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The Biologics Price Competition and Innovation Act: Potential Problems in the Biologic-Drug Regulatory Scheme

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Potential Problems in the Biologic-Drug Regulatory Scheme**

Ryan Timmis



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By Ryan Timmis*

In 2010, Congress passed the Patient Protection and Affordable Care Act, often referred to as “Obamacare.” Though little noticed in the fanfare surrounding this event, Title VII, the Biologic Price Competition and Innovation Act (BPCIA), was arguably one of the most important provisions. The BPCIA represents one of the more significant overhauls to the pharmaceutical industry in recent decades. For the first time, federal law established a pathway for the creation of generic versions of drugs produced by biotechnological means. Congress hoped by legalizing the production of generic biological drugs, generally known as “biosimilars,” that consumer prices for a variety of important drugs would decrease.

In 1983, the Hatch-Waxman Act created a pathway to market for generic versions of traditional small-molecule drugs. Small-molecule drugs, which comprise the majority of commonly used drugs, are created by purely chemical processes and have relatively simple structures. As Congress hoped, Hatch-Waxman has had considerable success in lessening the cost of many pharmaceuticals. For instance, a Federal Trade Commission (FTC) study found that the entry of multiple generics into the market under the Hatch-Waxman Act reduced the price of some drugs by up to 80%.

But consumers are unlikely to see comparable biosimilar price reductions resulting from the BPCIA’s enactment. First, biologic drugs are inherently more difficult and costly to manufacture than traditional pharmaceuticals, providing barriers to entry that the BPCIA cannot effectively address. Second, compared to Hatch-Waxman, the BPCIA imposes much longer exclusivity periods for both reference drugs and the first biosimilar produced. This will, at a minimum, delay the cost benefits stemming from increased competition. Lastly, the interchangeability provisions, which allow for automatic substitution of reference products similar to generic chemical drugs under Hatch-Waxman, are much stricter for biologics regulated under the BPCIA.

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I. INTRODUCTION

¶1 In 2010, Congress passed the Patient Protection and Affordable Care Act, often referred to as “Obamacare.”¹ Though little noticed in the fanfare surrounding this event, Title VII, the Biologic Price Competition and Innovation Act (BPCIA), was arguably one of the most important provisions.² The BPCIA represents one of the more significant overhauls to the pharmaceutical industry in recent decades. For the first time, federal law established a pathway for the creation of generic versions of drugs produced by biotechnological means.³ Congress hoped by legalizing the production of generic biological drugs, generally known as “biosimilars,” that consumer prices for a variety of important drugs would decrease.⁴

¶2 Modern biotechnology drugs, or “biologics,” have been a major part of the U.S. drug market since the Federal Drug Administration (FDA) approved the use of human insulin in 1982.⁵ Biologic drugs are expected to gain an even larger share of the U.S. economy with time.⁶ They already include many of the most commonly used drugs in America, including four of the top ten most common drugs sold.⁷ Approximately 20% of all drugs on the market in 2009 were biologics.⁸

¹ Sheryl Gay Stolberg & Robert Pear, *Obama Signs Health Care Overhaul Bill, with a Flourish*, N.Y. TIMES, Mar. 23, 2010, at A19, available at http://www.nytimes.com/2010/03/24/health/policy/24health.html?_r=0.

² JUDITH JOHNSON, CONG. RESEARCH SERV., RL34045, FDA REGULATION OF FOLLOW-ON BIOLOGICS 12 (2010), available at http://primaryimmune.org/advocacy_center/pdfs/health_care_reform/Biosimilars_Congressional_Research_Service_Report.

³ Richard A. Epstein, *The Constitutional Protection of Trade Secrets and Patents Under the Biologics Price Competition and Innovation Act of 2009*, 66 FOOD & DRUG L.J. 285, 286 (2011).

⁴ See Letter from Rep. Anna Eshoo et al. to President Barack Obama (Oct. 14, 2011), available at <http://patentdocs.typepad.com/files/house-letter.pdf>.

