Health Care and Life Sciences Alert

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FDA Accepts First Biosimilar Application under New Approval Pathway

July 24, 2014 was a landmark day in the biotechnology industry: Sandoz (the generic arm of Novartis) announced that the U.S. Food and Drug Administration (FDA or "the Agency") had accepted the first application for a U.S. biosimilar approval, for a biosimilar version of Amgen's Neupogen (filgrastim). This marks the first application filed and accepted pursuant to the approval pathway established by the Biologics Price Competition and Innovation Act of 2009 (BPCIA). Sandoz now enters unchartered territory, as FDA has yet to finalize its policies on biosimilars and the standards for their approval.

The BPCIA created a pathway to market for biological products that are "biosimilar" to, or "interchangeable" with, a reference FDA-licensed biologic. Biosimilars are manufactured with the goal of closely mirroring a licensed reference biological product—a complex medicine manufactured from living organisms. We do not know how quickly other biosimilar applications will be filed, but companies have clearly been laying the groundwork for submitting applications. During Fiscal Year 2013, FDA received 93 submissions for biosimilars in development and completed 81 actions related to these submissions.[1] In connection with these biosimilars in development, FDA conducted three reviews of proprietary biosimilar product names and held 27 meetings—a mix of Initial Advisory Meetings and Type 2, Type 3 and Type 4 meetings within the Biosimilar Product Development (BPD) phase.[2]

FDA Implementation of Biosimilars Pathway

Sandoz's application, which the company apparently filed in May, is further evidence that companies are pushing forward absent clear U.S. regulatory guidelines. FDA is still developing guidance implementing the new BPCIA pathway, which could take years to finalize. The Agency issued three Draft Guidances in February 2012, but only in May of this year released a Draft Guidance that delves more deeply into the studies needed to show biosimilarity. The Guidance topics, and release dates, include:

[1] FY 2013 Performance Report to the President and Congress for the Biosimilar User Fee Act, available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/ Reports/UserFeeReports/ PerformanceReports/UCM384179.pdf.

[2] A Biosimilar Initial Advisory Meeting is "limited to a general discussion regarding whether licensure under section 351(k) of the Public Health Service Act may be feasible for a particular product, and, if so, general advice on the expected content of the development program"; a BPD Type 1 Meeting is "necessary for an otherwise stalled drug development program to proceed . . ., a special protocol assessment meeting, or a meeting to address an important safety issue"; a BPD Type 2 Meeting is "a meeting to discuss a specific issue (e.g., proposed study design or endpoints) or questions where FDA will provide targeted advice regarding an ongoing biosimilar biological product development program"; a BPD Type 3 Meeting is an "in-depth data review and advice meeting regarding an ongoing biosimilar biological product development program"; and a BPD Type 4 Meeting is "a meeting to discuss the format and content of a biosimilar biological product application or supplement submitted under 351(k) of the PHS Act." FY 2013 BsUFA Performance Report at B-1, B-2.

- **Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (Draft Guidance):** Intended to assist sponsors of a 351(k) biosimilar application in demonstrating that a proposed therapeutic protein product is biosimilar to a reference product. *Issued February 2012; Formal comment period ended April 16, 2012*.

- **Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product (Draft Guidance):** Provides analytical factors that FDA will consider in assessing whether a proposed therapeutic protein product is highly similar to a reference product. *Issued February 2012; formal comment period ended April 16, 2012*.

- **Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (Draft Guidance):** Outlines FDA's interpretation of the BPCIA, in the form of answers to common questions from potential biosimilar application sponsors, biologics application (BLA) holders and other stakeholders. *Issued February 2012; formal comment period ended April 16, 2012.*

- **Formal Meetings between the FDA and Biosimilar Biological Product Sponsors or Applicants (Draft Guidance):** Provides recommendations to stakeholders on formal meetings between FDA and biosimilar sponsors or applicants during the biosimilar product development phase. *Issued March 2013; formal comment period ended May 31, 2013.*

- **Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (Draft Guidance):** Provides a stepwise process—which includes clinical pharmacology studies—for demonstrating that a proposed biosimilar product is highly similar to a reference product, pursuant to a "totality of evidence" standard. *Issued May 2014; formal comment period ends August 12, 2014*.

In the absence of finalized FDA policy, many questions remain. In particular, FDA has yet to come down on whether biosimilars should have distinct nonproprietary names from the reference product. This topic has garnered significant interest nationally—both in Congress and within executive agencies including the Federal Trade Commission (FTC). The FTC hosted a workshop earlier this year that considered naming as part of a broader analysis of competition issues surrounding biologic and biosimilar products. The World Health Organization (WHO) is also considering the issue from an international perspective.

Another other key issue that may be addressed during the review of Sandoz's application is "interchangeability," whereby FDA concludes that the biologic can be expected to produce the same clinical result as the reference product in any given patient. Although Sandoz has declined to state whether it seeks an interchangeability designation, such a designation would allow Sandoz's product to be widely substituted for the reference product. FDA has informally indicated its preference that sponsors first obtain biosimilar approval before requesting that FDA make a determination as to interchangeability, so it is possible that Sandoz will seek an interchangeability designation at a later time.

Patent Implications

A section 351(k) application can also be the triggering event for biosimilars patent litigation. Under the BPCIA, the 351(k) applicant has 20 days after filing to provide its application to the branded manufacturer. The branded manufacturer then has 60 days to provide a list of patents that it believes it could reasonably assert, kicking off a series of exchanges between the parties that determines which patents will be litigated in an immediate infringement suit prior to FDA approval of the biosimilar. Whether or not the Sandoz filgrastim application leads to patent litigation, the line-up of other biosimilars in development means that the first biosimilars patent lawsuit to test these provisions of the BPCIA is likely not far off.

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