

Biosimilars Pathway: A Far Cry From Hatch-Waxman

Law360, New York (March 30, 2010) -- On March 23, 2010, President Obama signed into law Pub. Law. No. 111-148, the APPROVAL PATHWAY FOR BIOSIMILAR BIOLOGICAL PRODUCTS (i.e., Biosimilars Pathway), a component of the Patient Protection and Affordable Care Act. This legislation creates, for the first time, a pathway for the production, use and sale of follow-on biologic therapeutics in the United States.

The U.S. is now among many countries in the world having a pathway for biosimilar products, including those in the EU that, in 2004, adopted biosimilars legislation and subsequently approved numerous biosimilar products for commercialization.

The Biosimilars Pathway is perhaps the most important piece of legislation impacting the IP rights of researchers, as well as the developers of biological products in U.S. history, and it will directly impact the IP rights of biologics manufacturers throughout the world seeking to safely market biological products in the U.S.

While many major biological medicines currently on the market in the U.S. were approved over 12 years ago, the exclusivity period will not apply, and so as they approach the end of their patent protection, drug manufacturers around the world, including traditionally “innovator” or “brand” companies are exploring the possibility of producing and selling biosimilars.

The Pathway was developed with an understanding that biosimilars are not generic versions of innovator products, and a demonstration of therapeutic equivalence based on pharmaceutical equivalence and bioequivalence will not suffice.

Biosimilars, historically referred to as “follow-on-biologics” in the U.S., are biological products that are sufficiently similar to their previously approved reference biologic that the same clinical outcome can be expected.

These criteria are based on the term of art “highly similar,” which is the established comparability standard for innovator biologics subject to a manufacturing change by their own sponsor. The requirements are set forth and submitted in a detailed application for a separate marketing license by the new sponsor in anticipation of the patent term expiration of the reference product.

The public policy behind the Biosimilars Pathway is generally to preserve incentives that encourage continued biologics innovation while assuring patient safety and expanding access to life-saving biological therapeutics by maintaining the same fundamental requirements of all biologics sponsors of a demonstration of safety, purity and potency.

The Biosimilars Pathway defines a biosimilar as a “biological product [that] is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and requires that there be “no

clinically meaningful differences between the biological product in terms of the safety, purity, and potency of the product.”

A new Pathway was necessary because the Hatch Waxman amendments, which created the U.S. generic drug pathways, applied to those products regulated under the Federal Food, Drug and Cosmetic Act and, except for one provision on patent term restoration, not to those products regulated under the Public Health Service Act.

Also with the experience gained with using comparability (an FDA guidance issued in 1996), and the European biosimilars pathway, it became clear that this approach could be usefully applied to the comparison of products from different sponsors.

The active substance in a product regulated as a drug can usually be, but not always be, defined at a molecular level, whereas many, but not all biologics, are more complex and are sometimes mixtures.

Even so, the use of comparability principles with most recombinant products to make manufacturing changes, such as expanding capacity by bringing new facilities on line, by their original sponsors demonstrates that these well-characterized biologics are well understood and that, just like in Europe, those approved earliest, e.g., epoetin and filgrastim, may likely be the first candidates as reference products for biosimilars.

The manufacturing processes are far more complex and expensive for many biologics than for small molecules, and historically biologics have and are subject to so called establishment licenses as well as product licenses (both having been combined to form the biological license, but the constituent requirements being unaltered).

Because of the differences between the requirements for generic drugs and biosimilars, the Biosimilar Pathway and the Hatch-Waxman Act should not be confused or analogized — they create fundamental, different expectations for the regulatory filings, and the new pathway for biosimilars does not set forth a different or lesser standard than that required of an innovator biologic, even though the data submitted to demonstrate the achievement of that standard is different.

Key features of the U.S. Biosimilars Pathway include provisions relating to the assessment of biosimilarity, a reference product exclusivity period of at least 12 years after the date on which the reference product was first licensed, a first interchangeable biosimilar exclusivity period of at least one year, and regulations regarding patent listings and alleged patent infringement actions.

