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From Interchangeability To Invisibility: FDA Wipes Designation From Biosimilar Labels

New Draft Guidance Urges Removal Of Interchangeability Designation From Biosimilar Labeling

by David Wallace

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.

Ever since its introduction, the US Food and Drug Administration's interchangeability designation for biosimilars has been a much-debated topic among industry stakeholders. But now, the latest FDA draft guidance has recommended removing the designation from biosimilar labels altogether.

Citing the difficultly of appropriately labeling interchangeable biosimilars and updating labeling "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explaining the designation is "not likely to be useful to prescribers" – the FDA made the move as part of its *latest draft guidance on labeling for biosimilar and interchangeable biosimilar products*.

Key Takeaways:

- New US FDA draft guidance has recommended removing details of interchangeability from biosimilar labels
- The FDA suggested the interchangeability designation had been a source of confusion for prescribers

Moreover, the FDA has explicitly specified

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."

- The agency said prescribers could be equally confident in the safety and effectiveness of biosimilars with or without the designation

A *docket* is now open for interested parties to submit comments on the newly-published draft guidance on biosimilar labeling, with the FDA specifically asking for feedback on biosimilarity statements and how clarity around biosimilarity can be improved.

Interchangeability A Legal, Not Clinical Distinction

Interchangeability for biosimilars is defined by the Biologics Price Competition and Innovation Act framework as separate to biosimilarity, requiring a product to not only be deemed biosimilar to its reference brand but also to "produce the same clinical result as the reference product in any given patient."

Rather than an additional clinical standard to biosimilarity, the designation represents a legal distinction that means biosimilars designated as interchangeable are eligible for pharmacy-level substitution, subject to US state law (*see sidebar*).

The first interchangeable biosimilar version of a reference product also benefits from a year of interchangeable exclusivity before a rival biosimilar of the same presentation can receive an interchangeability designation.

To be granted a designation of interchangeability, the BPCIA specifies that "for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product" must not be "greater than the risk of using the reference product without such alternation or switch."

Cutting Through The Confusion On US Biosimilar Interchangeability

By David Wallace

05 Aug 2022

Amid ongoing confusion around the US interchangeability designation for biosimilars, Joseph Park and Gillian Woollett of Samsung Bioepis talk to *Generics Bulletin* about the risks of misinformation, the importance of educational efforts, and how language is shaping certain misunderstandings around biosimilars.

Read the full article here

Biosimilar developers have therefore been required to conduct additional switching studies, over and above those required for a product to be licensed as a biosimilar, to win an interchangeability designation – although last year's designation for Coherus BioSciences' Cimerli (ranibizumab-eqrn) as the first interchangeable biosimilar to Lucentis showed that a switching study is not always essential. (Also see "*Cimerli Interchangeable Biosimilar Approved Without Switching Data*" - Generics Bulletin, 4 Aug, 2022.)

> ***"Determining how to appropriately label such products and keep labeling up to date without causing undue confusion has proven challenging."***

Explaining its reasoning in *a Federal Register notice on 18 September*, the FDA suggested that the interchangeability designation was causing challenges and confusion for biosimilars stakeholders, while also implying that it could a false impression of a separate clinical standard for interchangeable biosimilars, compared to biosimilars without the designation.

"Eight years have passed since FDA approved the first biosimilar product," the agency recalled. "In this time, FDA has approved over 40 biosimilar products, including multiple interchangeable biosimilar products, and has gained valuable experience about labeling considerations for biosimilar and interchangeable biosimilar products, including labeling statements in the 'highlights of the prescribing information' that explain biosimilarity and interchangeability."

"First, it has become clear that an applicant may choose to submit a single 351(k) biologics license application seeking to license both biosimilar and interchangeable biosimilar products. Draft labeling for such applications would need to address both biosimilar and interchangeable biosimilar products, and the status of a particular product within such a BLA can change over time, for example, as relevant exclusivities expire."

"Determining how to appropriately label such products and keep labeling up to date without causing undue confusion has proven challenging," the FDA admitted. (Also see "*Confusion Persists Over US Biosimilar Interchangeability*" - Generics Bulletin, 23 Jun, 2022.)

"Moreover," the agency said, "a labeling statement noting that certain products within a 351(k) BLA have been approved as interchangeable, and explaining the interchangeability standard, is not likely to be useful to prescribers, who 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."

For years, debate has continued over the merits of the US interchangeability designation, with some industry stakeholders suggesting that it could falsely imply that biosimilars that are not designated as interchangeable are somehow inferior, potentially causing confusion in the market (*see sidebar*).

So far, three molecules have seen biosimilars granted the interchangeability designation. These are Viatris/Biocon's Semglee (insulin glargine-yfgn) rival to Lantus, the first biosimilar to be designated as interchangeable (Also see "*Viatris Wins Landmark First US Interchangeability Designation For Semglee*" - Generics Bulletin, 29 Jul, 2021.), which was later followed by Eli Lilly's Rezvoglar (insulin glargine-aglr) version (Also see "*Lilly Gets Second Interchangeable Insulin Glargine In US*" - Generics Bulletin, 18 Nov, 2022.); Boehringer Ingelheim's Cyltezo (adalimumab-adbm) version of Humira (Also see "*First Interchangeable Humira Biosimilar Approved In US*" - Generics Bulletin, 18 Oct, 2021.); and Cimerli. (Also see "*Coherus Shakes Up Ranibizumab Competition With First Interchangeable US Biosimilar*" - Generics Bulletin, 3 Aug, 2022.)

Biosimilar Interchangeability: A Blessing Or A Curse?

By David Wallace

09 Jul 2021

Biosimilar interchangeability is a hot topic in the US, with the first FDA decision on a formal interchangeability designation expected this month. But across the industry, views differ dramatically on the desirability and likely impact of this additional standard to biosimilarity.

Read the full article here

'Purple Book' More Appropriate For Interchangeability Information

The FDA also suggested that its Purple Book database of licensed biologics could be a more apt venue for interchangeability information, noting that it had "evolved as a resource for patients, pharmacists, physicians, and other health care providers to easily identify approved biosimilar and interchangeable biosimilar products." (Also see "*FDA Overhauls Its Purple Book*" - Generics Bulletin, 25 Feb, 2020.)

"Because the Purple Book is available as an easy-to-use resource for pharmacists, and interchangeability, as defined in section 351(i)(3) of the PHS Act, pertains to substitution of an interchangeable biosimilar product for its reference product 'without the intervention of the [prescribing] health care provider' (i.e., pharmacy-level substitution)," the agency concluded, "information about interchangeability is more appropriately located in the Purple Book rather than labeling."

"Consistent with this evolution in our thinking, the draft guidance states that both biosimilar and interchangeable biosimilar products should contain the same biosimilarity statement in the

'highlights of the prescribing information.' This statement is applicable to biosimilar and interchangeable biosimilar products."

Accordingly, the FDA has withdrawn from an *updated draft Q&A document on biosimilar development* certain questions and answers regarding the inclusion of an interchangeability statement in the labeling of products licensed as interchangeable.

With the docket on the new draft guidance on labeling now open, "we invite comment on biosimilarity statements, such as a statement described in section IV.C.1.b of the draft guidance, in the 'highlights of the prescribing information'," the FDA specified.

"Specifically, FDA invites comment on how useful such biosimilarity statements have been for healthcare practitioners and the public, whether such statements can be improved to provide more clarity on what biosimilarity means, and whether biosimilar and interchangeable biosimilar product labeling should include such a statement at all."