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BIOSIMILARS VS. GENERICS – MAJOR DIFFERENCES IN THE REGULATORY MODEL

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On February 9, 2012, the U.S. Food and Drug Administration (FDA) published its long-awaited biosimilar guidance documents as a follow-up to the Biologics Price Competition and Innovation Act of 2009 (Biosimilars Act) that was signed into law by President Obama on March 23, 2010. The legislation, which was inspired by the 1984 Hatch-Waxman Act establishing a generic pathway for small molecule drugs, provides a new biosimilar pathway for the approval of large molecule (biologic) drugs.

While there are important similarities in the two regulatory schemes, there are many more differences. Generic manufacturers who are familiar with Hatch-Waxman and are looking for expedited entry into the biosimilars market may be disappointed.

Overview

Hatch-Waxman created two generic approval pathways for small molecule drugs – 505(b)(2) applications (so-called "paper NDAs") and ANDAs, with the latter requiring only bioequivalence studies to be considered therapeutically equivalent and fully substitutable by pharmacies for the pioneer drug. The Biosimilars Act also establishes two categories of generic biologics under a similar scheme – biosimilars and "interchangeable" biologic products with only the latter requiring clinical trials to be considered fully substitutable for the pioneer biologic by pharmacies.

A biosimilar product is defined as one that is "highly similar" to the pioneer product notwithstanding minor differences in clinically inactive components and where there are no clinically meaningful differences in terms of safety, purity and potency. An interchangeable biological product is one found to be biosimilar which means it is expected to produce the same clinical result as the pioneer in any given patient and, if administered more than once to an individual the risk in terms of safety or diminished efficacy of alternating or switching between use of the product and the pioneer is no greater than the risk of using the pioneer without such alteration or switch.

Both Hatch-Waxman and the Biosimilars Act provide pioneer, generic, and pediatric exclusivities to protect innovator and "first mover" investments. In addition, both Acts allow for the challenge of pioneer patents prior to launch but patent litigation under the Biosimilars Act is more complicated and risky than under Hatch-Waxman. In addition, Hatch-Waxman provides for the public listing of pioneer patents in the Orange Book and for automatic 30-month stay of FDA approval during patent litigation, whereas the Biosimilars Act has no comparable features.

Pioneer Exclusivities

Like Hatch-Waxman, the Biosimilar Act provides pioneer companies that invest in and develop biological drug products with an exclusivity period so that they can recoup their investment.

Hatch-Waxman provides a five-year marketing exclusivity for new active moiety as compared to the Biosimilar Act, which has a 12-year marketing exclusivity for new "biological structures." If a biosimilar application is filed by the same sponsor or manufacturer of the pioneer product (or a related party), the changed biological structure must also result in a (1) change in indications, route of administration, dosing schedule, dosing form, delivery system, delivery device or strength or (2) change in safety, purity or potency for a new 12-year exclusivity period to be awarded.

Under Hatch-Waxman, a generic can file an application after four years of new active moiety (5-year) exclusivity provided a patent challenge accompanies the filing. Under the Biosimilars Act, an applicant can file after four years of biologic structure (12-year) exclusivity.

Both laws include opportunities for pediatric exclusivity. Under Hatch-Waxman, pediatric exclusivity adds six months to all exclusivities and to Orange Book listed patents. The pediatric exclusivity under the Biosimilars Acts adds six months to 12-year exclusivity and six months to the four-year filing restriction.

Generic Exclusivities

The first generic filer to certify under Paragraph IV (challenging the pioneer's Orange Book patents) receives six months of generic exclusivity. The Biosimilar Act provides broader exclusivity incentives to the first approved "interchangeable" biologic product. Once the first interchangeable product has been approved, no subsequent interchangeable applications will be approved until one year after the first commercial marketing by the first licensee. That timetable is extended in the event of litigation against the first licensee.

The Biosimilar Patent Dance

Pioneer manufacturers are given procedural rights to litigate drug patents prior to generic launch under both Acts, but that is where the similarity ends. Under Hatch-Waxman, pioneers are required to list all patents that claim the drug or method of using the drug in the Orange Book and generic applicants seeking to enter the market prior to expiration are required to notify the pioneer and provide a detailed analysis as to why it believes each challenged patent is invalid or will not be infringed. If the pioneer files suit within 45 days of such notice, the FDA is required to suspend review and approval of the ANDA for 30 months unless shortened or lengthened by court order.

