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More Than Just Humira: US Biosimilars Enjoy An Eventful 2023

Adalimumab Competition Hits, Firms Settle On Stelara And New First Biosimilars Approved

by David Wallace

The launch of competition to Humira was the main event for US biosimilars this year – but a number of other key developments also took place in 2023, including settlements on Stelara that set up a series of launches in 2025, as well as first approvals for ustekinumab, natalizumab and tocilizumab biosimilars.

In 2023, one story dominated the headlines for the US biosimilars sector: the debut of biosimilar competition to AbbVie's top-selling Humira (adalimumab) immunology brand.

A series of patent settlements between biosimilar sponsors and the originator had paved the way for multiple launches throughout this year, with competition eventually materializing in the form of an initial launch by Amgen of its Amjevita (adalimumab-atto) version at the end of January, followed by a second wave of several Humira rivals that launched simultaneously at the start of July (*see sidebar*).

Amgen's initial launch met with a reasonably muted response, with Amjevita bringing in $51m in its first two months on the market. (Also see "*Amgen Reveals First Figures For US Humira Rival*" - Generics Bulletin, 28 Apr, 2023.)

Fresh Wave Of Adalimumab Biosimilars Hits US

By David Wallace

However, the effect on AbbVie's Humira sales was immediate, with the originator reporting first-

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quarter brand revenues in the US that were down by just over 26% – roughly in line with AbbVie's expectations – at just under $2.95bn. (Also see "*AbbVie Gets Humira Erosion Right, But Skyrizi/Rinvoq Disappoint Investors*" - Scrip, 27 Apr, 2023.)

Amgen had the biosimilar adalimumab market to itself for several months – but when the second wave of launches arrived in July, competition intensified considerably.

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As launch dates arrive under settlement agreements with Humira originator AbbVie, multiple firms have introduced adalimumab biosimilars in the US, confirming launch and pricing details – with one biosimilar following in the footsteps of Coherus by announcing an 85% discount to the originator.

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In the space of just a few days, launches were confirmed for Biocon's Hulio (adalimumab-fkjp); Boehringer Ingelheim's Cyltezo (adalimumab-adbm); Celltrion's Yuflyma (adalimumab-aaty); Coherus's Yusimry (adalimumab-aqvh); Fresenius Kabi's Idacio (adalimumab-aacf); Samsung Bioepis and Organon's Hadlima (adalimumab-bwwd); and Sandoz's Hyrimoz (adalimumab-adaz), with all of these biosimilars battling for a share of the market.

Differentiation efforts revolved around multiple factors, but one of the most important aspects was price. Amgen had launched its initial biosimilar with a dual pricing strategy – offering two versions at wholesale acquisition cost list prices that were set at 5% and 55% below the Humira list price respectively, albeit with the higher-priced version accompanied by a significant undisclosed rebate.

This approach, Amgen explained, was designed to "address the complexity of the US market," notably the preferences of pharmacy benefit managers. "PBMs have a business model that requires that they negotiate rebates with manufacturers," Amgen's management acknowledged, "and so they would prefer a high list price and negotiate rebates to net the price down and then pass those rebates through to their upstream employer clients." (Also see "*Amgen Talks Dual Pricing Strategy For Amjevita*" - Generics Bulletin, 1 Feb, 2023.)

Other biosimilar sponsors followed suit once they hit the market, with several adopting dual pricing strategies of their own. Meanwhile, others preferred to simply set a deep discount at the list price level, with Coherus announcing that it would be selling Yusimry at a massive 85% discount to Humira, as well as partnering with Mark Cuban's Cost Plus Drugs company to sell the biosimilar at an even steeper discount. (Also see "*Coherus Plots 'Lowest Price Adalimumab' With Huge Discount, Ties Up With Mark Cuban*" - Generics Bulletin, 1 Jun, 2023.)

