Blinded by (a Lack of) Science: Limitations in Determining Therapeutic Equivalence of Follow-On Biologics and Barriers to Their Approval and Commercialization

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ABSTRACT

Over the past twenty years, an increasing number of disease therapies based on recombinant DNA technology have been developed and commercialized. These treatments, commonly known as biologics, can be very effective. They can also be extraordinarily expensive. In an effort to ensure the availability and affordability of biologics, Congress enacted the Biologics Price Competition and Innovation Act (BPCIA) in 2010. The BPCIA was designed to strike a balance between facilitating the approval of generic biologics with a new regulatory pathway and protecting innovation of new biologics by offering a period of regulatory exclusivity much as the Hatch-Waxman Act (HWA) had done for small-molecule drugs.

This Article takes the position that, because of differences between the composition and features of small-molecule drugs and biologics, as well as between the abbreviated-approval pathways instituted by the BPCIA and the HWA, pioneer and generic manufacturers seeking to market biologics will face distinct regulatory and patent litigation considerations when compared with small-molecule drugs. First, it considers the important technical differences between small-molecule drugs and biologics and how these differences are likely to be reflected in different regulatory approaches under the HWA and BPCIA abbreviated-approval pathways. Second, the Article considers the particular role that production methods play in determining the characteristics of biologics. The complexity of these production methods can make it difficult to evaluate the presence of therapeutic equivalence between pioneer and generic biologics because it is difficult to ensure that production methods used by different manufacturers are identical. Process patents will also be litigated in distinct ways under the HWA and the BPCIA. Third, the Article argues that, as currently structured, the BPCIA is not likely to result in the dramatic reductions in healthcare costs that some of its proponents expect. This will be because of both difficulties in guaranteeing equivalence between pioneer and generic biologics and the strong protection offered to pioneer biologics manufacturers.

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by process patents. The best way to ensure that the introduction of generic biologics can help meet the price reduction goals of the BPCIA is to work toward improvements in technical and regulatory procedures for determining equivalence between pioneer and generic biologics.

INTRODUCTION

Gaucher disease is a progressive metabolic disorder that results from the absence of glucocerebrosidase, an enzyme needed to break down an intracellular lipid. Patients with the disease accumulate lipid in their livers and spleens and develop anemia and bone problems. Without treatment, patients become progressively incapacitated and often die in early adulthood. Genzyme, a biotechnology company based in Massachusetts, conducted clinical trials using glucocerebrosidase purified from human placentas and received Food and Drug Administration (FDA) approval to market the enzyme as a replacement therapy for Gaucher disease in 1991. Because purification of the enzyme from human tissue was challenging and expensive, Genzyme developed Cerezyme, a genetically engineered version of the drug, receiving FDA approval for the treatment in 1994. Regular treatment with Cerezyme is effective and results in the amelioration of most of the symptoms and signs of Gaucher disease. The price of this life-saving treatment is high, however, with the cost of the recommended dose sometimes exceeding $300,000 per patient each year.

Cerezyme is far from an isolated example of a costly, but effective, treatment produced by sophisticated recombinant DNA technology. These agents, belonging to the therapeutic class collectively known as biologics, are now typically produced by genetically modifying cell lines to manufacture large amounts of specific proteins. Biologics cost on average more than $16,000 per patient each year, more than twenty times the cost of traditional, small-molecule drugs, making

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3 See id.
6 See Neal J. Weinreb et al., Effectiveness of Enzyme Replacement Therapy in 1028 Patients with Type 1 Gaucher Disease After 2 to 5 Years of Treatment: A Report from the Gaucher Registry, 113 AM. J. MED. 112, 117–18 (2002).
them one of the most expensive items in the U.S. healthcare budget.\textsuperscript{11} Total expenditures on biologics are increasing rapidly and may have exceeded $100 billion in 2011.\textsuperscript{12}

Driven in large part by calls to reduce the cost of biologics by increasing market competition,\textsuperscript{13} Congress enacted the Biologics Price Competition and Innovation Act (BPCIA or the Act) in 2010,\textsuperscript{14} a pathway to facilitate the approval of generic versions of biologics, as part of the Patient Protection and Affordable Care Act.\textsuperscript{15} This new regulatory pathway was designed to strike a balance between allowing for the production of less expensive versions of biologics and protecting innovation by the pioneer entities responsible for first developing these breakthrough therapies.\textsuperscript{16} This balance is achieved by, at least in theory, allowing generic biologics manufacturers to rely on information previously submitted by the pioneer manufacturer, but granting a “data protection” period of twelve years before such information becomes available to support generic biologics applications.\textsuperscript{17} The BPCIA was modeled, at least in part, on the abbreviated new drug application (ANDA) pathway for small-molecule drugs enacted in the Drug Price Competition and Patent Term Restoration Act of 1984,\textsuperscript{18} popularly known as the Hatch-Waxman Act (HWA).\textsuperscript{19}

While there is an expectation that the BPCIA will result in substantial healthcare cost savings,\textsuperscript{20} there is also considerable uncertainty as to precisely how the Act will operate in practice because the FDA has not yet promulgated regulations setting out precisely what factors will be taken into account during the approval of generic biologics.\textsuperscript{21} Further, the contours of judicial interpretations of the Act will likely take years to emerge.\textsuperscript{22} As has been the case for generic small-molecule drugs attempting to enter the marketplace in the face of patented pioneer drugs,\textsuperscript{23} it is very likely that pioneer biologics manufacturers will attempt to enforce patents that they believe protect their products. Generic biologics manufacturers likewise will try to avoid that fate, by claiming that their products do not infringe, or that the patents are not valid.\textsuperscript{24}

This Article takes the position that because of differences between the composition and features of small-molecule drugs and biologics, as well as between the abbreviated-approval pathways instituted by the BPCIA and the HWA, pioneer and generic manufacturers seeking to market...
biologics will face distinct regulatory and patent litigation challenges compared with small-molecule drugs. In particular, consideration of manufacturing methods will play an important role in achieving regulatory approval for generic biologics by the FDA and in patent litigation between pioneer and generic biologic manufacturers in ways that they have not in the small-molecule drug context. Part I discusses the important technical differences between small-molecule drugs and biologics and how these differences are likely to be reflected in different regulatory approaches under the ANDA and BPCIA abbreviated-approval pathways. It also considers some of the ways patent litigation is expected to develop under the BPCIA. Part II considers the particular role that production methods play in determining the characteristics of biologics and how difficult it may be to evaluate the presence of therapeutic equivalence of a pioneer and a generic biologic product, given the difficulty of ensuring that production methods used by different manufacturers are identical. Further, it discusses differences in the ways that production method patents may be invoked in patent litigation disputes under the ANDA and BPCIA approval pathways. Part III argues that in the near term the BPCIA, as currently structured, is not likely to result in the dramatic reductions in healthcare costs that some of its proponents seem to expect. Because of difficulties in guaranteeing equivalence between pioneer and generic biologics, and the strong protection likely to be offered to pioneer biologics producers by process patents, entry of generic biologics to the U.S. market will most probably bring limited price competition for those therapeutic goods. The Article concludes that the best way to ensure that the introduction of generic biologics can help meet the price reduction goals of the BPCIA is to work toward improvements in technical and regulatory procedures for determining equivalence between pioneer and generic biologics. Without such improvements, patent litigation and regulatory barriers to biologics market competition likely will remain high.

I. DEVELOPING GENERIC BIOSIMILARS: BARRIERS TO DETERMINING THERAPEUTIC EQUIVALENCE

The United States approach to drug approval differs from that used in other countries. The U.S. regulatory framework involves two different statutes: the Federal Food, Drug, and Cosmetic Act (FD&CA) and the Public Health Services Act (PHSA). After it has completed the pre-clinical and clinical testing needed to demonstrate safety and effectiveness, the sponsor of a novel small-molecule drug seeking marketing approval does so by submitting a new drug application (NDA) under the FD&CA. The great majority of novel biologic agents, on the other hand, are approved by sponsors that submit biologics license applications (BLAs) under the PHSA. While the language of the PHSA requires that new biologics be reviewed for safety, purity, and potency (rather than for safety and efficacy as for an NDA), in practice, FDA procedures for reviewing NDAs and BLAs are similar. When the ANDA pathway for generic drugs was introduced under the HWA, Congress gave pioneer drug sponsors limited-term guarantees of drug exclusivity, in return giving generic drug ANDA applicants permission to rely upon clinical safety and efficacy studies submitted with the NDA for the reference pioneer drug. Access to this data allows generic drug applicants to avoid costly clinical trials and obtain marketing approval at dramatically lower cost.

