Biosimilars

The Next Big Thing?

By Henninger S. Bullock and Andrew J. Calica

Despite the opportunities presented by this nascent marketplace, players in this arena still face legal, regulatory, and economic uncertainty.

The individual mandate dominated the headlines before and after the recent U.S. Supreme Court decision upholding the Patient Protection and Affordable Care Act. Though less publicized, that decision also preserved an equally interesting piece of legislation aimed at reducing health-care costs—the Biologics Price Competition and Innovation Act of 2009 (BPCIA). Biologics Price Competition and Innovation Act, Pub. L. No. 111-148, 123 Stat. XXX, (codified at 42 U.S.C. §262). The BPCIA, section 351 of the Public Health Service Act, 41 U.S.C. 262(i)(1), signed into law on March 23, 2010, provides an abbreviated pathway for "biosimilars," a generic form of innovative biologic products, to enter what could become the next frontier for new drugs and therapies for patients.

Although conceptually similar to the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. 98-417, 98 Stat. 1585, referred to as the "Hatch-Waxman Amendments," which established the abbreviated approval pathway for generic drugs in the small molecule market, there are important and, in some instances, still developing, differences in the language and potential implementation of the BPCIA that promise to raise critical legal, economic, and practical issues for the pharmaceutical industry.

Biologics, defined to include viruses, therapeutic serums, toxins and antitoxins, blood and blood components, vaccines, allergenic products and proteins, except for chemically synthesized polypeptide, are typically generated through the use of the biologic processes of a living organism, or through biotechnology such as recombinant DNA technologies. 42 U.S.C. §262(i)(1). Uses for biologics are varied, with examples including the treatment of rheumatoid arthritis (Humira, Enbrel, and Remicade), cancer (Avastin, Herceptin), and diabetes (Lantus). The molecular structures of biologics are far more complex than small molecule drugs; their molecules can be between 100 and 1,000 times larger. As discussed below, this scientific and technical complexity presents unique challenges for the safety, efficacy, and interchangeability of products,

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and also provides fertile ground for unique and developing legal issues and strategies.

Biologics are also big business, accounting for 10–15 percent of the global pharmaceuticals market. The combined sales of the top 12 biologics in the United States reached an estimated $30 billion in 2010, and one calculation put the worldwide total for the one year period ending June 2011 at a staggering $148.2 billion. Andrew F. Bourgoin, *What You Need to Know About the Follow-On Biological Market in the U.S.: Implications, Strategies, and Impact* 5 (Thomson Reuters 2011); Thomas M. Burton & Jonathan D. Rockoff, *FDA Sets Path for Biotech Drug Copies*, Wall St. J., Feb. 10, 2012. The opportunity for generic competition beckons. Between 2011 and 2015, more than 30 branded biologics are expected to lose patent protection in the United States. Generics and Biosimilars Initiative, Global Biosimilar Market to Grow to US $3.7 Billion in 2015, Aug. 4, 2011.

Anticipating the potential for a new frontier, and perhaps in response to other factors such as the end of patent exclusivity for statins and an uncertain drug pipeline, biotechnology and pharmaceutical companies, both brand and generic, have engaged in a flurry of activity including acquisitions, mergers, and strategic partnerships. Eli Lilly's 2008 acquisition of ImClone elevated biologics to nearly half of its drug pipeline. Pfizer formed a strategic partnership with Biocon to compete in the recombinant human insulin market, primarily in emerging markets, but eventually in the United States as well. Teva and Lonza have undertaken a joint venture involving biologics, and Amgen recently announced a partnership with Watson Pharmaceuticals aimed at developing biosimilars to treat cancer.

Despite the opportunity for a new frontier, as discussed further below, players in this market still face uncertainty—legal, regulatory, and economic—at nearly every turn.

The Biologics Price Competition and Innovation Act

Spurred by a desire to decrease the cost of expensive biologic therapies and, therefore, increase patient access to treatment for often serious and life-threatening conditions, the BPCIA offers a framework for the approval of biosimilar products for the first time in the United States. Under the act, a so-called 351(k) applicant demonstrates that its product is biosimilar to a licensed biological product, the "reference product," if its product is "highly similar" to the reference product and there are "no clinically meaningful differences" between the two products in the areas of safety, purity, and potency. 42 U.S.C. §262(i)(2). Generally, an applicant must establish that (1) the biosimilar product uses the same mechanism of action as the reference product; (2) the condition of use in the proposed labeling has been previously approved for the reference product; (3) the route of administration, dosage form, and strength are the same; and (4) the facility for manufacturing, processing, packing, or holding meets standards designed to assure that the product remains safe, pure, and potent. 42 U.S.C. §262(k)(2)(A)(i). The U.S. Food and Drug Administration (FDA), in its discretion, may determine that one or more of these elements are unnecessary for a particular application. *Id.* An applicant must make the required showing with data derived from analytical studies, animal studies, and, notably, its own clinical studies. *Id.* Here a 351(k) application begins to diverge from a traditional Abbreviated New Drug Application (ANDA) submitted under the Hatch-Waxman Amendments. ANDA applicants typically rely exclusively on clinical studies conducted by the New Drug Application (NDA) holder.

