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Learning from our neighbors about regulation of biosimilar drugs

The experience of foreign regulatory agencies may play an important role as the FDA develops its own standards.

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The recent enactment of the Biologics Price Competition and Innovation Act of 2009 has left several unanswered questions as to the U.S. regulatory future for follow-on versions of biologics, also known as "biosimilars." The BPCIA establishes the framework for an abbreviated approval process for biosimilars, and the U.S. Food and Drug Administration is tasked with developing regulatory standards for approval. The European Union and other countries have already adopted approval guidelines for biosimilars, which may help the FDA and corporate counsel address the many challenges that the abbreviated approval of biosimilars presents.

The European Union has led the way in establishing a regulatory framework for the approval of biosimilars. Under the E.U. regulatory framework, the European Medicines Agency can approve "similar biological medicinal products." See Committee for Medicinal Products for Human Use, Guideline on Similar Biological Medicinal Products, CHMP/437/04 (Oct. 30, 2005) (E.U. Guidelines). The guidelines interpreting the E.U. regulatory framework explain that "similar biological medicinal products" are distinct from "generic medicinal products" because of the subtle differences inherent in biological medicinal products synthesized by different manufacturers or when compared against reference products. E.U. Guidelines, at § 2.1.

These differences have also been noted by other countries and regions. In 2006, Australia's Therapeutic Goods Administration adopted the European Union's guidelines on the approval of biosimilars. See Australian Government, Department of Health and Ageing, Therapeutic Goods Administration, European Union Guidelines Adopted in Australia. Since then, regulatory authorities for other countries — including Argentina, India, Japan, Mexico and Turkey — have issued draft or final guidelines on the issue. See Barbara Mounho et al., "Global Regulatory Standards for the Approval of Biosimilars," 65 Food & Drug L.J. 819, 824 (2010).

In 2009, the World Health Organization's Expert Committee on Biological Standardization issued its Guidelines on Evaluation of Similar Biotherapeutic Products. World Health Organization, Expert Committee on Biological Standardization,

Guidelines on Evaluation of Similar Biotherapeutic Products (October 2009) (WHO Guidelines). According to the WHO, the guidelines provide "globally acceptable principles" for the approval of biosimilar products and can be adopted or used by regulatory authorities around the world in establishing regulatory frameworks for the approval of these products. Id. at § 2.

The regulatory frameworks already in place abroad can provide the FDA with guidance on the most effective aspects of the regulatory approval process for this emerging trend in medical treatment. An initial task for the FDA will likely be to develop a specific definition of, and criteria for, biosimilarity. Under the BPCIA, a biosimilar product is "highly similar to the reference product notwithstanding minor differences in clinically inactive components" with "no clinically meaningful differences" between the two products with respect to the "safety, purity, and potency of the product." 42 U.S.C. 262(i)(2). The level of data required to demonstrate "highly similar," "minor differences" and "meaningful" may make all the difference and has yet to be determined.

CLINICAL TRIALS

Industry and consumer representatives have raised concerns regarding the safety risks posed by biosimilars and are urging the FDA to require clinical trials to establish biosimilarity. See, generally, U.S. Department of Health and Human Services and FDA Approval Pathway for Biosimilar and Interchangeable Biological Products Public Hearing (Nov. 2-3, 2010). Europe's experience with biosimilars suggests that clinical trials could provide valuable information in the approval of biosimilars in the United States. One commentator noted unexpected clinical outcomes for approximately half of the biosimilars developed in Europe. Bronwyn Mixter, "Biosimilars Pathway Should Require Clinical Trials, Unique Names, Industry Says," BNA Life Sciences Law & Industry Report, Nov. 5, 2010, at 4 LSLR 1031.

To establish that a product is biosimilar to a reference product, regulatory agencies abroad tend to require strict scientific guidelines and in-depth comparisons of the properties of each product. See Mounho, supra, at 825-26; WHO Guidelines at § 6. Proponents should support their biosimilarity claims with analytical data demonstrating the similarity of the proposed biosimilar and reference product. See Mounho, supra, at 827.

For example, Health Canada's information and submission requirements for subsequent-entry biologics provide that a sponsor of a subsequent-entry biologic must provide "extensive data on the demonstration of similarity with the reference biologic drug, including characterization studies conducted in a side-by-side format." See Health Canada, Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics, at § 2.3.1 (2010). Demonstration of similarity is the basis for allowing an abbreviated approval process. See Mounho, supra, at 827.

Regulatory processes abroad suggest that the exact level and type of nonclinical and clinical studies required for approval of a biosimilar should be determined on a case-by-case basis, depending on a comparison of the product to the reference product. See WHO Guidelines, at § 5 (noting that the "ability for the [similar biotherapeutic product] to be authorized based on reduced non-clinical and clinical data depends on proof of its similarity to an appropriate [reference biotherapeutic product]"). Nonclinical and clinical data often include studies considering pharmacodynamics, pharmacokinetics, toxicology and efficacy. See WHO Guidelines, at §§ 9.2, 10.

The FDA may need to evaluate the level of data supporting biosimilarity in light of the distinct qualities of each biologic product. Likewise, the BPCIA allows the FDA to waive any of the requirements of a biosimilar application if it determines that it is "unnecessary." 42 U.S.C. 262(k)(2)(A)(ii). Thus, the language of the BPCIA suggests that a similar case-by-case approach could be used in the United States.

CRITERIA FOR INTERCHANGEABILITY

The BPCIA includes a notable distinction from many foreign regulatory processes for biosimilars in that the act sets a standard by which a biosimilar can be determined to be "interchangeable" with the reference product. 42 U.S.C. 262(i)(3). If a product meets the standards for interchangeability, the biosimilar product may be substituted for the reference product without the prescribing physician's involvement. Id.

Many other jurisdictions do not designate biosimilars as interchangeable with their reference product. For example, the European Union's guidelines state that biosimilars should not be considered to be generic medicinal products because of the subtle differences in similar biological products. E.U. Guidelines, at § 2.1.

Other countries have specifically cautioned against such automatic substitution of biosimilars. For instance, under South Africa's guidelines, biosimilars cannot be considered interchangeable and should not be automatically substituted for referenced products. Republic of South Africa, Department of Health, Medicines Control Council, Guidelines for Similar Biological Medicines, at § 5.3 (2010). Thus, the FDA lacks the benefit of foreign experience in determining the level of data that will be required to support interchangeability.

In sum, regulatory authorities across the globe try to balance the need for lower-cost therapies with concerns about product efficacy and patient safety. Several key aspects of regulatory approval processes and guidelines relating to biosimilars have been adopted fairly consistently by other jurisdictions. The FDA may choose to follow the lead of these jurisdictions and require rigorous analytical data comparing the proposed biosimilar and the reference product, supported by both nonclinical and clinical studies, although the FDA regulatory approval process for biosimilars may differ in certain key respects, including the possible recognition of interchangeability with reference products. The future of the U.S. biosimilars market ultimately hinges on the details of the regulatory framework that the FDA adopts. As the FDA develops its own guidance and regulations on the approval process for biosimilars, the experience of foreign regulatory agencies may play an important role in defining its standards in this developing area of medicine.

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