Biosimilar Approvals in the US and Canada – the 'Patent Dance'

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The US and Canada each provide an abbreviated pathway (or shortcut) for a biosimilar manufacturer to get a product approved.[1] The shortcut allows for a biosimilar product to rely on a reference product's clinical trial data to help get biosimilar marketing authorization from the FDA or Health Canada. The reference product is the one that incurred the substantial time and expense of full clinical trials. Reducing the biosimilar manufacturer's requirement to generate clinical and efficacy data saves it a tremendous amount of cost and time. The government policy goal of the shortcut is to get lower priced medicines on the market faster.

As part of the process for this shortcut to the market, the governments try to determine that the reference product's patents would be infringed by considering patent issues *before* approval of the biosimilar drug. This safeguard involves an interaction, or 'patent dance', between the reference product owner and the biosimilar manufacturer.

In the US, the patent 'dance floor' is open to the companies once an application for biosimilar drug approval is submitted to the FDA. The *Biologics Price Competition and Innovation Act*[2] (**BPCIA**) provides a complex information exchange process in which reference product sponsors and biosimilar applicants may engage before commencing any patent infringement litigation.[3] The process will be shown in this article by reference to the first publicly available example. In *Amgen Inc. et al. vs Apotex Inc. et al.*[4], the BPCIA patent information exchange step was completed. Apotex submitted an abbreviated biologic license application (**aBLA**) to the FDA for a biosimilar version of Amgen's Neulasta (pegfilgrastim). In December 2014, the parties exchanged information and statements as required by the BPCIA, and subsequently agreed to include two U.S. patents in a patent action. Amgen had standing to bring the patent infringement action because it was an act of potential infringement by Sandoz to submit an aBLA to the FDA seeking approval of its pegfilgrastim when Amgen, the reference product owner, had patents listed with the FDA under the BPCIA.

Here are the steps in the patent dance as they occurred between Amgen and Apotex, as stated in the Amgen Complaint:

"…46. On December 16, 2014, Amgen received a letter from in-house counsel for Apotex Inc., notifying Amgen that the Apotex BLA had been accepted for review by FDA and that Apotex intended to provide Amgen the Apotex BLA pursuant to 42 U.S.C. § 262(l)(2).

47. Subsequently, Amgen received a copy of the Apotex BLA under the confidentiality provisions set forth in 42 U.S.C. § 262(*l*)(1).

48. Pursuant to 42 U.S.C. § 262(l)(3)(A), on February 27, 2015, Amgen provided Apotex a list of patents for which it believed a claim of patent infringement could reasonably be asserted against the Apotex Pegfilgrastim Product ("Amgen's (*l*)(3)(A) list"). Amgen's (*l*)(3)(A) list included the Patents in Suit.

49. On April 17, 2015, Apotex provided Amgen with its statements designated as being in accordance with 42 U.S.C. § 262(*l*)(3)(B).

50. On June 16, 2015, Amgen provided Apotex with a detailed statement, pursuant to 42 U.S.C. § 262(*l*)(3)(C).

51. Between June 22, 2015 and July 7, 2015, Amgen and Apotex engaged in good faith negotiations, pursuant to 42 U.S.C. §

262(l)(4). On July 7, 2015, Amgen and Apotex agreed that the Patents in Suit should be the subject of any patent infringement action brought pursuant to 42 U.S.C. § 262(l)(6)(A)…"

Subsequent to the Complaint, Amgen filed its Answer with Counterclaims in October 2015. Although Apotex agreed with Amgen on the patents to be included in BPCIA litigation, Apotex denied infringing, and asserted that the patents are invalid. Apotex also asserted that Amgen was violating the Sherman Act (US competition law) by launching suit for one of its method of manufacture patents. Apotex alleged that it provided Amgen with clear and irrefutable proof of noninfringement during the information exchange. Apotex believes that competition law applies if Amgen included this patent for the purpose of significantly delaying resolution of patent litigation, and Apotex's biosimilar entry into the market. There are also a number of issues raised by Apotex about BPCIA procedures. Apotex requested a declaration that a notice of commercial marketing to Amgen[5] is not mandatory, so that non-compliance cannot be basis for an injunction.[6] The parties will most likely go to a judge's decision to resolve the dispute, though a settlement is possible.

In Canada, there is also a patent review system, or dance, but it is potentially light on information exchange about the biosimilar product and its manufacturing process and heavier on litigation. The system is informally called the "NOC Regulations."[7] In order to receive marketing authorization, the biosimilar company must address freedom-to-operate with respect to patents listed with Health Canada on its Patent Register (click here for more information about the process). The first biosimilar case under the NOC Regulations involved Teva's biosimilar version of filgrastim[8]. Amgen had the first approved filgrastim product in Canada, under the brand name NEUPOGEN, with a patent that expires on July 31, 2024. Teva provided a notice alleging that it did not infringe any valid patent claims listed with Health Canada. Amgen then started litigation under the NOC Regulations in an attempt to block Teva's biosimilar filgrastim. In defence, Teva had alleged that claims of the Amgen patent in issue were invalid, infringed or not relevant. The case was settled in August 2013. The terms of the Canadian settlement are unknown.

The patent systems of both countries show that companies need to plan ahead and be prepared to address patent issues with regulators and each other. Resolution of patent issues can become the last hurdle to biosimilar market entry so the stakes of the dance are high.

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1 For more information about biosimilars generally, click here.

2 H.R. 3590, 111th Cong. (2010).

3 All the litigation provisions are found within 42 U.S.C. § 262(*l*) (2103).

4 *Amgen et al. v. Apotex Inc. et al.* U.S. District Court for the Southern District of Florida; Case 0:15-cv-61631-JIC.

5 42 U.S.C. § 262(*l*)(8)(A).

6 Apotex did acknowledge that other penalties potentially apply under 42 U.S.C. § 262(*l*)(9)(B).

7 *Patented Medicines (Notice of Compliance) Regulations*, SOR 93-133.

8 *Amgen Canada Inc. et al. v. Teva Pharmaceutical Industries Ltd. et al.* (T-989-12).