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Cutting Through The Confusion On US Biosimilar Interchangeability

Experts Offer Clarity Amid Misunderstandings Over US FDA Designation

by David Wallace

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.

With the first three interchangeability designations having been granted for biosimilars by the US Food and Drug Administration and one of them being an interchangeable Humira (adalimumab) biosimilar, plus multiple adalimumab biosimilars lined up for launch in 2023, the US interchangeability designation is attracting more and more attention among industry stakeholders.

However, with confusion persisting over interchangeability in the US – including the misleading implication that biosimilars without the designation are inferior to those with it, as well as the FDA's designation of interchangeability differing from how similar language is used to describe biosimilars in other global regions – there is a risk that the US market could become distorted by misunderstandings and misinformation.

Speaking with Joseph Park, senior manager of regulatory affairs at Samsung Bioepis, and Gillian Woollett, the firm's head of regulatory strategy and policy – authors of a recent article on the subject (*see sidebar*) – several aspects of

Confusion Persists Over US Biosimilar Interchangeability

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interchangeability were highlighted to *Generics Bulletin* as being particularly important for stakeholders to grasp.

These include the fact that the US FDA interchangeability designation for biosimilars is a legal rather than clinical distinction, allowing pharmacists (subject to state law) to substitute a biosimilar for its reference biologic without consulting the original prescriber.

They also include the idea that the underlying science means that all biosimilars can be considered as interchangeable as a clinical matter – in the sense of being safe and effective to substitute for their reference brands – even if sponsors have not pursued the formal FDA designation of interchangeability.

By David Wallace

23 Jun 2022

The US biosimilars industry is being constrained by misunderstandings stemming from the country's interchangeability designation, a new paper in *BioDrugs* has highlighted, citing an urgent need for clarity over the misperception that interchangeable biosimilars are superior to biosimilars without the designation.

Read the full article here

However, to effectively convey these ideas to stakeholders – particularly healthcare providers – there will need to be a renewed emphasis on education efforts, especially from the FDA itself, Park and Woollett believe.

A Legal, Not Clinical, Distinction

Asked how well stakeholders understood the idea that the US interchangeability designation was a legal rather than clinical distinction – the central thrust of the recent *paper published in BioDrugs* – Park acknowledged that "there is still a lot of confusion over the interchangeability designation in the US, and apparently some physicians have been led to believe that the FDA interchangeability designation is relevant to their prescribing decisions, whereas it is only about switching patients by [a mechanism] other than the prescriber."

"That's why we wrote the paper in the first place," he explained. "I think without the background on the regulatory pathway for interchangeable biologics, because the term is used commonly to define that [products] can be switched for patients, I think that caused the most confusion to the physicians."

Touching on the potential for interchangeable biosimilars to be seen as superior to biosimilars without the designation, he said that "without any background, if you just hear about it, it

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sounds like a better biosimilar product. But it isn't."

The difference between the US FDA interchangeability designation and the European conception of interchangeability was also a complicating factor, Woollett suggested.

"The EU regulators *came out with arguably the common use of the term*, rather than the legal use," she explained, with European regulators effectively considering every biosimilar to be interchangeable in the sense of being able to be switched with its reference product and other biosimilar versions, while leaving the actual decisions over specific substitution mechanisms to individual EU member states.

Woollett also pointed to a *2020 BioDrugs pape*r led by Sandoz's Hillel Cohen that offered further context on the risks of misinformation, adding that "the FDA has begun to allude to it as well."

One such example of misinformation highlighted by Woollett was a *misleading paper on so-called 'non-medical switching'*. "FDA has not commented on this paper per se," she said, "but they are aware that such papers are being published on an ongoing basis."

FDA Must Provide Education To Stakeholders

Asked about how misinformation around biosimilars could be countered, Park was clear that "education to all the stakeholders is the key factor," with Woollett highlighting in particular the need for education geared towards healthcare providers.

"I think all of them should be aware that an interchangeable biologic is not a better biosimilar," Park said. "With physicians, I think they are waiting for the interchangeability designation before prescribing a biosimilar, because they have a perception that it might help with their decisions. However, that is not a very wise approach, because not all biosimilars will pursue that designation. Largely because they are already physician-administered in clinics, so there is no opportunity for [the product] to be switched other than by the physicians themselves."

