Biosimilars FORUM

August 31, 2020

Dr. Stephen Hahn
Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: Comments to Notice: "Examination of Secondary Claim Disclosure and Biosimilar Disclosures in Prescription Drug Promotional Materials" (Docket No. FDA-2020-N-1307)

Dear Dr. Hahn,

The Biosimilars Forum ("The Forum") appreciates the opportunity to provide comment on the Food and Drug Administration's (FDA or the Agency) Notice, "Examination if Secondary Claim Disclosure and Biosimilar Disclosures in Prescription Drug Promotional Materials."

The Forum is a non-profit organization whose mission is to promote biosimilars-related education and policy advancement in the United States with the intent of expanding access and availability of biological medicines and improving health care. The Forum works on a consensus basis to develop policy positions to ensure the United States has a competitive, safe and sustainable biosimilars market, providing more options to patients and physicians.

The members of the Forum produce the majority of the biosimilars currently approved and marketed in the U.S. Our members have a deep knowledge of biosimilar development, the approval process, and marketing challenges that exist in the US. The Forum is committed to ensuring that patients and prescribers have complete, truthful and non-misleading information about biosimilars.

General Comments

In a Notice posted on July 7, 2020 in the Federal Register (FR) that is entitled "Examination of Secondary Claim Disclosure and Biosimilar Disclosures in Prescription Drug Promotional materials,"[1] the FDA announced that they are planning to initiate research on the impact of disclosure statements that could be included in biosimilar promotional materials. We understand that this research will be conducted by the Office of Prescription Drug Promotion (OPDP) of the FDA.

As described in the FR Notice, the proposed biosimilar-focused research will assess the impact of a disclosure designating the product as a biosimilar as well as varying basic factual statements about biosimilars. As described in the Notice, it will examine the impact of:

"(1) adding a disclosure designating the product as a biosimilar;

[1] https://www.regulations.gov/document?D=FDA-2020-N-1307-0001

(2) adding general informational statements about biosimilars; and
(3) naming a reference product.
This approach allows us to examine the effect of disclosing biosimilar status, examines the additive effect of including one, two, or three additional basic statements of information about biosimilars, and measures the effect of naming the reference product. Our proposed main outcome measures are perceptions of and attitudes toward the biosimilar product and the disclosure."

The proposed Phase 2 Interview Guide – Draft v2 (referred to within this comment letter as the **"**questionnaire") contains three draft disclosure statements.

The first proposed disclosure statement would focus on the similarity of biosimilars and the fact that healthcare professionals (HCPs) and patients can expect the same safety and effectiveness after using biosimilars. Four options are proposed for comparison:

- This biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from Humira, an existing FDA-approved reference product.
- This biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product.
- This biosimilar is a safe and effective medication and provides the same treatment benefits as an FDA-approved original biologic.
- This biosimilar is a safe and effective medication and provides the same treatment benefits as Humira, an FDA-approved original biologic.

The second proposed disclosure statement would focus on the "source" of the biosimilar and reference product. The following four wording options are proposed:

- Biosimilars are made from the same types of sources as the FDA-approved reference product.
- This biosimilar is made from the same types of sources as Humira.
- Biosimilars are made from the same types of sources as the FDA-approved original biologic.
- This biosimilar is made from the same types of sources as Humira.

The third proposed disclosure statement would focus on dosing and administration. The following four options are proposed:

- [DRUG NAME] has the same route of administration, dosage form, and strength as an existing FDA-approved reference product.
- [DRUG NAME] has the same route of administration, dosage form, and strength as Humira.
- [DRUG NAME] is given the same way and has the same strength and dosage as the FDA-approved original biologic.
- [DRUG NAME] is given the same way and has the same strength and dosage as Humira.

In general, the Forum requests that the FDA explain the added value and appropriateness of including disclosure statements in biosimilar product promotional materials. The Forum does not object to inclusion of statements that would help allay concerns that patients may have about safety or effectiveness. However, such statements must not be couched in cautionary or negative terms or include statements that are ambiguous or of minimal relevance to patients.

The Forum is offering comments that we believe will enhance the quality, utility, and clarity of the information to be collected in this study.

We offer our comments on the following:

(1) The nature of the individuals to be included in the study
(2) Impact of identifying the product as a biosimilar
(3) Identification of the reference product
(4) Tone of the disclosure statements
(5) Suggested messages that should be included in the disclosure statements
(6) Messages that are overly complex and that should be avoided
(7) Messages that should be avoided because they are unclear or of minimal value
(8) Duration

1. Individuals to be included in the study

Several questions within the questionnaire (e.g. Question S3) make it clear that the proposed study will focus primarily on HCPs and not on patient perceptions. The Forum believes that while the views and perceptions of HCPs are very important, it is critical to assess the impact of disclosure statements on patients. In the six years since the Forum was founded, we have found that while knowledge and perceptions of HCPs have increased over time, knowledge levels of patients are still low. The Forum therefore urges FDA to focus this study on patients instead of HCPs, or perhaps to conduct separate but parallel studies of both HCPs and patients.

