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Wallflowers: biosimilars don't dance – they go to the PTAB

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By **Erik Paul Belt** and **Maria Laccotripe Zacharakis**

Biologics are drugs produced from microorganisms or that contain components of microorganisms (eg, antibodies, proteins, stem cells and nucleic acids) and are often made through biotechnology processes, such as gene editing and cloning. Examples of biologics include Humira, a monoclonal antibody used in treating autoimmune diseases such as rheumatoid arthritis, and Avonex, made from interferon and used to treat multiple sclerosis. Biosimilars are drugs that are designed to be 'highly similar' to the brand-name patented biologic, meaning that there are no meaningfully significant differences between the approved biologic and the biosimilar in terms of the safety, purity and potency of the product.

The Biologics Price Competition and Innovation Act established a 'patent dance' between biologics innovators and biosimilars. This patent dance is similar to the interplay between drug innovators and generics under the Hatch-Waxman Act and could involve years of litigation. But biosimilar companies are increasingly opting out of this patent dance and are instead challenging the innovator patents in post-grant proceedings at the USPTO. Indeed, while post-grant proceedings are typically filed in parallel with patent infringement litigation in federal court, most of the post-grant proceedings challenging biologics patents are filed before, or instead of, federal court litigation. This chapter explores possible reasons for this disparity, as well as strategies that brand innovators can pursue to protect their biologics patents from invalidation in these post-grant proceedings.

I Can't Dance: biosimilars seek to avoid the patent dance

The Hatch-Waxman Act 1984 created a pathway for makers of generic versions of traditional drugs (eg, drugs synthesised from chemicals and compounds) to seek quicker US Food and Drug Administration (FDA) approval by filing what is known as an abbreviated new drug application (ANDA). The ANDA allows the generic to piggyback on the clinical data produced by the brand innovator, thus avoiding the need for years of its own clinical trials. But at the same time, this pathway often involves expensive and lengthy patent litigation between the generic and the brand innovator that can delay FDA approval for years.

In 2009, Congress enacted a similar abbreviated pathway, the Biologics Price Competition and Innovation Act, for makers of biosimilars to seek FDA marketing approval. Under the act, which took effect in 2010, the biosimilar applicant and the biologic brand innovator (known as the 'sponsor') exchange information and initiate patent litigation in a series of statutorily choreographed steps that occur over about an eight-month period, not including the patent litigation itself, which can take two to three further years. These choreographed steps are known as the 'patent dance'.

For example, after the FDA accepts for review an application for approval of a biosimilar, the applicant has 20 days to send the sponsor the biosimilar application along with information on how the biosimilar product is manufactured. The sponsor then has 60 days to provide a list of patents that it believes to be infringed. The applicant then has 60 days to provide arguments

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on why the biosimilar does not infringe or why the listed patents are invalid. This exchange of information goes back and forth several more times over a period of months before the music stops. This patent dance creates an 'artificial' infringement that allows the biologics sponsor to sue for patent infringement based on the mere filing of the biosimilar application, without having to wait for the applicant to actually make or sell the product.

But what happens when the biosimilar applicant does not want to dance? That is, the applicant may try to avoid the choreographed exchange of information to speed up the process, to provoke an earlier patent fight or for other strategic reasons. The applicant would want to avoid the dance or provoke an earlier fight so that it might market its biosimilar drug sooner, without the uncertainty of an 'at risk' launch (meaning without the risk that could lead it to be sued for infringement after it began commercial production and sales). That is what happened in a dispute between Amgen (the sponsor/patent owner) and Sandoz (the biosimilar applicant) concerning Sandoz's Zarxio product, which is a biosimilar to Amgen's Neupogen, a biologic used to stimulate the production of white blood cells. Sandoz refused to send Amgen its biosimilar application and information about the product. Amgen went to court to seek an injunction forcing Sandoz to dance. The case went all the way to the US Supreme Court. In 2017, the court held that Amgen could not force Sandoz to participate in the dance (at least under federal law) and that its only remedy was to file a type of patent litigation known as a declaratory judgment action. This ruling was good and bad for both the biologic and the biosimilar manufacturers. On the one hand, it established a precedent in which biosimilar makers could, in effect, opt out of the time-consuming patent dance. On the other hand, in opting out, the biosimilar cedes control of the patent litigation to the sponsor/biologic maker and has less say in the parameters of the litigation.

