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Biosimilar Interchangeability: A Blessing Or A Curse?

As Industry Awaits First FDA Decision, Views Are Mixed On Interchangeability

by David Wallace

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.

When the US Biologics Price Competition and Innovation Act set out the country's biosimilars framework in 2009, it contained within it a significant provision that would set the US apart from other markets in its treatment of biosimilarity, in the form of an additional designation for "interchangeable" biosimilars.

Interchangeability is defined by the BPCIA as a separate standard to biosimilarity, and requires 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."

Moreover, 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" if the biosimilar is to be granted a designation of interchangeability.

This therefore puts a significant burden on developers in terms of conducting additional studies, over and above those required for a product to be licensed as a biosimilar, if they are to win an interchangeability designation – albeit with the potential for pharmacy-level substitution as an advantageous prize.

While views have differed over the US interchangeability designation for biosimilars, up until now the arguments have been largely academic, as no biosimilar has yet been officially deemed interchangeable by the US Food and Drug Administration.

But that could be set to change very soon. In July, *Viatris* expects the first FDA decision on interchangeability to be made for its insulin glargine and insulin aspart biosimilars. (Also see "*Viatris Expects First Interchangeable Biosimilar Designations For Insulins In July*" - Generics Bulletin, 13 May, 2021.)

"Our 351k [biologics license application] for insulin glargine for interchangeability is on track for a July FDA goal date," Viatris president Rajiv Malik confirmed during the firm's first-quarter earnings call in May. Meanwhile, "our insulin aspart is also tracking towards its FDA goal date in July and is expected to include interchangeability."

And Viatris expects the designation to provide a significant boost to its efforts to penetrate the insulins market. "Once we have an interchangeable aspart, once we have interchangeability around there, it's an opportunity to basically relook into this, the challenges which we have faced so far in picking up the market share," Malik said. "We have been slowly and steadily picking up," he added, putting Viatris' current share of the insulin glargine market at around 2.5%.

Some have even gone as far as to suggest that insulin biosimilars should automatically be deemed interchangeable in the US, with draft legislation advanced in the hope of achieving this goal. (Also see "*US Bill Urges Automatic Insulin Interchangeability*" - Generics Bulletin, 18 Sep, 2020.)

Notably, Viatris partner *Biocon* has previously pointed to the relative lack of complexity of insulins compared to other biologics, insisting that "insulins are simple proteins and the regulatory requirements should be proportional to the complexity." (Also see "*FDA Is Urged To Make All Biosimilar Insulins Interchangeable*" - Generics Bulletin, 13 Jun, 2019.)

Lack Of Regulatory Clarity Called Out By Industry

In terms of the broader view of the FDA's regulatory approach to interchangeability, the biosimilars industry has in recent years pointed to a continuing lack of clarity around the subject from the US agency.

Industry body the Biosimilars Forum recently pointed out that "while FDA has published several guidance documents related to biosimilars, industry continues to struggle with the lack of clarity regarding the agency's policy on certain aspects of interchangeability as well as regulatory expectations for certain post-approval changes for biosimilar or interchangeable products" (*see sidebar*).

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Meanwhile, *Sandoz* has asked for specific interchangeability guidance addressing issues around promotion and advertising; labeling; product presentation; and post-approval process changes, with the firm insisting that "closing the gap of understanding regulatory requirements is essential to reduce development risks for our products."

And Biocon has pointed out that "for companies seeking interchangeability approval for their biosimilars, clear guidance to industry on remaining issues will significantly facilitate development and regulatory review, leading to increased patient access to valuable therapies."

Interchangeability, Meetings And Access Among BsUFA III Priorities

By Akriti Seth

14 Jan 2021
Industry stakeholders have offered their views on key priorities for the BsUFA biosimilars user-fee program ahead of its reauthorization.

Read the full article here

The perceived lack of regulatory clarity is not for want of trying on the part of the FDA. Major guidance on interchangeability published by the agency in May 2019 was welcomed by industry, not least for the decision to allow the use of comparator biologics not licensed in the US. (Also see "*FDA's Interchangeability Improvements Impress Industry*" - Generics Bulletin, 13 May, 2019.)

