

# GENERIC BIOLOGIC DRUGS WHAT'S IN A NAME?

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If you haven't encountered biosimilars yet, you will soon. Generic small-molecule pharmaceuticals gained prominence after passage of the Hatch-Waxman Act in 1984,<sup>1</sup> and Congress is currently considering similar legislation to authorize accelerated Food and Drug Administration (FDA) approval of biosimilars—generic biopharmaceuticals. Patents for various FDA-approved biopharmaceuticals will expire soon, and generic versions may become available. Although the Hatch-Waxman framework worked well for small chemically synthesized drugs, it may not be adequate in the context of biosimilars.

Biosimilars are biopharmaceuticals—nucleic acid or protein-based medications derived through manipulation of living organisms—that are “similar” to patented, FDA-approved biopharmaceuticals. Some examples of biopharmaceuticals and their uses include: recombinant human insulin (diabetes); erythropoietin (anemia due to cancer therapy); tissue plasminogen activator (stroke); rituximab (non-Hodgkin's lymphoma and rheumatoid arthritis); infliximab (Crohn's disease); pegfilgrastim (neutropenia due to cancer therapy); and  $\beta$ -glucosidase (Gaucher's disease).

Biopharmaceuticals are the fruits of biomedical research, and have become an essential part of the modern pharmacopoeia. They are also expensive. Traditional pharmaceuticals are chemi-

cally synthesized and possess distinct, relatively simple structures. Biopharmaceuticals, though, are derived from living organisms, are about 100 to 1,000 times larger than chemically synthesized pharmaceuticals, possess complex three-dimensional structures, and may exist as mixtures of isoforms. The high cost of developing and testing biopharmaceuticals is reflected in their annual per patient treatment costs, which can vary from about \$1,000 for recombinant human insulin (one of the first biopharmaceuticals available) to more than \$30,000 for newer anticancer biopharmaceuticals (e.g., humanized monoclonal antibodies). The global market for biopharmaceuticals was estimated in fall 2007 at \$56 billion per year. They are the fastest-growing component of the pharmaceutical industry, and may comprise about 60 percent of pharmaceutical companies' revenues by 2010.

With so much at stake, it's no surprise that manufacturers of innovator biopharmaceuticals and manufacturers of biosimilars disagree over the level of regulation that should be required. Innovator companies generally assert that even the best analytical methods currently available cannot adequately predict safety and efficacy of biosimilars, without reference to data from clinical trials. For innovator companies, such data are vital for gaining FDA approval in the first instance, for monitoring variation between product batches over time, and for verifying product safety and efficacy should the manufacturing process ever change. According to innovator companies, they are also trade secret information. In other words, if biosimilar manufacturers want FDA approval they will have to conduct (and

pay for) their own full clinical trials. Biosimilar manufacturers, in contrast, argue that current analytical techniques are sufficient to demonstrate the degree of similarity of most biopharmaceuticals, and would prefer to conduct targeted—not full—clinical trials.<sup>2</sup>

Unlike small-molecule drugs, which are approved under the Food, Drug and Cosmetic Act (FDCA),<sup>3</sup> most biopharmaceuticals are approved under the Public Health Service Act (PHSA).<sup>4</sup> Congress amended the FDCA in 1984 to allow submission of an abbreviated new drug application (ANDA) for generic versions of innovator drugs.<sup>5</sup> ANDAs are not generally required to include expensive preclinical (animal) and clinical (human) data to establish safety, purity, and potency. Instead, an ANDA must provide data demonstrating the generic drug's structural and biological equivalence (“bioequivalence”) with a reference drug already approved by the FDA. The FDA defined bioequivalence as “the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.”<sup>6</sup> Bioequivalence studies require much less time and cost than the randomized clinical trials required for new drug applications. 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 innovator drugs, Congress helped lower generic drug costs and speed them to market.

The PHSA has no comparable

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provisions, so biosimilar manufacturers seeking FDA approval must file completely new applications. Biosimilar manufacturers cannot rely on a reference biopharmaceutical's application data, and must instead conduct their own preclinical and clinical trials. Thus, manufacturers of approved pioneering biopharmaceuticals can continue to enjoy market exclusivity despite expiration of any relevant patent rights. Not surprisingly, Congress is under pressure to establish an expedited process for FDA approval of biosimilars, and four such bills have been introduced since February 2007. An analysis of the bills, though, reveals that application of the ANDA paradigm may not be entirely appropriate to approval of biosimilars.

Representative Henry Waxman introduced the Access to Life-Saving Medicine Act in February 2007.<sup>7</sup> The bill would allow submission of "Abbreviated Biological Product Applications" demonstrating that a biosimilar is "comparable to or interchangeable with" a reference biopharmaceutical, and that they "contain highly similar principal molecular structural features, notwithstanding minor differences in heterogeneity profile, impurities, or degradation patterns." The bill defines "comparable" as the absence of clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product based upon data derived from chemical, physical, and biological assays, and other nonclinical laboratory studies; and data from any necessary clinical study or studies sufficient to confirm safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and intended to be used.

Importantly, the bill explains that biosimilars and their reference products "shall . . . contain highly similar principal molecular structural features" despite the existence of structural differences due to: "post-translational events, infidelity of translation or transcription, or minor differences in amino acid sequence; and differences in post-polymerization modifications

of polysaccharide biological products." The Waxman bill would also allow the FDA to define other situations in which biosimilars and their reference products would "contain highly similar principal molecular structural features."

