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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the Biosimilars Council to Docket No. FDA-2016-D-0643, Labeling for Biosimilar and Interchangeable Biosimilar Products; Draft Guidance for Industry; and Docket No. FDA- FDA-2011-D-0611, Biosimilarity and Interchangeability: Additional Draft Q&As on Biosimilar Development and the BPCI Act; Draft Guidance for Industry

The Biosimilars Council is pleased to submit comments on the draft guidance, *Labeling for Biosimilar and Interchangeable Biosimilar Products* ("Draft Labeling Guidance" or "Labeling Guidance")[1] and on the related draft guidance, *Biosimilarity and Interchangeability: Additional Draft Q&As on Biosimilar Development and the BPCI Act* ("Draft Q&A Guidance").[2]

The Biosimilars Council works to increase patient access to lifesaving, affordable biosimilar medicines. The Council is a division of the Association for Accessible Medicines, an organization dedicated to improving access to safe, quality, effective medicine. The Biosimilars Council strives to create a positive regulatory, reimbursement, political and policy environment to assure biosimilars thrive, providing billions in savings to patients and the health care system. In fact, the use of biosimilars has saved nearly $24 billion for patients and taxpayers since 2015. Our members include biosimilar manufacturers and stakeholders working to promote biosimilar products.

The Biosimilars Council appreciates FDA's issuance of an updated draft guidance on labeling for biosimilar and interchangeable biosimilar products to reflect FDA's experience over the past eight years with the approval of over 40 biosimilar products, including multiple interchangeable biosimilar products.[3] As FDA has observed, determining how to appropriately label such products and keep labeling up to date without causing undue confusion has proven challenging,[4] and the draft guidance will help industry to continue to develop appropriate labeling for these types of products. The Biosimilars Council particularly applauds the FDA for its work to clarify that, as a scientific matter, there is no difference between biosimilars and interchangeable biological products, and this draft guidance is another important step forward.

[1] See Notice of Availability ("NOA"), 88 FR 63957 (September 18, 2023).
[2] FDA did not issue a separate Notice of Availability for the Draft Q&A Guidance. Instead, in the NOA for the Draft Labeling Guidance, the Agency indicated it was revising the Draft Q&A Guidance to remove Q.I.27 and Q.I.28 and leaving the remaining questions and answers in that draft guidance unchanged. *Id.* at 63959.
[3] When finalized, the Draft Labeling guidance will revise and replace the July 2018 guidance for industry "*Labeling for Biosimilar Products.*"
[4] NOA at 63959.

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The Biosimilars Council also appreciates FDA's proposed changes to the November 2020 draft Q&A guidance in conjunction with its publication of the Draft Labeling Guidance. Removal of questions Q.I.27 and Q.I.28 from that guidance and incorporation of the relevant language in the new, more comprehensive draft Labeling Guidance is appropriate.

The Biosimilars Council and its members provide the following comments on the two draft guidances for FDA's consideration.

General Comments

We recommend the final Labeling Guidance provide additional background on the updated thinking and changed perspective of FDA from July 2018 to September 2023. FDA guidances are intended to convey Agency thinking so sponsors can make informed decisions when designing development programs and determining regulatory strategies, and this updated guidance does not make clear what has changed. Although the Introduction lists some "significant changes" from the July 2018 guidance (see lines 27-38), the list is vague, and the draft guidance does not indicate what specifically changed in the areas listed. We recommend that the background section of the guidance be revised to include the information from the NOA that describes the evolution in FDA's thinking and to more specifically describe the changes between the July 2018 guidance and the current guidance.

In particular, the expanded background section should note that FDA now recommends that an interchangeability statement not be included in labeling, an important change explained in the NOA and effectuated by the removal of Q.I.27 and Q.I.28 from the Draft Q&A Guidance.[5] We fully support removal of the "interchangeability statement" from labeling, and the guidance should so state.

In addition, in response to FDA's request for comment on the usefulness of "biosimilarity statements,"[6] we recommend that such statements also be removed from biosimilar and interchangeable biosimilar labeling. As FDA states in the NOA, the Purple Book is well-suited to relay information on biosimilarity and interchangeability.[7] Removal of these statements from labeling also would align with generic drug labels, which do not include comparable statements or therapeutic equivalence ratings. We feel that biosimilarity and interchangeability statements do not improve patient or healthcare provider understanding and instead could be read to incorrectly suggest that biosimilar and interchangeable biosimilar products are different from their reference products, potentially leading to confusion and contributing to reluctance to prescribe biosimilar and interchangeable biological products.

