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US Biosimilars Enjoy A Year Of Firsts In 2021

Two Interchangeable Biosimilars And First Ophthalmic Biosimilar Approved

by David Wallace

While US biosimilar approvals have been somewhat thin on the ground in 2021 – with multiple products seeing action delayed due to the FDA's inability to conduct certain facility inspections during the COVID-19 pandemic – the market has nevertheless seen several firsts this year, including two interchangeability designations and the first ophthalmic biosimilar approval.

With biosimilars increasingly gaining traction in the US in recent years thanks to multi-source competition on certain key products, as well as healthy uptake in treatment areas such as oncology, 2021 saw the US biosimilars market take further steps forward with a number of firsts.

These included the first US Food and Drug Administration designations of biosimilar interchangeability, the launch of the first interchangeable biosimilar, and the first biosimilar to be approved by the FDA for ophthalmic indications.

However, at the same time several biosimilar developers saw their efforts to reach the market frustrated by delays to FDA approvals, caused by the agency's inability to conduct certain necessary facility inspections due to pandemic-related travel constraints.

Semglee Insulin Glargine Is First Interchangeable Biosimilar

The first US biosimilar approval of the year came in July, with the FDA's formal designation of Viatris' Semglee (insulin glargine-yfgn) biosimilar as interchangeable with Sanofi's Lantus blockbuster. (Also see "*Viatris Wins Landmark First US Interchangeability Designation For Semglee*" - Generics Bulletin, 29 Jul, 2021.)

To meet this additional standard to biosimilarity, a product must not only be deemed biosimilar to its reference brand but must also demonstrate that it will "produce the same clinical result as the reference product in any given patient."

Moreover, "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."

While industry views are still to some extent mixed on the desirability and necessity of interchangeability as a separate standard to biosimilarity in the US, the designation brings valuable prizes for successful applicants in the form of pharmacy-level substitution as well as a year of interchangeable biosimilar exclusivity for the first interchangeable biosimilar version of each product, dating from commercial launch of the interchangeable biosimilar. (Also see "*Biosimilar Interchangeability: A Blessing Or A Curse?*" - Generics Bulletin, 9 Jul, 2021.)

In Viatris' case, the launch of the interchangeable insulin glargine biosimilar – which followed some months after approval, in November (Also see "*First Interchangeable Biosimilar Launched In US*" - Generics Bulletin, 16 Nov, 2021.) – offers the opportunity to build on the relatively low market share captured so far by the non-interchangeable version of Semglee, which is due to be rapidly phased out.

The company has also taken the step of launching the interchangeable biosimilar in both branded and unbranded versions, with the unbranded version offered at a wholesale acquisition cost of $147.98 for a pack of five 3ml pens and $98.65 per 10ml vial, representing a 65% discount to the list price of Lantus.

Meanwhile, the branded version of interchangeable Semglee comes in at a price that is a lot closer to the reference brand, with a WAC of $404.04 per pack of five 3ml pens and $269.38 per 10ml vial. (Also see "*Viatris CEO Talks Integration, Roadmap And Interchangeable Biosimilars*" - Generics Bulletin, 22 Nov, 2021.)

Humira Gets First Interchangeable Biosimilar Approval

Semglee was not the only biosimilar to be formally designated as interchangeable by the FDA in 2021. Several months later, in mid-October, the agency announced that Boehringer Ingelheim was to be the second recipient of an interchangeability designation, for its Cyltezo (adalimumab-adbm) rival to Humira.

The biosimilar – which was initially approved by the FDA in August 2017 – is currently scheduled to be among a chasing pack of Humira biosimilars that are expected to hit the US market in 2023, after Amgen launches its Amjevita (adalimumab-atto) version at the beginning of the year, under

a series of settlement deals between biosimilar sponsors and originator AbbVie.

Boehringer Ingelheim has an expected launch date of 1 July 2023, putting it just after Samsung Bioepis on 30 June. (Also see "*First Interchangeable Humira Biosimilar Approved In US*" - Generics Bulletin, 18 Oct, 2021.)

It remains to be seen how interchangeability will affect the biosimilars market more broadly and the biosimilar Humira market specifically. However, with so many adalimumab competitors expected to launch in the US from 2023, interchangeability and Boehringer Ingelheim's year of interchangeable exclusivity could prove to be a significant differentiator.

Samsung Bioepis Bags First Ophthalmic Biosimilar

Another first for US biosimilars came in September, when Samsung Bioepis – the joint venture between Samsung Biologics and Biogen – announced that it had received the FDA's first approval for a biosimilar with ophthalmic indications, its Byooviz (ranibizumab-nuna) rival to Lucentis. (Also see "*FDA Approves First Ophthalmic Biosimilar With Samsung Bioepis' Lucentis Rival*" - Generics Bulletin, 20 Sep, 2021.)

While biosimilar versions of Avastin (bevacizumab) are already available in the US – and, like the reference brand, are used off-label to treat eye disease – this has led to criticism from some quarters given the relative lack of supporting data in ophthalmic indications. (Also see "*US Ophthalmology Association Warns Against Untested Avastin Alternatives*" - Generics Bulletin, 8 Sep, 2021.)

