

BIOBUSINESS BRIEFS

PATENT WATCH

Have the biosimilar floodgates been opened in the United States?

It took 5 years from the effective date of the Biologics Price Competition and Innovation Act (BPCIA) — the legislation introduced to create a pathway for the approval of biosimilar products — for the US Food and Drug Administration (FDA) to approve the first biosimilar product. In March 2015, Sandoz gained approval for filgrastim-sndz (Zarxio), a biosimilar version of Amgen's filgrastim (Neupogen).

Will a flood of other biosimilars follow?

There are three main hurdles a biosimilar product must clear to enter the US market — regulatory exclusivity periods, regulatory 'biosimilarity' requirements and patent exclusivity periods. The BPCIA provides regulatory exclusivity to reference products by preventing the FDA from approving a biosimilar application until at least 12 years after approval of the reference product. The BPCIA also requires clinical biosimilarity, which the FDA assesses on the basis of "data derived from analytical studies; animal studies; and a clinical study or clinical studies, including the assessment of immunogenicity and [pharmacokinetics] and [pharmacodynamics]". However, even if a biosimilar product can clear these two BPCIA hurdles, it may face patent infringement litigation, either from the reference product sponsor or from a third party.

For example, although Sandoz's filgrastim-sndz has been approved as a biosimilar of Amgen's filgrastim, Amgen has asserted that at least one of its patents covers the product, and is seeking to prevent Sandoz from entering the market until that patent dispute is resolved (the patent expires in December 2016). Likewise, Celltrion is seeking approval of a biosimilar of Janssen Biotech's infliximab (Remicade), but Janssen has asserted that Celltrion's product infringes six of its patents (which expire in 2015, 2016, 2018, 2022, 2023 and

2027). Although the BPCIA includes a framework for resolving patent disputes, all of the litigation to date has stemmed from biosimilar applicants trying to avoid the BPCIA's complicated information exchange and negotiation processes, and attempting to side-step its requirements to disclose confidential manufacturing and development processes.

Along with litigation, we anticipate an increasing number of patent challenges in the US Patent and Trademark Office, with biosimilar competitors bringing *inter partes* (between the parties) review (IPR) proceedings to invalidate patents on the grounds that the patent does not differ enough from prior art. We expect biosimilar competitors to use IPRs to attain earlier market entry, by invalidating core patents and later-expiring 'improvement' or 'selection' patents. Any would-be competitors may have an incentive to challenge core patents, which usually have earlier expiration dates, as such patents probably cover any product that could be approved as a biosimilar. Competitors who are furthest along in biosimilar product development may be most likely to bring IPRs, whereas those at earlier stages may wait for the patent landscape to be cleared before making substantial additional investments in their own product development and freedom-to-operate efforts. However, even if one biosimilar competitor has filed an IPR petition, another biosimilar competitor may want to file its own IPR petition to preserve its rights to challenge the patent on similar grounds and participate in any settlement discussions.

Even biologics that retain patent protection may not be immune from biosimilar competition, especially if the US Federal Circuit upholds recent district court and FDA decisions that found the patent dispute resolution procedures of

the BPCIA to be optional. Unlike the Hatch–Waxman Act, the BPCIA does not require biosimilar applicants to state in their applications that they will give notice to the reference product sponsor of any assertions that the relevant patents are invalid or will not be infringed. Although the BPCIA does state that the biosimilar applicant shall provide a copy of its application to the reference product sponsor, the US District Court for the Northern District of California has held that this requirement is optional, and the FDA has refused to impose such a requirement administratively. This means that it could be up to reference product sponsors to police the market for potential biosimilar competitors and to race to the courthouse to assert their patents before biosimilar products that infringe their patents are approved and marketed.