[5] Id.
[6] Id. See also Draft Guidance, section IV.C.1.b, lines 389-424.
[7] NOA at 63959.

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Furthermore, the final guidance should address products that currently have an interchangeability statement in their labeling. It should recommend that the statements be removed at the next labeling update for the reasons described previously for eliminating those statements and to ensure labeling consistency across biosimilar and biosimilar interchangeable products.

FDA also should clarify in the final guidance that safety or clinical updates to biosimilar labeling must be preceded by updates to reference product labeling, consistent with FDA's policy and practice. Indeed, FDA recommends that biosimilar and interchangeable biosimilar labeling incorporate relevant data and information from the reference product labeling, with appropriate modifications, and it describes the modifications that would be appropriate.[8] In addition, the BsUFA III Commitment Letter recognizes that biosimilar and interchangeable biosimilar license holders should wait until the reference product license holder updates the labeling before adding new safety information. The letter creates a new category of supplement, Category A, a supplement that seeks to update the labeling for a licensed biosimilar or interchangeable product with regard to safety information that has been updated in the reference product labeling. The Commitment Letter provides for a short turnaround time — a 3-month goal date — for these supplements in recognition of the need to act quickly to ensure that the labeling of the biosimilar or interchangeable biosimilar is accurate and up to date once the reference product labeling is updated.

Furthermore, biosimilar manufacturers do not have access to the clinical trial data FDA relied upon to deem their reference products safe and effective and to approve reference product labeling. Biosimilar license holders therefore are not well-suited to making labeling updates before such updates have been made to reference product labeling.

With regard to the Draft Q&A Guidance, in addition to removing Q.I.27 and Q.I.28, we recommend that FDA also revise Q.I.25, which is outdated and should be clarified. Since the Draft Q&A Guidance was written, new commitments were negotiated in conjunction with the reauthorization of the Biosimilar User Fee Amendments of 2022 ("BsUFA III"), and FDA issued a new draft guidance, *Classification Categories for Certain Supplements Under the Biosimilar User Fee Amendments of 2022* ("Draft Classification Guidance") that addresses Category F supplements, supplements seeking an initial determination of interchangeability.[9] We recommend that Q.I.25 be reworded to address Category F supplements, and that the answer include four scenarios:

- Initial application seeking biosimilarity only
- Initial application seeking biosimilarity and interchangeability
- Initial application seeking interchangeable biosimilarity only
- Supplemental application seeking interchangeability for an already approved biosimilar product.

[8] Lines 110-115.
[9] See Notice of Availability, 88 FR 54626 (August 11, 2023), and the Draft Classification Guidance at lines 308-315.

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Supplemental applications seeking interchangeability would be considered Category F supplements under the BsUFA III Commitment Letter.

We also recommend that FDA have sponsors clearly note on their applications "BIOSIMILARITY ONLY", "BIOSIMILARITY AND INTERCHANGEABILITY", "INTERCHANGEABLE BIOSIMILARITY ONLY", or "CATEGORY F" on the cover letter for consistency.

In addition, we recommend that the various Q&A guidances on biosimilar and interchangeable products be combined into one document, with 3 sections: "Final", "Draft", and "Withdrawn." If someone searches online, they could easily pull up the November 2020 version of the Q&A guidance and have no idea that FDA's thinking has changed. If all Q&As were combined in one document, the historical integrity could be kept, and sponsors would not have to review multiple documents, losing information along the way when questions are withdrawn. As currently written, the draft guidance makes this recommendation for only one of the four possible scenarios: "Interchangeability Only".

Although Q&A guidances are useful vehicles to quickly address questions that arise after a comprehensive guidance is published without having to constantly amend the initial guidance, it is good practice to do as FDA has done here, incorporating substantive information from Q&A guidances into the more comprehensive guidance documents when they are revised. When all of the questions from a Q&A guidance have been incorporated in related guidance documents, the Q&A guidance can be phased out.

More generally, we recommend that FDA develop a method of cross-referencing directly related documents on its web page so that if someone opens a guidance that is in the process of being replaced, like the July 2018 Biosimilar Labeling guidance, their attention would be directed to the publication of the draft replacement guidance. Otherwise, they might not be aware that FDA's thinking has changed and could follow outdated recommendations in their development programs.

