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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Subject: DOCKET NO. FDA-2015-P-2000

Transparent labeling of biosimilars

Dear Sir or Madam:

Amgen is pleased to have the opportunity to offer comments regarding the appropriate framework for labeling of biosimilars in the United States, as put forth in the Citizen Petition from AbbVie.¹

As a developer and manufacturer of innovative and biosimilar medicines, Amgen has a keen appreciation for the role of product labeling in the use of medicines. Not only is the product label intended to provide the information that a prescriber would need to make an informed prescribing decision, but the label also serves as an important source of information for formulary decisions. Just as the practice of medicine is an exercise in medical judgment and reasonable experts can differ on a recommended course of treatment, so too can individual prescribers or formulary committee members differ in what they consider relevant for clinical decision making. Particularly as the nascent biosimilars market in the US is formed, we believe transparent labeling will advance stakeholders' understanding of biosimilars and thereby increase public confidence in these medicines, an essential precursor to robust uptake of biosimilars.

For the reasons set forth herein, Amgen supports the policy approach that AbbVie advocates in its Citizen Petition. We thus respectfully urge FDA to promulgate a labeling policy that begins with transparency, supports consumer confidence, and facilitates appropriate use.

- 1. Biosimilar labels should include a clear statement that either (a) the product is approved as a biosimilar but not designated as interchangeable or (b) the product is approved as interchangeable with the reference product**

A thorough understanding of what biosimilars are and are not is essential to appropriate use and consumer confidence in these medicines. One source of confusion with the US law is the concept of biosimilarity as distinct from interchangeability. The generic drug paradigm is the dominant point of reference for most prescribers and patients; generic drugs are required by law to have the same active ingredient, and the vast majority of generics are determined by FDA to be therapeutically

¹ Docket no. FDA-2015-P-2000 (AbbVie CP).

equivalent.² However, biosimilar active substances are neither expected nor required to be structurally identical to their reference products, and equivalent bioavailability is not a sufficient condition for biosimilarity, let alone interchangeability. Instead, the law establishes a separate standard and designation of interchangeability for products that are demonstrated to be sufficiently similar to the reference product to be substituted for the reference product without the intervention of the prescriber.³ There is a steep learning curve for American prescribers and patients with regard to the significant differences between the concepts “biosimilar” and “interchangeable” as it relates to biologic medicines. Indeed, FDA has needed to publicly explain the differences between biosimilarity and interchangeability at the EP2006 ODAC⁴ and during the FDA media briefing after approval of Zarxio.⁵

The status of a product as biosimilar or interchangeable is important for the safe treatment of patients. While both biosimilar and interchangeable products will be safe and effective options for patients, only interchangeable products will have been evaluated and deemed by FDA to be safe and effective for a patient to experience multiple switches. The generic drug experience is instructive in this context, as patients may receive a different generic of a drug with each refill. Such repeated switching among different products is deemed safe for generic drugs; such switching is not appropriate for biosimilars, in part because the relationship between the reference product and the biosimilar does not imply a relationship between two biosimilars to the same reference product. Indeed, absent information that a biosimilar is interchangeable with the prescribed biological product—and thus has been approved for repeated switching between the reference and the interchangeable product—prescribers must direct product changes from one biologic to another. A clear indication of the biosimilar or interchangeable status on the label is a critical tool in helping prescribers know what is appropriate and supported by data.

Identifying the biosimilarity/interchangeability status of a product only in the *Purple Book* is not sufficient to ensure this important information is readily accessible to prescribers. In order to effectively communicate to a stakeholder group, communication should use the language and medium common to that constituency. Although *pharmacists* commonly use the *Orange Book* (the generic drug resource that is comparable to the *Purple Book*), *physicians* do not. In fact, many physicians are not aware of the Orange Book or its purpose and therefore are unlikely to look for a similar resource for biologic medicines. A more robust, failsafe solution is needed to convey the biosimilar or interchangeable status to prescribers. An explicit designation of biosimilarity or interchangeability on the label can serve to notify prescribers of this distinction and to inform prescribing decisions.

² FDA, *Approved Drug Products with Therapeutic Equivalence Evaluations* (the “Orange Book”), Introduction, at vii states that “FDA classifies as **therapeutically equivalent** those products that meet the following general criteria: (1) they are approved as safe and effective; (2) they are **pharmaceutical equivalents** in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity; (3) they are **bioequivalent** in that (a) they do not present a known or potential bioequivalence problem, and they meet an acceptable in vitro standard, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard...” (emphasis added) Available at

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf> (accessed 7/16/2015).

³ 42 U.S.C. §§ 262(k)(4)(A) and 262(k)(4)(B).

⁴ FDA CDER ODAC Meeting Transcript, at 60 (starting at line 15). Available at

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM436387.pdf> (accessed 7/16/2015).

⁵ FDA Media Briefing: First Biosimilar Approval in the United States, at 17. Available at

<http://www.fda.gov/downloads/NewsEvents/Newsroom/MediaTranscripts/UCM437548.pdf> (accessed 7/16/2015).