Pointing to the importance of pharmacists, Park suggested that "going forward, I think pharmacists will play a larger role, as they are often the most well-informed and trusted health

Interchangeability Designation For Semglee

By David Wallace

29 Jul 2021

Viatris has revealed its commercial strategy for its Semglee insulin glargine biosimilar in the US after winning a landmark first designation of interchangeability for the product from the FDA that will allow pharmacy-level substitution with a year of exclusivity.

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care provider. So, I think going forward the role of pharmacists will grow."

"Pharmacists have been interested in biosimilars since the beginning," Woollett added. "And they know about drugs – that's their job. They don't have to deal with the other aspects of treating patients. And for retail, they're the ones in the community so they are already known."

Ultimately, she said, it came back to "this prescribing versus dispensing distinction that we are trying to make in the paper."

And in terms of who should be leading education efforts, Woollett was clear that "the big one is the FDA, always," with the US agency spurred on by legislation aimed at bolstering education around biosimilars. (Also see "*Biosimilar Education And Innovation Bills Head To Biden's Desk*" - Generics Bulletin, 20 Apr, 2021.)

"I think that is where the more explicit direction is probably coming from – stepping up in response to that and expanding their materials," Woollett suggested. "And they have a lot of stuff on their website – FDA.gov I think just helps with the credibility."

Referring to contracts already in place for biosimilar education programs (Also see "*Medscape To Develop FDA Biosimilars Educational Program*" - Generics Bulletin, 21 Feb, 2022.), Woollett urged a focus on clarity around the purpose of the interchangeability designation. "It's particularly this aspect of interchangeability not being relevant for prescribing, but being critical to dispensing, that we flag; while of course recognizing that state laws govern both physicians and pharmacists, just separately."

There was a risk, Woollett cautioned, that progress for biosimilars could be stalled due by physicians choosing to "wait for the designation."

> ***"I would suggest as a scientific matter, if any product was to pursue interchangeability and fail, they would have actually proven that they were not biosimilar in the first place."***

Asked whether a deeper understanding of the scientific and regulatory processes underpinning both originator biologics and biosimilars – in particular, the concept of comparability that allows manufacturing changes for biologic brands to be authorized – could help stakeholders to understand ideas around interchangeability for biosimilars, Park attested that "the scientific and

regulatory principles are the same."

"Consistent regulatory and scientific principles should be applied to all biologics, not just biosimilars, so I think going forward it should be implemented that way," he stated.

Woollett noted, "that was another *paper I wrote with Chris Webster in BioDrugs* discussing comparability versus biosimilarity and saying they essentially have to be the same: you either believe in quality attributes to define a biologic [originator or biosimilar] or you don't."

"The challenge we've got in the US," she highlighted, "is that the use of comparability on a particular product is not public," in contrast to Europe *where such data is more transparent.*

"Even though the [originator] products continue to match over their lifetimes, for example between the Europe and the US, it cannot be definitively stated by a third party that there has been a manufacturing change to any biologic by referencing the US regulatory history because such changes are trade secrets," Woollett explained.

"So it's back to Joseph's point: regulatory consistency and the same science for everybody. The business model is actually not relevant to the FDA."

Touching further on the differences between the way the US interchangeability designation differs from the way interchangeability is considered in Europe, Woollett recalled that "the European regulators *wrote in 2017* that they consider every biosimilar to already be interchangeable," with specific policy decisions around actual switching left to individual EU member states.

In Europe "the law is silent, the European Medicines Agency is not saying either way," she said. But in the US, "we have this in-between opportunity that therefore implies that the biosimilars without the designation are not interchangeable. And that's the really incorrect message – they are just not designated as interchangeable."

To emphasize this point, she added, "I would suggest as a scientific matter, if any product was to pursue interchangeability and fail, they would have actually proven that they were not biosimilar in the first place."

How Will Interchangeability Influence Humira Biosimilars?