The Patient Protection and Innovative Biological Medicines Act of 2007,<sup>8</sup> introduced by Representative Jay Inslee, is far more stringent than any other biosimilars bill. The Inslee bill would require that applications for biosimilars contain: "data demonstrating stability, compatibility, and biological and physicochemical integrity of the active ingredient of the similar biological product; data from physical, chemical, and biological assays fully characterizing the similar biological product, in comparison with the reference product, at both the active ingredient and finished product levels; data from comparative nonclinical studies demonstrating that the similar biological product and the reference product have similar profiles in terms of pharmacokinetics, pharmacodynamics, toxicity, immunogenicity, and other relevant factors; data from comparative clinical trials demonstrating that the similar biological product and the reference product have similar profiles in terms of safety, purity, and potency, including pharmacokinetic studies, pharmacodynamic studies, and trials of sufficient size and duration to demonstrate that the products are similar in their safety (in terms of nature, seriousness, and frequency of adverse reactions), purity, and potency profiles; and a postmarket safety-monitoring plan."

The Biologics Price Competition and Innovation Act of 2007,<sup>9</sup> introduced by Senator Edward Kennedy, proposes similar standards for equivalence as the Waxman bill. The Kennedy bill 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." Nevertheless, the Kennedy bill would also grant the FDA the discretion to determine that any or all of these showings are not required.

Representative Anna Eshoo introduced the Pathway for Biosimilars Act, in March 2008.<sup>10</sup> The bill would require analytical studies demonstrating that the biosimilar is "highly similar"—a term that is not defined—to a reference product, "notwithstanding minor differences in clinically inactive components; animal studies," and at least one clinical study comprising "the assessment of immunogenicity and pharmacokinetics or pharmacodynamics . . . sufficient to demonstrate safety, purity, and potency."

The Hatch-Waxman pathway to approval of generic small-molecule drugs works well because demonstrating bioequivalence between these drugs and their reference compounds is relatively simple. Demonstrating comparability between biosimilars and innovator biopharmaceuticals, though, will be far more difficult because of their greater complexity and heterogeneity. The bioequivalence standard will not be adequate in the context of biopharmaceuticals because we cannot assume that two biopharmaceuticals with identical pharmacokinetic profiles will be equally safe and effective. 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, but if they are directed against endogenous ("self") proteins, they also may produce serious clinical consequences. Relatively minor differences between protein products—including sequence variations, post-translational modifications, contaminants, impurities, and formulation differences—can have profound effects on their immunogenicity.

The history of recombinant human erythropoietin (epoetin) is a case in point. Between 1998 and 2000, the instance of antibody-associated pure red-cell aplasia (PRCA, a rare form of anemia in which bone marrow ceases production of red blood cells) increased dramatically in patients receiving recombinant epoetin.<sup>11</sup> In these patients, PRCA was associ-

ated with the production of neutralizing antibodies against epoetin. Although the exact mechanism responsible remains unclear, changes to the epoetin formulation (human serum albumin stabilizer was replaced with polysorbate 80 and glycine), the route of administration (subcutaneous), and storage and handling procedures were implicated.

Because relatively minor changes to biopharmaceuticals, like epoetin, may cause profound changes in immunogenicity, and because an individual's immune system can respond to alterations that current analytical techniques cannot detect, it appears likely that biosimilars will require more extensive clinical testing for FDA approval than generic drugs do. The only certainty is that an extraordinary level of cooperation between Congress, the FDA, and the biopharmaceutical manufacturers (innovator and biosimilar alike) will be required

to ensure that biosimilars are safe and effective. After all, physicians and patients are likely to have concerns about the actual equivalence of biosimilars with their innovator biopharmaceuticals. Despite FDA approval, physicians could be reluctant to prescribe biosimilars, and patients could be reluctant to take them unless their safety and effectiveness are adequately addressed. ♦

## Endnotes

1. Drug Price Competition and Patent Term Restoration (Hatch-Waxman) Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified at 21 U.S.C. § 355(b), (j), (l); 35 U.S.C. §§ 156, 271, 282).

2. Letter from Kathleen D. Jaeger, President and CEO, Generic Pharmaceutical Association, to Food and Drug Administration (March 16, 2005), available at [www.fda.gov/ohrms/dockets/dockets/04n0355/04n-0355-c000015-01-vol4.pdf](http://www.fda.gov/ohrms/dockets/dockets/04n0355/04n-0355-c000015-01-vol4.pdf).

3. Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 *et seq.*

4. Public Health Service Act, 42 U.S.C. § 201 *et seq.*

5. Drug Price Competition and Patent Term Restoration (Hatch-Waxman) Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified at 21 U.S.C. § 355(b), (j), (l); 35 U.S.C. §§ 156, 271, 282).

6. 21 C.F.R. § 320.1.

7. Access to Life-Saving Medicine Act, H.R. 1038, 110th Cong. (2007).

8. Patient Protection and Innovative Biological Medicines Act of 2007, H.R. 1956, 110th Cong. (2007).

9. Biologics Price Competition and Innovation Act of 2007, S. 1695, 110th Cong. (2007).

10. Pathway for Biosimilars Act, H.R. 5629, 110th Cong. (2008).

11. Charles L. Bennett et al., *Pure Red-Cell Aplasia and Epoetin Therapy*, 351 *NEW ENG. J. MED.* 1403 (2004).