Furthermore, because most biologic medicines are dispensed in settings outside of a retail pharmacy (e.g., hospitals, clinics), when more than one biologic is available, a discussion between physicians and other members of the care team (e.g., pharmacists, formulary committee members) regarding which biologic medicine should be administered to an individual patient may occur. The omission of a clear statement of biosimilarity or interchangeability on the label will hinder the prescriber's informed engagement with other members of the care team.

As AbbVie has articulated, physician survey data and statements from multiple organizations of physician specialties that routinely treat patients with biologics support the need for including a statement on the biosimilarity or interchangeability status in the product label. Indeed, as stated by senior FDA staff, "Recognition that two products are biosimilar will give clinicians far more information than the mere knowledge that they were developed for the same indication."⁶ FDA's current position that, "The purpose of Highlights is to provide immediate access to the information to which practitioners most commonly refer and regard as most important"⁷ and, "Highlights should be a concise, informative summary of crucial prescribing information"⁸ further supports a statement of biosimilarity/interchangeability in the label, and specifically the Highlights section, as a necessary tool for clinicians to reference. Physicians are asking for label transparency, and providing that transparency will ultimately help foster confidence. As a developer of biosimilars, Amgen is committed to supporting robust understanding of and confidence in biosimilars; transparency in labels will advance this effort.

2. Clinical data generated by the reference product sponsor should be clearly identified as such

As AbbVie asserts⁹ in its petition, the generic construct for labeling biosimilars risks confusion due to the ambiguity in the source of the clinical data presented in the biosimilar label. In the generic drug context, it is well understood that there are no safety/efficacy data¹⁰ generated in patients by the sponsor of the generic, and thus the data on the label must have come from clinical studies with the brand. The biosimilar approval process stands in sharp contrast: because biosimilars are neither expected nor required to be structurally identical to the reference product, any structural differences must be interrogated and clinical data are likely to be generated. It is reasonable to anticipate that the clinical data from head-to-head studies supporting a determination of equivalent efficacy and non-inferior safety and immunogenicity will be of interest to prescribers. The existence (or potential existence) of data related to a biosimilar approval makes the source of the data on the label ambiguous unless such data are clearly identified. Lack of clear identification around the source of the data is confusing at best and could potentially be construed as misleading or otherwise misinterpreted. Consequently, the lack of transparency could undermine confidence in biosimilars overall, inadvertently deterring uptake. Identifying data in a clear and easily understandable manner is consistent with sound scientific practices and facilitates informed medical judgment.

As a developer of biosimilars, Amgen believes including pivotal clinical data in a biosimilar label and clearly identifying its source as distinct from the reference product data will foster confidence in the biosimilar paradigm. Practically speaking, when healthcare providers have an understanding of biosimilar development requirements and approval standards, transparent labeling can be expected

⁶ Kozlowski et al. Developing the Nation's Biosimilar Program. N Engl J Med 2011; 365:385-388 [August 4, 2011](#).

⁷ FDA, *Guidance for Industry on Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements*, at 6. Available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075082.pdf> (accessed 7/16/2015).

⁸ *Id.*

⁹ AbbVie CP, at 15-16.

¹⁰ Rather, if *in vivo* data are generated by a sponsor of a therapeutically equivalent generic, such data are to support a bioequivalence determination.

to provide prescribers with all they need to make confident choices among biosimilars and support their appropriate uses.

3. Clinical data generated by a biosimilar sponsor need to be referable

Amgen recognizes that label transparency, including the clear identification of clinical data generated with the biosimilar, is a more complex exercise than simply inserting additional data or titles in a reference product label. As a biosimilar manufacturer, Amgen is also aware that in the context of biosimilars, more clinical data are not necessarily “better.”

Biosimilars are new to US prescribers, and it is reasonable to expect that prescribers will want to understand the basis of FDA’s approval. A prescriber could ask, for instance, how a biosimilar was studied; this legitimate scientific question is harder to address in a meaningful way if these data are not in the label.

Parallel-arm clinical studies that have a single transition from the reference product to the biosimilar candidate are being conducted by some biosimilar manufacturers.¹¹ This testing addresses the likely medical question regarding the safety implication of a single transition for patients who are currently responding to the reference product. Prescribers may consider data generated by these studies relevant to their choosing the biosimilar for broader use than with solely naïve patients. Society benefits from a single transition study because outstanding questions are resolved rather than postponed for consideration after product approval; adoption of biosimilars in the market is thereby facilitated. Notably, however, this benefit can only be fully realized if the transition data are included on the label.

As a developer of biosimilars with over 30 years’ experience with innovative biologics, Amgen appreciates the complexities in labeling policy for biosimilars and supports the policy approach that AbbVie advocates in its Citizen Petition. We thus respectfully urge FDA to promulgate a labeling policy that begins with transparency, supports consumer confidence, and facilitates appropriate use.

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 is based first became known to me on or about June 2nd, 2015. 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: Amgen Inc. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Should you need any additional information regarding this submission, please contact Michael Malecki by telephone at 805-447-4723 or by email at mmalecki@amgen.com.

Sincerely,



Steven Galson, M.D., M.P.H.
Senior Vice President, Global Regulatory Affairs and Safety
Amgen Inc.

¹¹ For example, see <https://clinicaltrials.gov/ct2/show/NCT01936181> (accessed 7/16/2015).