Because a number of blockbuster biologic drugs that have been in use for at least 12 years are coming off patent in the coming months, these drugs — and their established revenue streams — are prime targets for biosimilar competition. For example, Apotex, with Intas Pharmaceuticals Ltd, has developed a biosimilar of Amgen's pegfilgrastim (Neulasta) and submitted a biosimilar application in December 2014, and Hospira has developed a biosimilar of epoetin alfa (marketed by Amgen as Epogen and by Janssen Products as Procrit), and submitted a biosimilar application in December 2014. Sandoz is working on a biosimilar version of epoetin alfa as well.

Biosimilar antibody product development has been of particular interest in view of the impending 'patent cliff' (TABLE 1). In addition to the upcoming end to the infliximab patent, AbbVie's adalimumab (Humira) may be off-patent as soon as 2016, and already a number of companies are developing biosimilar versions — including Amgen, ▶

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Table 1 | Selected biosimilar antibodies in development

Reference product (manufacturer)	Active biologic agent	Biosimilar competitors worldwide	Example territories with biosimilar approval	IPR filings (petitioner)	Annual US sales (US\$)*
MabThera, also known as Rituxan (Roche)	Rituximab	Amgen/Actavis, Sandoz, Boehringer Ingelheim, Pfizer Inc., Celltrion, Merck & Co., Stada Arzneimittel, Dr. Reddy's Laboratories, BioXpress Therapeutics and Biocad	India and Russia	Yes (Boehringer Ingelheim)	\$3.6 billion
Humira (AbbVie)	Adalimumab	Amgen, Sandoz, Zydus Cadila, Boehringer Ingelheim, Samsung Bioepis, Epirus Switzerland GmbH, Oncobiologics, Mochida/LG Life Sciences, Pfizer Inc., Coherus BioSciences, AET BioTech/BioXpress Therapeutics SA and Fujifilm Kyowa Kirin Biologics	India	No	\$6.5 billion
Remicade (Janssen Biotech, Inc.)	Infliximab	Celltrion, Amgen, Hospira, Alvogen, Biogen/Samsung Bioepis, Ranbaxy, Epirus Switzerland GmbH, Nippon Kayaku, Pfizer Inc. and BioXpress Therapeutics	Europe, Canada, Japan, Turkey, India and Korea	No	\$4.2 billion
Avastin (Genentech Inc.)	Bevacizumab	Amgen/Actavis, Biocad, Boehringer Ingelheim, Pfizer Inc. and Fujifilm Kyowa Kirin Biologics	None	No	\$2.9 billion
Herceptin (Genentech Inc.)	Trastuzumab	Amgen/Actavis, Biocad, Hospira, Celltrion, Samsung Bioepis, Pfizer Inc., PlantForm, Stada Arzneimittel, Hanwha, BioXpress Therapeutics and Biocon/Mylan	South Korea and India	Yes [†] (Phigenix, Inc.)	\$2.1 billion

IPR, *inter partes* review. *Data obtained from BioMedTracker. [†]Phigenix, Inc. filed two IPRs against Herceptin-related patents, and one was instituted.

Sandoz and Zydus Cadila, which has launched its product, Exemptia, in India. Genentech's bevacizumab (Avastin) may be off-patent in 2019, and Amgen and Biocad are reported to have biosimilar versions in development. Genentech's trastuzumab (Herceptin) may also be off-patent in 2019, and Amgen, Actavis and Synthron are jointly developing a biosimilar version, as are Biocad, Hospira and Celltrion.

If Europe is any predictor, we can expect to see a flood of biosimilars entering the US market over the next few years. There are 17 biosimilar products approved in Europe for 7 different active substances. Companies with approved biosimilar products in Europe or in another country probably have a head

start on product development, and only need to clear regulatory and patent hurdles before selling their products in the United States. Although biosimilar product pricing will not be as reduced as for generic drugs, the BPCIA will probably meet its goal of reducing the costs of biologic drug products, and will hopefully do so without undermining the incentives to develop new products.

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FURTHER INFORMATION

US Food and Drug Administration information on biosimilar applications: <http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologic-applications/biosimilars/default.htm>
PharmaPatentsBlog on biosimilars: <http://www.pharmapatentsblog.com/category/biosimilars/>

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