June 25, 2024

Dockets Management Staff (HFA–305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Comments from the Biosimilars Council to Docket No. FDA–2019-D-5473; Promotional Labeling and Advertising Considerations for Prescription Biological Reference Products, Biosimilar Products, and Interchangeable Biosimilar Products: Questions and Answers; Revised Draft Guidance for Industry

The Biosimilars Council is pleased to submit comments on the revised draft guidance, *Promotional Labeling and Advertising Considerations for Prescription Biological Reference Products, Biosimilar Products, and Interchangeable Biosimilar Products: Questions and Answers* ("Draft Guidance").[1]

The Biosimilars Council, a division of the Association for Accessible Medicines, represents the manufacturers of biosimilar medicines, which are FDA-approved, safe and effective, lower cost versions of brand biologics. The Council works to increase patient access to lifesaving, affordable generic and biosimilar medicines.

Biosimilars are the key to reducing prescription drug costs and increasing access to care, generating about $24 billion in savings since market introduction in 2015. To date, biosimilars have been used in roughly 700 million days of patient therapy.[2] Because of their lower costs, they have increased patient access to therapy, generating more than 344 million days of patient therapy that would not have been otherwise provided in the United States if no biosimilar was available.[3] These savings and increased access are critical, as spending on biologic medicines now accounts for 46% of all spending on pharmaceuticals in the United States.[4]

The Biosimilars Council applauds FDA's continued commitment to combatting misinformation about biosimilars, and we strongly support the revised Draft Guidance. Misinformation has been a significant impediment to use of safe and effective lower priced biosimilars, and the revised guidance will help ensure that sponsors engage in truthful and non-misleading communications regarding biosimilars, including interchangeable biosimilars ("interchangeables"), and their reference products.

[1] See Notice of Availability ("NOA"), 89 FR 31757 (April 25, 2024).
[2] Association for Accessible Medicines, The U.S. Generic & Biosimilar Medicines Savings Report, at 9. https://accessiblemeds.org/sites/default/files/2023-09/AAM-2023-Generic-Biosimilar-Medicines-Savings-Report-web.pdf. Accessed May 6, 2024.
[3] *Id.*
[4] IQVIA Institute for Human Data Science (2023). Biosimilars in the United States 2023-2027. https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/biosimilars-in-the-united-states-2023-2027 Accessed June 20, 2024.

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Importantly, the Draft Guidance makes clear that there are no clinically meaningful differences between a biosimilar product and its reference product in terms of safety, purity, and potency,[5] and the Draft Guidance clearly conveys that it would be false or misleading to suggest that biosimilars are less safe and effective than interchangeables or than their reference products.[6] The Draft Guidance also clarifies that it is appropriate to communicate that a biosimilar may be prescribed to treat patients that are not only new to a therapy but also that are switched from the reference product.[7]

Nevertheless, the guidance would benefit from an affirmative statement from FDA that interchangeability does not represent a higher standard or convey increased quality, safety, or efficacy than biosimilarity, and that a healthcare provider can be just as confident in prescribing a biosimilar as an interchangeable, regardless of whether the patient is new to treatment or is currently being treated with the reference product. FDA staff have made similar statements in various contexts,[8] but it would be helpful to include such a statement in the revised guidance.

The Biosimilars Council also provides the following text-specific comments.

Additional Text-Specific Comments

Lines	Current Language	Comments
118-121	Also, if promotional communications describe, for example, a study supporting a demonstration of biosimilarity or interchangeability in which a non-U.S.-approved biological product was used as a comparator (or otherwise mentions such a product), FDA recommends that the product be accurately identified as a non-U.S.-approved biological product.	We disagree with the recommendation that a promotional communication identify when a non-U.S.-approved product was used as a comparator. FDA requires a biosimilar applicant to build a data bridge between the ex-U.S. comparator and the U.S.-licensed reference product that demonstrates the relevance of the data generated with the ex-U.S. comparator. When FDA determines that the product is biosimilar to (or interchangeable with) the U.S.-licensed reference product, it has determined that the data are adequate to support the determination. Referring to a non-U.S.-approved comparator will unnecessarily sow confusion and decrease confidence in biosimilars. At minimum, the draft guidance should make clear that this recommendation applies equally to reference products. It is not uncommon for non-U.S. products to be used to support 351(a) BLAs and be referenced in

[5] Draft Guidance, lines 232-235.
[6] *Id*. at lines 223-230 and lines 322-327.
[7] *Id.* at lines 266-283.
[8] See, for example, Q&A with FDA Podcast/Transcript, Switching Between Biosimilars and Their Reference Counterparts with Dr. Sarah Yim, https://www.fda.gov/drugs/news-events-human-drugs/switching-between-biosimilars-and-their-reference-counterparts-dr-sarah-yim. Accessed June 18, 2024. See also, T.M. Herndon et al., Safety outcomes when switching between biosimilars and reference biologics: A systematic review and meta-analysis, PLoS One, 18(10) (2023).