29 See id. at 885.
30 See id.
31 See Thomas, supra note 17, at 13.
To receive approval under the ANDA pathway, a generic small-molecule drug sponsor must be able to demonstrate both that “the active ingredient of the new drug is the same as that of the listed [reference] drug,” and that “the new drug is bioequivalent to the listed drug.” Bioequivalence means that “the rate and extent of absorption of the drug do[es] not show a significant difference from the rate and extent of absorption of the listed drug.”

In contrast, under the BPCIA, generic biologics are required to satisfy substantially more stringent criteria to demonstrate “biosimilarity” to a reference biologic. A biosimilar product is “highly similar to [a] reference product.” Further, there must be “no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.” In addition to having a generic biologic being regarded as biosimilar to a pioneer product, the BPCIA also provides for a new classification: interchangeability. A biologic is interchangeable with a reference product if it meets requisite safety standards and “may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.”

Under the framework established by ANDA approvals and because it is difficult to establish that a derivative biologic is “the same” as a pioneer, the term “generic biologic” is now disfavored and the term follow-on biologic (FOB) is preferred. The remainder of this Article follows this usage.

A. Physico-Chemical Characteristics Increase the Difficulty of Determining Therapeutic Equivalence Between Pioneer and Follow-On Biologics

Because small-molecule drugs such as aspirin or statins have simple chemical structures, it is relatively easy to establish chemical identity between a generic competitor and its corresponding reference product. Establishing bioequivalence for a small-molecule drug is similarly straightforward, with the generic product sponsor having only to conduct tests on as few as twenty-four people, showing blood levels of the generic drug that are within twenty percent of those achieved with the reference product.

In contrast to their small-molecule drug counterparts, biologics are generally large protein molecules that display structural, chemical, and functional complexity. The most basic, and easiest to detect, type of variation between proteins occurs at the sequence level, either in changes that

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31 Id. at § 262(i)(2)(A)(v).
32 Id. at § 262(i)(3).
34 See Sahr, supra note 9, at 8 (noting that aspirin has only twenty-one atoms and a molecular weight of 180 Daltons); FTC FOB REPORT, supra note 32, at 8 & fig.1-2 (characterizing statins as “small” and “simple” with molecule weights of only approximately 400 Daltons).
35 See Morrison, supra note 8, at 465.
37 Id. at § 355(i)(2)(A)(iv).
38 Id. at § 355(i)(8)(B)(i).
39 See Steven A. Nash & Rebecca Workman, A New Pathway for Follow-On Biologics, 20 FED. CIR. B.J. 193, 198–99 (2010) (noting that the FDA will likely require analytical studies, animal experiments, and clinical trials before determining that a biologic is biosimilar to a reference product).
40 Id. at § 262(i)(2)(A) (Supp. III 2007–2010).
41 See Morrison, supra note 8, at 465.
42 Id. at § 262(i)(2)(B).
44 Morrison, supra note 8, at 465.
manifest directly in the sequence of amino acids that constitute the protein or in so-called “silent” variants in the underlying DNA sequence that do not change the amino acid sequence but can alter the control of protein synthesis.\textsuperscript{45} Three-dimensional protein structure, dependent upon correct folding of an amino acid chain, remains a poorly characterized process, but it is clear that protein misfolding can occur in some cell types,\textsuperscript{46} suggesting that differences between cell lines used to produce pioneer and follow-on biologics could result in the production of dysfunctional proteins. After amino acids have been linked into chains and folding of those chains has occurred, proteins are also subject to an extensive variety of chemical modifications known as post-translational modifications, most notably glycosylation.\textsuperscript{47} Here again, differences between cell lines used to produce pioneer and follow-on biologics can produce differences in patterns of protein modification, that are sometimes dramatic.\textsuperscript{48}

Beyond the complexities attributable directly to the composition of the biologics themselves are those that arise as a consequence of the multi-factorial nature of the manufacturing substrates and methods used to produce the proteins. Cell lines that produce therapeutic proteins are grown under artificial conditions. Even slight variations in cell culture conditions, including temperature, pH, atmospheric composition, and nutrients, can have effects on cell growth and protein production.\textsuperscript{49} Even when secreted directly into the culture medium, biologics are present in complex mixtures also containing a large range of nontherapeutic proteins and other impurities.\textsuperscript{50} A variety of purification technologies and analytical techniques are regularly used to minimize the chance that biologics are contaminated by extraneous proteins and other undesired molecules.\textsuperscript{51} Additionally, because of concerns about the possibility of contamination with viruses or other pathogens,\textsuperscript{52} ultrafiltration and other techniques are commonly used to help ensure the production of high-quality biologics.\textsuperscript{53}

It is easy to appreciate that an FOB might fail to satisfy biosimilarity requirements if it lacked potency, because of abnormal patterns of chemical modification or protein misfolding, or if it was unsafe because the biologic was contaminated with a pathogenic virus. In fact, however, a more problematic issue is probably that of immunogenicity, whereby a patient develops antibodies against the biologic with which she has been treated.\textsuperscript{54} These antibodies may bind to the biologic, thus neutralizing or eliminating it, or, less commonly, bind to the endogenous counterpart of the biologic, exacerbating the condition that the biologic was being used to treat.\textsuperscript{55} The conditions under which antibodies directed toward exogenous therapeutic proteins form are not yet well understood, but

\textsuperscript{45} See Ryan Hunt et al., Silent (Synonymous) SNPs: Should We Care About Them?, 578 METHODS IN MOLECULAR BIOLOGY 23, 35 (2009) (noting the ability of both nonsynonymous (amino-acid sequence altering) and synonymous (DNA changes that do not alter amino acid sequence) to affect protein structure and function).

\textsuperscript{46} See Nigel Jenkins et al., Post-Translational Modifications of Recombinant Proteins: Significance for Biopharmaceuticals, 39 MOLECULAR BIOTECHNOLOGY 113, 114 (2008).

\textsuperscript{47} See id. at 113.


\textsuperscript{50} See, e.g., Stephen Flatman et al., Process Analytics for Purification of Monoclonal Antibodies, 848 J. CHROMATOGRAPHY B: ANALYTICAL TECHS. BIOMEDICAL & LIFE SCI. 79, 84 (2007) (describing the range of impurities commonly encountered during monoclonal antibody purification).

\textsuperscript{51} See David M. Dudzinski, Reflections on Historical, Scientific, and Legal Issues Relevant to Designing Approval Pathways for Generic Versions of Recombinant Protein-Based Therapeutics and Monoclonal Antibodies, 60 FOOD & DRUG L.J. 143, 221–24 (2005).

\textsuperscript{52} See Mahmood Farshid et al., The Clearance of Viruses and Transmissible Spongiform Encephalopathy Agents from Biologics, 16 CURRENT OP. BIOTECHNOLOGY 561, 561 (2005).


\textsuperscript{55} Id.
likely include factors such as protein aggregates, post-translational modifications, and extraneous contaminants.\textsuperscript{56}

The issue of immunogenicity is important when considering FOBs because of the possibility that a pioneer biologic and its cognate follow-on product may have different immunogenicity profiles. In a well-known example, a cluster of patients being treated with a recombinant form of erythropoietin developed anemia due to failure of red blood cell production because of neutralizing antierythropoietin antibodies.\textsuperscript{57} Patients being treated in Europe with Eprex, one form of recombinant erythropoietin, developed antierythropoietin antibodies at a rate ten times greater than did U.S. patients treated with Epogen, another form of the biologic.\textsuperscript{58} Although the precise reason is not known for the increased formation of antierythropoietin antibodies in patients treated with Eprex,\textsuperscript{59} in light of these events, Eprex would fail to be classified as biosimilar to Epogen on both safety and potency grounds.\textsuperscript{60} With current analytical approaches and levels of scientific understanding, laboratory experimentation alone cannot be used to predict whether an FOB will have the same immunologic profile as a pioneer agent.\textsuperscript{61} Clinical trials capable of detecting evidence of antibodies directed at exogenous therapeutic agents or their innate equivalents remain necessary.\textsuperscript{62}

Emblematic of the complexity and variability inherent in its composition and manufacture, an average biologic requires two hundred fifty or more tests, compared with the forty to fifty tests needed to demonstrate the safety of a typical small-molecule drug.\textsuperscript{63} And these estimates reflect only the number and type of investigations that scientists now know to perform.\textsuperscript{64} Presumably, with increases in the scientific understanding of the factors involved in determining the safety and potency of biologics, an even greater number of tests will need to be performed to adequately characterize FOBs in the future.