⁵ See JOHNSON, *supra* note 2, at 1.

⁶ *Id.*

⁷ Biologic drugs sold under the brand names Humira, Enbrel, Remicade and Neulasta are the third, seventh, eighth, and ninth most prescribed drugs in the United States, respectively, as of the third quarter of 2013. In addition, the tenth most sold drug, Copaxone, though approved under a New Drug Application per the FDCA, is a protein-based drug with characteristics strongly similar to biologics. See *U.S. Pharmaceutical Sales: Q4 2013*, DRUGS.COM, <http://www.drugs.com/stats/top100/sales> (last visited Jan. 29, 2013).

⁸ WENDY H. SCHACHT & JOHN R. THOMAS, CONG. RESEARCH SERV., RL33901, FOLLOW-ON BIOLOGICS: INTELLECTUAL PROPERTY AND INNOVATION ISSUES 1 (2009), available at http://assets.opencrs.com/rpts/RL33901_20090803.pdf.

¶3 However, prices for commonly used biologics are often prohibitive. For instance, the Crohn's disease drug Humira—the most commonly sold biologic drug in the United States⁹—costs patients \$51,000 on average annually.¹⁰ Other biologics cost even more, sometimes reaching six figures.¹¹ Consequently, insurers adopted numerous strategies to pass costs on to consumers, potentially locking out the less fortunate.¹² It was against this background that Congress passed the BPCIA.

¶4 In 1983, the Hatch-Waxman Act created a pathway to market for generic versions of traditional small-molecule drugs.¹³ Small-molecule drugs, which comprise the majority of commonly used drugs, are created by purely chemical processes and have relatively simple structures. As Congress hoped, Hatch-Waxman has had considerable success in lessening the cost of many pharmaceuticals. For instance, a Federal Trade Commission (FTC) study found that the entry of multiple generics into the market under the Hatch-Waxman Act reduced the price of some drugs by up to 80%.¹⁴

¶5 But consumers are unlikely to see comparable biosimilar price reductions resulting from the BPCIA's enactment for various reasons.¹⁵ First, biologic drugs are inherently more difficult and costly to manufacture than traditional pharmaceuticals, providing barriers to entry that the BPCIA cannot effectively address. Second, compared to Hatch-Waxman, the BPCIA imposes much longer exclusivity periods for both reference drugs and the first biosimilar produced. This will, at a minimum, delay the cost benefits stemming from increased competition. Lastly, the interchangeability provisions, which allow for automatic substitution of reference products similar to generic chemical drugs under Hatch-Waxman, are much stricter for biologics regulated under the BPCIA.

¶6 Part II of this Comment provides an overview of both the regulation of biologics in general and the BPCIA in particular. Although biologic and pharmaceutical drugs have traditionally been regulated under different statutes, the Hatch-Waxman Act only amended the statute regulating pharmaceuticals. Consequently, until the passage of the BPCIA, no pathway existed for approving biosimilars of most biologic drugs.

¶7 Part III analyzes the BPCIA's likely minimal impact on biologic drug prices. There are numerous structural impediments in the production of biosimilars that do not exist for generics, of which regulation cannot easily fix. Moreover, specific provisions of the BPCIA will not only greatly delay market entry, but also reduce the ability of biosimilars to gain market share relative to generics. Part IV concludes by examining the BPCIA's potential impact on future innovation.

⁹ *Id.*

¹⁰ See JOHNSON, *supra* note 2, at 1.

¹¹ *Id.*

¹² *Id.* at 2.

¹³ *Id.* at 1.

¹⁴ FED. TRADE COMM'N, EMERGING HEALTH CARE ISSUES: FOLLOW-ON BIOLOGIC DRUG COMPETITION 12 (2009) (hereinafter FTC Report), available at <http://www.ftc.gov/reports/emerging-health-care-issues-follow-biologic-drug-competition-federal-trade-commission-report>.

¹⁵ See *infra* Part III for more explanation.