And since then, further guidance on interchangeability has continued to be developed by the FDA, including a Q&A document on applications and labeling that was published in late 2020 (Also see "*FDA Offers Clarity On Biosimilar Interchangeability*" - Generics Bulletin, 20 Nov, 2020.), as well as pending guidance over how the agency will implement the one-year exclusivity award to which first interchangeable biosimilars are entitled. (Also see "*Biosimilars: US FDA Developing Guidance For First Interchangeable Exclusivity*" - Generics Bulletin, 20 Nov, 2020.)

Implies Inferiority Of Non-Interchangeable Biosimilars

Even regardless of the specifics of FDA guidance, the concept of interchangeability has proved controversial, with the very existence of the separate standard cited as a cause for concern by some prominent biosimilars players.

Sandoz biopharmaceuticals executive director for scientific affairs, Hillel Cohen, last year emphasized in an interview with *Generics Bulletin* that while interchangeability is a "different regulatory category than biosimilarity and requires additional and different clinical data," the quality standards for biosimilars and interchangeable biologics were "absolutely identical."

Nevertheless, he said the firm had concerns that the separate standard "could suggest that the quality of a biosimilar that is not designated as interchangeable is lower in some manner." (Also see "*Sandoz Talks US Biosimilars And Misinformation*" - Generics Bulletin, 13 Aug, 2020.)

“Furthermore, a US interchangeability designation is only relevant for drugs administered in a retail or specialty pharmacy setting,” Cohen observed, with products administered by a provider in out-patient clinics or in doctors’ offices offering no opportunity for a pharmacists to substitute reference biologics and biosimilars, thus making it unlikely that an interchangeability designation would be pursued in the first place, given the additional regulatory and cost burden.

> *“The US interchangeability designation is an unnecessary procedure.”*

Other firms have also lined up to criticize the implications of US interchangeability for biosimilars.

Samsung Bioepis recently suggested that the separate interchangeability standard “may cause misunderstanding and misinterpretation of the scientific rigor that goes into biosimilar development [and] approvals,” insisting that an interchangeability designation is not necessary to drive uptake in the US. (Also see "*Samsung Bioepis Raises Fresh Questions For Biosimilar Interchangeability*" - Generics Bulletin, 14 May, 2021.)

“Biosimilars have been around now for more than a decade around the world. Until now, there has been no evidence on altered pharmacokinetics data, or heightened immunogenicity response, or increased safety risk, or improved or diminished efficacy in patients who switch back and forth between, from a reference drug to a biosimilar or in between biosimilar drugs,” the firm’s commercial vice-president Albert Kim observed.

“We have seen no such data prove that point and we don’t see [that the] interchangeability designation is a necessity to drive the biosimilar uptake in the US.”

Another major biosimilars player, *Celltrion*, has also called interchangeability into question. In a recent interview with *Generics Bulletin*, HoUng Kim, head of Celltrion Healthcare’s medical and marketing division, said the firm “believes that the US interchangeability designation is an unnecessary procedure,” citing the potential for the designation to “cause confusion by inaccurately implying a higher quality standard than biosimilarity.”

“Also,” Kim pointed out, “as the first interchangeable biological product receives up to one year of exclusivity over subsequent follow-on biologics, this could consequently delay competing biosimilar drugs entering the market.” (Also see "*Celltrion’s Kim Emphasizes Innovation As*

Pipeline Grows" - Generics Bulletin, 29 Jun, 2021.)

Some See Interchangeability As Unnecessary To Compete On Humira…

Biosimilars specialist *Coherus BioSciences* has also spoken out against interchangeability, recently confirming that it is not seeking to conduct any interchangeability studies for its proposed biosimilar Humira (adalimumab) product ahead of US market formation in 2023, maintaining that the designation will not be required in order for the company to be competitive.

"I think it's important to keep in mind that interchangeability thus far has not been a requirement at all to support biosimilar adoption," the firm's chairman, president and CEO Denny Lanfear Lanfear observed. "What we'd say is that our payer research indicates that interchangeability will not be a major impediment to biosimilar adoption specifically in the Humira market."

Coherus, he said, expected the payer to be "very, very active in that market, but we don't expect any requirement to be interchangeable or not."

Lanfear also pointed to the absence of any such requirement in Europe, where adalimumab biosimilars were launched almost three years ago. "That hasn't impeded biosimilar adoption there whatsoever," he reasoned. "So, we don't really think so; and, no, we are not seeking any biosimilar interchangeability study or to invest in such. We don't believe it's required." (Also see "*Coherus Distances Itself From Biosimilar Interchangeability*" - Generics Bulletin, 7 May, 2021.)