Specific Comments:

DRAFT LABELING GUIDANCE		
Line Number(s)	**Current Language**	**Comment/Proposed Change**
194-196	The illustrative examples in this section use a fictional reference product JUNEXANT (replicamab-hjxf) and a fictional biosimilar product NEXSYMEO (replicamab-cznm).	Some reference products do not have a four-letter suffix at this point. We recommend that the examples include products that do not have a four-letter suffix or that the guidance include a footnote addressing these products.
Footnote 24	*Core name* means the component shared among an originator biological product and any	We recommend deleting the references to actual products and using only fictitious products instead as in the

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	related biological product, biosimilar product, or interchangeable biosimilar product as part of the proper names of those products. Two examples of a core name are trastuzumab and adalimumab… Two examples of a proper name are trastuzumab-dkst and adalimumab-atto.	previously cited examples. Citing actual products could be seen as promoting or endorsing those products when fictitious examples would serve just as well here.
Footnote 25	…To illustrate, *replicamab products* refers to the reference product replicamab-hjxf and the licensed biosimilar product, replicamab-cznm; it would not, however, include a product with two biological product components, e.g., a biological product with the proper name replicamab and drugimab-xxxx, or a drug-biologic combination product.	We recommend the following change for clarity: "To illustrate, *replicamab products* refers to the reference product replicamab-hjxf and the licensed biosimilar product, replicamab-cznm; ~~it~~ *replicamab products* would not, however, ~~include~~ be appropriate to use when describing a product with two biological product components, e.g., a biological product with the proper name replicamab and drugimab-xxxx, or a drug-biologic combination product."
302-308	In rare circumstances, none of the above approaches for product identification may be appropriate. For example, if the reference product labeling describes a clinical study conducted with a non-U.S.-approved product (e.g., a clinical study conducted to support the safety, purity, and potency of the reference product was conducted with a non-U.S.-approved product, with an appropriate scientific bridge), the biosimilar or interchangeable biosimilar product labeling should incorporate the same terminology as the reference product labeling (see Table 3 for an example).	We recommend deleting this section. To our knowledge, originator biologic product labels do not address the source of the clinical study material, and it should not be addressed in biosimilar or interchangeable biosimilar labeling.
365-374	To help further illustrate, the labeling of JUNEXANT states that in nine clinical trials in adult patients with rheumatoid	We note that "and other indications" has been used in FDA-approved labeling to anonymize when licensure is sought for fewer indications than are approved for

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	arthritis, ulcerative colitis, or Crohn's disease, the rate of serious infection was 6.7 per 100 patient-years in 583 patients treated with JUNEXANT. If a biosimilar or interchangeable biosimilar product applicant sought licensure only for the rheumatoid arthritis and ulcerative colitis indications, the labeling should also convey that in the nine clinical trials, the rate of serious infection was 6.7 per 100 patient-years in 583 patients treated with replicamab-hjxf (i.e., the data should not be recalculated to remove the data based on adult patients with Crohn's disease, and the term Crohn's disease as used in the reference product labeling should be appropriately anonymized in the biosimilar or interchangeable biosimilar product labeling).	the reference product. We request that FDA specify this as an acceptable way to anonymize and provide an example Table. See for example, the Idacio label, section 5.2 Malignancies available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761255s000lbl.pdf : *Non-Melanoma Skin Cancer* During the controlled portions of 39 global adalimumab clinical trials in adult patients with RA, PsA, AS, CD, UC, Ps, **and other indications**, the rate (95% confidence interval) of NMSC was 0.8 (0.52, 1.09) per 100 patient-years among adalimumab-treated patients and 0.2 (0.10, 0.59) per 100 patient-years among control-treated patients. Examine all patients, and in particular patients with a medical history of prior prolonged immunosuppressant therapy or psoriasis patients with a history of PUVA treatment for the presence of NMSC prior to and during treatment with IDACIO. *Lymphoma and Leukemia* In the controlled portions of clinical trials of all the TNF-blockers in adults, more cases of lymphoma have been observed among TNF-blocker-treated patients compared to control-treated patients. In the controlled portions of 39 global adalimumab clinical trials in adult patients with RA, PsA, AS, CD, UC, Ps, **and other indications**, 2 lymphomas occurred among 7973 adalimumab-treated patients versus 1 among 4848 control-treated patients. (Emphasis added).
411-418	*Biosimilar means that the biological product is approved based on data demonstrating that	If FDA does not remove the "biosimilarity statement" then we recommend the following minor change