B. Regulatory Standards for Determining Biosimilarity and Interchangeability: Experience from ANDA Approvals and Statutory Requirements Under the BPCIA

Although most biologics are approved under the PHSA, a small number of relatively simple recombinant DNA-created proteins have been approved under the FD&CA.\textsuperscript{65} During the 1970s the

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\item \textsuperscript{56} See Anne S. De Groot & David W. Scott, \textit{Immunogenicity of Protein Therapeutics}, 28 TRENDS IN IMMUNOLOGY 482, 483–85 (2007).
\item \textsuperscript{57} See Nicole Casadevall et al., \textit{Pure Red-Cell Aplasia and Antierythropoietin Antibodies in Patients Treated with Recombinant Erythropoietin}, 346 NEW ENG. J. MED. 469, 469–70 (2002).
\item \textsuperscript{58} See Charles L. Bennett et al., \textit{Long-Term Outcome of Individuals with Pure Red Cell Aplasia and Antierythropoietin Antibodies in Patients Treated with Recombinant Epoetin: A Follow-Up Report from the Research on Adverse Drug Events and Reports (RADAR) Project}, 106 BLOOD 3343, 3344 (2005).
\item \textsuperscript{59} Although Epogen and Eprex were both produced by recombinant DNA technology and had identical amino acid sequences, there were differences in the way each biologic was manufactured. Jeanne Yang, Note, \textit{A Pathway to Follow-On Biologics}, 3 HASTINGS SCH. & TECH. L.J. 217, 226 (2011). One such difference was that Eprex was produced using the compound polysorbate 80 as a stabilizer (compared with Epogen, which used human serum albumin in this role). See Kati Boven et al., \textit{The Increased Incidence of Pure Red Cell Aplasia with an Eprex Formulation in Uncoated Rubber Stopper Syringes}, 67 KIDNEY INT’L 2346, 2347 (2005). Eprex was dispensed in prefilled syringes with rubber stoppers and in vitro experiments demonstrated that polysorbate 80 could leach impurities from the rubber stoppers that had the effect of increasing immunogenic reactions. See id.
\item \textsuperscript{60} See 42 U.S.C. § 262(b)(2)(A)-(B) (Supp. II 2007-2010). Eprex would not be regarded as potent because the neutralizing antierythropoietin antibodies would reduce the available and efficacious amount of Eprex in the body; it would not be safe because the antibodies would also degrade the body’s own naturally occurring erythropoietin, causing anemia. See Bennett, supra note 58, at 3346.
\item \textsuperscript{61} See Shankar, supra note 54, at 275.
\item \textsuperscript{62} See id. at 276–77.
\item \textsuperscript{64} See Christopher Webster et al., \textit{Biologics: Can There Be Abbreviated Applications, Generics, or Follow-On Products?}, BIOPHARM INT’L (July 1, 2003), http://biopharminternational .findpharma.com/biopharm/article/articleDetail.jsp?id=73785 (“Manufacturers do not test for all the impurities in a biologic—they test for those impurities that they know to be relevant to the process used and for which analytical tools (usually dedicated and specially developed) are available.”).
\item \textsuperscript{65} See Omnitrope’s U.S. Appl Set No Precedents for Biogenerics, Says Wood Mackenzie, PHARMA MARKETLETTER, June 19, 2006, available at 2006 WLNR 24314948 [hereinafter Omnitrope] (noting that, as of 2006, the FDA had
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FDA granted NDAs to a limited number of peptides and hormones under the FD&CA.\(^6^6\) Omnitrope (a recombinant version of human growth hormone), was granted approval as an FOB under what is known as the section 505(b)(2) pathway.\(^6^7\) The FDA was forced to concede, albeit reluctantly,\(^6^8\) that prior findings of safety and efficacy for biologics approved under the FD&CA could be relied upon when the Agency considered FOBs for licensure.\(^6^9\) However, the FDA also made clear that neither the ANDA pathway enacted under the HWA nor the 505(b)(2) pathway applied to biologics that had been approved under the PHSA.\(^7^0\)

Even though the BPCIA has granted the FDA statutory authority to review and approve applications, the Agency has not yet developed a standardized approval process for FOBs.\(^7^1\) The position adopted by the FDA in its detailed implementation guidelines will be critically important to FOB sponsors because the amount of clinical information required to demonstrate biosimilarity and interchangeability will be a major determinant of the cost associated with gaining FOB approval. As might be expected, pioneer manufacturers and some patient interest groups emphasize the importance of comprehensive safety testing including clinical trials, while FOB manufacturers would prefer to be allowed to rely on existing knowledge and non-clinical testing.\(^7^2\)

The FDA has taken steps to implement the BPCIA by creating the Biosimilar Implementation Committee, an internal working group chartered with evaluating the Act and developing FOB review and approval policies.\(^7^3\) The FDA also held a public hearing in November 2010 to gather information and solicit opinions regarding implementation of the BPCIA.\(^7^4\) Input was specifically requested on scientific and technical matters related to developing standards for biosimilarity and interchangeability.\(^7^5\)

Given the apparent specificity required of a BLA for an FOB compared with one for a pioneer biologic, claims about needing clarity in implementing the new FOB pathway seem superfluous. The PHSA requires that issuance of a BLA for a pioneer biologic only demonstrate that the product be “safe, pure, and potent.”\(^7^6\) On the other hand, the BPCIA amendments to the PHSA require that biosimilarity be proven by data that includes: (1) analytical studies demonstrating that the biological product is highly similar to the reference product; (2) animal studies, including assessment of toxicity; and (3) clinical studies, including the assessment of immunogenicity sufficient to demonstrate safety, purity, and potency.\(^7^7\) In fact, the apparent simplicity of the “safe, pure, and potent” requirement for pioneer biologics is illusory because, under the FDA Modernization Act of 1997, the FDA is approved four recombinant biologics under the FD&CA).\(^7^8\)

\(^{66}\) See id. (stating that the approved molecules included insulin, glucagon, and human growth hormone).

\(^{67}\) See Little, supra note 11, at 1108–09. Section 505(b)(2) of the FD&CA has been codified as 21 U.S.C. § 355(b)(2) (2006).

\(^{68}\) See Sandoz, Inc. v. Leavitt, 427 F. Supp. 2d 29, 36–38 (D.D.C. 2006) (holding that the FDA had a statutory obligation to act on Sandoz’s NDA within 180 days); see also Omnitrope, supra note 65 (“In August 2004, the Food and Drug Administration announced that it had failed to reach a decision, citing unresolved scientific and legal issues. In September 2005, Sandoz [Omnitrope’s sponsor] responded by filing a law suit that aimed to force a decision from the FDA.”).


\(^{70}\) See Sahr, supra note 9, at 27–28 (citing a website that is no longer active that contained an FDA Q&A) (“There is no abbreviated approval pathway analogous to 505(b)(2) or 505(j) [the ANDA pathway] of the Act for protein products licensed under section 351 of the Public Health Service Act. Such a pathway for the approval or licensure of follow-on protein products under the Public Health Service Act would require new legislation.”). Of course, such legislation has since been enacted in the form of the BPCIA.

\(^{71}\) See Vatland, supra note 21.

\(^{72}\) See Little, supra note 11, at 1108–10.

