GENERICS BULLETIN
CITELINE COMMERCIAL

24 Nov 2023 | **Analysis**

Generics Bulletin Explains: Removing Interchangeability Information From US Biosimilar Labels

Biosimilars Industry Backs Latest FDA Labeling Guidance – But Originators Disagree

by David Wallace

A clear divide between the biosimilars sector and the brand industry has been demonstrated by responses to a consultation over FDA draft guidance recommending that biosimilar labels remove information on interchangeability. *Generics Bulletin* explains the opposing positions.

A clear split between the biosimilars industry and the branded biologics sector has emerged in comments submitted to the US Food and Drug Administration over draft guidance around biosimilar labeling and interchangeability.

The FDA recently issued revised draft guidance that recommended removing details of the designation from biosimilar labels altogether.

Key Takeaways

- The AAM's Biosimilars Council and the Biosimilars Forum industry associations are supportive of draft FDA guidance recommending that details of interchangeability designations be removed from biosimilar labels.

Citing the difficultly of appropriately labeling interchangeable biosimilars and updating labels "without causing undue confusion" – as well as suggesting that a labeling statement indicating interchangeability and explaining the designation is "not likely to be useful to prescribers" – the agency suggested that its Purple Book database of licensed biologics could be a

more appropriate repository for interchangeability information (*see sidebar*).

Responses to the FDA's *docket* showed overwhelming support from off-patent industry bodies the Biosimilars Council and the Biosimilars Forum as well as individual biosimilars firms, while opposition to the removal of interchangeability information was voiced by brand industry bodies the Biotechnology Innovation Organization (BIO) and the Pharmaceutical Research and Manufacturers of America (PhRMA).

- Several biosimilars firms also responded individually, also backing the FDA's suggestion and pointing out unintended negative consequences caused by the interchangeability designation.

- However, brand industry bodies BIO and PhRMA disagree with the FDA's recommendation, suggesting that information around interchangeability belongs on biosimilar labels.

Biosimilars Council Backs Labeling Change

Responding to the draft guidance, the Association for Accessible Medicines' Biosimilars Council said it "applauds the FDA for its work to clarify that, as a scientific matter, there is no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."

With the latest draft guidance reflecting "FDA's experience over the past eight years with the approval of over 40 biosimilar products, including multiple interchangeable biosimilar products," the Biosimilars Council said, "as FDA has observed, determining how to appropriately label such products and keep labeling up to date without causing undue confusion has proven challenging, and the draft guidance will help industry to continue to develop appropriate labeling for these types of products."

However, the Council did suggest that the final guidance be updated to provide "additional background on the updated thinking and changed perspective of FDA from July 2018 to September 2023," suggesting that the guidance document itself "does not make clear what has changed."

From Interchangeability To Invisibility: FDA Wipes Designation From Biosimilar Labels

By David Wallace

18 Sep 2023

Amid continuing stakeholder confusion over the meaning and significance of the US FDA's interchangeability designation for biosimilars, the agency has now recommended omitting altogether details of interchangeability from biosimilar labels.

Read the full article here

While the introduction to the latest updated guidance lists some "significant changes" from the July 2018 guidance, the Council said, "the list is vague, and the draft guidance does not indicate what specifically changed in the areas listed." However, information from the Notice of Availability published in the *Federal Register* more clearly "describes the evolution in FDA's thinking [and] more specifically describes 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," the Biosimilars Council pointed out.

Furthermore, the Council suggested going further than the FDA's guidance and removing "biosimilarity statements" from labels as well as interchangeability information.

"As FDA states in the NOA, the Purple Book is well-suited to relay information on biosimilarity and interchangeability," the Council concurred. "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."

Finally, the Council also recommended that 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."

Biosimilars Forum Supports FDA Rationale

Similarly, the Biosimilars Forum backed the FDA's latest thinking in its own response to the guidance.

Suggesting that the US had seen a "significant amount of misinformation surrounding interchangeability" – and that "as the number of biosimilar treatment options has grown, it has also amplified the questions and implications around biosimilars and the ability to receive an 'interchangeable' designation for pharmacy substitution" – the Forum said the agency's latest position "will help with combatting misinformation and confusion surrounding an interchangeable designation."

"The Biosimilars Forum supports the FDA's rationale that the interchangeability standard is not likely to be useful to prescribers, who can prescribe either a biosimilar or an interchangeable biosimilar with equal confidence that they are as safe and effective as their reference products," the industry association said.

It also voiced support for the agency's recommendation to include information about interchangeability in the Purple Book, and – similar to the Biosimilars Council – recommended "removing the 'biosimilarity statement' from biosimilar package inserts as well."

"The Purple Book is appropriately suited to relay information on biosimilarity and interchangeability," the Forum said." Removal of these statements aligns with generic labels, where there is no 'generic statement' and therapeutic ratings are not noted. We feel that the statements do not help with patient or healthcare provider understanding, instead calling out that biosimilar and interchangeable biosimilar products are different from their reference products."

Coherus, Organon, Samsung Bioepis And Sandoz Weigh In

Individual biosimilars firms also lined up to comment on the FDA's latest draft guidance.