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	it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product. Biosimilarity of *[BIOSIMILAR OR INTERCHANGEABLE BIOSIMILAR PRODUCT'S PROPRIETARY NAME]* has been demonstrated for the condition(s) of use (e.g., indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information.	to this statement, for readability and to save a few words in the label: *Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological reference product, ~~known as a reference product~~, and that there are no clinically meaningful differences between the biosimilar product and the reference product. Biosimilarity of *[BIOSIMILAR OR INTERCHANGEABLE BIOSIMILAR PRODUCT'S PROPRIETARY NAME]* has been demonstrated for the condition(s) of use (e.g., indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information.
480	Table 4: Examples of Pediatric Use Statements, Row 1, Column 3 The safety and effectiveness of NEXSYMEO (for Indication Y) have been established in pediatric patients aged 6 months and older. Use of NEXSYMEO for this indication is supported by NEXSYMEO's approval as a biosimilar to replicamab-hjxf and evidence from adequate and well-controlled studies of replicamab-hjxf in adults with additional pharmacokinetic and safety data in pediatric patients aged 6 months and older.	We recommend deleting mention of "NEXSYMEO's approval as a biosimilar to..." and mention of the reference product later in the sentence. It does not seem necessary or consistent with the rest of the recommendations for the labeling, and we are unaware of any regulatory requirements for pediatric labeling that make this extra statement necessary. The sentence would be revised as follows: "The safety and effectiveness of NEXSYMEO (for Indication Y) have been established in pediatric patients aged 6 months and older. Use of NEXSYMEO for this indication is supported by ~~NEXSYMEO's approval as a biosimilar to replicamab-hjxf and~~ evidence from adequate and well- controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients aged 6 months and older."
489-506	…the Agency has the following recommendations with respect to incorporating relevant	We recommend clarifications to this section. As currently written, the bullets are confusing. The guidance should

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	immunogenicity data and information from the reference product labeling: • For a reference product with labeling consistent with FDA's recommendations as described in the Immunogenicity Labeling draft guidance, when finalized, the biosimilar or interchangeable biosimilar product labeling generally should follow the same content and format recommendations described in that guidance. The biosimilar or interchangeable biosimilar product labeling should also incorporate the appropriate modifications recommended in this guidance (e.g., the approaches to product identification in section IV.A., Recommended Approaches to Product Identification). • If the reference product labeling is not consistent with FDA's recommendations as described in the Immunogenicity Labeling draft guidance, when finalized, FDA recommends that the biosimilar or interchangeable biosimilar product applicant incorporate relevant immunogenicity data and information from the reference product labeling, with appropriate modifications (e.g., the approaches to product identification in section IV.A., Recommended Approaches to Product Identification). [Footnotes omitted]	explain that if the reference product labeling is not consistent with the draft guidance, *Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling — Content and Format* ("Immunogenicity Labeling draft guidance") when it is finalized, the biosimilar labeling should follow the labeling of the reference product and not follow the recommendations in the final Immunogenicity Labeling guidance. In other words, the biosimilar should follow the reference product labeling as closely as possible, even if it is not consistent with the Immunogenicity Labeling guidance, and it should also be consistent with the current draft guidance on Labeling Biosimilar and Interchangeable Products regarding Product Identification.
560-618	Text too extensive to include	We recommend including references to additional guidances on labeling topics, such as the BsUFA Supplement Classification draft guidance.

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Draft Q&A Guidance		
Line Number(s)	**Current Language**	**Comment/Proposed Change**
101-106	A BLA submitted under section 351(k) (a "351(k) BLA") of the PHS Act must contain, among other things, information demonstrating that the biological product is biosimilar to a reference product based upon data derived from analytical studies, **animal studies**, and a clinical study or studies (see section 351(k)(2)(A)(i)(I) of the PHS Act), unless FDA has determined that an element described in section 351(k)(2)(A)(i)(I) is unnecessary (see section 351(k)(2)(A)(ii) of the PHS Act). (**Emphasis added**)	We recommend changing "animal studies" to "an assessment of toxicity" consistent with the change to the Public Health Service Act ("PHS Act") enacted in section 3209 of the Consolidated Appropriations Act, 2023, Public Law 117-328, amending section 351(k)(2)(A)(i)(I) of the PHS Act (42 U.S.C. § 262(k)(2)(A)(i)(I)(bb)).

In conclusion, the Biosimilars Council appreciates the opportunity to submit comments on the two draft guidances, and we look forward to continuing our dialogue with the FDA to further increase competition and increase access to quality biosimilar medicines for America's patients.

Sincerely,

Craig Burton
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