The Biosimilars Act does not provide anything comparable to the Orange Book. Instead, a biosimilar applicant learns of the patents that protect the pioneer biologic only after providing the pioneer with confidential access to its application and related manufacturing process. The biosimilar applicant and pioneer then undertake a complex exchange of patent information (the "patent dance") over an approximate two-month period to compile a list of "agreed to" patents that will be subject to a "first wave" of pre-launch litigation. The pioneer then has 30 days to file suit on those patents to enjoin biosimilar launch or else only royalties can be obtained in subsequent litigation on those patents.

The Biosimilars Act also provides for a "second wave" of pre-launch litigation by requiring the biosimilar applicant to notify the pioneer a second time at least 180 days prior to launch. Patents that were disclosed, but not on the "agreed to" list during the first dance, are eligible for possible injunctive relief, and applicants can file Declaratory Judgments during this second wave on patents that the pioneer elects not to pursue.

The Long-Awaited FDA Guidance

There are no approved biosimilars in the U.S. yet, as the industry has been waiting for the recently released FDA guidelines on the scientific and technical data the agency will require of applicants to gain market approval. The new guidelines provide valuable insight into the more complex biosimilar process. Let's compare.

- *Demonstrating Generic Small Molecules Bioequivalency*

To be approved, generic drug applicants must demonstrate "bioequivalency" in addition to providing information regarding the labeling, chemistry, manufacturing, and quality of its drug product. Instead of conducting extensive clinical testing, ANDA applicants can rely on the clinical trials, including the safety and efficacy results obtained by the reference pharmaceutical product.

A generic drug is bioequivalent when the rate and extent of absorption of the drug (its "bioavailability") are not significantly different from those of the reference drug. The type of studies demonstrating bioequivalency depend upon the dosage form and route (e.g. oral versus injectable), but generally the standards of proving equivalence are well established (provided in FDA guidance and the U.S. Pharmacopoeia). These include certain simple *in vitro* studies and *in vivo* biostudies. Overall, demonstrating bioequivalency is relatively straightforward and not expensive.

- *Demonstrating Biosimilarity: A More Complex Endeavor*

Biosimilar product applicants have a more involved (and more expensive) approval process. The FDA has proposed a "stepwise" approach to demonstrating biosimilarity, starting with extensive structural and functional characterization of the proposed and referenced product. This characterization is the "foundation" of a biosimilar development program and informs the type and extent of additional studies that the FDA will require.

The structural characterization should use state of the art technology comparing primary structure, higher order structure, enzymatic post-translational modifications, and other potential variants and modifications. Also, this characterization should be performed on several lots to determine if the manufacturing process will result in variability. The functional characterization involves comparing the proposed and reference product to show that the biologic activity and potency are highly similar, there are no clinically meaningful differences, and the mechanism of action is the same.

The FDA also proposes that applicants conduct animal studies, including animal toxicity studies, to demonstrate biosimilarity. Animal toxicity studies are useful when the structural and functional characterization leave uncertainties about the safety of the proposed product that need to be addressed before initiating clinical studies in humans. However, if the biosimilar product is shown to be highly similar, applicants need not conduct the vast animal safety studies required for the original approval of the biologic, e.g., nonclinical safety pharmacology, reproductive and developmental toxicity, and carcinogenicity studies.

The animal studies envisioned by the FDA will likely include pharmacokinetic (PK) and pharmacodynamics (PD) studies, which can be incorporated into a single animal toxicity study if appropriate. Although animal immunogenicity studies are generally not predictive of potential responses in humans, if there is a concern of immunogenic reactions from impurities or excipients, animal studies may be required.

Applicants will generally be required to conduct clinical studies sufficient to demonstrate safety, purity, and potency for the intended use. The scope will depend upon the uncertainty level about the biosimilarity after structure and functional characterization and animal studies. The FDA has emphasized that human PK and PD studies, as well as immunogenicity comparisons, will generally be required, as these cannot be adequately predicted from functional assays and studies in animals.

Beyond these, additional clinical studies may be required to demonstrate safety and effectiveness, but the FDA envisions discussing the type and extent of further studies with the applicant depending upon what residual uncertainties remain about biosimilarity.

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