The FDA anticipates that demonstrating biosimilarity will be more cumbersome than demonstrating bioequivalence. Even slight differences in the structure of a biologic can produce significant therapeutic differences. In turn, these therapeutic differences can affect safety, purity, or potency. Manufacturing differences and environmental factors such as light and temperature can have a similar effect. As a result, unless the FDA deems them unnecessary, one or more clinical studies will be required to demonstrate biosimilarity.

In determining biosimilarity, the FDA proposes to use a risk-based totality-of-the-evidence approach. The FDA will evaluate the different information provided by an applicant—clinical studies, animal studies, knowledge of human pharmacokinetics—in reaching an overall assessment on whether or not a product is biosimilar to a reference product. The FDA has suggested that it will not apply a single one-size-fits-all analysis.

In February 2012, the FDA unveiled guidance documents informing the industry that the first step in this approach is to characterize the structure and function of a proposed biosimilar and the reference product and then to compare them. Ctr. for Drug Evaluation and Research, Ctr. for Biologics Evaluation and Research, U.S. Dep't of Health and Human Services, U.S. Food and Drug Admin., *Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* 7 (2012). This characterization will be used as a guide in developing the scope and extent of animal and human clinical studies necessary to determine biosimilarity. *Id.* ("For example, if rigorous structural and functional comparisons show minimal or no difference between the proposed product and the reference product, the stronger the scientific justification for a selective and targeted approach to animal and/or clinical testing to support a demonstration of biosimilarity."). The FDA has noted that an applicant may be able to demonstrate biosimilarity even if the biosimilar and the reference product exhibit "formulation or minor structural differences," as long as the applicant demonstrates that they are not clinically meaningful. *Id.* at 8. The agency further advised that a clinically meaningful difference could include a difference in the "expected range of safety, purity, and potency" of the two products, but that "slight differences in rates of occurrence of adverse events between the two products ordinarily would not be considered clinically meaningful differences." *Id.*

Next, an applicant should consider the role of animal studies in addressing toxicity and in developing additional support for biosimilarity. *Id.* at 7. In the third step, the applicant conducts human pharmacokinetics studies and, when appropriate, pharmacodynamic studies. *Id.* Fourth, an applicant compares the clinical immunogenicity of the two products. *Id.* If after these steps residual uncertainties remain regarding biosimilarity, an applicant "should then consider what comparative clinical safety and efficacy data" may be necessary. *Id.*; Rachel E. Sherman, Assoc. Dir. for Medical Policy, Ctr. for Drug Evaluation and Research, U.S. Food and Drug Admin.,

Biosimilar Biological Products: Biosimilar Guidance Webinar 13 (2012). As one might expect, the FDA has encouraged applicants to consult with the agency in developing a clinical program after completing the comparative structural and functional analysis. Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, *supra*, at 7–8.

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Biosimilarity and Interchangeability

At the end of this process, a product deemed biosimilar will become eligible for marketing approval by the FDA. But approval does not ensure instant market penetration at the expense of the reference product. Unlike a classic generic product, a biosimilar product may *not* be substituted for a reference product without the intervention of the prescribing health-care provider. In other words, generic substitution laws, enacted in most states, will not permit pharmacists to substitute biosimilars for a reference product as they do in the small molecule market. Once again, it is the complexity of biologics that drives this different dynamic.

However, the BPCIA contains a second designation. Once biosimilarity is established, the FDA may determine that a product is "interchangeable" with the reference product. Interchangeability requires a determination that (1) the biosimilar can be expected to produce the same clinical result as the reference product *in any given patient*, and (2) for a biological product that is administered more than once, that the risk to the patient in terms of safety or diminished efficacy of altering or switching between use of the biosimilar product and the reference product is not greater than the risk of not switching. 42 U.S.C. §262(k)(4). An interchangeable product *may* be substituted for the reference product automatically and without the intervention of a health-care provider.

Progress Toward Implementation of the BPCIA

Implementation of the act has been measured. In February 2012, the FDA issued three draft guidance documents on biosimilar product development. First, Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, is intended to assist companies drawing up a 351(k) application in demonstrating that a proposed therapeutic product is a biosimilar. This draft guidance describes the FDA's totality-of-the-evidence approach, discussed above. Second, Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product, details the analytical factors considered when assessing biosimilarity. Third, Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, is intended to supply answers to common questions from applicants. The Q & A document provides the beginnings of a roadmap for navigating the application process. The FDA is now in the process of receiving and reviewing public comment on these documents.