\(^{73}\) See Sahr, supra note 9, at 27–28 (citing a website that is no longer active that contained an FDA Q&A) (“There is no abbreviated approval pathway analogous to 505(b)(2) or 505(j) [the ANDA pathway] of the Act for protein products licensed under section 351 of the Public Health Service Act. Such a pathway for the approval or licensure of follow-on protein products under the Public Health Service Act would require new legislation.”). Of course, such legislation has since been enacted in the form of the BPCIA.


\(^{75}\) See Sahr, supra note 9, at 27–28 (citing a website that is no longer active that contained an FDA Q&A) (“There is no abbreviated approval pathway analogous to 505(b)(2) or 505(j) [the ANDA pathway] of the Act for protein products licensed under section 351 of the Public Health Service Act. Such a pathway for the approval or licensure of follow-on protein products under the Public Health Service Act would require new legislation.”). Of course, such legislation has since been enacted in the form of the BPCIA.

\(^{76}\) Nash & Workman, supra note 36, at 200.

\(^{77}\) See id. at 61,498–99.


required to use parallel processes when reviewing pioneer BLAs and NDAs, thus incorporating the considerably more detailed drug approval processes laid out for NDAs.\(^78\)

There is, however, also the potential for the abbreviated pathway to be less burdensome than it could be because of a provision in the BPCIA that allows the requirements for laboratory, animal, or clinical studies to be waived when making a determination of biosimilarity.\(^79\) Thus, although the FDA appears to have discretion as to the nature and amount of information needed to support an abbreviated BLA application, given congressional intent to make biologics available at lower cost, the amount of data needed for an FOB approval will likely be significantly less than for approval of the reference product.\(^80\)

Interestingly, there is no FDA requirement for specific types of studies to classify an FOB as interchangeable. Instead, the sponsor is required to show that the FOB: (1) is biosimilar to the reference product; (2) can be expected to have the same clinical result as the reference product; and (3) does not compromise safety and efficacy when alternated with the reference product in cases where the biologic is administered more than once.\(^81\)

A possible avenue for gaining experience with the abbreviated-approval process is one in which FOB sponsors and the FDA will start with “baby steps,” initially considering less complex biologics, such as those molecules that can be produced in bacterial cells and have a lower risk of immunogenicity because they do not undergo post-translational glycosylation.\(^82\) The BPCIA also makes provision for the FDA to issue product-class-specific guidance documents, disclosing criteria for whether a product meets biosimilarity and interchangeability standards.\(^83\) Thus, it is likely that as the FDA gains experience in judging whether an FOB is biosimilar to and interchangeable with a reference biologic, it will share that experience with the biogenerics industry, with subsequent FOB approval applications benefiting from the FDA’s experience. As familiarity is achieved with the important issues involved in assessing biosimilarity and interchangeability, it is possible that in vitro analytical methods and animal studies will provide enough information to reliably predict FOB safety and efficacy without the need for expensive clinical trials.\(^84\)

The BPCIA also gives the FDA authority to impose Risk Evaluation and Mitigation Strategies (REMS) on biologics licensed under the abbreviated pathway.\(^85\) REMS programs could allow FOB sponsors to gather postmarketing clinical data in the place of comprehensive premarketing clinical data.\(^86\) Similarly, postmarketing studies might also be used to evaluate any immunogenicity problems in the context of switching between follow-on and reference biologics rather than having to perform that assessment before product launch.\(^87\) This latter possibility makes a great deal of sense because

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\(^80\) See James N. Czaban, et al., Panacea or Poison Pill? Making Sense of the New Biosimilars Law, 8 PHARM. L. & INDUS. REP. 698 (2010) (“The assumption, which has yet to be proven, is that the quantum of data necessary for a biosimilar approval will be substantially less than that originally required in support of approval of the reference product.”); Alexandra McTague, The Biologics Price Competition and Innovation Act: The Pros and Cons of Biosimilar Approval, 9 PHARM. L. & INDUS. REP. 151 (2011) (“If substantial clinical trials are required to show biosimilarity, the BPCIA hardly will differ from the current BLA procedure and thus would not produce moderately priced biologics. Thus, it is likely that Congress intended something less onerous than full clinical trials.”).

\(^81\) 42 U.S.C. § 262(k)(4)(A), (B).

\(^82\) See Decision Resources Director Michael Malecki quoted in In Vivo Magazine, DECISION RESOURCES, INC. (Oct. 1, 2010), http://decisionresourcesinc.com/News-and-Events/In-The-News/Malecki-In-Vivo-100110 [hereinafter Decision Resources].

\(^83\) See 42 U.S.C. § 262(k)(8)(D).

\(^84\) 42 U.S.C. § 262(k)(5)(C).


\(^86\) See id.
problems with immunogenicity may have a low incidence and may not become apparent until a relatively large number of patients have been treated with a biologic.\textsuperscript{87}

Despite the lack of certainty about how approval procedures will be implemented, the FDA is apparently ready to accept FOB applications and will operate directly from the statute until regulations are established or guidance documents have been issued.\textsuperscript{88} In the interim, FOB manufacturers are taking different approaches, with some preparing to move ahead with the new approval pathway\textsuperscript{89} and others electing to submit full BLAs until detailed implementation rules have issued.\textsuperscript{90} Whatever guidance the FDA issues, it is likely, as one commentator suggests, that “demonstrating comparability remains a sponsor’s burden and one that needs to be met case-by-case on a data-driven basis.”\textsuperscript{91}

\textbf{C. The BPCIA Establishes a Complex Set of Patent Litigation Procedures}

Given the high stakes involved, it is likely that, as has been the case for generic small-molecule drugs,\textsuperscript{92} patent litigation will arise between pioneer and follow-on biologics manufacturers. Rather than following the patent litigation procedures established by the HWA, Congress elected to adopt an even more intricate patent litigation system for biologics.\textsuperscript{93} In overview, the Act provides for several steps before litigation commences: (1) the FOB applicant has to disclose its application to the pioneer entity; (2) each party has to identify relevant patents; (3) the parties trade briefs regarding validity and potential infringement of those patents; (4) the parties confer on which patents will be litigated; and (5) the parties concurrently exchange patents selected for litigation if they cannot jointly agree as to which patents should be litigated.\textsuperscript{94} A detailed analysis of all of the patent litigation provisions in the BPCIA is beyond the scope of this Article.\textsuperscript{95} Instead, this Article will consider aspects of the BPCIA that differ from the HWA and relate to therapeutic equivalence between pioneer and follow-on biologics.

Under the ANDA framework, generic drug manufacturers were placed on notice about which patents relating to a pioneer drug its manufacturer intended to assert by requiring that those patents be listed in a publication known as the “Orange Book.”\textsuperscript{96} As part of an NDA, a pioneer drug sponsor must submit a list of any patent “which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted.”\textsuperscript{97} Through regulation, the FDA established three

\textsuperscript{87} See Sahr, supra note 9, at 53.

\textsuperscript{88} See Nash \& Workman, supra note 36, at 200.

\textsuperscript{89} See, e.g., Decision Resources, supra note 82 (noting that Merck BioVentures announced in June 2010 that it was preparing to file for approval of an FOB application under the BPCIA even in the absence of implementation guidelines and was believed to be in the final stages of preparing to file for a Neupogen biosimilar).


\textsuperscript{91} John M. Engel, Biosimilars Approvals in the US: The Path Forward, 23 BIOPHARM INT’L 46, 48 (2010).


\textsuperscript{93} See Czaban et al., supra note 80 (“As complex as traditional Hatch-Waxman litigation can be . . . . Congress, in the Biosimilar Act, has created an even more complex and process-bound system for resolving patent disputes involving biosimilar products.”).

\textsuperscript{94} See THOMAS, supra note 17, at 777.


classes of patents that can be presented with an NDA: “drug substance (active ingredient), drug product (formulation and composition), and method-of-use patents.”

The BPCIA, on the other hand, makes no provision for an equivalent to the Orange Book for biologics. In its place, under the BPCIA, the FOB applicant must provide a copy of its application to the reference biologic sponsor within twenty days of filing the application. The reference product sponsor then has sixty days to respond with a list of the patents for which it “believes a claim of patent infringement could reasonably be asserted.” Only then is the FOB applicant in a position to develop a clear understanding of whether its product might infringe patents held by the reference product sponsor.

