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Provisionally Interchangeable? FDA Weighs 'Requirements' For Pfizer's Adalimumab

FDA-Approved Abrilada 'Meets The Standards As An Interchangeable Biosimilar'

by Dean Rudge

Pfizer has responded to *Generics Bulletin's* queries regarding its bid to win an interchangeability designation for its Abrilada (adalimumab-afzb) biosimilar to AbbVie's Humira reference product.

With biosimilar interchangeability in the US in its infancy, *Pfizer Inc.* appears to have been caught in the controversial designation's evolving and somewhat indeterminate landscape, in its bid to win interchangeability for the firm's already approved Abrilada (adalimumab-afzb) biosimilar.

Almost exactly a year ago, Pfizer announced US Food and Drug Administration filing of a prior approval supplement for the low concentration 40mg/0.8ml Abrilada as an interchangeable biosimilar to AbbVie's Humira (adalimumab) reference product. (Also see "*FDA To Review Pfizer's Abrilada For Humira Interchangeability*" - Generics Bulletin, 3 Mar, 2022.)

A biosimilar with an interchangeable designation can be substituted for its reference product at the pharmacy, without additional approvals from the prescribing physician, subject to state law.

With a Biosimilar User Fee Act goal date scheduled for the fourth quarter of 2022, no announcement was made going into the end of February 2023.

Responding to *Generics Bulletin* enquiries, a Pfizer spokesperson disclosed: "We are pleased to share that the FDA completed their review and provisionally (*Pfizer's emphasis*) determined that Abrilada meets the standards as an interchangeable biosimilar to Humira."

"However," the firm continued, "discussions with the FDA are ongoing to determine requirements and timeframes for the full approval of the interchangeable application."

Abrilada is bidding to be the first interchangeable adalimumab biosimilar that can be administered in an auto-injecting pen.

While Pfizer continued to look forward to launching Abrilada in the US in the second half of 2023, under the terms of the company's November 2018 licensing deal with AbbVie, the Pfizer spokesperson told *Generics Bulletin*, "As we have additional updates, we will share more."

FDORA Looks To Fill In Gaps

Pfizer's quandary may be that the FDA has already approved a low-concentration interchangeable adalimumab biosimilar – Boehringer Ingelheim's Cyltezo (adalimumab-adbm).

The approval grants Cyltezo a year of exclusivity, seemingly foreclosing Pfizer from final interchangeability approval despite Cyltezo not being granted license to launch until July 2023.

Unlike Abrilada, with its proprietary auto-injector pen, pre-filled syringe and vial formulations, Cyltezo is only approved as a single-use pre-filled glass syringe.

Seeking to address novel and confusing potential dilemmas for the FDA, tweaks in the recent Food and Drug Omnibus Reform Act of 2022 (FDORA) handed the agency more approval authority around interchangeable biosimilars, including for the FDA to approve 'tentatively' a subsequent interchangeable biosimilar while a first interchangeable biosimilar's exclusivity is in effect.

Meanwhile, following FDORA's signing into law on 29 December, the FDA can approve multiple interchangeable biosimilars and allow them to share exclusivity if they are approved on the same day. (Also see "*Generic Policy Tweaks In Omnibus Legislation Include Processes Improvements On Late-Stage Label Changes, 505(b)(2) TE Designations*" - Pink Sheet, 23 Dec, 2022.)

Emphasizing the potential complications for sponsors in an exclusive interview with *Generics Bulletin* last year, Samsung Bioepis' Gillian Woollett commented, "It doesn't block another biosimilar being approved, it only blocks another interchangeable being approved during that window of the exclusivity. So, what becomes key is when does that window start?"

"There seem to be various interpretations," she indicated, "because back during the negotiations – and I was there at many of them – there was no awareness of delays post-approval before launch. So that becomes fundamental to whether the incentive even exists if the exclusivity has been burned through before anybody launches."

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Pfizer Switching Data Hits FDA Guide

With biosimilar sponsors having to generate ancillary clinical trial data to achieve a designation, Pfizer's PAS was supported by positive topline data from its REFLECTIONS B538-12 interchangeability study evaluating "multiple switches" between Abrilada and Humira in rheumatoid arthritis patients.

Overall, the study was split up into four 'treatment' periods and one safety follow-up period, over a period of 36 weeks. The study as a whole took just under 18 months to complete.

According to the US-based firm, the study demonstrates "pharmacokinetic equivalence in patients who switched multiple times between treatment" with Abrilada and Humira.

"Based on results, the researchers have decided that switching between Abrilada and Humira does not make any clinically meaningful difference compared to continuous treatment with Humira," Pfizer concluded.

Pfizer's *study* comparing the level of adalimumab in the blood between two groups of participants saw the first group receive Humira throughout the study, while the second started on Humira and then switched to Abrilada for a total of three times during the study.

Of the 213 participants in the switching arm, 201 finished the study, and 12 stopped treatment early.

The latest FDA guidance directs that in a study seeking to demonstrate interchangeability, the switching arm is "generally expected to incorporate at least two separate exposure periods (switch intervals) to each of the two products" – i.e., at least three switches.

"In addition to establishing biosimilarity, a manufacturer of an interchangeable biosimilar needs to submit information to show that the proposed product can be expected to produce the same clinical result as the reference product in any given patient," the FDA adds.

"Also, for certain interchangeable biosimilars, FDA evaluates information on the effects of switching between the reference product and the interchangeable biosimilar."