As part of its February 2012 rollout, the FDA reported that it had already received 35 pre-Investigational New Drug (IND) meeting requests for proposed biosimilar products corresponding to 11 reference products, held 21 pre-IND sponsor meetings, and received 9 INDs. *See* Sherman, *supra*. No biosimilar applications have yet been received in the United States. In Europe, the European Medicines Agency approved its first biosimilar in 2006—Sandoz's Omnitrope, used to treat growth hormone deficiency. Since then, 13 additional biosimilars have received approval.

The FDA anticipates receiving only two biosimilar applications annually and only one application requiring a determination of interchangeability annually. Agency Information Collection Activities; Proposed Collection; Comment Request; General Licensing Provisions; Section 351(k) Biosimilar Applications, 77 Fed. Reg. 88,80, 88,82 (Feb. 15, 2012). But these estimates are based on the FDA's review of the expiration dates for patents related to potential reference products and general market interest in biological products that could be candidates for 351(k) applications. *Id.* The number of meeting requests and INDs received in the two years since the act's passage may suggest that the FDA has underestimated the market's interest in biosimilar and interchangeable products. Then again, the requests might signal a rush to market by key players already well positioned to enter the fray. Time will tell.

Of note, the FDA has succeeded in implementing a user fee program to fund its review of 351(k) applications. Food and Drug Administration Safety and Innovation Act of 2012, Pub. L. No. 112-144, XXX Stat. XXX (codified in scattered sections of the U.S.C.); Rachel Slajda, *FDA User Fee Bill Keeps Rocketing Through Congress*, Law360 (June 20, 2012). The new biosimilar user fee program is similar to the prescription drug user fee program but permits the collection of fees during the pre-application development phase to generate revenue in the near term and to enable the FDA to meet with applicants early in the development of potential products. 76 Fed. Reg. at 76,425. Within five days of FDA acceptance of a request for a product development meeting, or upon the filing of an IND, the sponsor must pay an initial biosimilar biological product development fee. Food and Drug Administration Safety and Innovation Act, §744H(a)(1)(A). The sponsor must then pay an annual development fee each fiscal year thereafter. *Id.* at §744H(a)(1)(B). The Food and Drug Administration Safety and Innovation Act also calls for application and supplement fees, an annual biosimilar biologic product establishment fee to be paid by any facility engaged in the manufacture of a biosimilar product for which an application has been approved, and an annual biosimilar biologic product fee. *Id.* at §§744H(a)(2), 744H(a)(3), 744H(a)(4). Congress has authorized the FDA to use these fees for all aspects of the review of applications, including the development phase and post-marketing surveillance.

The FDA estimates that the burden, in terms of hours, associated with the review of a biosimilar application will not differ from the review of first-generation biologic products. 77 Fed. Reg. at 88,81. As one might then expect, biosimilar application, establishment, and product fees will be equal to the fees established under the prescription drug user fee program for human drug applications, which includes new biological product applications, for any fiscal

year. Food and Drug Administration Safety and Innovation Act, §744H(b)(1); 76 Fed. Reg. at 76,425–26. Fees collected during the development phase are set at ten percent of those set for a human drug application. *Id.* Finally, the bill commands the FDA to produce written reports each fiscal year detailing the FDA's progress in achieving established review goals, its implementation of the user fee program, and how it used the fees collected during that fiscal year. Food and Drug Administration Safety and Innovation Act, §744I(a), §744I(b).

Notwithstanding the above, issues remain that could interrupt the implementation of this new regulatory scheme. For example, in April 2012 Abbott Laboratories filed a petition with the FDA requesting that the agency decline approval of any biosimilar application referencing Humira®, or any other product whose BLA was submitted prior to the BPCIA. The petition contends that approval would work a taking of the reference product sponsor's trade secrets without just compensation. Further, having reasonably relied upon the FDA's specific lack of authority to approve a biosimilar application, Abbott argued that the use of information provided to the FDA as a part of a pre-BPCIA BLA would frustrate the discreet investment-backed expectations of reference product sponsors. This issue, among others, could eventually result in litigation.

Barriers to Entry

Despite the market opportunities and a developing framework for seeking approval, the barriers for biosimilar products remain high. Some estimates for developing a biosimilar product are as high as $10 to $40 million, compared to $1 to $2 million for a traditional generic. Estimates have anticipated that biosimilar products will involve higher manufacturing costs than traditional generics generate. Biologics probably will also generate higher distribution costs than small molecule drugs because biologics are less stable and have shorter shelf lives. These heightened costs will translate into a smaller price difference between biosimilars and reference products than in the typical brand-generic market. For example, Sandoz launched Omnitrope in Europe at only a 20–30 percent discount to its reference product, Eli Lilly's Humatrope. *Drug Appraisal: Assessing the Efficacy and Safety of Omnitrope*, 2 Brit. J. Clin. Pharmacology 298, 300 (2010).