2. Impact of identifying product as a biosimilar

The FR Notice announcing this research undertaking specifies that *"We propose to examine seven different disclosure conditions plus a control with no disclosure for a total of eight test conditions*." However, when reviewing the draft questionnaire we did not observe a control group. Inclusion of a control group is important because the first two proposed disclosure statements immediately identify the product as a biosimilar. We urge FDA to include a control group that will not identify a given product as a biosimilar to allow for an assessment of whether or not the very inclusion of a statement that the product is a biosimilar will have an impact on HCP/patient perception. Further, the Forum urges FDA to ensure that this control group is sufficiently large to allow definitive conclusions to be drawn to address this question.

3. Identification of the reference product

The Prescribing Information (PI) for a biosimilar includes a statement that identifies the product as a biosimilar. This statement is appended as a footnote to the summary page and does not identify the reference product. If the PI does not identify the reference product by brand name, it is unclear why the FDA would deviate from this practice and instead mandate identification of the brand of the reference product in biosimilar promotional materials. By way of comparison, reference products are not required to be included in generic drug promotional materials but are commonly included in promotional materials for over-the-counter medications.

The Forum is concerned that identifying a specific reference product by brand name in biosimilar promotional materials is itself promotion of the reference product. In addition, because the reference product is licensed and marketed widely, identifying the reference product by brand name within the survey may bias the survey results.

Therefore, the Forum strongly urges that if mention of the reference product is to be included in disclosure statements, the reference product should only be referred to in general terms.

4. Tone of the disclosure statements

As a part of efforts to educate the public about biosimilars, Forum member companies have held multiple educational exchanges with many stakeholder groups over the past six years. We have also monitored the biosimilar information disseminated by other organizations. We have learned that it is critical to explain concepts in positive and easy to understand wording, because negative message framing of factual statements can create a negative perception.[2] It has been demonstrated that negative patient or HCP perceptions may lead to negative treatment outcomes, a phenomenon known as the nocebo effect.[3] We

As an example, the BPCIA specifies that biosimilars must have "*no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product*." This is wording that is incorporated into some options for the first disclosure statement. While intended to reassure patients and their providers of the safety, effectiveness and quality of biosimilars, we have learned in discussions with stakeholders that they believe this specific wording is complex, confusing and perhaps negative in tone. It is clearer, simpler and more reassuring to state that "*patients can expect that biosimilars will provide the same safety and effectiveness as their reference products*."

We appreciate that one of the options for the first disclosure statement is that "*This biosimilar is a safe and effective medication and provides the same treatment benefits as an FDA-approved original biologic*." The Forum agrees that this statement is positive in tone although it is more complex in sentence structure as compared to the text we proposed in the paragraph above.

5. Suggested messages that should be included in the disclosure statements

Based on the educational efforts undertaken by Forum member companies in the past six years, we have identified key messages that we believe are of greatest value to inform, educate and reassure patients and their HCPs about use of biosimilars.

We propose the following key messages in order of importance for inclusion in the study:

(1) Patients can expect that biosimilars will provide the same safety and effectiveness as the reference product.

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[2] Cohen HP and McCabe D. The importance of countering biosimilar disparagement and misinformation. BioDrugs. 2020. 34:407-414

[3] Rezk MF, Pieper B. To see or NOsee: the debate on the nocebo effect and optimizing the use of biosimilars. Adv Ther. 2018;35:749–53. https ://doi.org/10.1007/s1232 5-018-0768-z.
Kristensen LE, Alten R, Puig L, et al. Non-pharmacological effects in switching medication: the nocebo effect in switching from originator to biosimilar agent. BioDrugs. 2018;32:397–404. https ://doi. org/10.1007/s4025 9-018-0306-1.
Pouillon L, Danese S, Hart A, et al. Consensus report: clinical recommendations for the prevention and management of the nocebo effect in biosimilar-treated IBD patients. Aliment Pharmacol Ther. 2019;49:1181–7. https ://doi.org/10.1111/apt.15223 .

(2) The FDA has a rigorous review and approval process, applying the same high-quality standards to both biosimilars and reference products
(3) Patients have been benefitting from the use of biosimilars for many years.

6. <u>Messages that should be avoided</u>

The approval process for biosimilars is relatively new and there are numerous concepts that the FDA and Forum member companies have found are challenging to explain in a simple and succinct manner. These are discussed as "Conceptual Challenges" in a recent Forum publication, and they are areas in which we have seen biosimilar disparagement and misinformation, whether unintentional or otherwise. [4] We urge FDA not to require inclusion of statements about the topics listed below as they cannot be easily explained in one or two sentences.

(1) Interchangeability
(2) Extrapolation of indications

We have noted that Q12 asks: "*[DRUG NAME] and [the reference medication/Humira] can be used interchangeably*." The concept of interchangeability is unprecedented and often misunderstood. We encourage the FDA to continue to work with stakeholders to determine the best path forward to educate patients and providers about interchangeability. It is important that the FDA standardize language around interchangeability that manufacturers can use in future promotional materials.