An application submitted for biosimilar approval under the Pathway may not be submitted until four years after “the date on which the reference product was first licensed ...,” which is a period of time during which a prudent biosimilar applicant would prepare an application and litigation strategy.

Importantly, included in the patent provisions of the legislation is a unique scheme for the confidential exchange of information regarding patent rights relevant to the subject biosimilar and reference (i.e., branded) product.

This submission of this information is not based on information made available in the Orange Book under Hatch-Waxman regarding the patent term and exclusivity periods, given that PHS Act biologics are not listed in the Orange Book, and is one reason parallels between the Hatch-Waxman Act and the Biosimilar Pathway should not be drawn.

Under the default Biosimilar Pathway information exchange scheme, after filing of an application with the FDA, the applicant must provide the reference product sponsor (i.e., the innovator) with a copy of the biosimilar application, the manufacturing process used in the production of the subject biosimilar and, optionally, any

additional information requested by the reference product sponsor (i.e., innovator), must be provided to the sponsor by the applicant.

The Pathway does not indicate how much information requested by a sponsor must be provided by the applicant, other than that it include a copy of the entire biosimilar application submitted, and the Pathway does not limit the amount or quality of such information.

Due to the narrow window of time (60 days) in which an applicant must respond to such a request, it is important that an applicant anticipate what information may be requested (e.g., significantly detailed information regarding manufacturing processes) based on the nature of the biotechnology well in advance of filing.

It is possible that the request for information could include information pertinent to variants or alternative forms of the biosimilar product, which could lead to the exchange of sensitive information unduly prejudicing the applicant, as well as the IP of the biosimilar applicant with respect to, for instance, state of the art manufacturing methods.

Subsequently, the sponsor must provide the applicant with a list of patents which the sponsor believes a claim of infringement could reasonably be asserted if the biosimilar was engaged in making, using, offering to sell, selling or importing into the U.S. the biosimilar product applied for.

Regarding the list of patents, due to the nature of biotechnology and the volume of claims necessary to adequately disclose many biotechnology inventions, it is likely that numerous patents will be listed. For example, patents containing claims directed to methods for manufacturing biological products, which are not uncommon in biotechnology patent portfolios, should be included on the list.

In contrast, the Hatch-Waxman Act does not permit the listing of patents directed to methods of manufacturing approved drugs in the Orange Book. In addition, sponsors must work with in-house counsel and litigation counsel who appreciate the nature of biotechnology to immediately determine whether or not patents directed to subsequent generation products, which are lucrative patents in numerous biotechnology portfolios, should be included.

In addition to the list of patents, a sponsor must provide an applicant with a list identifying the patents that the sponsor would be prepared to license to the applicant. This is radically different from the Hatch-Waxman Act.

In response, the applicant is required to provide the sponsor with a detailed statement that describes, on a claim by claim basis, the factual and legal bases why the sponsor's patents are invalid, unenforceable or will not be infringed by the commercial marketing of the biosimilar product, or a statement that the applicant does not intend to commercialize the biosimilar product in the U.S. before the date that all asserted patents expire.

If the applicant provides a detailed statement setting forth the factual and legal bases of invalidity, unenforceability or noninfringement, such statements must be accurate and sustainable if litigation arises. Extreme care should be taken in developing a litigation strategy before filing the application.

Interestingly, within 60 days after having received the applicant's detailed statement and response, the sponsor must provide the applicant with a "detailed" statement that describes, for each listed asserted patent, on a claim by claim basis, the factual and legal basis of the opinion of the sponsor concerning infringement and validity of the claims.

In preparing this detailed statement, the sponsor must develop and articulate in good faith, counter arguments regarding invalidity, unenforceability or noninfringement (if alleged by the applicant) which could require extensive litigation and preparation. There is no parallel Hatch-Waxman provision.

While it remains unclear whether guidelines will be issued by the FDA concerning the data necessary to adequately support approval of an application filed under the Biosimilar Pathway, the standards for a biosimilar will match those of a innovator biologic, namely safety, purity and potency.

It is also clear that IP management strategies for biosimilars should include an appreciation of the unique nature of biosimilar technologies and immediate consideration of the applicant and sponsor's intellectual property portfolio's strengths, weaknesses and scope.

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