The BPCIA provides strong incentives for the pioneer sponsor to disclose all relevant patents at this stage because, if it fails to list a patent, it is barred from suing for infringement of that patent.

Another important difference between the ANDA and FOB approval pathways is that under the HWA, method-of-production (or process) patents cannot be asserted. In contrast, the BPCIA allows infringement actions against an entity “making” the allegedly infringing product, so method-of-production patents can be asserted against FOB sponsors.

The importance of process patents will be discussed in more detail in Part II of this Article.

In addition to providing a copy of its biologics application to the reference product sponsor, the FOB applicant must also provide “such other information that describes the process or processes used to manufacture the biological product” to the pioneer sponsor. This requirement has been challenged as forcing the FOB manufacturer to risk the disclosure of trade secret information. The Act attempts to minimize any such risk by limiting disclosure of manufacturing process information to one in-house counsel employed by the reference product sponsor and one or more attorneys serving as outside counsel. Recipients of this information are only permitted to use it to determine if a claim of patent infringement could reasonably be asserted and are even prohibited from sharing the information with outside scientists. Thus, while biosimilars sponsors may complain about having to disclose manufacturing information they would rather keep confidential, pioneer sponsors may be hampered in their technical ability to determine whether FOB manufacturing processes infringe their methods patents.

The BPCIA features an involved process for determining which patents will be litigated in a dispute between pioneer biologic and FOB sponsors that is quite unlike anything provided for under the HWA. Both parties are required to undertake good-faith negotiations to decide which, if any, patents should be litigated. Should these negotiations fail, the FOB sponsor must inform the pioneer biologic sponsor of the number of patents that it believes should be litigated in an

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99 See Dougherty, supra note 95, at 234.
102 See Czaban et al., supra note 80 (“[B]iosimilar applicants are on their own, when developing a biosimilar product, in determining which patents must be avoided or challenged.”).
infringement suit. Not more than five days later, the parties must simultaneously exchange lists of the patents they believe should be litigated, but the number of patents each party submits cannot be greater than the number proposed by the FOB applicant (unless the FOB applicant states that it believe no patents should be litigated, in which case the pioneer biologic sponsor may nominate one patent for litigation). After the lists have been exchanged, the reference sponsor must bring a patent infringement action within thirty days for each patent on the lists. This elaborate dance gives significant power to the FOB sponsor because it can set an upper limit on how many patents can be litigated.

While the FOB applicant has substantial influence on the number of patents that can be litigated in immediate patent infringement actions, the pioneer sponsor does have the possibility of later recourse. Under the BPCIA, an FOB applicant must provide the reference product sponsor 180-day notice before the commercial sale of the FOB. This event can then trigger a second phase of patent litigation because once notice of imminent commercialization has been received, the pioneer sponsor may seek a preliminary injunction, asserting any of the patents that it previously identified during the patent-list exchange.

Because of the complexity of the patent litigation provisions in the BPCIA, it is not yet known whether the Act might tilt patent battles in favor of either pioneer or follow-on biologic sponsors. What is clear is that strategic considerations as to which patents are to be litigated will be of great importance to both parties and careful deliberation will be given when deciding which patents to nominate for litigation.

II. PRODUCTION METHODS WILL PLAY IMPORTANT ROLES IN DETERMINING BIOSIMILARITY AND IN FOB PATENT LITIGATION

The large-scale manufacture of biologics is challenging. Federal regulations prescribe detailed guidelines on how to maintain good manufacturing processes and quality assurance so that products will consistently meet design specifications. Pioneer manufacturers argue that because the steps involved in making biologics are so complex it is very difficult to ensure comparability of pioneer and follow-on biologics. Understanding regulatory efforts to measure biosimilarity, and intellectual property law efforts to protect pioneer biologics, requires that regulators and litigators pay careful attention to biologics production methods.

A. Changes in Production Methods Impact the Ability to Manufacture Biosimilar Therapeutic Agents

Small changes in a biologic’s structure can affect its clinical safety and efficacy. In fact, according to the FDA, “[i]ssuance of a biologics license is a determination that the product, the

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117 See Dougherty, supra note 95, at 238.
120 See Czaban et al., supra note 80 (noting that the provisions relating to the identification of which patents will be litigated “pose significant strategic challenges in uncharted territory for both reference product sponsors and biosimilar applicants”).
123 See Sahr, supra note 9, at 12; also supra notes 45–63 and accompanying text.
manufacturing process, and the manufacturing facilities meet applicable requirements to ensure the continued safety, purity and potency of the product.” An unsettled question in the FOB field is how often differences in manufacturing processes cause clinically significant changes in therapeutic biologics. Although they all recognize the importance of production methods in the manufacture of safe and effective biologics, authorities differ on whether it is possible to produce biosimilar products without precise process identity.

Those who oppose ready determinations of biosimilarity between pioneer and follow-on biologics contend that slight changes in process can produce significant changes in the character of a biologic. Part of the problem is that, at least in some cases, it is not even possible for the manufacturer to identify which changes in production method might be responsible for alterations in end-product quality. For example, efalizumab, an immunosuppressive monoclonal antibody that was recently removed from the market because of serious side effects, was originally developed by XOMA. Large-scale manufacturing of efalizumab was subsequently moved to XOMA’s partner, Genentech. Even though it had access to all of the documentation and experience XOMA had accrued during its development of the monoclonal antibody, Genentech was unable to precisely replicate the manufacturing process. While not apparent on analytical and animal studies, human studies revealed differences between the two formulations, and the FDA required supplemental Phase III clinical studies before the product was approved. Similarly, Genzyme ran into difficulties when it attempted to transfer the manufacture of Myozyme, an enzyme replacement therapy, from one facility to another. Even though Genzyme had access to all original information about the drug, changes made in transferring to the new facility and increasing the scale of manufacture were enough to change the recombinant protein. Citing changes in the structure of the protein, the FDA determined that Myozyme produced in the new facility would have to be treated as a different product and that additional clinical studies were needed prior to marketing.

The Genentech and Genzyme examples demonstrate that problems can arise even when the biologics producer has unfettered access to the manufacturing protocols and scientific know-how involved in making the recombinant protein. This type of issue is likely to be an even greater concern when different companies are attempting to produce versions of the same biologic. That possibility was confirmed with the differences in immunogenicity that were observed between versions of the same biologic when different companies are attempting to produce versions of the same biologic. Those who oppose ready determinations of biosimilarity between pioneer and follow-on biologics contend that slight changes in process can produce significant changes in the character of a biologic.


125 See Regulation of “Biosimilars” in the European Union, HOGAN & HARTSON, LLP 2 (June 18, 2004), available at http://www.hoganlovells.com/files/Publication/88bedf36-dc7b-4263-a4a4-2f2776a956014/Presentation/PublicationAttachment/078fe85f-a0d5-4ccc-a96f-afec79554fbd/1475_040618_reg_biosimilars_eubulletin.pdf (“For biological drugs, there are always differences among different manufacturers’ products, and ‘the process is the product, and the product is the process.’”).


129 See id.

130 See id.; see also Liang, supra note 9, at 364 n.9.


132 See id.

133 See id. The FDA even required that the new product be launched under a new brand name. See Engel, supra note 91, at 48.