While not mentioned in the proposed draft questions, the Forum believes that extrapolation is another topic that should be avoided because it is overly complex for routine inclusion in all promotional materials. Extrapolation of indications in the context of biosimilars is based on structural and functional similarity and PK/PD data and not between the indications of the reference product. However this is often not well understood, as the indications of originator biologics are obtained by separate and unique clinical studies. It is understandable that patients and their healthcare providers might prefer a drug explicitly studied in each indication when they lack an understanding and appreciation of how extrapolation is applied towards biosimilars. Furthermore, we have noted that in the past some organizations and individuals have called for identification of indications studied directly versus those obtained via extrapolation. Such requests are no more than thinly veiled efforts to sow doubts about biosimilars.

7. <u>Messages that should be avoided because they are unclear or are of minimal value</u>

The second disclosure statement that is proposed deals with the "source" of the biosimilar and reference product. Both are manufactured by use of biotechnology. They may be manufactured by use of similar cells, but the cells lines themselves and the fermentation and purification processes will be different. However, these facts are irrelevant to patients and likely to many HCPs. As a result, the Forum believes that the "source" of biosimilars and their reference products are not facts that need to be disclosed in promotional materials.

The third disclosure statement focuses on the route of administration, dose forms, and strength as their reference product. By definition, these must be identical for both the biosimilar and reference product. As a result, patients who are switched to biosimilars from reference products will not see a change in

[4] Cohen HP and McCabe D. Ibid.

these parameters, and this information is not relevant to patients receiving biosimilars who had not previously received reference product.

8. Duration

The FR Notice does not specify if the proposed disclosure statements are to be permanent features of all biosimilar promotional materials or if a requirement to include such statements will be retired after a set period of time. The Forum recommends that a set period of time (e.g. 3 years) be established after implementation of a requirement to include disclosure statements in biosimilar promotional materials, after which the FDA should consider deleting any such requirement. For example, if this requirement were to be implemented in 2021, FDA would reconsider in 2024 whether or not the requirement is still of value.

Summary and Conclusions

Based on the extensive experience of Forum member companies in discussing and educating a wide variety of stakeholders, the Forum urges that focus be placed on three topics that would be of greatest value to patients and their HCPs in helping them understand the basic principles of biosimilars:

(1) Patients can expect that biosimilars will provide the same safety and effectiveness as the reference product.
(2) The FDA has a rigorous review and approval process, applying the same high-quality standards to both biosimilars and reference products
(3) Patients have been benefitting from use of biosimilars for many years.

We reiterate the importance of positive framing of the key concepts that highlight the quality and benefits of biosimilars.

The Forum is concerned that confusing or negative statements may lead to unwarranted concerns that patients will not attain maximal efficacy on a biosimilar or may have an adverse event that they would not have had with the reference biologic. Patients may fear that they will receive an ineffective, inferior, or unsafe product. Patients could specifically request not to be treated with a biosimilar, or if they do receive a biosimilar, a negative preconceived opinion of the biosimilar may lead to poor clinical outcomes.[5]

Based on what has been observed to date, it is possible that confusing and negative statements may be used by some to disparage and spread misinformation about biosimilars.[6]

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[5] Kristensen LE, Alten R, Puig L, et al. Non-pharmacological effects in switching medication: the nocebo effect in switching from originator to biosimilar agent. BioDrugs. 2018;32:397–404. https ://doi.org/10.1007/s4025 9-018-0306-1.
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[6] Cohen and McCabe, *ibid*

Inclusion of confusing or negative statements in promotional materials has potential to slow adoption of biosimilars, diminishing opportunities to increase patient access and help generate healthcare system savings on pharmaceutical expenditures.[7]

Biosimilar education has always been an important priority for the Biosimilars Forum. The suggestions and proposals that we have offered in this comment letter are based on the many educational interactions we have had with a wide variety of stakeholders. The Biosimilars Forum believes that this research could help ensure accurate information about biosimilars is communicated to patients, healthcare professionals and others who have a role in adoption of biosimilars in the US. We appreciate the positive steps FDA has already taken to examine instances where false and misleading information has had a negative impact on perception and utilization of biosimilars.

The Forum looks forward to continuing to work with the FDA as it advances this research and assesses the findings. If you have any questions regarding this response, please contact Andrea Maresca at amaresca@thornrun.com

Sincerely,

Andrea Maresca
On behalf of The Biosimilars Forum

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"The importance of countering biosimilar disparagement and misinformation" by Hillel Cohen and Dorothy McCabe, *BioDrugs,* July 2020. 34:407-414

[7] Citizen Petition from Pfizer Inc. August 22, 2018. https ://www.regul ation s.gov/docum ent?D=FDA-2018-P-3281-0001. Accessed 19 Mar 2020.
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