Manufacturers of reference products can also be expected to defend their turf. They may decide to produce increasingly complex products to discourage biosimilars or take aggressive approaches to pricing. Reference product manufacturers may also seek to develop second generation products of their own and encourage physicians to switch to those products rather than to biosimilars.

Some generic manufacturers will no doubt seek to leverage their experience in Europe and other developing markets. Some generic manufacturers that have achieved approval for biosimilar products in other regulated markets have already started to work toward launch of a U.S. product, including Teva, Sandoz, Hospira, and Actavis. For example, Hospira's biosimilar for Epogen to treat anemia is in the clinical trial phase in the United States. Others now seek strategic partnerships to shore up product development, technological innovation, and marketing and distribution needs.

Still, regulatory and commercial uncertainty looms large. Combine those pressures with the reality that it appears that companies do not have enough potential biosimilar opportunities to launch new products continually and some companies may decide not to pursue biosimilar development.

Some manufacturers may instead opt to file a Biologics License Application (BLA), positioning a drug as a reference product rather than using the abbreviated pathway for a biosimilar. The advantages of marketing a second-generation product, or "biobetter," including market exclusivity and the ability to file at any time, may outweigh the burdens discussed above. Generics and Biosimilars Initiative, US Biosimilars Pathway Unlikely to Be Used, March 18, 2011; Michael McCaughan, *Follow-On Biologics: Is there a Pathway?*, In Vivo Blog, May 20, 2010. One report has noted that Sandoz, which has more biosimilar launches in regulated markets outside of the United States than any other company, has opted to file BLAs in the United States. Bourgoin, *supra*, at 5. Teva, the largest generic manufacturer in the world, also elected to file a BLA for a granulocyte colony-stimulating factor called Neutroval shortly before the passage of the BPCIA, rather than wait for the availability of the abbreviated pathway. *Id.* at 5.

Legal Landscape

The BPCIA raises some familiar legal issues but differs in structure and application from the Hatch-Waxman Amendments. We endeavor below to provide a primer on some of the most pressing issues, although we acknowledge that there is ample room for commentary in this still developing field.

Patent Protection and Market Exclusivity

Similar to the Hatch-Waxman Amendments, the BPCIA uses market exclusivity and the patent laws together to achieve the twin aims of fostering new drug innovation and patient access to lower cost products. However, once again, the complexity and variability of biologics has, in part, led Congress to take a different approach to exclusivity and patent dispute resolution regarding biologics.

Reference Product Exclusivity

The BPCIA authorizes a 12-year period of exclusivity for reference products. Biosimilar applications may not be submitted until four years after the date of first licensure of the reference product. 42 U.S.C. §262(k)(7)(B). Afterward, the FDA may not approve a biosimilar application until 12 years after the date of first licensure of the reference product. 42 U.S.C. §262(k)(7)(A). The reference product will enjoy an additional six months of exclusivity over and above these four- and 12-year time periods if the FDA determines that information related to the use of a biologic product will produce health benefits in the pediatric population and the sponsor completes the additional requested studies for that group. 42 U.S.C. §262(m)(2), §262(m)(3).

The 12-year exclusivity term received bipartisan support in Congress, but unsurprisingly, industry viewpoints varied considerably. Andrew Pollack, *Biologic Drugs May Get Less Protection*, N.Y. Times, Jan. 14, 2010. In 2008, the Biotechnology Industry Organization proposed a 14-year period of exclusivity. Bourgoin, *supra*, at 2 (citing H. Grabowski, Data Exclusivity for New Biological Entities, Duke Univ. Dep't of Economics Working Paper, June 2007). Advocates argued that biosimilar produc-

ers would market products that would have similarities to but that would not duplicate reference products, which would limit the patent protection of a reference product. Fed. Trade Comm'n, Emerging Health Care Issues: Follow-on Biologic Drug Competition 32–33 (2009). Some proponents also argued that incentivizing innovator firms to invest in research and development for new therapies and post-approval research to develop new uses for existing therapies required a longer period of market exclusivity. *Id.* at 39–41.

The FDA anticipates that demonstrating biosimilarity will be more cumbersome than demonstrating bioequivalence.