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		their labeling. For example, the USPI for Rituxan (rituximab) repeatedly refers to studies conducted with "RITUXAN or non-U.S.-licensed rituximab" and this should be referenced in promotional labeling if it is to be required of biosimilar products. To address this concern, the guidance could be revised as follows: "Also, if promotional communications describe, for example, a Phase III study supporting approval of a new indication for a reference product in which a non-U.S.-approved biological product was used as a comparator or a study supporting a demonstration of biosimilarity or interchangeability in which a non-U.S.-approved biological product was used as a comparator (or otherwise mentions such a product), FDA recommends that the product be accurately identified as a non-U.S.-approved biological product."
139-144	In general, a biosimilar product's FDA-approved labeling contains data and information from the CLINICAL STUDIES section of the reference product's FDA-approved labeling for the conditions of use for which the biosimilar product is licensed and also generally includes data and information from the reference product's FDA-approved labeling regarding clinical pharmacology studies, immunogenicity, and toxicity, among other information.	We suggest revising the latter part of the sentence as follows to clarify that this information also pertains to studies conducted with the reference product: "In general, a biosimilar product's FDA-approved labeling contains data and information from the CLINICAL STUDIES section of the reference product's FDA-approved labeling for the conditions of use for which the biosimilar product is licensed and also generally includes data and information from the studies that supported licensure of the reference product as described in ~~from~~ the reference product's FDA-approved labeling regarding clinical pharmacology studies, immunogenicity, and toxicity, among other information."
167-173	Although assessment of each promotional communication involves a fact-specific determination, representations or suggestions that create an impression that there are clinically meaningful differences between the reference product and a product that has been approved as biosimilar to that	While we recognize that FDA has interpreted "no clinically meaningful differences… in terms of the safety, purity, and potency of the product" to include immunogenicity, it would be helpful to clarify that in the context of promotional communications. We recommend revising the guidance to read:

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	reference product, such as promotional communications representing or suggesting that the reference product is safer or more effective than the biosimilar product or that the biosimilar product is safer or more effective than the reference product, are likely to be false or misleading	"... representations or suggestions that create an impression that there are clinically meaningful differences (including with respect to immunogenicity) between the reference product and a product that has been approved as biosimilar to that reference product ..."
205-215	In some cases, presenting otherwise accurate information about a reference product or about a biosimilar product could contribute to a misleading presentation when provided in a comparative context. For example, presentations in promotional communications for a reference product that include a comparison of the number of indications for which the reference product is licensed to the number of indications for which the biosimilar product is licensed in a manner that creates the overall impression that the biosimilar product is less safe or less effective than the reference product simply because the biosimilar product is licensed for fewer indications than the reference product would be misleading. Representations or suggestions in promotional communications for the reference product that the biosimilar product is less safe or less effective than the reference product in any of the indications licensed for the biosimilar product because the licensure pathway for the biosimilar product differs from that for the reference product also would be misleading.	The 2020 draft guidance expressly referred to the scenario when a biosimilar is not studied directly in each licensed indication of the reference product and the biosimilar's licensure is based in part on extrapolation (2020 Draft Guidance lines 210-214). We recommend reincorporating that text as an example here—i.e., clarifying that it would be misleading to suggest that a biosimilar is less safe or effective because it has not been directly studied in all of the licensed indications. Accordingly, we recommend revising the guidance to add an additional sentence beginning on line 210 as follows: "Similarly, presentations that imply that the biosimilar is less safe or less effective because it has not been studied for all of the indications for which it is licensed would be misleading because the licensure pathway for the biosimilar product differs from that of the reference product (e.g., a biosimilar may not be directly studied in a particular indication with licensure based, in part, on extrapolation)." In addition, we recommend adding an additional sentence after line 215 that addresses when a biosimilar is not approved for all of the strengths, dosage forms, and routes of administration: "Similarly, promotional communications that create an overall impression that biosimilars are less safe and effective because they are not licensed in all of the strengths, dosage forms, and routes of administrations as their reference products would be misleading."
223-230	When multiple products are licensed as biosimilar to and interchangeable with or biosimilar to but not interchangeable	Consistent with our general comments above, we recommend including an explicit statement that it would be misleading for a reference product sponsor to suggest that a

