Implications of the BPCIA on the IP Strategies of Brand Companies and Biosimilar Developers

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The enactment of the Biologics Price Competition and Innovation Act ("BPCIA") in 2010 established for the first time ever in the US an abbreviated pathway for obtaining FDA approval of a new biological product that is deemed biosimilar to an already licensed biological. Although the BPCIA became law in 2010, the first biosimilar product approved under the new abbreviated pathway did not hit the market until five years later. Since the introduction of Sandoz's Zarzio® in 2015, the US biosimilar industry has grown rapidly. The US biosimilar market was $436M in 2018, but it is projected to reach nearly $18B by 2026.

Key Differences Between the BPCIA and Hatch-Waxman

From the outset, it was clear that the BPCIA's abbreviated pathway for biosimilars is fundamentally different from the abbreviated pathway for small molecule drugs established by the Hatch-Waxman Act in 1984. Although both statutes provide a mechanism by which patent disputes can be litigated and resolved prior to the actual launch of the biosimilar or generic product, there are few other similarities between the two statutes. Importantly, whereas Hatch-Waxman established the "Orange Book," which provides a publicly-available listing of patents covering the brand product, no equivalent public patent listing is provided under the BPCIA. Instead, the BPCIA provides for a complicated mechanism involving the private exchange of information and patent lists between the biosimilar applicant and the reference product sponsor (known colloquially as the "Patent Dance") which is designed to enable the parties to jointly identify and agree on the patents that will be the subject of the statutory litigation. Further, although the Hatch-Waxman Act prohibits process/manufacturing patents from being listed in the Orange Book, and consequently included in the ANDA litigation, the BPCIA contains no such restriction. This, combined with the significantly more complex nature of biological molecules and the fact that they are generally covered by many more patents, has led to a dramatic increase in the number and variety of patents that are asserted in the typical BPCIA litigation as compared to ANDA suits.

An Illustrative Case - Humira®

Indeed, a review of the BPCIA litigations to date related to antibody products showed that on average 20 patents are asserted in such litigations. In Abbvie's BPCIA litigation with Amgen related to Amgen's application to market Amjevita™, a biosimilar of Humira®, currently the world's top selling drug, Abbvie identified a total of 61 patents that it said were infringed by Amjevita™. Only one of the 61 patents claimed the antibody itself. The other 60 patents were directed to dosing regimens (12 patents), indications (12 patents), formulations (8 patents), pharmaceutical compositions (9 patents), and manufacturing processes (19 patents). Moreover, only one of the 61 patents identified by Abbvie as infringed by Amgen was even in force on the date Humira was first approved by the FDA in 2002. The other patents were either pending applications at that time or were filed after Humira's approval.

The case of Humira® illustrates two key implications of the BPCIA for brand companies. First, the importance of the core patents directed to the biological molecule itself is diminished under the BPCIA as compared to Hatch-Waxman. Because these patents are almost always filed very early in the development of the biologic product, they are often expired by the time the 12-year exclusivity period provided by the BPCIA has passed, which is the earliest point at which the FDA can approve a biosimilar. Conversely, the value of patents directed to other aspects of the reference product, such as methods of treatment, dosing regimens, manufacturing processes, etc., are significantly increased under the BPCIA as they are more likely to be the patents still in force at the time the biosimilar is approved.

Second, an innovator is wise to implement a robust patent-life cycle management strategy and consider patenting the full spectrum of innovations that occur throughout the development and commercial life of the biological product. In addition to the core biological molecule and the primary indication, consideration should be given to filings patent applications directed to:

- New indications
- Routes of administration (*e.g.,* subcutaneous)
- Manufacturing processes
- Mechanisms of action
- Formulations
- Combination products
- Combination therapies
- Biological profiles
- Delivery devices (*e.g.,* prefilled syringe)
- Companion diagnostics

Insights from the FDA's Guidance Documents for Biosimilars

Additional IP implications can be gleaned from the "Guidance for Industry" documents that the FDA has issued for biosimilars since the BPCIA was enacted. The FDA issued several important Guidance documents in 2012, including: (1) Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; (2) Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product; (3) Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product; and (4) Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 Guidance for Industry.