In contrast, the Generic Pharmaceutical Association (GPhA) argued that a period similar to Hatch-Waxman's five years of market exclusivity provided the incentives necessary to promote innovation while ensuring timely patient access to less costly biosimilars. The GPhA was wary of an absolute shield that would bolster what it characterized as reference product sponsors' weaker patents. Press Release, Generic Pharmaceutical Association, GPhA Statement on BIO's Flawed Data Exclusivity White Paper (Jan. 30, 2009). Other advocates for a shorter exclusivity period, such as the Federal Trade Commission (FTC), argued that because competition in the biosimilar market was more likely to resemble brand-to-brand competition than traditional brand-to-generic competition, the patent regime would protect developers sufficiently to spur innovation without an extended period of exclusivity. Emerging Health Care Issues: Follow-on Biologic Drug Competition, at 35–37.

The Obama administration took a position somewhere in the middle. In a letter to Representative Henry Waxman, the White House endorsed an exclusivity period of seven years. Lisa Richwine, *White House: 7 Years Enough to Shield Biotech Drugs*, Reuters (June 25, 2009). Given the nascent state of the biosimilar industry in the United States, exactly how the 12-year period of exclusivity granted by Congress will affect the development of the market remains to be seen.

First Interchangeable Exclusivity

The first biosimilar determined to be interchangeable with a particular reference product will enjoy a period of exclusivity during which time the FDA cannot license other biosimilar products as interchangeable. The exclusivity calculus is based on the date of approval, the date of first commercial marketing, and certain patent litigation milestones. The period of exclusivity ranges in length from a minimum of one year after the date of the first commercial marketing of the biosimilar product as interchangeable with the reference product, to a maximum of 42 months after the approval of the first interchangeable biosimilar product if patent litigation is instituted and remains ongoing. 42 U.S.C. §262(k)(6).

Opponents of this type of exclusivity pointed out perceived abuses and anticompetitive behavior attributed to the corollary 180-day period of exclusivity under Hatch-Waxman. After the U.S. Court of Appeals for the District of Columbia Circuit ruling in *Mova Pharmaceutical Corp. v. Shalala*, an ANDA applicant only needed to be the first to file a Paragraph IV certification with respect to a particular drug to receive 180-day exclusivity. *Mova Pharmaceutical Corp. v. Shalala*, 140 F.3d 1060, 1076 (D.C. Cir. 1998). Critics argue that this has promoted a litigation cottage industry in the small molecule market. They contend that some generic companies have taken opportunities to attack brand patents and settle disputes in exchange for agreements to delay entry of the generic form to the market, which they view as a business strategy as lucrative as the business of manufacturing generic drugs. Wendy H. Schacht & John R. Thomas, Cong. Research Serv., RL31379, The "Hatch-Waxman" Act: Selected Patent-Related Issues 12–13 (2002); Bethany McLean, *A Bitter Pill*, Fortune, Aug. 13, 2001. Some were concerned that this same dynamic could play out with biosimilars.

Proponents argued that market participants would be reluctant to invest the substantial resources necessary to establish interchangeability without the added certainty of recouping the costs associated with development and patent challenges. Emerging Health Care Issues: Follow-on Biologic Drug Competition, at 66–67. The decision to provide a period of exclusivity for the first product actually approved as interchangeable, rather than the first to challenge a reference product's patents, applying only to interchangeable products, as opposed to interchangeable and biosimilar products, arguably promotes the desire to incentivize development without engendering anticompetitive behavior.

The cost and complexity of establishing interchangeability and the anticipated narrow price differential between reference and biosimilar products suggests that this exclusivity period may not have a substantial impact on the market. Indeed, the first interchangeable product may experience de facto exclusivity as some have projected that only a few interchangeable products likely will enter the market. *Id.* at 67–68.

Disclosure of Competitively Sensitive Information and Multiple Litigations

The most significant difference between the small molecule patent dispute resolution approach and the BPCIA approach to patent dispute resolution is that the latter makes information-sharing compulsory and could lead to multiple litigations. Within 20 days of receiving a notice from the FDA that a biosimilar sponsor's application has been accepted for review, the applicant must provide the reference product sponsor a copy of the application and additional information describing the process used to manufacture the proposed biosimilar. 42 U.S.C. §262(l)(2). Although not explicitly stated, this manufacturing information will likely consist of what is known in the small molecule market as chemistry, manufacturing, and controls, or "CMC" information.

This information is to be turned over to the reference sponsor's in-house and outside counsel, as long as the attorneys do not engage in patent prosecution related to the reference product, for the exclusive purpose of determining whether a claim of patent infringement could reasonably be asserted. 42 U.S.C. §262(l)(B)(ii), §262(l)(C), §262(l)(D). If the reference product sponsor is the

licensee of a particular patent, the information may be turned over to the licensor provided that the licensor has retained the right to assert the patent or participate in litigation and provided that the licensor has agreed to be subject to the act's confidentiality provisions. 42 U.S.C. §262(l)(B)(iii).

