeable with the reference product, (3) transparently identify, in the Clinical Studies section of the labeling, the studies that were conducted with the reference product to support its approval; (4) include a description of the key studies on which the biosimilarity determination was based, and (5) reflect the postmarket information specific to the biosimilar.

A. FDA Should Require Biosimilar Labeling to Identify the Product as a Biosimilar.

Genentech agrees with AbbVie that biosimilar labeling should disclose that the product is a biosimilar. Genentech also recommends that this statement identify the reference product by proprietary and nonproprietary name. We agree with FDA's view, articulated in draft guidance published in 2012, that this information is "necessary for a health professional to make prescribing decisions."[7] Identifying the product as a biosimilar will alert physicians to consult other aspects of the labeling, as described below, to understand the data supporting the biosimilar and whether the biosimilar is interchangeable with the reference product.

Genentech also shares AbbVie's belief that the indications section of the biosimilar labeling should clearly identify the indications for which the biosimilar was approved. Listing only those indications for which the biosimilar is licensed is most consistent with prescribers' expectations and enables informed treatment decisions. Instead of requiring the Indications and Usage section to state that the biosimilar is licensed for fewer than all reference product indications (where applicable), however, Genentech recommends that the Clinical Studies section of the labeling describe the indications in which the biosimilar *was* studied, as well as the design of those studies. This description will implicitly disclose those indications for which licensure was based on extrapolation.

B. FDA Should Require Biosimilar Labeling to Include a Clear Statement Regarding Interchangeability or Lack Thereof.

Genentech agrees that biosimilar labeling should state whether (or not) FDA has determined that a biosimilar is interchangeable with the reference product. Omitting information on interchangeability from biosimilar labeling might prompt prescribers to conclude that the biosimilar has been shown interchangeable when it has not, leading to unintended substitution. This misimpression is especially likely if the biosimilar labeling otherwise is the same as that of the reference product.

Specifically, Genentech recommends that labeling for biosimilars that have not been determined interchangeable include the following text in the Warnings and Precautions section of the labeling: "Substitution by any other biological product requires the consent of the prescribing physician. Caution should be taken because [no/limited] switching data are available to support interchangeability of [brand name biosimilar] with the reference product or another biosimilar to the same reference product."

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[7] FDA, Draft Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference product (Feb. 2012) at 21 (Draft Scientific Considerations Guidance).

Including a statement on interchangeability in biosimilar labeling is consistent with FDA's prior recognition that communicating a biosimilar's interchangeability status is critical.[8] It is also in accord with FDA's previously articulated concerns about the potential patient safety risks of inadvertently switching patients between non-interchangeable products.[9] Whereas FDA will have determined that patients may safely and effectively alternate between a reference product and its interchangeable biosimilar, no such assurance will exist with ordinary biosimilars. Therefore, a clear indication of the biosimilar or interchangeable status in the labeling is an important tool in helping prescribers know when switching a patient is appropriate and supported by data. Finally, to maximize prescriber convenience and understanding of whether a particular product is substitutable for the reference product, information on interchangeability should appear in the document that FDA has identified as the primary mechanism for communicating critical information to prescribers: the product labeling.

C. FDA Should Require Biosimilar Labeling to Explain That the Clinical Data Are Derived from Studies of the Reference Product and that the Product is Biosimilar to the Reference Product Based on Comparative Studies.

Genentech agrees that the Clinical Studies section of biosimilar labeling should identify the specific product(s) studied in each described trial. We believe this approach is most transparent and will avoid confusion about the source of data discussed. We also recommend that the labeling explain that a biosimilar is approved based on a showing that it is highly similar to, and has no clinically meaningful differences from, the reference product. This approach best reflects the unique regulatory pathway of biosimilars and the fact that their approval is based, in part, on the fact of FDA's prior licensure of the reference product as safe, pure, and potent.

Genentech generally recommends that in describing pharmacokinetics, immunogenicity, safety, and efficacy, the biosimilar labeling include: (1) a statement that, based on a biosimilarity study (with a description of the study design), the biosimilar product has been shown to have no clinically meaningful differences from the reference product in the specific attribute (pharmacokinetics, immunogenicity, safety, or efficacy); and (2) the data available for the reference product for that attribute (as included in the reference product labeling), with a clear introductory statement noting that the data were generated with the reference product. For example, Genentech recommends that the Clinical Studies section of the labeling include:

- A statement that biosimilarity to the reference product was demonstrated in a comparative study or studies with a description of the study design (which would describe the indication/population studied, the primary endpoints, and whether the study was designed as an equivalence or non-inferiority study);

- A statement that, based on these study results, the biosimilar has no clinically meaningful differences from the reference product in terms of effectiveness;

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[8] *See id.* at 21.

[9] *See, e.g.*, 75 Fed. Reg. (October 5, 2010) (seeking public comment on the following question: "What safeguards should the agency consider to assist the healthcare community when prescribing, administering, and dispensing biological products to prevent unsafe substitution of biological products?").

- A statement that the effectiveness profile of the reference product previously was established; and

- Restatement of the Clinical Studies section of the reference product labeling (for the indications for which the biosimilar is approved) that clearly identifies the reference product by proprietary and nonproprietary name.

