Supplement to the Los Angeles and San Francisco
Daily Journal
AUGUST 27, 2014

BIOTECH: THE BATTLE OVER BIOSIMILARS

Biosimilars and the new road to FDA approval

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Biologics are a class of medicines that include protein-based products used to treat a disease or health condition. However, they differ from more traditional "small-molecule" drugs in that they are made by cellular processes or biotechnology. Biologics are large, complex molecules that are difficult to manufacture, characterize and compare to one another, and are extremely expensive to develop. While biologic products have revolutionized patient therapies for a variety of cancers and inflammatory diseases (such as breast cancer and rheumatoid arthritis, respectively), the lengthy time and enormous costs to discover, produce and obtain U.S. Food and Drug Administration approval for these products have contributed to high prices and limits on their access to patients.

Intended to reduce prices and expand access to biologics, the Biologics Price Competition and Innovation Act (BPCIA) was enacted as part of the Patient Protection and Affordable Care Act (PPACA). It amended the Public Health Service Act (PHSA) to establish an abbreviated pathway for FDA licensure of biological products. However, while the BPCIA has been in place for over four years, nearly all of the essential determinants of how it will be administered remain largely undecided.

The BPCIA provides two tiers of regulatory approval: A biologic may be demonstrated to be either "biosimilar" or "interchangeable" to a reference biologic. A "biosimilar" designation means the two compounds are "highly similar" and there are "no clinically meaningful differences" between them. An "interchangeable" designation means the two compounds "can be expected to produce the same clinical result" and the risk of diminished safety or efficacy by switching between them is no greater than the risk of using the reference biologic.

The BPCIA provides several types of regulatory exclusivity. First, the reference biologic receives "data exclusivity," under which a biosimilar application may not be submitted to the FDA within four years of first licensure of the reference. Second, the reference biologic receives "market exclusivity," under which a biosimilar application may not be approved until 12 years after first licensure of the reference. Third, the first licensed interchangeable biologic receives a period of market exclusivity, under which a second biosimilar may not be found interchangeable until one year after first commercial marketing of the interchangeable, or different periods depending on the outcome of related patent litigation.

However, many fundamental issues concerning the BPCIA remain unresolved, making this regulatory pathway unattractive to some potential biosimilar manufacturers. At one level, as with any new regulatory pathway, there are costs, risks and uncertainties in the face of a completely unknown and untested procedural approval process. The rulemaking process for the BPCIA is still in its relatively early stages. The FDA was slow to provide *any* guidance to industry regarding the biosimilars pathway, and the several draft guidances issued to date leave many questions open about how the BPCIA regulatory licensure process will actually play out. The guidances so far indicate a case-by-case process, which does not help for planning purposes until sufficient cases proceed through the process.

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Other important issues that remain largely undecided include: (a) by what processes and guidelines biosimilars will be named, and (b) whether and how biosimilars and/or interchangeables may be substituted at the pharmacy, which is a matter of state law. Some states have already passed legislation prohibiting pharmacists from substituting interchangeable biosimilars for a reference biologic without physician approval.

The regulatory challenges ahead for potential biosimilar manufacturers remain significant. The FDA has explained that it will evaluate biosimilars under a four-part standard for biosimilarity: (1) not similar, (2) similar, (3) highly similar and (4) highly similar with a fingerprint-like similarity. However, the actual definitions of these categories will only be determined over time as the FDA proceeds with evaluation of various biosimilar products.

Although the BPCIA was enacted into law more than four years ago, it should not be surprising in view of these uncertainties surrounding regulatory approvals that only two applications for biosimilars have been recently submitted, both for products that have already been approved and marketed as biosimilars in many other countries.

On July 24, Sandoz Inc., a unit of Novartis AG, announced that the FDA had accepted its application for a biosimilar for Amgen's Neupogen, which is indicated for the treatment of neutropenia, a granulocyte disorder. The FDA acceptance was a U.S. landmark in that it is widely believed to be the first of any biosimilar application. More than 40 other countries have already approved the biosimilar, which is marketed by Sandoz as Zarzio.

On Aug. 11, South Korea-based biosimilar manufacturer Celltrion Inc. announced that the company is seeking FDA regulatory approval for Remsima as a biosimilar for Johnson & Johnson affiliate Janssen Pharmaceutical's Remicade, a monoclonal antibody indicated for treatment of rheumatoid arthritis, ankylosing spondylitis, ulcerative colitis, Crohn's disease, plaque psoriasis and psoriatic arthritis. More than 50 countries have already issued regulatory approval for Remsima, including the first approval of any monoclonal antibody biosimilar through the European Medicines Agency (EMA) regulatory pathway in the fall of 2013. It is expected that Celltrion will launch the biosimilar in the European Union in 2015 when the reference product comes off patent.

Having proven "biosimilarity" under the EMA biosimilars pathway, both the Sandoz and Celltrion biosimilar products are believed to have a higher chance than most for success under the new U.S. licensure pathway.

The BPCIA also provides a specific process for patent litigation. Similar to Hatch-Waxman — which addressed generic drugs — a biosimilar application is deemed an act of infringement, and the litigation is slated to proceed through a case management scheme prescribed by statute. However, unlike Hatch-Waxman, there is no Orange Book — which lists FDA-approved drugs, their generic equivalents, and patents alleged to cover each drug — for biosimilars, resulting in a biosimilar patent litigation process that includes a cumbersome series of exchanges of product information and patent contentions between the parties to identify the patents to be litigated. One apparent requirement under the biosimilars statute is that the biosimilar manufacturer must provide a copy of its FDA filing to the innovator/patent holder of the originally approved biologic. Turning over such highly sensitive and confidential information may be viewed as a showstopper to some companies developing biosimilars. Because of the complexity of this process, many commentators have derisively dubbed it the BPCIA "patent dance," and the process is viewed by many as so onerous that few are interested in testing the process.

Indeed, prior to both of the first two filings of Sandoz and Celltrion under the biosimilars pathway, both companies filed traditional declaratory judgment patent challenges to avoid the patent litigation process mandated by the statute after the filing of their biosimilars applications. The question whether such an action is cognizable is currently on appeal before the U.S. Court of Appeals for the Federal Circuit. It will be years before the courts decide the cases to specify whether the process provided in the statute can be avoided by traditional patent litigation or whether the statute mandates its litigation process as the sole remedy. Another wildcard is the potential for challenging patent validity outside of federal court proceedings, for example, through the USPTO's new post-grant proceedings.

The promise of reduced costs and increased access to biologic medicines remains the hope of patients, regulators and health care payors in the U.S., with biosimilars seen by many as a key part of that promise. 2014 has already become a landmark year with the filing of the first two U.S. biosimilars applications. Despite the complexities and uncertainties of this untested regulatory pathway, biosimilar enthusiasts are cautiously optimistic about the rapid approval in the U.S. of these initial products from Sandoz and Celltrion, which are considered by most to be high quality, well-tested biosimilars, already approved and marketed in many countries outside the U.S. There is more than a hope that 2015 will be a breakthrough year for biosimilars in the U.S.

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