Following this initial disclosure, the biosimilar applicant and the reference sponsor are to exchange information and patent lists in an effort to determine which patents, if any, should lead to an immediate infringement action. Sixty days after the initial disclosure, the reference sponsor must provide the applicant with a list of patents for which the reference sponsor believes it could reasonably assert patent infringement claims and must identify which patents the reference sponsor is willing to license to the applicant. 42 U.S.C. §262(l)(3)(A). In response, the applicant must provide the reference sponsor with a detailed statement that describes the factual and legal basis of the applicant's opinion, on a claim-by-claim basis, that one or more patents is invalid, unenforceable, or will not be infringed, or a statement that the applicant does not intend to market the product until the patent's expiration. 42 U.S.C. §262(l)(3)(B)(ii). The applicant must also list which patents it is willing to license from the reference sponsor, if any. 42 U.S.C. §262(l)(3)(B)(iii). Finally, the reference product sponsor must then respond with a detailed statement specifying the factual and legal basis of the opinion, on a claim-by-claim basis, of the reference product sponsor that one or more patents will be infringed by the marketing of the biosimilar product. 42 U.S.C. §262(l)(3)(C).

After this exchange, the parties must negotiate in good faith to determine which patents, if any, will be the subject of an immediate action for infringement. If a resolution is not forthcoming, provisions narrowing the number of patents at issue become applicable. 42 U.S.C. §262(l)(5), §262(l)(6). First, the biosimilar applicant decides *how many patents* it should litigate in an immediate infringement action; not which patents it should litigate, but only how many. 42 U.S.C. §262(l)(5)(A). Within five days, the reference sponsor and applicant must simultaneously exchange lists of patents, containing only the number of patents previously chosen by the biosimilar applicant, which each party believes should become the subject of an immediate action for infringement. 42 U.S.C. §262(l)(5)(B). If the biosimilar applicant decides that no patents should be litigated, the reference product sponsor may choose one patent to list. 42 U.S.C. §262(l)(5)(B)(ii). The reference product sponsor must then bring an action for each patent contained on bothlists within 30 days. 42 U.S.C. §262(l)(6)(B). All told, this exchange of patent lists and confidential information can last up to eight months.

All other patents for which the reference sponsor intends to assert claims would then be litigated in a second proceeding after the biosimilar applicant supplies the reference sponsor with a mandatory 180-day notice that it intends to market the product. 42 U.S.C. §262(l)(8)(A). Presumably, this would not occur until at least 180 days before the expiration of the reference sponsor's 12 years of exclusivity. Unless the biosimilar applicant decides to launch "at-risk," immediately on the expiration of the reference sponsor's exclusivity, the reference sponsor's exclusivity effectively would lengthen by the period of time that it takes to resolve the ensuing litigation.

In contrast, an ANDA applicant in the small molecule context does not have to make similar disclosures other than in a particular set of circumstances. ANDA sponsors must certify, with respect to each patent listed under the referenced drug in the "Orange Book," either that (1) the patent information has not been filed and listed, (2) the patent is expired, (3) the applicant does not intend to market the generic drug until after the patent's expiration, or (4) the patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted. 21 U.S.C. §355(j)(2)(A)(vii).

If an ANDA applicant elects to challenge a patent and makes a Paragraph IV certification, the sponsor must provide notice to the patent owner, and the holder of an approved application for the reference listed drug (RLD) if someone other than the patent owner, within 20 days of the FDA's acceptance of the ANDA. 21 U.S.C. §355(j)(2)(B). This notice must include a detailed statement of the factual and legal basis for the opinion that the patent is invalid or will not be infringed." 21 U.S.C. §355(j)(2)(B)(iv). The owner of the patent or the RLD holder then will have 45 days to commence an infringement action or the approval of the ANDA will take effect immediately. 21 U.S.C. §355(j)(5)(B)(iii). The ANDA applicant may not bring a declaratory judgment action for non-infringement unless the 45-day period has expired without either the patent owner or the RLD holder bringing an action for infringement. In addition, the ANDA sponsor's notice to the patent owner or the RLD holder must have included an offer of confidential access to the ANDA application so that the owner of the patent or the RLD holder may determine whether an action for infringement should be brought. 21 U.S.C. §355(j)(5)(C)(i)(I). If an infringement action is brought within 45 days the approval shall be made effective 30 months after the date of receipt of the notice, or a shorter or a longer period as a court may order because either party to the action failed to cooperate reasonably in expediting the action, or because the court makes a final determination regarding infringement. 21 U.S.C. §355(j)(5)(B)(iii).

