The Biologics Price Competition and Innovation Act of 2009: The Patent Battles Have Begun with the Very First Biosimilar!

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Neupogen® (filgrastim), marketed by Amgen Inc., is a 175-amino acid human granulocyte colony-stimulating factor (molecular weight: 18,800 daltons) used in the treatment of cancer. On March 6, 2015, the FDA approved the biosimilar of Neupogen®, the first of its kind. It is to be marketed by Sandoz under a "placeholder nonproprietary name filgrastim-sndz" and can prescribed for the same indications as Neupogen®[1]. The regulatory story is over (for now, anyway), but the legal battle has only just begun, and could delay the market entry of filgrastim-sndz.

[1]FDA approves first biosimilar product Zarxio. http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm436648.htm (retrieved March 8, 2015)

The Biologics Price Competition and Innovation Act of 2009 (hereinafter BPCIA), enacted into law as part of the Patient Protection and Affordable Care Act of 2010[2], established regulatory and legal pathways for the marketing of generic biologicals (hereinafter biosimilars). The U.S. Senate noted that the purpose of the BPCIA is to balance "innovation and consumer interests."[3] Clearly, the approval of biosimilars in Europe starting in 2006 put considerable political pressure on the Congress to act[4]. This short article focuses mostly on the patent provisions of the BPCIA[5]. To make it more readable and interesting to AAPS readership (mostly non-lawyers), the individual product names (i.e., Neupogen® and filgrastim-sndz) are worked into the text of these statutory provisions.

Biological products , with a few exceptions, have been approved under § 351 of the Public Health Service Act[6] . The BPCIA amended this section by adding two new sections: section (k) which provides definitions and licensure requirements for biosimilars and interchangeables (hence, an applicant for a license to market such products is designated as a subsection (k) applicant), and section (l) which describes the legal framework for patent protection for innovators in the

[2] http://www.hhs.gov/healthcare/rights/law/title/vii-improving-access-to-innovative.pdf (retrieved March 9, 2015)
[3] *Ibid*., Title VII, Sec. 7001 (b) Sense of the Senate
[4] Anon. Europe approves two follow-on human growth hormones. Nature Biotech. 24, 601-602 (2009).
[5] 42 U.S.C. § 262 (l)
[6] Codified under 42 U.S.C. § 262

area of biologicals. While the focus of this article is to describe patent provisions under the BPCIA, the (rather tortured)[7] distinctions between a biosimilar and an interchangeable (a "super" biosimilar, as it is defined) deserves comment. A biosimilar (filgrastim-sndz, in this case) is defined as a product that is "highly similar to the reference product [Neupogen®, in this case] notwithstanding minor differences in clinically inactive components (emphasis added)"[8] and "there are no clinically meaningful differences between [filgrastim-sndz] and [Neupogen®] in terms of safety, purity, and potency of the product." [9] An interchangeable, in addition to meeting the requirements of a biosimilar[10], "can be expected to produce the same clinical result as the reference product in any given patient"[11] (emphasis added) and "for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch (emphasis added)"[12]. The regulatory distinction between a biosimilar and an interchangeable appears clinically unnecessary since both products should be expected to produce the same therapeutic outcome. Such a distinction suggests

[7] Personal opinion
[8] 42 U.S.C. § 262 (i)(2)(A)
[9] 42 U.S.C. § 262 (i)(2)(B)
[10] 42 U.S.C. § 262 (k)(4)(A)(i)
[11] 42 U.S.C. § 262 (k)(4)(A)(ii)
[12] 42 U.S.C. § 262 (k)(4)(B)

additional studies for interchangeable licensure, making it needlessly far more expensive than its corresponding biosimilar. In this connection, under BPCIA (Federal law), an interchangeable "may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product."[13] Since pharmacy practice laws are the jurisdiction of individual states, many states have passed legislation to restrict substitution without the knowledge of the prescriber[14].

Under the BPCIA, the innovator company (Amgen in this case) and the subsection (k) applicant (Sandoz in this case) are required first to attempt to resolve potential patent infringement matters through a patent exchange process, before proceeding to litigation, only if necessary. Some have called these negotiations the BPCIA "patent dance"[15]. In this case, the process began when Sandoz was notified on July 7, 2014 that the FDA had accepted its application for filgrastim-sndz. [16] As per the BPCIA, Sandoz was required to provide Amgen with