Similar information would be included in each applicable section (e.g. pharmacokinetics, immunogenicity) of the labeling.

D. Biosimilar Labeling Should be Updated Independently from the Reference Product Labeling.

For two reasons, Genentech recommends that FDA require biosimilar and reference product sponsors to update and maintain their labeling separately. First, this approach will allow the labeling to account for differences in postmarket pharmacovigilance findings with respect to each product. For example, rare, but potentially serious, safety risks might not be detected during abbreviated preapproval clinical testing of biosimilars. If biosimilar-specific safety signals are observed in the postmarket phase, the biosimilar labeling should be promptly updated so doctors have all relevant information to make prescribing decisions. Second, separate updates are appropriate in light of the distinct life cycles of the biosimilar and reference product. Both products will change over time as they undergo post-approval manufacturing changes, potentially causing their safety and efficacy profiles to "drift" apart in the postmarket phase. The described approach will ensure that biologic product labeling provides prescribers with up-to-date, product-specific information that is necessary for the safe and effective use of the biologic.

III. FDA Should Publish Guidance on Biosimilar Labeling and Engage Stakeholders in the Development of its Policy on Biosimilar Labeling.

Genentech shares AbbVie's concern that FDA recently changed its position on biosimilar labeling without explaining this change or soliciting public comment on the agency's new position. As the AbbVie Petition notes, in a February 2012 draft guidance, FDA stated that biosimilar labeling "should include all the information necessary for a health professional to make prescribing decisions, including a clear statement advising that: This product is approved as biosimilar to a reference product for stated indications(s) and route of administration(s). This product (has or has not) been determined to be interchangeable with the reference product."[10] FDA's position on biosimilar labeling received broad public support across manufacturers, health care professionals and patient advocates.

Nevertheless, in March 2015, FDA approved the labeling of the first biosimilar without these statements and without explaining why they were omitted.[11] The labeling also did not explain that the pharmacokinetic, safety, efficacy, and immunogenicity data described in the

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[10] Draft Scientific Considerations Guidance at 21.

[11] Zarxio Prescribing Information (Mar. 2015).

labeling were developed with the reference product rather than the biosimilar. In April 2015, FDA finalized the above draft guidance without the discussion on labeling without explaining the omission.[12] In a June 2015 letter responding to questions from U.S. Senator Lamar Alexander, FDA stated that it deleted the labeling discussion because it was considered outside the scope of the particular guidance and noted that the agency has created the Purple Book to provide information on whether a biosimilar is an interchangeable product.[13]

Genentech is concerned by the process used to implement the agency's change in position and the fact that FDA is approving biosimilar labeling without articulating the agency's biosimilar labeling policy or providing an opportunity for public comment on that policy.[14] Consistent with FDA's commitment to transparency and its good guidance practices, Genentech urges FDA to timely issue its planned draft guidance on biosimilar labeling to allow stakeholder input on the agency's policy on biosimilar labeling going forward. Clear guidance on these issues is necessary for manufacturers, physicians, and patients, given the public health significance of labeling in communicating information to physicians and in the treatment decisions that result from those communications.

IV. Conclusion

Genentech generally supports the AbbVie Petition and recommends that FDA adopt a transparent labeling approach for biosimilars that reflects their unique scientific characteristics and statutory approval pathway. Specifically, Genentech recommends that FDA adopt a policy in which biosimilar labeling: (1) states that the product is a biosimilar to an identified reference product; (2) states whether or not FDA has determined that the biosimilar is interchangeable with the reference product; and (3) describes the design of the key biosimilarity studies and transparently identifies the studied drug when referring to clinical studies that supported approval of the reference product. In addition, Genentech recommends that biosimilar labeling be updated independently of the reference product labeling. Genentech believes that this policy best reflects the scientific and regulatory characteristics of biosimilars as highly similar to, rather than the same as, the reference product and provides the information necessary to enable informed treatment decisions and ensure the safe and effective use of biosimilars. Genentech also recommends that FDA promptly issue its planned draft guidance on biosimilar to permit meaningful public comment on the agency's overarching policy on biosimilar labeling.

V. Verification

Pursuant to 21 U.S.C. § 355(q)(1)(I): I certify that, to my best knowledge and belief: (a) I have not intentionally delayed submission of this document or its contents; and (b)

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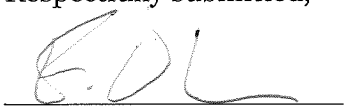
[12] Final Scientific Considerations Guidance.

[13] Letter from Thomas A. Kraus, Associate Commissioner for Legislation, Food and Drug Administration to Honorable Lamar Alexander, Chairman, Committee on health, Education, Labor and Pension, United States Senate (June 22, 2015) at 3.

[14] FDA has stated that it intends to issue a draft guidance document on biosimilar labeling in 2015, but this guidance has not yet been issued. *Id.*

the information upon which I have based the action requested herein first became known to me on or about March 6 (the date of the first biosimilar approval), April 30 (publication of final Scientific Considerations guidance), June 3 (posting of AbbVie citizen petition on regulations.gov), 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, Genentech, 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,



Eric Olson
Vice President
U.S. Product Development
Regulatory