One notable distinction between these two methods of resolution is that the BPCIA does not establish a 30-month stay of approval of a biosimilar application pending a judgment on the issue of infringement as in a small molecule patent infringement dispute. Michael P. Dougherty, *The New Follow-On-Biologics Law: A Section by Section Analysis of the Patent Litigation Provisions in the Biologics Price Competition and Innovation Act of 2009*, 65 Food & Drug L.J. 231, 234 (2010). Another is that the biosimilar applicant is required to turn over competitively sensitive information while the reference product sponsor doesn't have an equivalent pre-litigation disclosure obligation. However, this is balanced by the biosimilar applicant's ability to control the number of patents litigated in an immediate action and the timing of that litigation in relation to the expiration of the reference product sponsor's market exclusivity.

Though no 351(k) applications have yet been filed, the patent protection and exclusivity scheme may make applicants reluctant to use the abbreviated pathway and risk dissemination of sensitive information.

Lack of an Orange Book Equivalent

A final, significant difference between the small molecule scheme and the biosimilar

scheme is that the BPCIA does not require a listing of biosimilar or interchangeable products and their reference products and associated patents. Bourgoin, *supra*, at 3. In the small molecule market, an NDA must include information regarding any patent which claims the drug for which the application is submitted. 21 U.S.C. §355(b)(1). This information is published by the FDA in the Orange Book. When filing an ANDA, generic manufacturers can reference patents covering brand products in the Orange Book and, as previously noted, must make a certification regarding each patent listed in the Orange Book under a particular drug. Instead of publishing an Orange Book equivalent, the BPCIA relies on the exchange of patent information described above to identify relevant patents. Dougherty, *supra*, at 234.

The FDA may establish more stringent post-marketing surveillance requirements for biosimilars than for classic generic products.

In a letter to the FDA, three pharmacist trade organizations expressed support for the development of an FDA-compiled interchangeability reference list, something similar to the current Orange Book, to assist health-care providers. Letter from Am. Pharmacists Ass'n, Nat'l Ass'n of Chain Drug Stores, and Nat'l Cmty. Pharmacists Ass'n to U.S. Food and Drug Admin. 3 (May 25, 2012). This type of listing would also aid prospective applicants to identify patents that might become the subject of a dispute before filing an application. Others have expressed concern that establishing a similar patent listing system may result in the same kind of anti-competitive behavior experienced in the small molecule market, such as the phenomenon of brand manufacturers delaying generic entry by "later listing" patents after an ANDA has been filed. Emerging Health Care Issues: Follow-on Biologic Drug Competition, at 57. On the other hand, if the intent is to encourage follow-on manufacturers to design around branded manufacturers' patents, an Orange Book equivalent could aid in that process.

Potential Litigation Exposure and Regulatory Scrutiny

Because substitution of a biosimilar for a reference product requires specific intervention of a physician—the inverse in some respects of the "dispense as written" construct for traditional drugs—some commentators, and the European experience, have suggested that biosimilar manufacturers will be required to engage in promotional activities to achieve market penetration. Typically, generic manufacturers do not employ a sales force to promote their products, relying instead on price, timing of market entry, generic substitution laws, and placement on formularies to garner market share. Biosimilars may not enjoy those advantages, and price alone may not sufficiently motivate physicians to switch to biosimilars. Deploying so-called "detail men" may become necessary to ensure that physicians become comfortable with prescribing biosimilar products. Notwithstanding the advances in corporate compliance measures, operating a sales force carries inherent risks that could expose a company to the type of tort claims and regulatory scrutiny, for instance, for misbranding or off-label promotion, traditionally reserved for innovator companies.

The FDA may establish more stringent post-marketing surveillance requirements for biosimilars than for classic generic products. The FDA draft guidance suggests that in their post-market monitoring biosimilar applicants should take into consideration particular safety concerns associated with the use of the reference product and its class. Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, at 20. Biosimilar applicants are further advised to implement mechanisms to differentiate between adverse events associated with their products and those associated with the reference products, including events not seen with the reference products. Additional emphasis is placed on the detection of rare but potentially serious safety risks not identified during pre-approval testing. Biosimilars thus carry the potential for differing rates of particular adverse events from the reference products or for altogether different adverse events. Knowledge of these events, sometimes thought to reside only, or to a greater degree, with brand manufacturers, may instead reside with generic manufacturers. Biosimilars could, therefore, become targets for litigation in a way that small molecule generic manufactures are not accustomed. Similarly, Biosimilar manufacturers will have their own clinical trial experiences and may find themselves having to in some instances defend those trials in litigation.

Will *Mensing* Preempt Failure-to-Warn Claims Involving Biosimilars?

Another outstanding question is whether plaintiffs will be able to maintain state law failure-to-warn claims involving biosimilars, or whether the courts will deem those claims preempted by federal law. Assuming for present purposes that the act does not contain any express preemption provision, and we haven't found an obvious preemption clause, attorneys will fight on the battleground of implied or conflict preemption. To be sure, depending on the product at issue, other regulatory schemes may affect the biosimilar preemption analysis—the National Childhood Vaccine Injury Act, for instance—but we limit the discussion here to comparing biosimilars to products approved under Hatch-Waxman.