Dancing with Myself: biosimilars seek to dance on their own terms

Possibly as a result of the *Sandoz v Amgen* case, more biosimilar makers are avoiding the patent dance altogether and are instead challenging the sponsor's patents directly in special proceedings at the USPTO rather than in federal court litigation.

In 2011, Congress passed patent reform legislation known as the America Invents Act. The act introduced new litigation-like procedures in the USPTO PTAB that allow anyone (but usually companies accused of infringement or competitors that anticipate an infringement suit) to challenge the validity of another company's patents. These post-grant proceedings include *inter partes* reviews and post-grant reviews. Patent owners have likened these proceedings to death squads because they have a higher 'kill rate' than federal court litigation – that is, challenged patents are invalidated more frequently in these USPTO proceedings than in court litigation.

Inter partes reviews and post-grant reviews are essentially the same in terms of procedure, the major difference being that in *inter partes* reviews the validity challenge may only be based on prior art in the form of printed publications (eg, patents and technical articles published before the filing date of the challenged patent), while post-grant reviews include the full range of validity challenges available in federal court. *Inter partes* reviews may be filed against any patent, but post-grant reviews may only be filed against patents that were filed on or after 16 March 2013. *Inter partes* reviews and post-grant reviews are like litigation in that the parties file briefs, depose witnesses and argue to a panel of judges. But unlike federal court patent litigation, the proceedings concern only

the validity of the challenged patent and do not concern infringement, damages or injunctions. The proceedings are more compact and, from start to finish, take 18 months. In contrast, patent litigation can last two or three times as long. At present, *inter partes* reviews are far more common than post-grant reviews, so this chapter focuses on *inter partes* reviews, although most of the issues discussed below will apply equally to both.

One big difference between *inter partes* reviews and federal court litigation is that in litigation, patents are presumed valid and invalidity must be proved by clear and convincing evidence – a relatively high bar. In *inter partes* reviews, however, the patents are not presumed to be valid and the burden of proving invalidity is lower. Possibly for this reason, patents are invalidated more often in post-grant proceedings than in court litigation.

Because post-grant proceedings present a more attractive forum for challenging patents than federal court litigation, and given the higher success rate that patent challengers have in invalidating patents in these post-grant proceedings, it is no wonder that biosimilar makers have turned away from the patent dance and towards the PTAB.

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Dancing with Mr D: *inter partes* reviews result in high rates of invalidity

Since the Biologics Price Competition and Innovation Act took effect in 2010, there have been about 45 federal court litigations filed between sponsors and applicants involving biologics patents. Over the same period, however, biosimilar makers have filed about 120 *inter partes* review petitions challenging biologics patents. In most patent disputes in other industries and technologies, accused infringers typically file *inter partes* review petitions after federal court litigation has already begun or at least after being threatened with a lawsuit. In those situations, the accused infringer files the *inter partes* review petition for two reasons:

- the possibility of getting the court litigation stayed pending the outcome of the *inter partes* review; and
- the odds of invalidating the asserted patent are better at the USPTO than in federal court.

To save on judicial resources, some federal judges will push pause on the patent litigation pending the outcome of the *inter partes* review, although judges are more likely to pause the litigation in the early stages. As the litigation gets closer to trial and the court has already invested time in deciding substantive issues in the case, the likelihood that the case will be stayed pending a recently filed *inter partes* review decreases dramatically. In the biologics versus biosimilars realm, however, most *inter partes* reviews are filed before any court litigation and even before the biologics patent owner has been given a reason to file suit. In fact, the biosimilar makers appear to be filing *inter partes* reviews even before seeking FDA approval for their biosimilar products.