134 See supra notes 57–60 and accompanying text.
production methods as they can, while still fulfilling regulatory obligations to disclose manufacturing processes. The issue of manufacturing trade secrets will be discussed in more detail below.\(^\text{135}\)

Production methods, however, need not be the final determinant as to whether two products can be regarded as biosimilar. According to an FDA scientist, “at least for recombinant proteins (though not for naturally-derived products), the manufacturing process ‘impacts but does not necessarily define the product,’ and therefore ‘if you can define the desired endpoint (product), [you] can probably design the process to achieve that product (“reverse engineering”).’\(^\text{136}\) This suggests that, even without complete identity of manufacturing processes, it might be possible to produce biologics that could meet the biosimilarity standard. Support for this proposition comes from a D.C. Circuit Court ruling that absolute chemical identity was not required to support an ANDA.\(^\text{137}\) This case involved a generic version of female reproductive hormones prepared from the urine of postmenopausal women.\(^\text{138}\) The pioneer product manufacturer argued that differences in protein glycosylation patterns between the pioneer and generic products meant that the two products were not the same and that the ANDA application should be denied.\(^\text{139}\) The court deferred to the FDA’s finding that any variation between the two products was not clinically significant for the product’s intended uses.\(^\text{140}\)

The result in *Serono Labs.* is consistent with the FDA’s long-standing practice of allowing “well-characterized therapeutic recombinant DNA-derived and monoclonal antibody biotechnology products” to be marketed without requirement for lot-by-lot release (approval).\(^\text{141}\) This was justified because “greater control has been achieved by manufacturers over the production of biotechnology products through in-process controls, process validation, and advances in analytical techniques.”\(^\text{142}\) Similar concerns arise when a biologics sponsor seeks approval for a change in manufacturing processes. The FDA uses a “comparability protocol” for post-BLA approval process changes, with requirements for smaller amounts of laboratory and clinical data than required for a BLA.\(^\text{143}\) And, indeed, not all process alterations for approved biologics have required clinical trials.\(^\text{144}\)

FOB advocates contend that the comparability assessments performed in the assessment of production process changes, or batch-to-batch evaluations of approved biologics, are exactly the same type of considerations as when the FDA makes a determination of biosimilarity, or indeed, interchangeability.\(^\text{145}\) Pioneer companies counter by stating that only intracompany changes should

\(^{135}\) See infra notes 152–56 and accompanying text.


\(^{138}\) See Dudzinski, supra note 51, at 203.

\(^{139}\) See id.

\(^{140}\) See *Serono Labs.*, 158 F.3d at 1318.


\(^{142}\) Id.


\(^{144}\) See Little, supra note 11, at 1128.

\(^{145}\) Testimony of Rasmus Rojkjaer, Generic Pharmaceutical Ass’n, Part 15 Public Hearing on Approval Pathway for Biosimilar and Interchangeable Biological Products 331–32 (Nov. 3, 2010), available at http://www.regulations.gov/#documentDetail;D=FDA-2010-N-0477-0012 (“The FDA has been evaluating products for biosimilarity for years. Anytime a brand new biologic manufacturer has changed his manufacturing process, added new facilities, substituted an ingredient or changed the cell line, the FDA has used the same time honored data driven scientific standard: Comparability to analyze these changes. . . . [I]f this same approach can and should be applied to biogenetics.”). See also Pamela Jones Harbour, Comm’r, Fed. Trade Comm’n, Remarks at the ABA Sections of Antitrust and Intellectual Property Law Meeting: The Competitive Implications of Generic Biologies 11 (June 14, 2007), http://www.ftc.gov/speeches/harbour/070614genbioph.pdf (citing a generic pharmaceutical company’s belief that “[t]he science to create affordable generic biotech drugs exists today. . . . It is being done every time a brand manufacturer changes a
be used in comparability analysis because only then is all the necessary data available.\textsuperscript{146} It is impossible to know which of these positions the FDA will adopt. But, given the known issues with lack of comparability between different biologics preparations\textsuperscript{147} and the Agency’s strong interest in protecting public safety,\textsuperscript{148} it is probable that, until it has developed a body of experience with regards to the amount and kind of data needed to make comparability evaluations, the FDA will adopt a conservative approach and require at least some clinical studies before approving biologics under the BPCIA.

B. Protection of Production Methods Will Play a Significant Role in Efforts to Safeguard Pioneer Biologics

Patent protection is usually more difficult to secure for biologics than for small-molecule drugs.\textsuperscript{149} The products of biologics patents are generally closely related to substances that already exist in the human body and broad composition of matter claims are usually disallowed for proteins that already exist in nature.\textsuperscript{150} Because of this limitation, biologics developers may need to rely on protections offered by process patents.\textsuperscript{151}

Of course, even before a pioneer biologic sponsor might want to enforce a process patent, there is the issue of whether the sponsor would have sought patent protection for that process in the first place. In theory at least, an innovator can seek to protect a novel process by keeping it a trade secret rather than by applying for a patent.\textsuperscript{152} Trade secret protection can be useful in the case of proprietary know-how and has the potential advantage that the process would not become publicly available for anyone to use upon expiration of the patent.\textsuperscript{153} A disadvantage of relying on trade secret protection alone is that, as discussed above, the FDA requires disclosure of information relating to manufacturing processes to obtain a BLA.\textsuperscript{154} While the FDA has long treated trade secret information as confidential,\textsuperscript{155} innovators complain that their trade secrets are at risk when the Agency might use that information to assess FOB applications.\textsuperscript{156} Although it is difficult to know whether pioneer biologics sponsors intentionally keep details of their manufacturing processes secret manufacturing process or location and uses comparability to ensure the biotech drug will provide the same safety and efficacy. . . . [B]iotech firms routinely justify process and site changes via comparability studies. For example, if an innovator biotech company seeks changes in processes supporting the manufacture of their products, or seeks to change the manufacturing location of a product, comparability is the process by which the amended product is judged to provide the same clinical effect and safety profile”).

\textsuperscript{146} See Webster, supra note 64 (“The innovator has a comprehensive database of every step of the manufacturing process and key intermediates and has established many in-process controls and reference standards. Generally, changes are minor alterations to a well-understood, extensively validated and licensed process, with all other aspects of production remaining unchanged. The innovator is able to compare product made before and after the process change and show that the change has had no effect on the product made.”).

\textsuperscript{147} See supra notes 126–34 and accompanying text.

\textsuperscript{148} See 21 U.S.C. § 393(b)(1) (2006) (stating that the FDA’s mission is to “promote the public health”).


\textsuperscript{150} See id. at 2–3.

\textsuperscript{151} See id. at 3.

\textsuperscript{152} See 21 C.F.R. § 20.61(a) (2010) (“A trade secret may consist of any commercially valuable plan, formula, process, or device that is used for the making, preparing, compounding, or processing of trade commodities and that can be said to be the end product of either innovation or substantial effort. There must be a direct relationship between the trade secret and the productive process.”).

\textsuperscript{153} See David R. Hannah, Should I Keep a Secret? The Effects of Trade Secret Protection on Employees’ Obligations to Protect Trade Secrets, 16 ORG. SCI. 71, 73 (2005).

\textsuperscript{154} See Food & Drug Administration, supra note 124 and accompanying text.

\textsuperscript{155} See Peter Lurie & Allison Zieve, Sometimes the Silence Can Be Like the Thunder: Access to Pharmaceutical Data at the FDA, 4, at ¶¶ 12–29.

\textsuperscript{156} A full discussion of the questions as to whether the FDA might be responsible for an unconstitutional “taking” of trade secret information from innovator companies is beyond the scope of this Article. For a discussion of these issues, see Little, supra note 11, at 1110–14, 1118–25; Andrew Wasson, Note, Taking Biologics for Granted? Takings, Trade Secrets, and Off-Patent Biological Products, 2005 DUKE L. & TECH. REV. 4, at ¶¶ 12–29.
from the FDA, it is reasonable to suppose that some details of the procedures involved in the mass-production of biologics are not included in BLAs. There may well be a fuzzy line between disclosed details that the sponsor knows are important in manufacturing and details that are not known to alter the characteristics of the biologic and are not disclosed to the FDA.

¶44 A related issue can also arise if the innovator elects to protect its manufacturing methods with process patents. A company loses trade secret protection upon publication of the patent application.¹⁵⁷ So, again there may be some incentive to omit subtle process steps or factors from the patent application to prevent the entire process from becoming public knowledge. This could also be risky because if an adversary became aware that what turned out to be important process details were omitted from the written description of the patent, the validity of the patent could be challenged for lack of enablement.¹⁵⁸ Therefore, because of the intricacy of biologics manufacturing methods, a process patent would need to be narrowly tailored to maximize the likelihood that it would be held valid.¹⁵⁹ The problem with patents with limited scope is that they can be relatively easy to design around so that FOB manufacturers could avoid infringement.¹⁶⁰ This would require the FOB sponsor to be able to use manufacturing processes that were different enough not to infringe upon the innovators process patent, but comparable enough to produce a biologic that it would pass the FDA’s biosimilarity requirements.¹⁶¹ It is not yet apparent whether FOB sponsors would be able to thread this needle. It is likely that the precise treatment of process methods as they apply to FDA disclosure requirements, biosimilarity standards, and patent enablement will be subject to careful parsing of regulatory language and contentious litigation in the next several years.