Lucentis had previously been expected to face biosimilar competition in the US by the end of 2021. But as it received its Byooviz approval, Samsung Bioepis overturned these expectations by revealing that it would not launch the biosimilar before June 2022, following a hitherto undisclosed settlement with originator Genentech.

"Pursuant to a global license agreement entered into with Genentech," the company indicated, "Samsung Bioepis and Biogen will have freedom to market in the US as of June 2022." (Also see "*US Lucentis Competition Expectations Upended By Byooviz*" - Generics Bulletin, 22 Sep, 2021.)

Inspection Limitations Lead To Delays

Despite so many firsts for US biosimilars in 2021, some developers may see it as a year of missed opportunities to approve a greater number of biosimilars, after international inspection constraints related to the COVID-19 pandemic prevented the FDA from conducting certain necessary inspections, pushing back the potential approvals of multiple biosimilar candidates.

The first signs of this were seen at the very end of 2020, when Viatris and Biocon revealed that their bevacizumab candidate had been indefinitely delayed as the agency was unable to conduct

a facility inspection. (Also see "*Viatris And Biocon's US Bevacizumab Hit By Indefinite Delay*" - Generics Bulletin, 26 Dec, 2020.)

Then, in September, Alvotech revealed that its AVT02 adalimumab candidate – potentially the first US biosimilar version of the 100mg/ml higher-concentration presentation of Humira – had been similarly delayed. (Also see "*Alvotech Suffers Delay On Higher-Strength Adalimumab In US*" - Generics Bulletin, 21 Sep, 2021.) Alvotech had also been seeking interchangeability for its adalimumab biosimilar.

Notably, the FDA's current inability to approve these two biosimilars contrasts with the approach of the European Medicines Agency, which has seen fit to endorse both of these products this year. Viatris and Biocon gained approval for their bevacizumab biosimilar in April while Alvotech's filing for a higher-strength Humira biosimilar with partner Stada received a marketing authorization in November. (Also see "*Alvotech Welcomes EU Endorsement Of Higher-Strength Adalimumab*" - Generics Bulletin, 16 Dec, 2021.)

More recently, Fresenius Kabi acknowledged that its proposed pegfilgrastim biosimilar had suffered from the same uncertainty over the US agency's ability to conduct a necessary inspection, with the product pushed back to a likely FDA approval in 2022, from an originally expected date of 2020. (Also see "*Fresenius Delayed By FDA Inspection Uncertainty As It Works Towards US Pegfilgrastim Launch*" - Generics Bulletin, 12 Nov, 2021.)

And as the year drew to a close, an FDA goal date came and went without approval for the BAT1706 bevacizumab candidate developed by China's Bio-Thera Solutions. (Also see "*Bio-Thera's Bevacizumab US Action Date Passes Without Approval*" - Generics Bulletin, 1 Dec, 2021.)

Responding to queries over these biosimilar delays, the FDA said it was "actively working on an approach for addressing outstanding inspections."

"FDA is currently employing other tools to evaluate facilities, as appropriate," the regulator indicated, "such as requesting records and other information under section 704(a)(4) of the FD&C Act or reviewing trusted foreign regulator inspection records under existing mutual recognition agreements. These tools have, in many cases, successfully allowed us to take actions on applications in lieu of an FDA inspection."

"FDA continues to monitor the public health situation as well as public health advisory travel restrictions," the agency concluded. "Once safe travel can resume, inspections will be scheduled based on a number of factors including the public health impact." (Also see "*FDA Will Take Action On Biosimilars Delayed By Inspection Lag*" - Generics Bulletin, 21 Oct, 2021.)

Two Approvals In December Take Total To Four

However, the final days of 2021 demonstrated that even if biosimilar approvals have been somewhat muted this year – similar to 2020, when just three biosimilars were approved by the FDA (Also see "*US Biosimilars See A Banner Year Despite Few Approvals*" - Generics Bulletin, 26 Dec, 2020.) – the agency is still pushing ahead with reviewing and approving new products.

A second biosimilar version of insulin glargine was approved by the FDA in the form of Eli Lilly's Rezvoglar (insulin glargine-aglr) 3ml pre-filled pens, which unlike Semglee does not benefit from a designation of interchangeability. (Also see "*Will Eli Lilly's Rezvoglar Be Able To Compete With Interchangeable Semglee?*" - Generics Bulletin, 23 Dec, 2021.) Lilly has already marketed for years its Basaglar follow-on biologic version of insulin glargine, but not a biosimilar.

And a further adalimumab approval – this time, for Coherus BioSciences' Yusimry (adalimumab-aqvh) version – took the total number of FDA-approved Humira rivals to seven. (Also see "*Coherus Promises 'Compelling Value Proposition' After US Adalimumab Approval*" - Generics Bulletin, 20 Dec, 2021.) The approval sets up what could be the fiercest biosimilar battle in the US to date, as multiple developers line up launches in 2023.