[13] 42 U.S.C. § 262 (i)(3)
[14] Substitution allowed? State biosimilars laws are evolving. https://www.dlapiper.com/en/us/insights/publications/2014/09/ipt-news-23/substitution/(retrieved March 5, 2015)
[15]Federal Circuit Affirms Dismissal of First BPCIA "Patent Dance" Challenge, But Remains Mum on BPCIA Interpretation . . . At Least for Now. Kurt R. Karst – http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2014/12/federal-circuit-affirms-dismissal-of-first-bpcia-patent-dance-challenge-but-remains-mum-on-bpcia-int.html (retrieved March 6, 2015)
[16] http://www.fdalawblog.net/NEUPOGEN%20-%20Amgen%20PI%20Memo.pdf (retrieved March 7, 2015)

a copy of the biosimilar application and details of the manufacturing processes no later than July 28, 2014[17]. Sandoz did not comply with this requirement, which precipitated much litigation between these two pharmaceutical companies (discussed briefly, later). If Sandoz had complied with this first step, the timeline of events under the BPCIA would have been as follows: (1) On or before September 26, 2014: Amgen, based on information provided by Sandoz, would have provided Sandoz with a "list of patents" it might infringe in its efforts to market filgrastim-sndz[18], and identified those of the listed patents that Amgen would be willing to license[19]; (2) On or before November 25, 2014: Sandoz would have "provide[d] to [Amgen] with respect to each patent listed . . . a detailed statement that describes, on a claim by claim basis, the factual and legal basis of the opinion of [Sandoz] that such patent is invalid, unenforceable, or will not be infringed by the . . . marketing of [filgrastim-sndz][20] or stated that Sandoz "does not intend to begin . . . marketing the [filgrastim-sndz]" before the expiration of "such patent"[21]. Sandoz would have also responded to Amgen's offer, if any, to license its technology[22]. In addition, Sandoz had the option of providing its own

[17] 42 U.S.C. § 262 (l)(2) (A)

[18] 42 U.S.C. § 262 (l)(3)(A)(i)
[19]42 U.S.C. § 262 (l)(3)(A)(ii)
[20] 42 U.S.C. § 262 (l)(B)(ii)(I)
[21] 42 U.S.C. § 262 (l)(3)(B)(ii)(II)
[22] 42 U.S.C. § 262 (l)(3)(B)(iii)

list of patents that Amgen could have asserted against Sandoz in its marketing efforts.[23] (3) On or before January 26, 2015: Amgen would have provided Sandoz with "a detailed statement that describes with respect to each patent", why, in Amgen's opinion, each of its listed patents would be infringed by Sandoz, if it were to market filgrastim-sndz.[24] (4) At this stage, Amgen and Sandoz would "engage in good faith negotiations to agree on which, if any patents" listed by Amgen (see (1), this paragraph), or by Sandoz (see (2), this paragraph)[25] shall be the subject of patent infringement litigation. "If, within 15 days of" the commencement of these negotiations, both parties "fail to agree on a final and complete list of which, if any, patents, listed by [Sandoz and Amgen] shall be the subject of action for patent infringement"[26], the parties would move towards litigation. Before that, Sandoz "shall notify [Amgen] of the number of patents [it] will provide to [Amgen][27]. Within 5 days of such notification, both parties "shall simultaneously exchange a list of patents" (the second exchange) that Sandoz and Amgen believe "should be the subject of an action for patent infringement", and Amgen would then bring such action against Sandoz within 30 days of the second exchange.[28] If, on the other hand, both parties agree to patents that are in "play",

[23] 42 U.S.C. § 262 (l)(3)(B)(i)
[24] 42 U.S.C. § 262 (l)(3)(C)
[25] 42 U.S.C. § 262 (l)(4)(A)
[26] 42 U.S.C. § 262 (l)(4)(B)
[27] 42 U.S.C. § 262 (l)(5)(A)
[28] 42 U.S.C. § 262 (l)(6)(B)

Amgen would bring "an action for patent infringement" against Sandoz within 30 days of such agreement.[29]

Concerned that FDA approval of filgrastim-sndz is imminent (FDA FY 2014 performance goals call for "review[ing] and act[ing] on 70 per cent of original biosimilar biological product application submissions within 10 months of receipt") [30], and the filgrastim-sndz application was recommended for approval by the FDA Oncologic Drugs Advisory Committee on January 7, 2015[31], Amgen filed a motion for a preliminary injunction in United States District Court, Northern District of California, on February 5, 2015 to stop Sandoz from marketing filgrastim-sndz, citing, inter alia, that "Amgen Will Be Irreparably Harmed if Sandoz Enters the Market in Violation of the BPCIA"[32]. Sandoz's filed its opposing response on February 24, 2015 stating, inter alia, that Amgen declined several offers made by Sandoz to provide its biosimilar application, "subject only to reasonable confidentiality protections" and "Sandoz Fully Complied with the

[29] 42 U.S.C. § 262 (l)(6)(A)
[30]http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM281991.pdf
[31] http://www.novartis.com/newsroom/media-releases/en/2015/1885139.shtml
[32] http://www.fdalawblog.net/NEUPOGEN%20-%20Sandoz%20Opp%20to%20Amgen%20PI.pdf

BPCIA"[33]. A hearing is scheduled for March 13, 2015 at 10:00 AM on the motions by Amgen and Sandoz. Stay Tuned!

[33] http://www.fdalawblog.net/NEUPOGEN%20-%20Sandoz%20Opp%20to%20Amgen%20PI.pdf