The guidance documents emphasize that the FDA will use a *totality of the evidence approach* to review applications for biosimilar products, and encourage a *stepwise approach to demonstrating biosimilarity,* which with rare exceptions will include a comparison of the proposed biosimilar product with the reference product in terms of structure, function, animal toxicity, human pharmacokinetics (PK) and pharmacodynamics (PD), clinical immunogenicity, and clinical safety and effectiveness. This stepwise approach is intended to better address residual uncertainty about biosimilarity that might remain at each step of the approval process.

The guidance documents also give some indication of which characteristics of the reference product the FDA will analyze most closely in determining whether an aBLA meets the standard for demonstrating biosimilarity. Thus, the brand company should consider pursuing patent protection around these critical parameters to better ward off a biosimilar challenge. The Guidances identify the following aspects as particularly important to the agency's biosimilarity analysis:

Structural Identity

- *Guidance:* "In general, FDA expects that the expression construct for a proposed product will encode the same primary amino acid sequences as the reference product. . . .However, minor modifications such as N- or C- terminal truncations that will not effect safety and effectiveness may be justified. . . ." (Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, April 2015, at 9.)
- *Implication:* Exact structural identity (at AA level) may not be required to show biosimilarity – raising the possibility that patents reciting specific sequences of the reference product might be avoided (at least literally) by a biosimilar having minor sequence differences. This increases the importance of brand companies not relying too heavily on the core composition of matter patents to fend off biosimilar challenges. The brand company should pursue multiple layers of protection by patenting manufacturing methods, formulations, dosing regimens, etc.

Environmental Conditions

- *Guidance:* "Protein modifications and higher order structures can be affected by environmental conditions, including formulation, light, temperature, moisture, packaging materials, container closure systems and delivery device materials." (Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, April 2015, at 5.)
- *Implications:* Because these are all factors that could impact demonstrating biosimilarity, innovators should consider obtaining patents on these aspects of their product to increase the burden on biosimilar competitors. For example, patents directed to pre-filled syringes containing the reference biologic product increasingly are sought by brand companies.

Comparative Assays/Devices

- *Guidance:* "The stepwise approach should start with extensive structural and functional characterization of both the

proposed product and the reference product. . . . It may be useful to further quantify the similarities or differences between the two products using a meaningful *fingerprint-like* analysis algorithm that covers a large number of additional product features and their combinations with high sensitivity using orthogonal methods." (Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, April 2015, at 7.)

- *Implications:* Brand companies should consider patenting "fingerprints" and unique assays for characterizing their product.

Post-Translational Modifications

- *Guidance:* "Differences in certain post-translational modifications. . .*might not* preclude a finding of biosimilarity if data and information provided by the sponsor show that the proposed product is highly similar to the reference product." (Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, April 2015, at 8.)
- *Implications:* This language suggests that there is a presumption that at least some differences in PTMs between the reference product and the proposed biosimilar will likely prevent a finding of biosimilarity. Thus, brand companies should consider patenting important PTMs, such as glycosylation profiles, as part of the overall patent life cycle management strategy for the reference product.

Formulations

- *Guidance:* "Differences in formulation between the proposed product and the reference product are among the factors that may affect the extent and nature of subsequent animal or clinical testing." (Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, April 2015, at 10.)
- *Implications:* To the extent differences in formulation will result in additional clinical testing, which would increase both the cost and length of trials, biosimilar manufacturers will have a strong incentive to match the formulation of the reference product as closely as possible. This increases the value to the brand company of formulation patents covering the reference product.

Companion Diagnostics

- *Guidance:* "When selecting the study population for a comparative safety and effectiveness study, a sponsor should consider, for example, whether its study population has characteristics consistent with those of the population studied for the licensure of the reference product for the same indication . . . ."
- *Implication:* This illustrates the value of companion diagnostics to the brand company. If it is necessary for the biosimilar developer to use a companion diagnostic to recruit a similar study population as the reference product, then the sponsor's patent on the CDx would be an additional hurdle that the biosimilar developer must overcome to get their product on market.