Eventually, it became apparent that many of the biosimilars in the market were going to have to

compete at that kind of discount level to stay in the game. For example, Samsung Bioepis and Organon also offered their biosimilar at a 85% discount, while Sandoz and Biocon announced discounts of 81% and 85% respectively for their unbranded adalimumab products.

Price Not The Only Deciding Element

While price was a key factor, it was not the only element of differentiation between the various biosimilars on the market.

One aspect of interest was interchangeability, with Boehringer's Cyltezo the only biosimilar on the market in July with an interchangeability designation, which allows pharmacy-level substitution subject to US state law. Perhaps reflecting anticipation of gaining a key advantage from interchangeability, Boehringer offered a discount of just 5%-7% off Humira's price for its biosimilar.

Meanwhile, other suppliers hoped to gain an edge by offering a high-concentration 100mg/ml version of adalimumab – in line with the latest version of Humira – rather than the 50mg/ml lower concentration offered by many of the other biosimilars. Samsung Bioepis's Hadlima, Sandoz's Hyrimoz and Celltrion's Yuflyma were the only three biosimilars to have a 100mg/ml version approved at launch.

One biosimilar sponsor that had hoped to be able to offer both interchangeability and a high-concentration formulation was Alvotech, which had partnered with Teva for a planned US launch of its AVT02 adalimumab candidate as part of the July group. However, a series of US Food and Drug Administration complete response letters linked to its Reykjavik manufacturing facility prevented Alvotech from obtaining approval in time. (Also see "*Alvotech And Teva To Miss US Adalimumab Launch After Further FDA Setback*" - Generics Bulletin, 29 Jun, 2023.)

Nevertheless, Alvotech has pledged to compete in the market once the compliance issues are resolved, with management insisting that the story of Humira biosimilars in the US is "still being written." (Also see "*Alvotech Says Adalimumab Story Is 'Still Being Written' Ahead Of 'Critical' Inspection*" - Generics Bulletin, 8 Sep, 2023.)

Even for those firms that were able to enter the market, however, it was not necessarily a smooth ride. PBMs were selective about which biosimilars would be included on formularies – often only selecting two or three biosimilars for inclusion – and it appeared that Boehringer and Sandoz were frequently favored, with Sandoz recently claiming that it had "more lives covered than any other competitor" on adalimumab. (Also see "*Another PBM Favors Sandoz And Boehringer On Adalimumab*" - Generics Bulletin, 11 Jul, 2023.)

More recently, the market has been reshaped further after Pfizer was able to secure an interchangeability designation for its own biosimilar, Abrilada (adalimumab-afzb), making it

only the second interchangeable adalimumab available, after Boehringer's Cyltezo. (Also see "*FDA Decision On Interchangeable Exclusivity Allows Pfizer To Rival Boehringer On Adalimumab*" - Generics Bulletin, 9 Oct, 2023.)

As Pfizer revealed an October launch and a dual pricing strategy for Abrilada by the end of the year, Boehringer disclosed that it was bringing forward the launch of an unbranded version of Cyltezo from 2024 to 2023, with the product priced at a much steeper 81% discount than Cyltezo's initial 5%-7%. (Also see "*Boehringer Accelerates Adalimumab Dual Pricing Strategy With 81% Discount*" - Generics Bulletin, 5 Oct, 2023.)

In recent weeks AbbVie has also revealed the more serious impact that biosimilars have had on its branded Humira revenues since the onslaught of multi-source competition began in July. The originator reported US Humira sales that dropped by almost two-fifths in the third quarter, again in line with AbbVie's previously stated expectations. (Also see "*AbbVie Results Reflect Humira Hit In Q3*" - Generics Bulletin, 30 Oct, 2023.)

However, for many industry stakeholders, the anticipation is that 2024 will be when the true dynamics of the biosimilar adalimumab market begin to reveal themselves, as contracting cycles refresh and formularies prepare for the first full calendar year of competition to Humira.

Stelara Settlements Set Stage For 2025

Adalimumab was far from the only game in town for US biosimilars in 2023, however. Another major immunology brand – J&J's Stelara (ustekinumab) – was also the focus of plenty of attention.

