The Biosimilar Regulatory Pathway and the Patent Dance

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Biologic medicines, or "biologics," continue to show significant growth in the U.S. pharmaceutical market. This reflects a larger global trend, where the worldwide market for biologics was valued at $150 billion in 2011 and is expected to surpass $250 billion by 2017. And in the U.S., biologics already account for four of the top ten drugs by sales. Given these market conditions, industry participants should monitor the evolving regulatory framework established by the Affordable Care Act that established a pathway for biosimilars (medicines that are highly similar to the original biologic) to enter the market.

Biologics are large, structurally complex proteins derived from living cells that are used in the treatment, diagnosis or prevention of disease. Unlike the more common "small molecule" drugs (e.g., acetaminophen), biologics are manufactured within living organisms, such as bacteria, yeasts, or mammalian cells. Due to this complexity, the efficacy of biologic medicines are highly sensitive to their manufacturing conditions. Despite their growing popularity, biologics are neither new nor experimental; they treat chronic conditions such as cancer, rheumatoid arthritis, multiple sclerosis and others.

Regulatory Framework for Approving Biosimilars

The Affordable Care Act introduced a pathway for FDA approval of "abbreviated" applications for biological products that are shown to be "biosimilar" to an already-approved biologic ("reference product"). This abbreviated pathway is set forth in the part of the law called the Biologics Price Competition and Innovation Act (BPCI Act). This Act provides the framework for FDA licensure and patent litigation that results from biosimilar applications.

For example, under the BPCI Act, a biological product may be shown to be "biosimilar" if the submitted data indicates that the product is "highly similar" to the reference product. And, importantly, when the reference product is patent protected, submitting an abbreviated application under the BPCI Act triggers a series of events that may lead to patent litigation.

The Patent Dance

Once a biosimilar application has been submitted to the FDA, there is a procedure, commonly referred to as the "patent dance," for resolving any patent disputes. This procedure has strict timing and sequencing requirements and involves several rounds of information exchanges between the reference product sponsor (which is usually the innovator company) and the biosimilar applicant. Some of the key steps of this process include:

- Within 20 days after the FDA has accepted its abbreviated application, the biosimilar applicant must provide the reference product sponsor with confidential access to the biosimilar application and relevant manufacturing information for the proposed biologic.
- Within 60 days of receiving these materials, the reference product sponsor must provide to the biosimilar applicant: (1) a list of patents it believes are infringed, and (2) identify which, if any, of these patents it would be willing to license to the biosimilar applicant.
- Within 60 days of receipt of the patent list, the biosimilar applicant must provide the reference product sponsor a statement describing, on a claim-by-claim basis, the factual and legal basis as to why each patent is invalid,

unenforceable, and/or not infringed. Within this same 60 day period, the biosimilar applicant may provide to the reference product sponsor a counter list of patents that the biosimilar applicant believes could be subject to a claim of patent infringement.

- Within 60 days of receiving these materials, the reference product sponsor must provide a reciprocal statement describing, on a claim-by-claim basis, the factual and legal basis that each patent will be infringed, as well as a response to any statement regarding validity and enforceability.
- The parties then have up to 15 days to negotiate in good faith to arrive at a list of patents, if any, that should be subject to a patent infringement action.

  - If the parties reach agreement, then the reference product sponsor must bring an infringement action within 30 days for each patent on the negotiated list.
  - If the parties do not reach agreement, the biosimilar applicant must notify the reference product sponsor of the number of patents it will provide in a second list, and the parties then simultaneously exchange within 5 days of this notice a list of patents that each party believes should be the subject of the infringement litigation. Within 30 days after this exchange, the reference product sponsor must bring an infringement action on all the patents on the simultaneously exchanged lists.

There is no automatic regulatory stay of approval of the biological application during the course of the patent litigation. Thus, to prevent an "at risk" launch of the biologic, a reference product sponsor must be proactive in seeking and justifying preliminary injunctive relief. The ability to seek a preliminary injunction is built into the statute since the BPCI Act requires the biosimilar applicant to provide notice to the reference product sponsor at least 180 days before the biosimilar applicant's first commercial marketing of the biosimilar.

The regulatory framework surrounding the patent dance raises many important issues. For example, it only deals with contemplated patent litigation in the Federal Court system, and it is silent as to the use of other post-grant challenges that may be available to biosimilar applicants, such as inter partes review ("IPR") and post-grant review ("PGR"). These types of post-grant challenges are becoming popular and cost effective ways to invalidate patents.

Moreover, the intricacies and interplay of the patent dance is already being litigated. In a recent Northern District of California lawsuit, Amgen alleges that Sandoz, which filed the first U.S. abbreviated biosimilar application earlier this year (for a biosimilar of Amgen's Neupogen® (filgrastim) product), failed to "follow the rules" set forth by the BPCI Act by "refus[ing] to provide Amgen with the BLA and manufacturing information" and otherwise failing to comply with the statute. The Court's interpretation and application of the requirements of the BPCI Act will be instructive as other courts begin to grapple with the nuances of the patent dance.

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