II. BACKGROUND

A. Overview of the History and Regulation of Biologic Drugs

18 The FDA defines biologic drugs as those derived from biological processes and used therapeutically to treat diseases.¹⁶ This definition is extraordinarily broad, covering products ranging from blood components, to toxins like Botox, to viruses altered for use in gene therapy.¹⁷ Federal regulations differentiate between biologic drugs and chemical drugs, which are created by synthetic chemical processes.¹⁸ While the latter are regulated under the Food, Drug and Cosmetic Act (FDCA), biologic drugs are, for the most part, licensed for marketing under the Public Health Service Act of 1944 (PHSA).¹⁹ Amended by the FDA Modernization Act of 1997 to simplify the licensing process, the PHSA now requires the submission of only a single biologic-license application to market a biologic product, replacing the two-license system that had been in place.²⁰ A notable exception to the general rule that chemical drugs are regulated under the FDCA while biologics are regulated under the PHSA is the regulation of insulin.²¹ Used primarily to treat diabetes,²² insulin is a small protein that, along with glucagon, regulates blood-sugar levels and carbohydrate metabolism.²³

19 In 1921, Frederick Banting and Charles Best were the first to isolate insulin, extracting it from the pancreases of dogs in their lab at the University of Toronto.²⁴ Shortly thereafter, the insulin extract was used to treat Leonard Thomson, a 14-year-old boy dying from type-1 diabetes.²⁵ Though the initial treatment failed due to insufficient purity, a subsequent insulin injection was successful, returning the boy to health.²⁶ For his work in providing the first effective treatment to a condition that had previously been a death

¹⁶ FOOD & DRUG ADMIN., WHAT ARE “BIOLOGICS”: QUESTIONS AND ANSWERS (Apr. 14, 2009), available at <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm133077.htm>.

¹⁷ See 42 U.S.C. § 262(i)(1) (2012) (“[Biologics are] a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.”).

¹⁸ JOHNSON, *supra* note 2, at 1.

¹⁹ *Id.* at 5.

²⁰ *Id.* at 6.

²¹ *Id.*

²² Insulin is especially critical for treating individuals suffering from type-1 diabetes. Type 1 diabetes is an autoimmune disorder affecting the pancreatic islet cells that produce insulin. The beta cells are destroyed, resulting in lower insulin levels and higher blood sugar. Type-2 diabetes, by contrast, is caused by insulin resistance; the body still produces insulin at normal levels, but the cells that would normally be affected by it do so at a reduced level. See *Type 1 diabetes*, MAYO FOUND. FOR MED. EDUC. AND RESEARCH (Aug. 2, 2014), <http://www.mayoclinic.org/diseases-conditions/type-1-diabetes/basics/causes/con-20019573>.

²³ Proteins are large organic molecules composed of amino acids with distinct structure. The protein insulin is composed of 51 amino acids in two chains, though the specific structure differs somewhat between species. See Jean-Philippe Cartailier, *The Structure of Insulin*, BETA CELL BIOLOGY CONSORTIUM, http://www.betacell.org/content/articleview/article_id/8/ (last visited Mar. 12, 2015).

²⁴ Suzanne White Junod, *Celebrating a Milestone: FDA’s Approval of First Genetically Engineered Product*, UPDATE MAG. (2007), available at <http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/SelectionsFromFDLIUpdateSeriesonFDAHistory/ucm081964.htm>.

²⁵ KALAYYA KRISHNAMURTHY, PIONEERS IN SCIENTIFIC DISCOVERIES 266 (Mittal Publ’ns 2002).

