Follow-On-Biologics Framework: Overview and Comparisons

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In 1984, Congress passed the Hatch-Waxman Act, setting in motion more than 25 years of patent litigation between branded pharmaceutical companies and generic manufacturers and resulting in a significant expansion of generic drugs. Hatch-Waxman, however, only applied to small molecules prepared by chemical synthesis, not larger, more complex, biologic molecules isolated from natural sources. The absence of an abbreviated U.S. Food and Drug Administration (FDA) approval pathway for biologics was addressed in March 2010 when Congress passed the Biologics Price Competition and Innovation Act. Although both acts seek to simplify and expedite approval of generic drugs and follow-on biologics while simultaneously respecting patent protection for the innovator's branded products, the two acts contain very significant differences requiring careful strategic planning.

Two categories of biosimilar follow-on biologics

Follow-on biologics can be either biosimilar to the reference product or interchangeable with the reference product. Unlike an AB rated generic, a biosimilar follow-on biologic cannot be substituted by the pharmacist for prescriptions written for the reference product. Only an interchangeable follow-on biologic can be substituted when a prescription is written for a reference product.

Biosimilarity requires that the follow-on biologic be "highly similar" to the reference product and have no clinically meaningful differences in safety, purity, and potency from the RP. This undefined standard leaves a host of unanswered questions. What range of structural differences between the follow-on biologic and the reference product will be permitted by the FDA under the highly similar standard? What analytical testing will be required to meet that standard? What types of animal and clinical studies will be required to establish that there are no such clinically meaningful differences?

To be interchangeable, the follow-on biologic must not only be shown to be biosimilar to the reference product, but also must be expected to produce the same clinical result as the reference product in any given patient. If administered more than once to an individual, the risk of diminished efficacy or safety from switching between the follow-on biologic and the reference product must be shown to be no greater than the risk of using the reference product without such switch. Again, the factors to be considered in making such determinations have not yet been identified.

Although it is hoped that these uncertainties will be addressed by formal guidance from the FDA later this year, they very well may be resolved on a case-by-case basis. As a result, consideration should be given to the filing of a full Biologic License Application over the biosimilar route, particularly where the manufacture of a follow-on biologic is complex.

Comparison of exclusivity periods

Under Hatch-Waxman, generic drugmakers must wait at least four to five years from the approval date for the branded New Drug Application (NDA) to file their application. Additional branded exclusivity is available if certain supplemental NDAs are approved. Although a follow-on biologic application can also be filed four years
after the reference product licensing date, it cannot be made effective for 12 years after that date. Additional exclusivity periods are not permitted for supplemental applications on the reference product. Significantly, however, a modification to the structure of the reference product that results in a (currently unspecified degree of) change in safety, purity, or potency may allow for an additional 12 year period of exclusivity.

Given the length of the exclusivity period, careful strategic consideration should be given to the timing of filing patent applications, the order in which various types of patent applications should be filed, and their content. The potential for an additional 12 years of exclusivity should be considered in structuring ongoing research and development.

Under Hatch-Waxman, the first generic to file a substantially complete ANDA containing a Paragraph IV certification may receive 180-day generic market exclusivity. If a follow-on biologic is only biosimilar, there is no exclusivity against other biosimilars to the same reference product. However, if the follow-on biologic is interchangeable with the reference product, then it is possible that no subsequent interchangeable follow-on biologic could be approved until one year after the first interchangeable follow-on biologic is commercially marketed.

Patent litigation framework

The patent litigation framework for follow-on biologics is significantly different from the Hatch-Waxman procedure, and requires considerable interaction between the follow-on biologic applicant and the reference product sponsor before the initiation of litigation. Unlike with Hatch-Waxman, the reference product sponsor does not list patents in the Orange Book. Instead, the follow-on biologic applicant has the initial burden of identifying relevant patents during its development work. Shortly after acceptance of the follow-on biologic application by the FDA, the reference product sponsor and patent owner are entitled to confidential access to the follow-on biologic application and manufacturing information, even when the follow-on biologic applicant does not intend to market a product before patent expiration.

That disclosure then triggers a complicated exchange of information between the reference product sponsor and follow-on biologic applicant. This process begins with the reference product sponsor listing patents for which it believes a claim for patent infringement could reasonably be asserted. Unlike Hatch-Waxman, there is no limitation on the types of patents that can be included on the list. Failure of the reference product sponsor to timely list a patent potentially limits the remedies available to it for such late-listed patents.

Next, the follow-on biologic applicant, followed by the reference product sponsor, sequentially exchange a detailed statement of the factual and legal bases for their positions on each listed patent claim. The follow-on biologic applicant also may list any other patents of the reference product sponsor that it believes a claim for patent infringement could reasonably be asserted.

After these exchanges are completed, the reference product sponsor and follow-on biologic applicant negotiate to determine which patents will be litigated. If they fail to reach agreement, then another multi-step procedure occurs in which the follow-on biologic applicant can limit the number, but not identity, of patents that it believes should be litigated. At the conclusion of this procedure, the reference product sponsor must promptly file a patent infringement action on the identified patents or risk significantly limiting the remedies available to it.

While Hatch-Waxman patent litigations are usually filed within 45 days of the NDA holder receiving a Paragraph IV notice containing the ANDA holder's allegations of patent invalidity and/or non-infringement, for biologics the above procedure is likely to result in the passage of more than seven months before patent litigation begins. Such litigation could begin long before the 12 year exclusivity has expired. The follow-on biologic applicant effectively controls the timing of such litigation because the filing of its application with the FDA triggers the statutory procedure discussed above. Unlike Hatch-Waxman, there is no automatic 30 month stay of FDA approval of a follow-on biologic application pending resolution of the infringement action.

Interestingly, the Biologics Competition Act also provides for a second round of litigation. In particular, the follow-on biologic applicant must give the reference product sponsor an 180-day notice before the date of first commercial marketing of the follow-on biologic. The reference product sponsor may then seek a preliminary injunction against commercial manufacture or sale of the follow-on biologic with respect to any patent that was listed in the pre-suit exchanges, but not litigated. Declaratory judgment actions on such excluded patents by either the reference product sponsor or the follow-on biologic applicant are also permitted at this time.

Conclusion

The requirements for establishing biosimilarity or interchangeability between a follow-on biologic and reference product are more rigorous than establishing bioequivalency between a generic and branded drug. The degree of difficulty will remain uncertain until the FDA implements guidance and practice. While the market exclusivity period for biologics is significantly longer than for traditional pharmaceuticals, patent protection will still be important. A thorough understanding of the patent portfolios covering biologics products and processes will be required, including their scope of protection, remaining term, strength, and possible design-arounds before the first follow-on biologic application is even filed. The time to prepare for successful navigation through patent litigation on biologics is now.