In *Pliva, Inc. v. Mensing*, 131 S. Ct. 2567 (2011), the U.S. Supreme Court held that the federal regulatory scheme governing prescription drugs preempted state law failure-to-warn claims. The touchstone of *Mensing*-style preemption is an ANDA holder's federal duty of "sameness." To obtain FDA approval, a generic manufacturer ordinarily must show that its drug is bioequivalent to the brand-name product. As the Court observed, by eliminating the requirement that generic manufacturers independently prove the safety and efficacy of their products, the Hatch-Waxman Amendments allow manufacturers to bring generic drugs to the market less expensively than they could if they had to undertake independent safety studies. This

analysis is fairly straightforward in the traditional, small molecule context.

But, as discussed, the BPCIA establishes two tiers of similarity: biosimilarity and interchangeability. The first category, biosimilarity, may seem similar to bioequivalence, but it has important distinctions. The FDA draft guidance suggests that differences may exist in formulation between a reference product and a biosimilar. For example, a proposed biosimilar product may demonstrate biosimilarity even though it does not contain human serum albumin, which is part of the reference product's formulation. The second category, interchangeable products would seem to present the strongest argument for sameness, or at least most similarity, in comparison to reference products. Interchangeable biosimilars may be substituted for reference products without the intervention of a prescriber and are expected to produce the same clinical result in any particular patient. It remains to be seen whether courts will treat these tiers differently in a preemption analysis.

Mensing's duty of sameness extends to the product labeling as well. An ANDA holder cannot initiate labeling changes that would render its product information different from that of the NDA holder, or in some cases, a reference listed drug holder. Thus, except for small differences, such as a National Drug Code identifier, a generic manufacture must use the same label as the NDA at all times. The FDA has not yet made clear whether or to what degree this construct will apply to biosimilars.

All that the act requires is that an application include information demonstrating that "the condition or conditions of use prescribed, recommended, or suggested in the labeling proposed for a biological product have been previously approved for the reference product." 42 U.S.C. §262(k)(2)(A)(i)(III). The FDA draft guidance does not fill in the gaps for industry: "Labeling of a proposed product should include all the information necessary for a health professional to make prescribing decisions…" Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, at 21. Although it would result in practical difficulties, a case-by-case determination on labeling is not entirely out of the question, given the complexity of and uncertainty involved in biologics. Some industry groups have raised with the FDA the possibility that differing effects of biosimilars on patients could warrant labeling distinctions. As it currently stands, biosimilars will have a different naming convention than small molecule generics, suggesting another area of potential divergence from classic ANDA drugs.

Interestingly, the act does include an exception to the approval process permitting applicants in certain product classes to submit their applications under 505 of the FDCA. 21 U.S.C. §355. Because this application would fall within the same regulatory scheme addressed by the *Mensing* court, we have good reasons to think that preemption would apply to the labeling on these products. The exception is, however, time limited. Only applications submitted before approval of the act and those submitted no later than 10 years after enactment may be eligible.

Absent labeling sameness, the reasoning underpinning *Mensing* arguably will not translate to the biosimilar context. If a biosimilar contains its own precautions, warnings or adverse events, presumably only the biosimilar manufacturer, can initiate labeling changes, at least to those unique sections, setting aside the FDA's authority to do so on its own initiative for a moment.

How, if at all, the courts will apply the preemption doctrine to biosimilars may well have implications for manufacturers of reference products. NDA holders currently face claims by consumers of ANDA products that are premised on their ability or an ANDA's inability to alter drug labeling and the medical community's perceived reliance on information originating with an NDA holder. So-called brand or "innovator" liability is truly a minority position in the case law, but California courts have recognized it, for example. If labeling claims can proceed against biosimilars, litigants who ingested biosimilar products may not target reference product manufacturers, or reference product manufacturers may have defenses that differ from those available to innovator companies in the small molecule litigation.

Even setting preemption aside, reference product manufacturers may have powerful arguments in cases involving noninterchangeable biosimilars. Brand liability is premised on the notion that (1) an NDA holder's warning is addressed to the compound, not merely its own branded product; and (2) the substitution of a generic product by a pharmacy is a foreseeable event, happenstance, or both, and, therefore, does not break the causal chain. Neither premise may operate in the biosimilar context because each product may contain unique warnings, and pharmacies may not substitute biosimilars for reference products without physician intervention.

Conclusion

The United States is marching toward a biosimilar world. The opportunities for industry and the potential benefits for patients can hardly be ignored. Nonetheless, economic, regulatory, and legal uncertainty abounds and promise to shape the contours of this nascent marketplace. Will biosimilars indeed become the next big thing? Stay tuned.