²⁶ Michael Bliss, *Rewriting History: Charles Best and the Banting and Best Myth*, 48 J. HIST. MED. ALLIED SCI. 253, 254 (1993), available at <http://jhmas.oxfordjournals.org/content/48/3/253.full.pdf>.

sentence, Charles Banting received the 1923 Nobel Prize in Medicine along with J.J.R. Macleod, the director of the lab in which Messrs. Banting and Best worked.²⁷

¶10 The University of Toronto maintained the patent on insulin until it expired in 1941.²⁸ During this time, the University of Toronto tested every batch of insulin sold in the United States to ensure quality.²⁹ But with the patent's expiration looming, Congress worried that without the university's standardization and oversight the lives of diabetics and other insulin-dependent patients would be "immediately endangered."³⁰ Congress therefore passed the so-called Insulin Amendments to the FDCA two days before the patent expired, requiring the FDA to ensure the safety and effectiveness of each batch of insulin sold in the United States.³¹ When Congress passed the PHSA three years later, the FDA retained its authority to regulate insulin under the FDCA.

¶11 Modern biologic-drug technology has advanced significantly since the days of animal pancreatic extracts. In 1982, the FDA approved the first modern biotech drug, human insulin—or "Humulin," as marketed by Eli Lilly.³² Rather than rely on purification of insulin derived from animals, researchers at Genentech—a small biotechnology firm—used recombinant DNA technology to make a protein identical to insulin produced by the human pancreas.³³

¶12 Recombinant DNA is made by placing a designed nucleic acid sequence, known as an "intron," into a portion of DNA.³⁴ The portion of DNA is referred to as a "cloning vector," and is generally either a plasmid or a DNA-based virus, such as bacteriophage lambda.³⁵ One of the key aspects of the cloning vector is that it must be capable of independently reproducing inside of a host cell, such as an E. coli bacterium.³⁶ Typically, the DNA segment is introduced to the vector by first using a "restriction enzyme" to break apart both the original DNA strand and the introduced strand at a specific point in the sequence, allowing the two to combine.³⁷ The enzyme DNA-ligase then seals the strands together, causing the recombinant DNA to be treated as if it were part of the vector's DNA from the start.³⁸ As a result, the host-cell produces amino acids introduced by the DNA codes alongside the normally produced amino acids, creating the desired protein in a process known as "translation."³⁹ The cell will produce the protein indefinitely, and the protein can then be isolated and used as a drug in humans.⁴⁰

²⁷ *Id.* at 253; see also Louis Rosenfeld, *Insulin: Discovery and Controversy*, 48 CLINICAL CHEMISTRY 2270 (2002) (describing Macleod's contributions).

²⁸ 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, 153 (2005).

²⁹ *Id.*

³⁰ *Id.*

³¹ *Id.*

³² White Junod, *supra* note 24.

³³ Dudzinski, *supra* note 28, at 165. Animal insulin is similar, but not identical, to human insulin. *Id.*

³⁴ JEREMY M BERG, JOHN L TYMOCZKO & LUBERT STRYER, *BIOCHEMISTRY* § 6.2 (5th ed. 2002), available at <http://www.ncbi.nlm.nih.gov/books/NBK22480/>.

³⁵ *Id.* A Plasmid is a piece of DNA generally found in a bacterial host cell that is capable of independent replication. *Id.*

³⁶ *Id.*

³⁷ *Id.*

³⁸ *Id.*

³⁹ See *id.*

⁴⁰ *Id.*

¶13 Following the introduction of human insulin, the FDA approved human growth hormone in 1985, alpha interferon in 1986, tissue plasminogen activator in 1987, and erythropoietin in 1989.⁴¹ Today, modern biologics represent four of the ten most commonly used drugs in the United States by sales.⁴² As of 2006, eighteen different biotech drugs had annual sales of over \$1 billion.⁴³

¶14 Biologic drugs are used to treat a wide array of conditions, including rheumatoid arthritis, multiple sclerosis, neutropenia, various types of cancer, and diabetes. Due to the “constructed” nature of drugs produced by biotechnological processes, it is possible to make blockbuster drugs tailored uniquely to previously unmet medical needs.⁴⁴ In time, it may even be possible to modify a drug for a specific individual.⁴⁵ Thus, unlike the traditional model for pharmacological drugs, which typically targets common conditions and requires significant marketing expenditures, the model for biologic drugs allows for adaptability and individualization.⁴⁶