Coherus argued forcefully that the proposed labeling change "is not the remedy for the 'confusion' in 'explaining the interchangeability standard'," suggesting instead that "ideally, the solution should come from the legislative efforts to modify or even eliminate the concept of interchangeability which lacks scientific basis and consistency."

Nevertheless, backing the removal of the "interchangeability statement" – which the firm said had contributed to "inaccurate perceptions that interchangeable biosimilars are safer or more effective than biosimilars" – Coherus said that a revised footnote supporting the "biosimilarity statement" should be developed, including wording to make clear that "prescribers can prescribe both biosimilar and interchangeable biosimilar products in place of the reference product with equal confidence that they are as safe and effective as their reference products."

Organon also submitted comments on the draft guidance, indicating that it was "aligned with FDA's rationale in this regard and supports the proposed labeling changes."

"Organon believes that the FDA's robust biosimilar regulatory approval standard is sufficient to designate a biologic as both [emphasis Organon's] biosimilar and interchangeable through a designation," the firm said. "The creation of this interchangeable designation has unintentionally led to a barrier for biosimilar adoption in the US by inadvertently suggesting that it denotes a higher quality standard than biosimilarity. The lack of an interchangeability designation has been cited as a reason some providers are reluctant to use non-interchangeable biosimilars – even in the physician-infused setting."

"Nevertheless, we recognize the need to operate within the current legal construct and make additional investments to receive an interchangeable designation. The current requirements to pursue this designation are predicated on a legal, rather than clinical, basis and have created confusion across the provider and patient landscape. Organon supports prospective changes to streamline the ability to receive an interchangeable designation for future biosimilar applications, which appears to align with the FDA's position within this proposed guidance as well as recent comments and actions from the FDA."

The firm also said that the FDA's efforts to transition interchangeability information to the Purple Book, rather than being included on the label, "maintains safety and information standards for providers and pharmacists while reducing confusion around this designation."

"We support the FDA's goals and encourage the FDA to continue educating and clarifying how interchangeability impacts patients while reinforcing the value of biosimilars to the marketplace."

"That the reasoning for deleting the biosimilarity statement is the same as that proffered by the agency for the interchangeability statement suggests it would be efficient, and least likely to cause confusion, to remove all these superfluous statements."

Samsung Bioepis went even further with its comments, advocating removing the biosimilarity statement as well as interchangeability information. It suggested that "just as is acknowledged by FDA, in their statement made in the *Federal Register* notice, that the description of the interchangeability designation is not relevant nor useful for the prescriber, neither is the identification of a product as biosimilar."

"Any physician can prescribe any medicine, including both biosimilar and interchangeable biosimilar products for any appropriate purpose in place of the reference product," the firm stated. "And, in all cases, this is with equal confidence that they are as safe and effective as their reference products and each other."

"That the reasoning for deleting the biosimilarity statement is the same as that proffered by the agency for the interchangeability statement suggests it would be efficient, and least likely to cause confusion, to remove all these superfluous statements (and associated footnotes) for all 351(k) products at the same time."

“Such a cleaning up of the label could further include the removal of the suffix to the non-proprietary name,” Samsung Bioepis further mooted. These suffixes were “originally proposed in a time of early conjecture when it was thought that biosimilars might be treated more like generic small molecule drugs and less like branded drugs, and that differences between different biosimilars to the same reference could raise safety concerns especially if patients were switched.” But “this has not proven to be the case.” (Also see "*FDA Sticks To Its Guns On Biosimilar Naming*" - In Vivo, 20 Mar, 2019.)

“With more combination and multi-ingredient products envisaged, such a change back to the use of the United States Adopted Name (USAN) as the proper name would avoid the concatenation of suffixes and impossibly long proper names for many biologics, including biosimilars and interchangeable biologics. It would also avoid the same biologics being available concurrently with and without suffixes. And the need for exceptions within the data systems trusted with implementation of the naming conventions, both within the US and internationally would help those systems to remain efficient too.”

“In no case would any of these suggestions change the prescribing authority for physicians,” the firm underlined. “But by simplifying labels through the removal of extraneous information that invites confusion, the objectives of the label to provide critical information for prescribers would be maintained.”

While Sandoz did not submit its own comments to the docket, the firm’s CEO Richard Saynor recently set out his thoughts on the FDA’s latest position on interchangeability during the firm’s third-quarter results call.

“Honestly, I think from a personal point of view, I think the designation was more confusing than it actually helped,” Saynor suggested. “If you think about biosimilars in Europe, they’re automatically effectively designated interchangeable once they’re given an approval. And I think the fact that the US authorities created a position where one product was interchangeable specifically to one other actually causes more confusion than not.”

As such, he said, the FDA’s move to de-emphasize interchangeability “actually just brings the US much more in line with certainly the European regulators and thinking of in terms of how biosimilars are adopted and used.”

BIO And PhRMA Push Back Against FDA Position

Standing in opposition to the biosimilars industry responses to the FDA guidance were submissions from BIO and PhRMA.