Thus, the FDA's Guidance for Industry documents provide valuable insight into the factors the agency considers particularly important in assessing whether an aBLA submission meets the standard for biosimilarity required by the BPCIA. A reference product sponsor that is able to obtain additional patent protection around these key aspects of the brand product will increase the burden on companies seeking approval to market a competing biosimilar.

Protecting the Biosimilar Developer's Innovation

Due to the complex nature of biological molecules, a considerable amount of innovation can be involved in developing a biosimilar product. This was illustrated in *Momenta Pharmaceuticals, Inc. v. Amphastar Pharmaceuticals, Inc.,* 686 F.3d 1348 (Fed. Cir. 2012). The product at issue there was enoxaparin, an anticoagulant comprising low molecular weight heparin. It is made by cleaving raw heparin, which consists of sugar chains, into smaller chains. Lovenox®, marketed by Sanofi, was the reference product. Although not a typical biological product, the complexity of enoxaparin makes it more analogous to a complex biological than the usual small molecule drug. Indeed, the FDA cited the case of enoxaparin as instructive of how the agency would approach its review of aBLAs. *See*, Lee, S. *et al., Nature Biotech* 31:220-226 (2013).

Momenta and Sandoz both filed ANDAs to market generic Lovenox®. Due to the biochemical complexities of enoxaparin, it was difficult for ANDA filers to show the "sameness" required under Hatch-Waxman. Sanofi filed a Citizen's Petition with the FDA to prevent the approval of generic enoxaparin until the reference product could be further characterized. The FDA denied Sanofi's petition, but enumerated a list of criteria that had to be met for a generic applicant to show sameness to enoxaparin, including the nature and arrangement of components that constitute enoxaparin. To meet this criterion,

Momenta developed a new manufacturing control process to ensure each batch of its generic product included the same array of sugar chains characteristic of enoxaparin. Momenta sought and obtained patent protection for its proprietary process.

Momenta's ANDA was ultimately approved and it started marketing generic enoxaparin. The FDA also approved Amphastar's ANDA for enoxaparin. But Momenta immediately sued Amphastar for infringement of its process patent. The district court granted Momenta a preliminary injunction to prevent Amphastar from marketing its generic version of enoxaparin, finding a likelihood of success on the merits that Amphastar infringed Momenta's process patent. So, while the complexity of the reference product increased the difficulty for Momenta to show sameness, it compelled Momenta to develop an innovative assay that resulted in patents Momenta then asserted against another generic to keep competing generic products off the market. The preliminary injunction was ultimately vacated by the Federal Circuit on other grounds (*i.e.* that the district court had applied the wrong standard in rejecting Amphastar's defense under 35 U.S.C. §271(e)(2)). The court found that post-approval activity, such as batch testing, was not categorically outside the scope of the FDA safe harbor exemption from infringement. *Momenta Pharmaceuticals, Inc. v. Amphastar Pharmaceuticals, Inc.,* 686 F.3d 1348 (Fed. Cir. 2012).

Similarly, in *Coherus Biosciences, Inc. v. Amgen, Inc.,* No.1:19-cv-00139 (D. Del. Filed January 24, 2019), Coherus received FDA approval to market its adalimumab biosimilar and then immediately sued Amgen, which had previously been approved to market biosimilar adalimumab, for patent infringement. Specifically, Coherus asserted that Amgen's biosimilar infringed three patents Coherus had obtained on adalimumab formulations. Coherus alleged that Amgen's manufacture in the U.S. of Amjevita for sale in Europe infringed the patents. The parties subsequently settled the case before any substantive decision by the court on the merits.

The *Momenta* and *Coherus* cases show that the techniques and strategies used by aBLA applicants in developing their product and demonstrating that it meets the standard for biosimilarity required by the BPCIA can involve a significant level of innovation that creates patenting opportunities for the biosimilar developer that can in some instances can be asserted against companies seeking to market competing biosimilar products.