Once a patent challenger files an *inter partes* review petition, the patent owner may oppose, and the PTAB then decides whether to institute the *inter partes* review. Not all *inter partes* review petitions are granted, but because the standard for institution is relatively low, roughly 50% or more of *inter partes* reviews are instituted. In fact, more than 55% of *inter partes* reviews challenging biologics patents have been granted, while only about 35% have been denied. As for the remaining 10% of *inter partes* review petitions, the matters were settled before the PTAB ruled on the petitions. Of the *inter partes* reviews that were instituted, nearly 70% resulted in cancellation of all challenged patent claims. Overall, more than 80% of the instituted *inter partes* reviews resulted in cancellation of at least some, if not all, of the challenged claims.

Safety Dance: if you must dance with biosimilars at the PTAB, learn to dance safely

Given the high success rate that patent challengers have experienced when filing *inter partes* reviews, a biologics innovator should plan for, and be ready to defend its patent in, an *inter partes* review (or post-grant review, if applicable). Fortunately, new PTAB rules that took effect in January 2021 should help patent owners defend their patents.

In particular, patent challengers almost always support their *inter partes* review petitions with expert testimony. Until now, if the patent owner submitted its own expert testimony in its preliminary response to the petition, the PTAB would resolve any factual disputes created by the expert testimony in a light more favourable to the petitioner. This rule has led many patent owners to forego submitting expert testimony at the petition stage and even to forego filing any preliminary response at all. But as of January 2021, the rule has changed, meaning that the PTAB will no longer resolve factual disputes between experts in a light more favourable to the petitioner. Rather, the PTAB will now consider factual disputes when weighing whether the *inter partes* review petitioner has met its burden of proof. In other words, creating a dispute between experts could now help patent owners avoid institution of the *inter partes* review. The takeaway is that biologics innovators and patent owners should now retain experts in the patented technology and include the testimony of such experts as part of a preliminary response to an *inter partes* review petition. In fact, biologics innovators should not wait for the biosimilar makers to file *inter partes* review petitions. Rather, the innovators should assume that *inter partes* review petitions will be filed and should retain independent experts early and often so that the experts are familiar with the patents and technology well before having to rebut the biosimilar maker's expert.

Biologics innovators can take other steps to insulate their patents from invalidation in *inter partes* reviews or court litigation. One strategy is to create as much patent protection as possible for the biologic product. The more dance moves that the biologics innovator has in its repertoire, the easier it will be to out-dance the biosimilars applicant. For example, the biologics innovator may consider patenting variants of the biologic (eg, variants with a different sugar modification (ie,

glycosylation) pattern), manufacturing methods for producing the biologic product and even methods of using the biologic product for treating various conditions.

But just as important as filing multiple patents is the need to file stronger patents. Before filing the patent, the innovator should carefully review the prior art and make sure to tell a story in the patent about how the patented product or method is new and innovative over that prior art. The innovator should also disclose all of the prior art available during the examination of the patent application and make sure that the patent examiner actually considers it. Invalidation based on prior art is more likely when the patent examiner has not considered the prior art presented in the validity challenge. In both *inter partes* reviews and federal court litigation, that the USPTO considered the prior art will help minimise the possibility of invalidation.

Finally, another strategy to consider is to maintain some of the manufacturing steps as trade secrets, which may make it more difficult for the biosimilar applicant to figure out how to make the product in the first place.

Of course, before considering any of these strategies, the innovator should consult with its attorneys to ensure that the strategies are legally proper and effective.

Last Dance: conclusions

Biosimilar makers are increasingly turning to alternative strategies to get the upper hand on biologics innovators, including filing *inter partes* reviews at the USPTO in the hope of avoiding or short-circuiting the patent dance. Accordingly, biologics innovators should plan and be ready for these tactics and should consult with their attorneys to find the best legal strategies to strengthen their IP positions.

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