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Biosimilars IP playbook is being re-written by the rise of interchangeables

FDA's approval of the first interchangeable monoclonal antibody has highlighted the complexities of regulatory exclusivity, while the introduction of more such drugs will alter impact IP strategies in years to come.

The US interchangeable biosimilar market is gaining rapid momentum all of a sudden. Having waited more than a decade since the Biologics Price Competition and Innovation Act, the FDA **awarded** interchangeability status for the first time in late-July. Now, it has **approved** the second automatically-substitutable biosimilar, Boehringer Ingelheim's Humira imitation, Cyltezo.

The rise of interchangeable biosimilars promises to have important commercial ramifications for the US biologics market, which in turn has implications for the patent strategies of both originators and imitators. But the approval of Cyltezo also raises some more specific questions about the period of regulatory exclusivity that the first interchangeable version of a biologic is entitled to.

The recent designation of insulin glargine-yfgn (to be marketed as Semglee) as interchangeable was an important breakthrough, because it creates the US's first biosimilar that can be substituted for the relevant originator product without a change in prescription. While **other biosimilars** have tended to capture a relatively small market share and cause only a modest erosion in price, interchangeables have the potential to perform more like small-molecule generics, gaining a much larger portion of the market and cutting prices more steeply.

Biosimilar producers had not until recently sought to satisfy the extra testing requirements for interchangeability status. With six years having passed since the first biosimilar approval, spectators were beginning to wonder whether this route would remain unused. But with Semglee's approval, a trail had been blazed for other biosimilars. Its success could encourage more to follow this path.

Even more significant is last week's approval of Cyltezo as an interchangeable version of best-selling drug, adalimumab (marketed by AbbVie as Humira). This is important because Boehringer's product is a monoclonal antibody – a type of drug that accounts for the bulk of the biologics market and which is tougher to gain interchangeable status for than an insulin product. It is also noteworthy, because Cyltezo will be competing for a share of the substantial Humira market against at least eight other biosimilars from 2023.

As interchangeables reshape the dynamics of biologics competition, IP strategies will have to be re-examined. Leading in-house and private practice professionals **told *IAM* recently** that interchangeable biosimilars may be more inclined to launch at-risk, preliminary injunction hearings will become even more important in BPCIA suits, and trend towards patent thicketing may be compounded.

The rise of interchangeability will also increase the importance of biosimilar-versus-biosimilar IP strategy, argues **Aydin Harston** of Rothwell Figg. "It makes it even more important for biosimilar makers to carve out their own IP positions and to cover as much of the space as they can, whether it be formulation claims, methods of production, methods of purification, stability enhancement and delivery devices," he says.

"There may be increased litigation between the biosimilar competitors as they fight over a smaller share of the market with a large share of the market being met by the brand and the interchangeable products," Harston believes. "An arsenal of IP may make it easier to settle such litigations with cross-licences, whereas a biosimilar maker without any IP who is accused of infringing another biosimilar maker's IP will be in a difficult position."

However, Cyltezo's approval raises a more specific question about the regulatory exclusivity that the first interchangeable version of a drug is entitled to under the BPCIA. Such a product may benefit from up to one year on the market before the FDA is permitted to award interchangeability status to another biosimilar version of the same molecule. This could be extremely valuable to Boehringer given that Alvotech is also seeking interchangeability for its adalimumab biosimilar, AVT02, which has produced **positive top-line results** in a recent switching study. Locked in the last outstanding litigation with AbbVie, Alvotech is **hoping to beat** its biosimilar rivals to market in early-2023.

But it turns out there is a snag. The statute **states** that the first interchangeable drug qualifies for exclusivity (relative to other interchangeables) until the earliest of four dates: one year after commercial marketing; 18 months after a final court decision in, or dismissal of, patent infringement litigation against "the applicant that submitted the application for the first approved interchangeable biosimilar"; 42 months after interchangeability approval if litigation is ongoing; or 18 months after approval, if there is no litigation.

Given that Boehringer settled its litigation against AbbVie in May 2019, it appears that its product will not qualify for any exclusivity in relation to Alvotech's drug. However, given that Cyltezo was approved as a biosimilar in 2018 and received interchangeability on the basis of subsequent submissions, it could try to argue that its litigation with AbbVie did not relate to the "application for the first approved interchangeable biosimilar". On the face of it, though, this seems unlikely to succeed.

If Boehringer is denied meaningful exclusivity, this is something other biosimilar producers will need to factor into decisions about the timing of future patent litigation settlements.

Another important nuance to be considered is that exclusivity only applies in relation to other interchangeable biosimilars "relying on the same reference product". This could also become a bone of contention, because Alvotech has applied for approval as a biosimilar version of AbbVie's high concentration formulation of Humira, whereas Boehringer's approval pertains to the lower-concentration version. Boehringer has already

petitioned the FDA to treat the two formulations as the same product for all relevant purposes. But the issue has yet to be resolved.

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