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	with the same reference product, promotional communications should avoid representing or suggesting that any of these products (i.e., the reference product, any interchangeable biosimilar product(s), or any non-interchangeable biosimilar product(s)) are less safe or effective than each other for their approved uses based on their licensure pathways. In addition, promotional communications for a reference product should avoid representing or suggesting that a biosimilar product is less safe or effective than the reference product because the biosimilar product has not been licensed as interchangeable with the reference product.	HCP should not prescribe a biosimilar to patients currently being treated with the reference product because it has not been approved as interchangeable. We recommend the guidance be revised as follows: "When multiple products are licensed as biosimilar to and interchangeable with or biosimilar to but not interchangeable with the same reference product, promotional communications should avoid representing or suggesting that any of these products (i.e., the reference product, any interchangeable biosimilar product(s), or any non-interchangeable biosimilar product(s)) are less safe or effective than each other for their approved uses based on their licensure pathways, or that an HCP should not prescribe a biosimilar to patients currently being treated with the reference product because it has not been approved as interchangeable. In addition, promotional communications for a reference product should avoid representing or suggesting that a biosimilar product is less safe or effective than the reference product or should not be prescribed to patients currently being treated with the reference product because the biosimilar product has not been licensed as interchangeable with the reference product.
235-238	It is both normal and expected for biological products to have minor differences between batches. This means that biologics generally cannot be copied exactly, and that is why biosimilar products may not be identical to their corresponding reference product.	We recommend the following revisions to help further clarify and reiterate this important point regarding identity, particularly with respect to how product variability occurs in reference products: "It is both normal and expected for biological products, whether reference products or biosimilars, to have minor differences between batches (i.e., to not be identical), without any impact on safety, purity, or potency. This means that biologics generally cannot be copied exactly, and that is why biosimilar products may not be, and are not required to be, identical to their corresponding reference product."
279-282	Additionally, the promotional communications include a claim that HCPs can consider prescribing	We recommend revising the guidance to clarify that it would be acceptable to convey that HCPs can consider prescribing

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	NEXSYMEO to treat patients who are new to replicamab product therapy for an approved indication and for patients currently being treated with JUNEXANT for the same indication.	NEXSYMEO to treat patients who are currently being treated with another replicamab product for the same indication as follows: "…and for patients currently being treated with JUNEXANT or another replicamab product for the same indication."
284-302	In addition, the firm clearly and prominently provides contextual information about the study design and methodology, the role the study played in the biosimilarity evaluation, relevant data from NEXSYMEO's FDA-approved labeling, and any material limitations of the data. The firm also accurately describes the comparator used in the study as a non-U.S.-approved product.	For the reasons explained in our comments on lines 118-121, we recommend striking the last sentence referring to "non-U.S.-approved product."
317-320	It also misleadingly implies that there is a clinically meaningful difference between the products when the data presented in the promotional communications do not support this conclusion.	The misleading nature of the statement flows from FDA's approval of NEXSYMEO as biosimilar to JUNEXANT, which necessarily means that FDA has determined there are no clinically meaningful differences between the two products, regardless of what data are presented in the promotional communications. We recommend clarifying as follows: "It also misleadingly implies that there is a clinically meaningful difference between the ~~products when the data presented in the promotional communications do not support this conclusion~~, contrary to FDA's approval of NEXSYMEO as biosimilar to JUNEXANT."
322-327	Example 4: Promotional communications for HILEZEO state that, unlike patients using OMPIRAM, patients using HILEZEO can be assured of HILEZEO's safety and effectiveness because HILEZEO is licensed as interchangeable with CLAREXANT while OMPIRAM is not. This presentation misleadingly suggests that because HILEZEO is licensed as interchangeable with CLAREXANT and OMPIRAM is not, HILEZEO is superior in safety and effectiveness to OMPIRAM.	Consistent with the revisions we recommend on lines 223-230, we recommend reframing this example in terms of a reference product sponsor suggesting that that OMPIRAM is less safe and effective because it is not licensed as interchangeable and patients on CLAREXANT should not be prescribed OMPIRAM.

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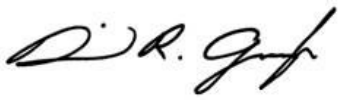
In conclusion, the Biosimilars Council appreciates the opportunity to submit comments on the revised Draft Guidance on behalf of its members, and we look forward to continuing our dialogue with the FDA to further increase competition and increase access to quality generic and biosimilar medicines for America's patients.

Sincerely,



David R. Gaugh, R.Ph.
AAM Interim President and CEO

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