PUBLICATION

Regulation of Biosimilars

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Congress is currently considering legislation similar to the Hatch-Waxman Act of 1984 to authorize expedited Food and Drug Administration (FDA) approval of generic biologic drugs, or “biosimilars.” Biosimilars are biologic drugs that are “similar” to their patented, FDA-approved biopharmaceutical counterparts. Although the expedited approval process works well for traditional chemically-synthesized drugs, it may not work as well for biopharmaceuticals.

Biopharmaceuticals are nucleic acid or protein-based medications derived from the manipulation of living organisms. They are the result of modern biomedical research and include many different kinds of medications. These include recombinant human insulin; erythropoietin (EPO); vaccines; and monoclonal antibodies. Unfortunately, biopharmaceuticals can also be very expensive, with some costing more than $100,000 per patient, annually.

As innovative biopharmaceuticals lose patent protection, the market for their biosimilar counterparts opens. However, there is no expedited pathway for FDA approval of biosimilars. Small-molecule chemically-synthesized drugs are approved by the FDA under the Food, Drug and Cosmetic Act (FDCA), which Congress amended via the Hatch-Waxman Act to provide for expedited approval of generic drugs. By limiting the degree of testing required for generic drugs, and by allowing reference to the FDA's prior findings of safety and efficacy for reference innovator drugs, Congress helped lower generic drug costs and sped the drugs to market. Almost all biopharmaceuticals, though, are approved under the Public Health Service Act (PHSA), which has no comparable provisions for expedited approval. Consequently, a manufacturer seeking FDA approval for a biosimilar is required to submit a completely new application — including the results of full clinical trials — without reference to the FDA's prior findings of safety and efficacy for a reference innovator biopharmaceutical.

Congress recognizes that an expedited FDA approval process is needed for biosimilars. In fact, four bills addressing this issue have been introduced since February 2007. An analysis of the bills, though, suggests that a limited testing paradigm — which works so well for small-molecule drugs — may not be so easy to legislate.

The “Access to Life-Saving Medicine Act” (H.R. 1038), introduced by Representative Henry Waxman in February 2007, would require a demonstration that a biosimilar is “comparable to or interchangeable with” a reference biopharmaceutical, and that it contains “highly similar principal molecular structural features, notwithstanding minor differences in heterogeneity profile, impurities, or degradation patterns.” The “Biologics Price Competition and Innovation Act of 2007” (S. 1695), introduced by Senator Edward Kennedy, is similar to the Waxman bill and would require a showing of “biosimilarity” based upon “analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; animal studies; and a clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency.” The “Pathway for Biosimilars Act” (H.R. 5629) introduced by Representative Anna Eshoo in March 2008, would require analytical studies demonstrating that the biosimilar is “highly similar” — a term that is not defined by the bill. Each of these three bills would grant the Secretary of the Department of Health and Human Services (DHHS) broad discretion to determine whether or not to waive certain requirements, including

laboratory studies, animal studies and clinical studies. In contrast, the fourth bill, known as the “Patient Protection and Innovative Biological Medicines Act of 2007,” (H.R. 1956) introduced by Representative Jay Inslee, contains none of the exceptions of the other three bills. The Inslee bill would require the submission of “data demonstrating the stability, compatibility … and biological and physiochemical integrity of the active ingredient,” results of “physical, chemical, and biological assays fully characterizing” the biosimilar, “data from comparative nonclinical studies,” “data from comparative clinical trials,” and “a plan for postmarketing safety monitoring.”

The Hatch-Waxman paradigm for approval of generic small-molecule drugs works well because demonstrating “bioequivalence” between these drugs and their reference compounds is relatively simple. Demonstrating bioequivalence requires, for example, administering the generic drug and the reference drug to volunteer subjects in a cross-over study, and then assaying plasma samples for drug (or metabolite) concentrations over time. The pharmacokinetic parameters derived from these data allow determination of the drugs' comparability.

Biopharmaceuticals, though, are far more complex than small-molecule drugs, and demonstrating simple “bioequivalence” may not be sufficient. Biopharmaceuticals are roughly 100 to 1,000 times larger than chemically-synthesized drugs, they possess complex three-dimensional structures, and may exist as mixtures of isoforms. A major shortcoming of biopharmaceuticals is their tendency to evoke an immune response (the formation of harmful antibodies). Not only can these antibodies affect drug efficacy by neutralizing the drug itself, they may produce serious clinical consequences if they are directed against endogenous (“self”) proteins. For example, beginning in 1998 the incidence of a rare form of anemia associated with the production of erythropoietin-neutralizing antibodies increased dramatically in patients receiving epoetin-a. While the causes remain unclear, they were positively correlated with changes to the product formulation, the route of administration, and storage and handling issues. The scientific and medical communities have learned that relatively minor differences between protein products — including sequence variations, posttranslational modifications, contaminants, impurities, and formulation differences — can have profound effects on their immunogenicity. Ironically, the Waxman bill would define biosimilars having differences “solely due to post-translational events, infidelity of translation or transcription, or minor differences in amino acid sequence,” as well as differences in glycosylation – all major determinants of immunogenicity – as containing “highly similar principal molecular structural features.”

Because relatively minor changes to biopharmaceuticals may cause significant alterations in immunogenicity, and because an individual's immune system can respond to alterations that current analytical techniques may not detect, it appears likely that biosimilars will require more extensive clinical testing than generic drugs. Consequently, the savings enjoyed with generic small-molecule drugs may not be realized with biosimilars, and biosimilars may not enter the market as rapidly as their generic small-molecule cousins.