¶45 The other arena in which intellectual property considerations relating to manufacturing processes are likely to arise in FOB approvals is in the selection of whether process patents are litigated in immediate infringement actions. As described above, under the BPCIA, FOB sponsors can limit to as few as one the number of patents for which the pioneer sponsor can initially assert infringement.¹⁶² In the situation that the FOB sponsor has successfully limited the number of patents in play, the pioneer sponsor has to plan very carefully which patents to assert. If only a single patent can be asserted, that patent most likely would have to claim the biologic molecule, even though process patents might afford stronger protection.¹⁶³ The reference product sponsor could also choose to delay assertion of some patents, including process patents, until it had received 180-day notice of commercialization of the FOB.¹⁶⁴

¶46 In the absence of any cases testing trial strategies for the BPCIA patent litigation procedures, it is impossible to predict exactly what factors will be most important in asserting patents for infringement actions. However, it is likely that the type of patents involved, including method and composition-of-matter patents, their apparent strength, and their expiration dates will be important considerations.¹⁶⁵

¹⁵⁷ See, e.g., Tewari De-Ox Sys., Inc. v. Mountain States/Rosen, L.L.C., 637 F.3d 604, 611–12 (5th Cir. 2011).
¹⁵⁹ See id. at 546.
¹⁶⁰ See id.
¹⁶¹ See Sahr, supra note 9, at 46.
¹⁶² See supra notes 111–16.
¹⁶³ See supra notes 149–51.
¹⁶⁴ See Czaban et al., supra note 80 (“[R]eference sponsors might seek to challenge biosimilar applicants to a game of ‘chicken’ by holding back certain patents from the initial litigation, with the implicit threat that such patents may be interjected via a preliminary injunction motion in the six months prior to the applicant’s announced commercial launch date.”).
¹⁶⁵ See id.
III. THE BPCIA WILL LIKELY HAVE LIMITED IMPACT ON THE PRICE AND AVAILABILITY OF BIOLOGICS UNTIL SCIENTIFIC METHODS AND REGULATORY PROCEDURES ALLOW EASY CONFIRMATION OF FOB BIOSIMILARITY AND INTERCHANGEABILITY

The small-molecule generic drug industry owes a great deal of its success to the comparative simplicity with which a generic drug sponsor can establish the technical basis for the similarity between its product and the corresponding reference drug.\(^\text{166}\) There is no doubt that the ANDA pathway has markedly affected pharmaceutical agent availability and cost. Generic pharmaceuticals account for fifty-six percent of U.S. drug prescriptions but only thirteen percent of prescription costs.\(^\text{167}\) Of the more than 11,000 pioneer drugs approved by the FDA, over seventy-five percent now have generic equivalents.\(^\text{168}\) Similarly, the BPCIA approval pathway is expected to result in the introduction of FOBs.\(^\text{169}\) But it is not obvious whether the advent of FOBs will result in significant healthcare cost savings.

The introduction of a pathway to FOB approval has been widely heralded as a way to improve access to expensive biologics by launching lower-cost alternatives.\(^\text{170}\) Because many pioneer biologics have already lost patent protection, or will do so within the next few years,\(^\text{171}\) they are ripe for displacement from the marketplace. Depending upon the models they employ, economists have developed estimates for the healthcare savings from FOBs that range from $43.2 billion\(^\text{172}\) to $108 billion\(^\text{173}\) over the first ten years.

Unfortunately, there are a number of forces at work that will likely blunt cost savings flowing from the BPCIA. Experience with small-molecule drugs has shown that generic competition has the greatest effect on drug prices when there are multiple competing generic products being sold. An FDA study of small-molecule drug prices showed that the price reduction attributable to competition was only six percent with a single generic producer, but rose to forty-eight percent with two generic producers, fifty-six percent with three, sixty-one percent with four, sixty-seven percent with five, and eighty percent with twelve.\(^\text{174}\) There are several reasons that there will most likely be a relatively small number of FOB competitors. First, as has already been discussed in this Article, FOB manufacturers face barriers to entry because of the technical complexity of producing biologics and the regulatory requirements associated with demonstrating therapeutic equivalence with reference products.\(^\text{175}\) Second, the cost of producing FOBs is expected to be much higher than the cost of making small-molecule generics. The average cost of bringing a biosimilar to market is estimated to be between $100 million and $200 million.\(^\text{176}\) This compares with prices ranging from approximately one million

\(^{166}\) See Morrison, supra note 8, at 465.

\(^{167}\) Id. at 464.

\(^{168}\) Id.

\(^{169}\) See Sahr, supra note 9, at 44.


\(^{171}\) See Dudzinski, supra note 51, at 244–52 app. A.


\(^{173}\) See SHAPIRO ET AL., supra note 10, at 13.


\(^{176}\) Sumanth Kambhammettu, The European Biosimilars Market: Trends and Key Success Factors, SCICASTS (Oct. 27, 2008), http://scicasts.com/specialreports/20-biopharmaceuticals/ 2152-the-european-biosimilars-market-trends-and-keysuccess-factors. Admittedly, this is substantially lower than the $1.2 billion it costs to develop a
dollars to five million dollars to develop a generic small-molecule drug.\textsuperscript{177} Third, manufacturing facilities capable of producing high-quality FOBs may be relatively scarce. A new biologics production plant can take three to five years to build and cost upwards of $250 million.\textsuperscript{178} Whether there is an absolute shortage of biologics production capacity is uncertain.\textsuperscript{179} As well as the cost of the production facilities themselves, the costs of materials for biologics production are twenty to one hundred times greater than those for small-molecule drugs.\textsuperscript{180} Finally, many biologics may not attract the interest of FOB manufacturers. A large number of biologics are “niche drugs” directed at the treatment of uncommon disorders affecting small numbers of patients.\textsuperscript{181} Only those products that produce sizeable revenues would be likely to draw generic competition.\textsuperscript{182}

Even assuming that barriers to entry would not prevent a reasonable number of FOB manufacturers from entering the market, it is still far from certain that substantial price reductions will result from generic competition. If the FDA fails to classify an FOB as interchangeable, pharmacists and hospitals are unlikely to routinely replace a pioneer biologic with a merely biosimilar FOB when they receive a prescription for the pioneer biologic.\textsuperscript{183} The automatic replacement of a brand-name prescription with a less expensive, generic equivalent is mandated in almost one-third of the states when a physician has not specifically signed for the brand-name product.\textsuperscript{184} An FOB that is not interchangeable will likely not meet this standard. This lack of free substitutability means that for a biosimilar FOB to succeed commercially, its sponsor will need to undertake expensive marketing campaigns to encourage physicians to prescribe its product instead of the pioneer biologic.\textsuperscript{185} Factors that may determine the success of an FOB could include order of entry into the market, results of clinical studies, number of sales personnel, direct-to-consumer advertising, and access to formularies.\textsuperscript{186} It has even been suggested that pioneer sponsors might try to out-market FOB competitors, driving up the costs of both the pioneer and follow-on biologics.\textsuperscript{187}

Although this analysis suggests that price reductions brought about by the advent of FOBs might be limited, even relatively small percentage discounts can amount to significant absolute cost savings.\textsuperscript{188} Based partly on experience from Europe, industry leaders expect that FOBs will cost approximately thirty percent less than pioneer biologics.\textsuperscript{189} Consider a blockbuster biologic like Enbrel, a therapy marketed by Amgen and Pfizer for the treatment of rheumatoid arthritis and other

