Portfolio Media. Inc. | 860 Broadway, 6th Floor | New York, NY 10003 | www.law360.com
Phone: +1 646 783 7100 | Fax: +1 646 783 7161 | customerservice@law360.com

2015 Will Be A Watershed Moment For Biosimilars

Law360, New York (February 03, 2015, 3:07 PM ET) -- The Biologics Price Competition and Innovation Act, enacted as a subsection of the Affordable Care Act and signed into law in March 2010, was designed to create an abbreviated pathway for U.S. Food and Drug Administration approval of biosimilar biologic drugs.[1] Such an abbreviated pathway had existed since 1984 for generic small-molecule drugs via the Hatch-Waxman Act,[2] but the BPCIA broke new ground for large-molecule, complex biologics.

Thomas H. Wintner

Despite the fanfare surrounding passage of the BPCIA, it was not until four years later, in 2014, that the first company actually filed a biosimilar application under the law's newly created pathway. Also in 2014, three additional companies filed applications for biosimilar versions of different FDA-licensed biologics. The year 2015 thus represents a watershed moment for biosimilars. These applications, known as §262(k) applications after the key section of the Public Health Services Act added by the BPCIA, will force both the FDA and courts to grapple with the meaning of the BPCIA on important issues that they previously have been able to defer.

The status of the four §262(k) applications from 2014 is as follows:

1. Sandoz's application for Zarxio, a proposed biosimilar of Neupogen (filgrastim), was accepted by the FDA for review in July 2014.
2. Apotex's application for a biosimilar of Neulasta (pegfilgrastim) was accepted by the FDA for review in December 2014.
3. Celltrion's application for Remsima, a biosimilar of Remicade (infliximab), was filed with the FDA in August 2014.[3]
4. Hospira's application for Retacrit (epoetin zeta), a biosimilar of Epogen and Procrit (epoetin alpha), was filed with the FDA in December 2014.[4]

Currently, Sandoz's application for Zarxio appears furthest along. On Jan. 7, 2015, an independent panel voted 14-0 to recommend that the FDA approve the Zarxio application, and formal approval from the agency appears possible as early as March 2015.

The Meaning of the BPCIA Is Finally Starting to be Litigated

The language of the BPCIA leaves ample room for interpretation. Yet with no biosimilar applications actually on file, it has been difficult for parties to test that language. That is now changing in light of the four §262(k) applications described above.

Litigating Outside the BPCIA's Framework

The BPCIA provides a framework for resolving allegations of patent infringement for patents related to a "reference product" (i.e., the product for which a biologics license application has already been granted) and to which the §262(k) biosimilar application is to be compared.[5] An initial wave of litigation focused on whether a prospective biosimilars applicant could challenge a reference product patent via a declaratory judgment action outside of the BPCIA framework. For example, in 2013, an attempt was made by Sandoz to press a declaratory judgment action on patents covering Enbrel prior to Sandoz's filing of a §262(k) application for a biosimilar version of the drug. This attempt was rebuffed on jurisdictional grounds by the district court, and the district court's decision was affirmed by the Federal Circuit.[6] In dismissing Sandoz's action, the district court invoked both traditional "case and controversy" principles as well as logic based on the language of the BPCIA. The Federal Circuit, however, affirmed exclusively on the former rationale, reasoning that the requisite "immediacy" was lacking because Sandoz had not filed a §262(k) application with the FDA for its proposed Enbrel biosimilar.[7]

Whether the Sandoz action would have come out differently before the Federal Circuit had its §262(k) application been on file at the time of suit remains an open question.[8] Questions have also arisen whether a different result should obtain if the declaratory judgment action is brought against the patent holder, as opposed to the reference product sponsor.[9] So far, however, the weight of decisions suggests that it will be difficult for biosimilars applicants and reference product sponsors (or patent holders, if they are different) to litigate patents entirely outside of the framework envisioned by the BPCIA (i.e., prior to filing and acceptance of a §262(k) application which triggers the BPCIA machinery).[10]

Litigating Within the BPCIA's Framework

Assuming the BPCIA continues to preempt the field as described above, interpretation of the law's provisions will take on heightened importance. The BPCIA's language is therefore being tested in a second wave of litigation, prompted by the FDA's first-ever acceptance of a §262(k) application in July 2014. Two broad sets of questions are emerging in this second wave.