While Stelara biosimilar launches had been expected to launch in the US as early as the end of 2023, a series of patent settlements with J&J struck by biosimilar sponsors this year has recalibrated expectations for the brand, giving five biosimilars confirmed launch dates in early 2025, assuming they receive FDA approval.

Amgen, which was first to settle with J&J, has gained a launch date of 1 January 2025 for its version. The firm is the first and so far the only sponsor to have garnered an approval for a Stelara rival, with the FDA authorizing its Wezlana

History Repeating: Will US Stelara Settlements Follow Humira's Lead?

By David Wallace

13 Jun 2023

Years before Humira rivals hit the US market in 2023, a series of litigation settlements between biosimilar adalimumab developers and originator AbbVie provided a roadmap for a succession of date-certain launches this year. Now, similar settlements over Stelara between J&J and ustekinumab developers are

(ustekinumab-auub) version as an interchangeable biosimilar at the end of October. (Also see "*Trailblazer Amgen Scoops First US Stelara Biosimilar – With Interchangeability*" - Generics Bulletin, 1 Nov, 2023.)

starting to fall into place for 2025.

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The Amgen settlement was followed by a J&J deal with Alvotech and US marketing partner Teva that offered a date no later than 21 February 2025 for their partnered AVT04 ustekinumab candidate.

Samsung Bioepis and Sandoz have a settlement offering launch a day later, on 22 February 2025. Celltrion's settlement with J&J has given the Korean firm a 7 March 2025 launch date for its CT-P43 version. And partners Fresenius Kabi and Formycon can enter the market on 15 April 2025 with their FYB202 biosimilar.

It remains to be seen whether other biosimilar sponsors will settle with J&J and gain similar launch dates, but at this point Stelara feels like it could be the next Humira in terms of fierce biosimilar competition with multiple rivals launching at around the same time.

First Natalizumab And Tocilizumab Biosimilars Also Approved

The back half of 2023 also saw two other first-time registrations for biosimilar molecules in the US, with Biogen's Tysabri (natalizumab) and Roche's Actemra (tocilizumab) both seeing their first rivals approved by the FDA.

In August, Sandoz received approval for the Tyruko (natalizumab-sztn) biosimilar rival to Tysabri that it will commercialize in conjunction with development partner Polpharma Biologics. (Also see "*FDA Approves Natalizumab For Sandoz And Polpharma Biologics*" - Generics Bulletin, 25 Aug, 2023.)

Although litigation with originator Biogen is still ongoing, Sandoz has set out plans to launch the biosimilar in the first half of 2024. (Also see "*Sandoz Mulls At-Risk Launch For US Natalizumab*" - Generics Bulletin, 30 Oct, 2023.)

Then in September, Biogen itself received approval from the FDA for the Tofidence (tocilizumab-bavi) version of Actemra that was developed by its partner Bio-Thera Solutions. (Also see "*Biogen Gets First US Tocilizumab Biosimilar*" - Generics Bulletin, 2 Oct, 2023.)

The partners have recently struck a settlement deal with Roche to end patent litigation over tocilizumab, with details of the launch date still unclear – although the originator indicated that it continued to expect competition to Actemra in the US "in 2024." (Also see "*Biogen, Bio-Thera*

Shake Hands On US Actemra Settlement" - Generics Bulletin, 27 Oct, 2023.)

And a final first for US biosimilars came in the last days of 2023, with Coherus Biosciences announcing on 26 December that it had obtained approval for a first rival to Amgen's Neulasta (pegfilgrastim) Onpro on-body injector device, using Coherus' Udenyca (pegfilgrastim-cbqv) biosimilar.

Coherus had only recently resubmitted a filing for Udenyca Onbody to the FDA, just weeks after a complete response letter from the agency knocked back the application due to an ongoing review of inspection findings at a third-party filler. (Also see "*Coherus Refiles US On-Body Pegfilgrastim, With Potential For 2023 Approval*" - Generics Bulletin, 9 Oct, 2023.)