\textsuperscript{177} FTC FOB REPORT, supra note 32, at 14.
\textsuperscript{178} See H. Grabowski, Follow-On Biologics: Data Exclusivity and the Balance Between Innovation and Competition, 7 NATURE REVIEWS DRUG DISCOVERY 479, 483 box 3 (2008) (noting also that this cost is not factored into the cost of developing FOBs).
\textsuperscript{179} Compare Design of a Large-Scale Biologics Manufacturing Facility, CH2M HILL LOCKWOOD GREENE, http://www.ch2m.com/corporate/markets/life_sciences/assets/ProjectPortfolio/HumanGenome.pdf (last visited July 12, 2012) (stating, in 2005, that there was a “worldwide shortage of biologics manufacturing capacity”), and Linda Lim, The Future of Biologics Manufacturing in Singapore, 4 INNOVATION (2003), available at http://www.innovationmagazine.com/innovation/volumes/v4n3/coverstory3.shtml (citing a “global shortage of biologics manufacturing capacity”), with Shapiro et al., supra note 10, at 9 (“[S]ome U.S. producers of biologics have idle production facilities that could be retrofitted to produce new biogenetics themselves or could subcontract from others, at much lower cost than required to build a new U.S. facility.”). It is also possible that foreign biologics manufacturers could elect to enter the U.S. FOB market, further increasing production capacity. See Shapiro et al., supra note 10, at 8–9.
\textsuperscript{180} See Shapiro et al., supra note 10, at 5.
\textsuperscript{182} See id.
\textsuperscript{183} See Czaban et al., supra note 80.
\textsuperscript{184} Timothy E. Welty, Pharmacy and Generic Substitution of Anti-Epileptic Drugs: Missing in Action?, 41 ANNALS PHARMACOTHERAPY 1065, 1066 (2007).
\textsuperscript{185} See Czaban et al., supra note 80.
\textsuperscript{186} FTC FOB REPORT, supra note 32, at 16.
\textsuperscript{187} See id. at 16 n.52.
\textsuperscript{188} See Harbour, supra note 145, at 19.
\textsuperscript{189} See Decisions Resources, supra note 82.
autoimmune diseases; in 2009, it had sales of $5.9 billion in the United States. Enbrel is due to lose patent protection in 2012. If FOB versions were produced, reduced average sales price by just ten percent, and took only twenty-five percent market share, then Enbrel would still stand to lose over $1.9 billion in sales. Because such large dollar sums are at stake, pioneer manufacturers are likely to do whatever they can to protect the market share of their products and delay the introduction of FOBs. These efforts will probably include patent enforcement lawsuits. Given current uncertainty about how the BPCIA patent litigation provisions will be implemented and interpreted, it will likely take several years for pioneer and follow-on biologics sponsors to grasp their complexities. Indeed, critics of the complexity of the patent litigation provisions of the BPCIA also suggest that, in some situations, FOB manufacturers might elect to file traditional BLAs instead of abbreviated applications to avoid the risk and intricacies of the biosimilar patent-challenge provisions.

Beyond just procedural jockeying though, pioneer biologics sponsors are also likely to engage in patent litigation on substantive grounds. Under ANDA, pioneer small-molecule drug manufacturers have been very effective at “evergreen[ing]” their drug patents by filing “improvement” patents on their original products, claiming new features such as different doses, extended release formulations, or novel modes of administration. In enacting the BPCIA, Congress recognized this problem, and provided that the twelve-year data protection period would only be granted for the first licensure of a reference biologic but would not be available for supplemental applications for the same product (which could be sought when process modifications were instituted) or for nonstructural changes to the reference biologic. However, just because a pioneer sponsor may not be able to evergreen its product by safeguarding its BLA application data, it may still be able to do so by litigating patents that claim process modifications. As discussed in Part II of this Article, the BPCIA creates a gray area around the amount of detail with which manufacturing processes are disclosed in regulatory filings to the FDA, enabled in patent applications, or held as trade secret information or proprietary know-how. It is highly likely that experienced patent litigators will exploit this zone of uncertainty and try to protect reference biologics through the assertion of process patents.

Despite the ways in which generic competition for biologics may be impeded by economic forces and patent litigation efforts, the BPCIA accelerated-approval pathway will probably meet with increasing success. This can be expected to occur as the FDA develops a body of experience in dealing with FOB applications and an understanding of what technical factors are most predictive of biosimilarity and interchangeability. One way that such advances could be hastened would be through the FDA’s development of guidance documents discussing important scientific and regulatory considerations in obtaining approval for follow-on versions of important classes of biologics.

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190 See Evans, supra note 175, at 98.  
191 Id.  
192 Cf. M. Sean Royall & Joshua Lipton, The Complexities of Litigating Generic Drug Exclusion Claims in the Antitrust Class Action Context, 24 ANTI-TRUST 22, 22 (2010) (noting, in the small-molecule drug context, that “[b]randed manufacturers thus have strong incentives to consider potential legal actions for defending their investments in franchise drug products, provided there are good-faith bases to do so. This often takes the form of patent enforcement lawsuits against prospective generic entrants”).  
193 See THOMAS, supra note 17, at 781 (“Resolution of the scientific and legal issues that this legislation raises will likely engage the courts and the FDA for many years to come.”).  
194 See Engel, supra note 91, at 50.  
198 See supra notes 152–61 and accompanying text.  
199 See Yang, supra note 59, at 240–41.
Ultimately though, the surest way to enable the FDA to make biosimilarity and interchangeability judgments for FOBs, without burdening their sponsors with requirements for expensive preapproval clinical trials, will be to improve the quality of the scientific data used to judge biosimilarity and interchangeability. One commentator has noted that “the quantity of data required to license follow-on biologics will vary for each product and will depend on each product’s complexity and on how much is known about the product’s mode of action.”200 Developing a better understanding of the factors that contribute to a biologic’s complexity will let scientists measure those parameters and regulators assess them. Knowing more about a biologic’s mode of action will provide greater insight into the issues that impact the product’s clinical safety and efficacy. Armed with tools that would allow them to assess FOBs for safety and efficacy problems without the need of expensive, preapproval clinical studies, generic biologic manufacturers would be better able to deliver these breakthrough medicines at lower cost.

CONCLUSION

Biologics play important roles in treating a range of medical conditions. But they are expensive, accounting for a significant proportion of healthcare costs in the United States. The BPCIA was enacted in the hope that generic, less expensive versions of biologics could be introduced to the U.S. market, increasing access and reducing healthcare expenditures. To minimize the chance that public safety will be compromised by the introduction of FOBs, strict comparability and interchangeability standards must be met for these biologics before they can be approved by the FDA under the BPCIA abbreviated-approval pathway.

A problem that risks circumventing Congress’s desire to deal with rising healthcare expenses comes from technical, regulatory, and legal challenges to FOB manufacturers being able to meet biosimilarity and interchangeability standards. The complex nature of the large molecules comprising biologics, together with an imperfect understanding of the factors that impact their synthesis in living cells, means that it is technically difficult to produce FOBs that are exact replicas of corresponding pioneer products. That difficulty is compounded by the lack of well-validated scientific tools that can detect differences between pioneer and follow-on biologics without the need for expensive, preapproval clinical trials.

Particular difficulties can be expected to arise with regards to minor deviations in biologics manufacturing processes between different varieties of a biologic. The existence of several examples of process variances resulting in changes in biologic characteristics that could, or did, impact patient safety have been of understandable concern to the FDA. Because of this, federal regulators will likely be reluctant to approve FOBs unless manufacturing processes closely mirror those of equivalent reference products. Pioneer biologics manufacturers may be able to extend patent protection of their products by asserting more current process patents, asserting infringement over manufacturing methods used by FOB manufacturers. These efforts will likely be more effective if litigators can take advantage of possible ambiguities in process descriptions required by regulatory disclosures and enablement requirements in patent applications.

Increasing utilization of the BPCIA accelerated-approval pathway for FOBs will require that the FDA and industry participants develop experience and knowledge about the scientific, regulatory, and legal aspects of the approval process. It is likely that the full promise of the BPCIA will only be delivered when improved analytical methods will allow the detection of subtle differences in biologics that could affect patient safety, obviating the need for clinical trials. Until then, there will be ample opportunities for pioneer and generic biologics manufacturers, FDA regulators, and patent lawyers to experience and challenge the intricacies of the exciting, but complex, new biologics abbreviated-approval pathway.

200 Webster, supra note 64.