More generally, Sandoz' new North America head Keren Haruvi recently pointed out in an interview with *Generics Bulletin* that the concept of interchangeability was generating uncertainty around US biosimilars. Moreover, she noted that "companies wishing to pursue an FDA designation of interchangeability would need to add tens of millions of dollars of US-specific development costs, according to the current guidance requirements." (Also see "*Sandoz Aims To Be 'First In And Last Out' In North America*" - Generics Bulletin, 15 Mar, 2021.)

…While Several Others Are Pursuing Interchangeable Adalimumab

However, biosimilars developers are far from united in their response to the US interchangeability standard, with many viewpoints more positive.

In April, *Boehringer Ingelheim* boosted its chances of winning a landmark interchangeability designation later this year for its Cyltezo (adalimumab-adbm) FDA-approved biosimilar to Humira, after reporting positive data from the firm's "first-of-its-kind" Phase IIIb Voltaire-X switching study.

Thomas Seck, the company's senior vice president for medicine and regulatory affairs, said the "first-of-its-kind switching study further reinforces our goal to broaden access to biosimilar

treatment options while contributing to the quality and sustainability of healthcare systems." (Also see "*Boehringer Makes Case For Interchangeable Adalimumab Biosimilar*" - Generics Bulletin, 26 Apr, 2021.)

Pfizer has also been named as among those firms pursuing an interchangeability designation as part of efforts to compete with Humira, for the firm's Abrilada (adalimumab-afzb) approved biosimilar. (Also see "*AmerisourceBergen Sees Momentum Build In US Biosimilars*" - Generics Bulletin, 3 Feb, 2021.)

And in the last month, *Alvotech* also celebrated primary completion of the company's landmark Phase III clinical switching study for its proposed high-concentration biosimilar version of Humira, with top-line results expected later this year.

AbbVie Assumes Two Interchangeable Humira Biosimilars In 2023

By Dean Rudge

03 Dec 2020

Amid several new and updated draft guidance documents and the potential approach of the first approval, interchangeability continues to be a buzzword in US biosimilars. AbbVie has projected that two Humira (adalimumab) biosimilars will hold the designation when they launch in 2023.

Read the full article here

While Alvotech's adalimumab biosimilar has not yet been approved by the FDA, the Icelandic firm said it was "the only known company that has both developed a biosimilar candidate for the higher-concentration Humira and is executing a switching study to support approval as an interchangeable product." (Also see "*Alvotech Adalimumab Biosimilar Switching Study Hits Key Date*" - Generics Bulletin, 16 Jun, 2021.)

Another major US biosimilars player, *Teva*, believes that in the next five to eight years biosimilars will have "migrated to be more like complex generics or AP-rated generics," as automatic substitution comes into play. (Also see "*Teva: Biosimilars In The US Will Become Like Complex Generics*" - Generics Bulletin, 13 Apr, 2021.)

Meanwhile, some industry players remain a little more ambivalent about the likely significance of interchangeability. Sandoz biopharmaceuticals chief Pierre Bourdage recently acknowledged that, given the lack of any formal FDA decision on interchangeability to date, "it's very difficult to determine what that designation could mean and how important and vital it is." (Also see "*Biosimilars Adoption In Europe, US: Some Wins, 'Incomplete' Policies*" - Generics Bulletin, 1 Jun, 2021.)

For its part, the Association for Accessible Medicines has remained even-handed and diplomatic

in its comments on interchangeability, in its role as a representative organization for the entire off-patent industry.

The AAM has welcomed earlier FDA guidance on interchangeability for providing additional clarity and insights on study design requirements, while at the same time making it clear that the separate designation should not be read as implying that non-interchangeable biosimilars are inferior to their interchangeable peers.

“While the interchangeability designation does not confer any additional quality or safety attributes for FDA-approved biosimilars,” the association emphasized, “we look forward to continue working with the agency to bring biosimilar medicines to America’s patients.”

Amid a host of conflicting views on the subject, it at least seems certain that the imminent FDA decision on Viatris’s insulins will cast some light on the subject by finally giving industry stakeholders a tangible view of what an agency decision on interchangeability looks like. And potentially – assuming a positive decision – how an approved interchangeable biosimilar behaves in the US market.