Asked about the potential effect of interchangeability designations on the various Humira (adalimumab) biosimilars that are expected to hit the US market in 2023, Park said "everybody is looking forward to seeing and interested to see what will happen." (Also see "*First Interchangeable Humira Biosimilar Approved In US*" - Generics Bulletin, 18 Oct, 2021.)

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"There's a lot of conjecture, of course, but as scientists and regulatory experts I don't think we have that kind of commercial insight."

Asked whether different stakeholder behaviors towards Humira biosimilars with an interchangeability designation – compared to those without the designation – could be a major test of the significance of interchangeability for the US market, Woollett said that "the challenge we've got is whether you can isolate that as the reason for anything you observe. There are so many other variables in the equation."

"And again, there's the European experience," she added, referring to biosimilar competition to Humira that has existed in Europe since late 2018.

Alvotech Humira Settlement Sets Up Interchangeable Adalimumab Showdown

By David Wallace

09 Mar 2022

Alvotech and AbbVie have settled all of their legal disputes over Alvotech's AVT02 biosimilar rival to Humira. With Alvotech seeking a coveted interchangeability designation for its higher-strength adalimumab, the firm's US entry date provided by the settlement matches that of Boehringer Ingelheim's interchangeable Cyltezo lower-strength adalimumab biosimilar.

Read the full article here

In Europe, she observed, "everything has turned out to give you the same clinical result, which is ultimately what is going to be probably the most important factor. So I think the good news is that we can see what happened in Europe."

The FDA were "quite intrigued by real-world evidence and what it can do," Woollett suggested. "And because of the nature of the healthcare systems in Europe you often have a more complete data set, even for smaller countries. Whereas we have 2,000 payers in the US."

Further Clarity Still Needed Over Interchangeable Exclusivity

Discussing the year of interchangeable exclusivity that is granted to the first biosimilar to a given reference product to be granted an interchangeability designation by the FDA, Park noted that the agency was expected to issue further guidance on exactly how the mechanism would function.

Expanding on the aspects that still require clarification, Woollett said that "in theory, the incentive was to encourage people to seek the designation. But 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?"

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"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."

In particular, she highlighted, the exclusivity did not block other biosimilars from competing with an interchangeable. "It blocks FDA issuing another interchangeability designation, but it doesn't stop anybody else from getting an approval and launching a biosimilar to the same reference product," she noted.

Shared First Interchangeable Biosimilar Exclusivity May Be Allowed Under US FDA User Fee Bill

By Derrick Gingery

04 May 2022
Legislation in development also could create an option for tentative approval of interchangeable biosimilars.

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And ultimately, she continued, "our paper argues, and the European regulators have argued, that they are all interchangeable. So the only place where the rubber hits the road on that would be the pharmacists' ability under state law to substitute. As a legal matter, if the FDA hasn't issued the designation, and the product wasn't labelled with 'this product is interchangeable with this reference', then the pharmacists wouldn't be able to substitute."

> ***"The bottom line is that the FDA's interchangeability designation is only relevant to pharmacy medicines. It's not relevant for physician-administered medicines, because it's about dispensing and not prescribing."***

"This is where, as I like to say, the science is the easy bit. Because Joseph and I as scientists could say 'well they are all, in the European sense of the word, interchangeable'. It's this legal bit and how it then runs through the various workflows etc. that is really important."

"And then there's the FDA's interpretation, because they've got all these things around first licensure and all these other aspects that FDA has the authority to interpret from the statute. And then presumably the courts will be involved when they make some of the decisions if people disagree with them."

Finally, asked whether the US interchangeability designation could ever be relevant outside the retail setting – given that its only function is to facilitate pharmacy substitution – Park was clear.

"The bottom line is that the FDA's interchangeability designation is only relevant to pharmacy medicines," he underlined. "It's not relevant for physician-administered medicines, because it's about dispensing and not prescribing."

Woollett concurred. "If we're being precise, that's right and that's why we wrote the paper," she said. However, she added, "if we're not in a precise world" – a world where misinformation and misperceptions can persist – then "you've got that fuzzying of the physician expectation."

"Which is why the paper's title – 'Interchangeability for Biologics is a Legal Distinction in the USA, Not a Clinical One' – says it all."