“Implementation of the Biologics Price Competition and Innovation Act (BPCIA), including the distinction between biosimilar and interchangeable products, remains of significant importance

to BIO members," the biotech association insisted, "and BIO wants to avoid any erosion of the distinction between biosimilar and interchangeable, even in labeling."

With an interchangeable biosimilar needing to meet additional statutory requirements to enable pharmacy substitution, BIO suggested that "by removing the clear identification of interchangeability from the product label, BIO believes that FDA undermines the statute by standardizing the label to 'biosimilar' thereby encouraging the perception that all biosimilars can be considered as interchangeable at the pharmacy."

"BIO is also concerned this change may lead to unintended consequences. For example, promotional labeling or advertising could imply that a biosimilar is interchangeable when it is not, mischaracterizing both the statutory distinction between a biosimilar and an interchangeable product and imply that the biosimilar has satisfied the requirements for interchangeability."

"Therefore, BIO recommends that FDA retain the interchangeability statement in the label for those products which have been determined to be interchangeable."

"Currently," BIO claimed, "there is no evidence that demonstrates interchangeability is the cause of: (1) any confusion to physicians and patients and (2) that the interchangeability designation is a barrier to biosimilar market uptake" – assertions that would likely be disputed by the biosimilars industry. Moreover, the association suggested that "misconceptions and confusion around interchangeability will not be addressed by eliminating information pertaining to the topic from product labels."

And in response to suggestions that interchangeability information move to the Purple Book, BIO said this was "not a routinely accessed source document used by patients and healthcare professionals and is not commonly recognized in the same way as the product label."

"In particular, physicians rely heavily on the label when prescribing medications and when looking for information about the product and have indicated their preference to refer to one source to obtain relevant information," BIO said. Therefore, "retaining the interchangeability statement in labeling and explaining the standard is an important step towards education around the meaning of the interchangeability standard."

> *"Misconceptions and confusion around interchangeability will not be addressed by eliminating information pertaining to the topic*

from product labeling."

Meanwhile, affirming its support for labels to contain a biosimilarity statement, originator body PhRMA said it was "concerned with FDA's proposal to eliminate the parallel interchangeability statement and footnote," recommending instead that this be "retained and refined."

"Inclusion of such a statement is necessary to provide context for biosimilar labeling," PhRMA argued. While the Purple Book "serves a complementary function, particularly for pharmacists, the labeling is the proper vehicle to convey this information to prescribers, consistent with FDA's regulations," the association argued.

It also suggested that "abolishing the biosimilarity statement would cause confusion because it would result in inconsistent labeling across different biosimilar products."

"Misconceptions and confusion around interchangeability will not be addressed by eliminating information pertaining to the topic from product labeling," PhRMA summarized. "Retaining the interchangeability statement in labeling and explaining the standard is an important step towards education around the meaning of the interchangeability standard."

Meanwhile, PhRMA said it "also has concerns that FDA apparently began implementing the draft guidance before the comment period closed" – pointing to the agency's recent approval of Amgen's Wezlana (ustekinumab-auub) as an example of the FDA "approving interchangeable products with only the biosimilar statement in the labeling" (Also see "*Trailblazer Amgen Scoops First US Stelara Biosimilar – With Interchangeability*" - Generics Bulletin, 1 Nov, 2023.) – which the brand industry association said "raises legal and policy concerns" and "undermines the public comment process and conflicts with statutory and regulatory provisions on guidance development."

FDA's Yim Sets Out Agency's Position

As the FDA mulls the feedback on its draft guidance, recent comments from Sarah Yim – director of the FDA Office of New Drugs' Office of Therapeutic Biologics and Biosimilars – have shed light on the agency's current thinking.

"We believe that statements in the prescribing information identifying that products have been approved as interchangeable with the reference product and describing the interchangeability standard are not necessary for informing the safe and effective use of the product to prescribing

health care professionals," Yim summarized (*see sidebar*).

As the FDA gains experience with licensing biosimilar and interchangeable products, she set out, the agency was finding that a single biosimilar application and associated prescribing information may include both biosimilar and interchangeable biosimilar products simultaneously.

"We have considered multiple approaches to accommodate this scenario, some of which raised a variety of concerns, including increased confusion," she explained. "Including biosimilarity statements in the prescribing information for both biosimilar and interchangeable biosimilar products is factually accurate and avoids these concerns."

Yim also added weight to claims that interchangeability statements could be contributing to inaccurate perceptions that interchangeable biosimilars are safer or more effective than those that are not approved as interchangeable. "The interchangeability designation does not indicate a higher level of biosimilarity," Yim underlined.

"Healthcare professionals can prescribe both biosimilar and interchangeable biosimilar products in place of the reference product with equal confidence that they are as safe and effective as their reference products."

FDA Officially Recommends Removal Of Interchangeability Designation From Biosimilar Labels

By Chloe Kent

02 Nov 2023

The US Food and Drug Administration has recommended that biosimilar drugs all use the same biosimilarity statement on their product information. Interchangeable products currently employ a separate interchangeability statement.

Read the full article here