¶15 However, biologic drugs are not without flaws. Because biologic drugs are extremely structurally complex, replication and mass production pose many challenges.⁴⁷ The extreme precision required to produce a biologic drug determines its development. In other words, “the manufacturing process for each biologic defines . . . the product.”⁴⁸ When combined with regulations requiring FDA approval of manufacturing processes and facilities—let alone the actual drug—this complexity ensures a significantly more expensive creation process than is common for traditional chemical drugs.⁴⁹ For instance, estimates place the cost of creating a manufacturing facility for a new biologic drug, excluding materials, between \$200 and \$400 million.⁵⁰ Normally taking ten to fifteen years,⁵¹ bringing a new biologic to market costs an estimated \$1.2 billion.⁵²

¶16 Unsurprisingly, biopharmaceutical firms on average spend roughly 30% of revenue on research and development (R&D), amongst the highest of any U.S. industry.⁵³ Some biopharmaceutical firms—typically those developing a drug for the first time without prior sales to offset costs—spend more than 100% of revenue on R&D.⁵⁴ Further, with roughly 75% of R&D funding spent on plans that ultimately fail and only 5%–10% of the drugs entering clinical trials receiving approval, most R&D projects provide no remuneration.⁵⁵

⁴¹ JOHNSON, *supra* note 2, at 1.

⁴² *See supra* note 7.

⁴³ Stacy Lawrence, *Billion Dollar Babies: Biotech Drugs as Blockbusters*, 25 NATURE BIOTECHNOLOGY 380, 380 (2007).

⁴⁴ *See id.*

⁴⁵ *Id.* at 382.

⁴⁶ *See id.* at 380.

⁴⁷ Kenneth J. Szeto & Marian Wolanski, *Initial Steps in the Regulation of Generic Biological Drugs: A Comparison of US and Canadian Regimes*, 67 FOOD & DRUG L.J. 131, 132 (2012).

⁴⁸ SCHACHT & THOMAS, *supra* note 8, at 24 (citing Christopher Webster et al., *Biologics: Can There Be Abbreviated Applications, Generics, or Follow-On Products?*, INT’L BIOPHARM MAG. (July 1, 2003), available at <http://www.biopharm-mag.com/biopharm/article/articleDetail.jsp?id=73785>).

⁴⁹ *Id.*

⁵⁰ *Id.*

⁵¹ Erwin A. Blackstone & Joseph P. Fuhr, *The Future of Competition in the Biologics Market*, 31 TEMP. J. SCI. TECH. & ENVTL. L 1, 3 (2012).

⁵² Henry Grabowski, Genia Long & Richard Mortimer, *Implementation of the Biosimilar Pathway: Economic and Policy Issues*, 41 SETON HALL L. REV. 511, 550 (2011).

⁵³ Blackstone & Fuhr, *supra* note 51, at 3–4.

⁵⁴ *Id.*

⁵⁵ Blackstone & Fuhr, *supra* note 51, at 4.

And making matters worse, the FDA has become more cautious than its prior 17%–20% approval rate in recent years,⁵⁶ sometimes even refusing their advisory panel's recommendations to grant licensure.⁵⁷ Because of these economic hurdles, the majority of biopharmaceutical firms report negative earnings.⁵⁸

¶17 Given the extraordinary costs and risks involved in developing biologics, the FDA's increased reluctance to approve new drugs seems perverse. Specifically, these FDA-exacerbated barriers to entry disproportionately affect small biopharmaceutical firms, which are generally far less financially stable than multibillion-dollar corporations like Merck.⁵⁹ Small firms, however, play a critical role in the biopharmaceutical industry. For instance, from 2006 to 2008, small firms discovered 50% of all new biologics and 56% of "orphan drugs" developed to treat rare diseases.⁶⁰ But without well-funded coffers, these small firms operate with little margin for error, making the degree of risk exponentially higher than for established drug makers. This burden, in turn, prompts business mergers to mitigate risk, thereby reducing competition and limiting the availability of new products available to consumers.⁶¹ Because of these barriers to entry, biologic drug prices are often extremely high,⁶² with many patients spending tens of thousands of dollars annually.⁶³