The first questions involve timing. The BPCIA, as written, envisions up to an eight-year period for patent resolution prior to FDA approval and launch of a biosimilar product. This derives from the BPCIA's exclusivity provisions, which prevent the FDA from accepting a §262(k) application until four years after the date of first licensure, and from approving it until 12 years after that same date.[11] In other words, in the eight-year window between acceptance and approval of the biosimilar application, the majority of patent issues should be resolved so that a clear launch is permissible at the 12-year point, absent a court's finding of infringement.[12] The initial round of §262(k) applications, however, has been for biologic drugs that were first licensed in the 1990s or early 2000s, which means that both the four-year and 12-year exclusivity periods have already expired, or will in the very near future.[13] The effect of this is to compress the patent resolution period from eight years to zero, or, at most, the 180-day window during which time the reference product sponsor may bring a preliminary injunction against the biosimilars applicant after receiving the statutorily required "notice of commercial marketing."[14] For example, in another action between Amgen and Sandoz, this one triggered by the FDA's July 2014 acceptance of Sandoz's §262(k) application for Zarxio (a proposed biosimilar of Amgen's Neupogen), a key dispute is over when the 180-day pre-launch notice period should commence: Does it commence as early as acceptance of the §262(k) application by the FDA (assuming 180-day notice of commercial marketing is given

at that point), or can it only commence upon the FDA's approval of the proposed biosimilar product?[15] The Federal Circuit never answered this question in the prior Sandoz/Amgen litigation because there the court's jurisdictional holding required no interpretation of the BPCIA.[16]

The second question involves remedies for noncompliance with the BPCIA's statutory provisions. In the case of Zarxio, after Sandoz's §262(k) application was accepted for review by the FDA, Sandoz did not provide Amgen with "a copy of the application" or "such other information that describes the process or processes used to manufacture the biological product" within the timeframe set forth under 42 U.S.C. §262(l)(2)(A).[17] Sandoz contends that the remedy for its refusal to provide the §262(k) application is supplied by the BPCIA itself, 42 U.S.C. §262(l)(9)(C), which provides that in the case of such refusal the BLA holder may bring a declaratory judgment action for "infringement, validity, or enforceability of any patent that claims the biological product or a use of the biological product," but not on patents directed toward manufacturing of the biological product.[18] Amgen contends that because the §262(k) application exchange is mandatory, and because the whole point of the BPCIA is to permit a BLA holder the opportunity to create a list of patents it can reasonably assert against (or offer for license to) the biosimilar applicant, including manufacturing patents, Amgen's remedy for Sandoz's breach should be broader than what is specifically permitted under §262(l)(9)(C).[19]

These questions of timing and remedies take on heightened importance when, as in the case of Zarxio, FDA approval and commercial launch of the proposed biosimilar product appear imminent.

Lessons from the FDA

The FDA, even more so than the courts, has been busy with implementation of the BPCIA and has issued draft guidance documents on various topics pertaining to biosimilars in 2012, 2013 and 2014.[20] While communications between prospective biosimilars applicants and FDA are generally not subject to public scrutiny, the public recently received a glimpse into the FDA biosimilars approval process via "briefing" documents submitted by the FDA and Sandoz on Jan. 7, 2015, regarding the company's biosimilar application for Zarxio.[21] These documents are highly product specific and cannot therefore serve as a definitive reference for other §262(k) applicants. But they nevertheless confirm certain key issues raised by the FDA in its prior guidance documents.

First, the briefing documents confirm the FDA's commitment to requiring the §262(k) applicant to supply the agency with a broad and robust showing of analytical similarity to the reference biologic.[22] Without such a showing, the application is doomed from the start. With such a showing, additional requirements, including clinical requirements, may be relaxed on a case-by-case basis.

Second, the briefing documents confirm that the FDA is willing to consider not just comparisons between the proposed biosimilar product and the U.S.-approved reference product, but also between the proposed biosimilar product and the reference product's EU-approved equivalent (if it exists and if appropriate "analytical bridge" studies are conducted).[23] This will be particularly appealing to any company considering a §262(k) application for which an equivalent biosimilar has already been approved, or is in the approval process, in Europe.[24]

Third, the briefing documents confirm that while the FDA will almost certainly require a §262(k) application to include at least one clinical study (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics), the applicant may be able to use the results of this and other studies to extrapolate across other approved indications for the reference listed product.[25]

Conclusion

The filing of the first §262(k) applications in 2014 represents the tip of the iceberg for biosimilars. In addition to the legal and regulatory tangles discussed above, further FDA guidance will almost certainly be required on the important issues of naming and labeling for biosimilars, as well as that of interchangeability. These issues, in turn, necessarily intersect with substitution at the pharmacy and/or clinic level, a process governed not by the FDA but by individual states.

Many state legislatures have within the past few years debated or passed substitution laws specific to biosimilars, but there will doubtless be issues that arise in their implementation once the first biosimilars are approved by the FDA and are permitted to launch. Still other important issues, such as the interplay of inter partes review proceedings with BPCIA patent infringement actions, will need to be addressed by both the courts and the U.S. Patent and Trademark Office. The years ahead should be interesting for biosimilars, to say the least.

—By Thomas H. Wintner, Mintz Levin Cohn Ferris Glovsky and Popeo PC

Thomas Wintner is a member of the firm in Mintz Levin Cohn Ferris Glovsky and Popeo's Boston office.