IRA Price Negotiation Casts Shadow Over Sector

Elsewhere in the US biosimilars sector, 2023 also saw biosimilar rivals to Lucentis (ranibizumab) start to capture market share in a more meaningful way than in 2022, with both Samsung Bioepis and Biogen's Byooviz (ranibizumab-nuna) and Coherus' Cimerli (ranibizumab-eqrn) making gains as the year went on.

While the two biosimilars each held just a 4% market share as of Q1 2023, the second quarter saw Cimerli shoot up to 17% while Byooviz boasted 8% of the market. (Also see "*Guidelines, Treatment Duration And Access All Key For Biosimilar Uptake, Says Samsung Bioepis*" - Generics Bulletin, 24 Oct, 2023.)

This year has also seen relatively new players in the biosimilars space begin to make their mark, such as Amneal making inroads with its initial trio of Alymsys (bevacizumab-maly), Releuko (filgrastim-ayow) and Fylnetra (pegfilgrastim-pbbk).

Amneal has also just struck a deal with mAbxience to gain US rights to two denosumab biosimilars referencing the Prolia and Xgeva brands that have annual US sales in excess of $4bn. Meanwhile, Meitheal recently announced a deal to bring in insulin aspart, insulin lispro, and insulin glargine candidates from Tonghua Dongbao Pharmaceutical. (Also see "*Amneal And Meitheal Join Biosimilars Forum*" - Generics Bulletin, 19 Oct, 2023.)

On the regulatory front, the FDA's approach to biosimilars continues to evolve, with the agency recently publishing guidance on labelling that suggests that the US interchangeability designation for biosimilars may become less prominent in future. The FDA has now recommended omitting details of interchangeability from biosimilar labels altogether, in favor of a statement of biosimilarity – although interchangeability information will still be contained within its online Purple Book database. (Also see "*From Interchangeability To Invisibility: FDA Wipes Designation From Biosimilar Labels*" - Generics Bulletin, 18 Sep, 2023.)

However, 2023 also brought a development that may cast something of a shadow over the future of the biosimilars sector, with both Stelara and Novo Nordisk's NovoLog (insulin aspart) being included in the initial Medicare price negotiation list under the Inflation Reduction Act. (Also see "*Price Negotiation Purgatory: Upcoming Biosimilars Couldn't Keep Stelara, NovoLog Off The List*" - Pink Sheet, 29 Aug, 2023.)

The move surprised some observers – with many assuming that biosimilar competition on the near-term horizon may disqualify these products from price negotiation – and could lead to a chilling effect on biosimilar development, with the US off-patent industry having long been opposed to the IRA and its price negotiation mechanism. (Also see "*AAM Laments Price Negotiation Legislation Passing US Senate*" - Generics Bulletin, 8 Aug, 2022.)

Another potential barrier for biosimilars is the continuing distortions caused by PBMs, with opaque rebates and contracting practices often making it difficult for new biosimilars to get traction in the market. (Also see "*AAM Calls For FTC Scrutiny Of Pharmacy Benefit Manager Practices*" - Generics Bulletin, 26 May, 2022.)

Meanwhile, oncology biosimilars – which saw great success on initial launch – have in recent quarters seen prices driven down as the presence of multiple players in the market intensifies competition. (Also see "*Amgen Builds Up Future Launches As Oncology Biosimilars Slide*" - Generics Bulletin, 2 Feb, 2023.)

At a transitional time for biosimilars – a time when the US is simultaneously being opened up to new biosimilar competition and seeing uptake and greater access, while also keeping in place mechanisms that make life tougher for biosimilar sponsors and which do not support the market beyond the first couple of biosimilars on a given molecule – the current state of the market was perhaps best summed up early this year by Craig Burton, executive director of industry body the Biosimilars Council: "In a word, complicated." (Also see "*'In A Word, Complicated' – AAM's Burton Talks US Biosimilars*" - Generics Bulletin, 21 Mar, 2023.)