Abrilada was approved as a biosimilar without an interchangeability designation in November 2019, presented in the lower concentration 40mg/0.8ml and 20mg/0.4ml strengths, as both a pre-filled pen and syringe. (Also see "*Pfizer's FDA-Approved Adalimumab Faces Four-Year Wait*" - Generics Bulletin, 18 Nov, 2019.)

Its approval was based on Pfizer's initial Phase III REFLECTIONS B538-02 comparison trial, which involved 597 rheumatoid arthritis patients and wrapped in December 2017.

Abrilada's FDA-approved label includes rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, adult Crohn's disease, ulcerative colitis, and plaque psoriasis indications.

Boehringer Chose 'Sensitive' Patient Population

Four months before Pfizer's PAS filing, Boehringer Ingelheim's lower-concentration Cyltezo emerged as the first Humira biosimilar granted an interchangeability designation, while offering the first ever-published data on what a successful switch study looks like.

Boehringer's landmark VOLTAIRE-X switching study, which the German firm described as establishing "no meaningful clinical differences in pharmacokinetics, efficacy, immunogenicity and safety between switching and continuous treatment groups," used a plaque psoriasis patient population.

"We chose plaque psoriasis for VOLTAIRE-X because it is the most sensitive population to allow for detection of differences as a result of switching between Humira and Cyltezo, and we aligned with the FDA on the plaque psoriasis population for this trial," Boehringer Ingelheim told *Generics Bulletin's* sister publication, the *Pink Sheet*.

"The VOLTAIRE program is comprehensive," Boehringer insisted, "and its design was the result of close and ongoing communication with FDA."

In addition, Boehringer previously conducted studies for biosimilarity designation "in three different therapeutic areas … to provide confidence to physicians in regard to their patient populations."

To date, only three other biosimilars have been designated interchangeable. Two of those are insulins, referencing Sanofi's Lantus: Biocon's Semglee (insulin glargine-yfgn) and Eli Lilly's Rezvoglar (insulin glargine-aglr). (Also see "*Lilly Gets Second Interchangeable Insulin Glargine In US*" - Generics Bulletin, 18 Nov, 2022.)

Only one other monoclonal antibody has been approved with an interchangeability designation, Coherus BioSciences/Formycon's Cimerli (ranibizumab-eqrn), referencing Genentech's Lucentis (ranibizumab).

In achieving it, the partners did not conduct a switching study, instead providing in the eyes of the FDA "sufficient justification" that Cimerli will produce the same clinical result in any given patient for each condition of use. (Also see "*Coherus Biosimilar Used 'Scientific Justification' To Skip Switch Study, Still Get Interchangeability With Lucentis*" - Generics Bulletin, 2 Sep, 2022.)

A multidisciplinary review *memo* published by the FDA unveiled several noteworthy insights for

biosimilar Lucentis sponsors, including that the US regulator and its counterpart in Europe, the European Medicines Agency, had different requirements in terms of the primary efficacy population and statistical analysis for the clinical comparability trial.

Guides, Proposals And Information

As players across the industry continue to get to grips with interchangeability, more and more information, guidance, and proposals are being published or pushed with the goal of facilitating approvals, driving uptake and resolving lingering questions.

Only last month, an FDA regulatory science pilot program under the third iteration of the Biosimilar User Fee Amendments, or BsUFA III, was launched, with one of its focuses "advancing the development of interchangeable products."

Acknowledging that the biosimilar and interchangeable landscape will continue to evolve, the FDA acknowledged that "both regulatory experience and policy development may inform and change the knowledge gaps for the research pilot program as BsUFA III progresses." (Also see "*BsUFA Research Roadmap Highlights Interchangeability And Reducing Trials*" - Generics Bulletin, 27 Jan, 2023.)

Moreover, under a *proposed rule* released by the Centers for Medicare and Medicaid Services late last year, Medicare Part D plans would, beginning in 2024, be permitted to substitute interchangeable biosimilars as soon as they are available, without waiting for the beginning of the next benefit year. (Also see "*Interchangeable Biosimilars May Qualify For 'Immediate Substitution' In Medicare Part D*" - Generics Bulletin, 21 Dec, 2022.)

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

And in a proposal that raises further questions of the designation's *raison d'être*, draft legislation introduced in the US senate, the proposed Biosimilar Red Tape Elimination Act, seeks to prohibit the FDA from requiring biosimilars to undergo switching studies to receive an interchangeability designation. (Also see "*US Bill Seeks To Eliminate Biosimilar Interchangeability Trial Burden*" - Generics Bulletin, 22 Nov, 2022.)

In a recent exclusive interview with *Generics Bulletin*, Fresenius Kabi's senior vice president for

US biosimilars Ali Ahmed summed up the company and other's position, saying, "I think there's a lot of confusion around what is and what is not interchangeability. The best way I can describe it is as more of a legal connotation than anything else."

"A biosimilar," he insisted, "is safe, it's effective, it is meant to be utilized according to its label and for the indications for which it was approved. And there shouldn't be any confusion that a biosimilar product is just as safe and just as effective as an interchangeable product and vice versa." (Also see "*Fresenius Kabi: Adalimumab Customers Want Supply Guarantee, We Can Provide That*" - Generics Bulletin, 25 Jan, 2023.)

[Editor's note: This article was updated 28 February to include data from Pfizer's Phase III switching study, a link to which can be found in the main article]