The opinions expressed are those of the author(s) and do not necessarily reflect the views of the firm, its clients, or Portfolio Media Inc., or any of its or their respective affiliates. This article is for general information purposes and is not intended to be and should not be taken as legal advice.

[1] See generally Biologics Price Competition and Innovation Act of 2009, Pub. L. No. 111-148, §§ 7001-7003, 124 Stat. 119 (2010). The BPCIA also created the designation of "interchangeable" biologics in addition to "biosimilar" ones. However, the FDA requires a "step-wise" showing of biosimilarity before an interchangeability designation can be obtained, and the agency has yet to release anticipated guidance on how interchangeability can be demonstrated. Because the FDA has to date focused almost exclusively on biosimilarity under the BPCIA, so too does this article.

[2] See generally Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984).

[3] As of this writing, Celltrion's application has yet to be accepted by the FDA for review.

[4] As of this writing, Hospira's application has yet to be accepted by the FDA for review.

[5] Compare 42 U.S.C. §262(a) (original, reference product application) with 42 U.S.C. §262(k) (biosimilar application).

[6] See Sandoz v. Amgen, No. 13-2904, 2013 U.S. Dist. LEXIS 161233 (N.D. Cal. Nov. 12, 2013), aff'd Sandoz v. Amgen, No. 2014-1693, 2014 U.S. App. LEXIS 22903 (Fed. Cir. Dec. 5, 2014).

[7] Sandoz, 2014 U.S. App. LEXIS 22903, at *18 ("The essential requirement for [early adjudication of a patent infringement action under 42 U.S.C. §262(e)(2)(C)] is the defendant's filing of the FDA application needed for market entry.").

[8] Id. at *19-20 ("We ... do not decide whether, once an application is filed under the BPCIA, that statute forecloses a declaratory judgment action concerning whether the ultimate marketing of the application-defined product would infringe under 35 U.S.C. § 271(a).").

[9] See, e.g., Celltrion Healthcare Co. v. Kennedy Trust for Rheumatology Research, No. 14-2256, 2014 U.S. Dist. LEXIS 166491 (S.D.N.Y. Dec. 1, 2014).

[10] See Sandoz, 2014 U.S. App. LEXIS 22903, at *18-20; see also Celltrion, 2014 U.S. Dist. LEXIS 166491, at *15 ("The BPCIA purposefully keys its dispute resolution procedures to the occurrence of certain events on the path to FDA approval. Celltrion has failed to show why this carefully crafted and well-timed procedure should be avoided here."). It is important to remember, however, that even if litigation outside of the BPCIA is precluded in federal court, challenges to the validity of patents covering a biologic reference product may still be brought via IPR proceedings before the USPTO.

[11] See 42 U.S.C. §262(k)(7)(A),(B).

[12] See 35 U.S.C. §271(e)(4)(D).

[13] But see FDA Citizen Petition No. 2012-P-0317 (Abbvie petition challenging the FDA's authority to accept or approve §262(k) applications based on reference products approved prior to the effective date of the BPCIA in 2010).

[14] See 42 U.S.C. §262(l)(8)(A),(B).

[15] See Amgen v. Sandoz, No. 14-04741 (N.D. Cal.).

[16] See Sandoz, 2014 U.S. App. LEXIS 22903, at *19 ("Our resolution of this case makes it unnecessary for us to address the district court's BPCIA rationale."); but see Sandoz v. Amgen, 2013 U.S. Dist. LEXIS 161233, at *6 (district court ruling that "notice of commercial marketing" under 42 U.S.C. §262(l)(8)(A) cannot as a matter of law be provided until such time as the biosimilar product is actually "licensed" by the FDA).

[17] See Amgen v. Sandoz, No. 14-04741 (N.D. Cal.) (Amgen Complaint ¶¶ 68-71).

[18] Id. (Sandoz Answer ¶¶ 6-7).

[19] Amgen is also seeking extra-statutory remedies for Sandoz's alleged violations of the BPCIA, including but not limited to damages and other relief under the California Unfair and Deceptive Practices Act. See id. (Amgen Complaint ¶¶ 72-76, 104-106 and pp. 36-37).

[20] See generally http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm290967.htm (last visited Jan. 21, 2015).

[21] See FDA Briefing Document for BLA 125553, available at http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/oncologicdrugsadvisorycommittee/ucm428780.pdf (last visited Jan. 21, 2015); see also Sandoz Zarxio Advisory Committee Briefing Materials, available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM428782.pdf (last visited Jan. 21, 2015).

[22] See Jan. 17, 2015, FDA Briefing Document at 13-28.

[23] See Jan. 17, 2015, FDA Briefing Document at 8-9, 13, 28.

[24] There currently are almost 20 EU-approved biosimilars, in five different product classes. The EU has had an abbreviated biosimilars approval regime in place since 2003, well before passage of the BPCIA in the U.S.

[25] See Jan. 17, 2015, FDA Briefing Document at 10, 60.