B. Overview of the Biologic Price Competition and Innovation Act of 2010

1. Licensure & Disclosure

¶18 Congress passed the Biologic Price Competition and Innovation Act as Title VII of the Patient Protection and Affordable Care Act to provide a pathway for the licensure of follow-on biologic drugs.⁶⁴ This pathway is analogous to that provided for generic drugs by the Drug Price Competition and Patent Term Restoration Act of 1984, more commonly referred to as the Hatch-Waxman Act.⁶⁵ Hatch-Waxman allowed for the filing of Abbreviated New Drug Applications (ANDAs), which have much lower evidentiary requirements for approval than traditional New Drug Applications used for pioneering drug research. Because ANDAs require only a showing of equivalency with a given reference drug rather than independent proof of safety and efficacy,⁶⁶ the process of bringing a new drug to market via an ANDA is consequently much cheaper and less burdensome than doing so with a traditional New Drug Application. The ANDA process takes only a few

⁵⁶ *Id.*

⁵⁷ *Id.* The authors mention the case of Esbriet, a chemical drug designed to treat idiopathic pulmonary fibrosis. Though their advisory panel had advised approval and there was a clear medical need for the drug, the FDA refused approval and demanded a new study in early 2010.

⁵⁸ *Id.* at 3–4 (citing Steven Silver, *Biotechnology*, STANDARD & POOR'S INDUS. SURVEYS (Feb. 24, 2011), available at <http://www.scribd.com/doc/49646708/bio-0211>).

⁵⁹ *See id.* at 5.

⁶⁰ *Id.*

⁶¹ *Id.*

⁶² Alfred Engelberg, Aaron S. Kesselman & Jerry Avorn, *Balancing Innovation, Access and Profits: Market Exclusivity for Biologics*, 361 NEW ENG. J. MED. 1917, 1918 (2009).

⁶³ *Id.* On the extreme end, imiglucerase, a drug sold under the brand names Cerezyme and Genzyme for the treatment of Gaucher's disease, costs roughly \$200,000 annually. *Id.*

⁶⁴ Stolberg & Pear, *supra* note 1, at 1.

⁶⁵ JOHNSON, *supra* note 2, at 1.

⁶⁶ Holly Soehnge, *The Drug Price Competition and Patent Restoration Act of 1984: Fine-Tuning the Balance Between the Interests of Pioneer and Generic Drug Manufacturers*, 58 FOOD & DRUG L.J. 51, 54 (2003).

years and costs \$1–\$2 million by some estimates, resulting in a continuous influx of generic-drug manufacturers to the industry.⁶⁷

¶19 For biologics regulated under the FDCA, Hatch-Waxman’s 1983 enactment similarly provided a generic pathway via the use of ANDAs.⁶⁸ But prior to the BPCIA’s adoption, there was no direct pathway for approval of follow-on biologics under the PHSA.⁶⁹ And because the PHSA regulates the vast majority of biologics, additional legislation was needed to form a similar avenue for biologic follow-ons.⁷⁰

¶20 Congress passed the BPCIA to bring the regulation of biologic follow-ons in line with that for traditional chemical drugs, albeit more than a quarter century later. The BPCIA divides follow-on biologics into two categories—interchangeable follow-ons and biosimilar follow-ons—based on their relationship to an original, pioneering biologic drug, known as a “reference product” for purposes of the statute.⁷¹ Interchangeable follow-ons are identical to a reference product and can substitute for a reference product under any circumstances.⁷² Biosimilar follow-ons must both be “highly similar to the reference product notwithstanding minor differences in chemically inactive components” and have “no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency of the product.”⁷³

¶21 To license a product as biosimilar or interchangeable, the application must meet five criteria.⁷⁴ First, the biologic must be substantially similar to the reference product based on data derived from (1) analytical chemical studies showing the products are “highly similar,” (2) animal studies including toxicity assessments, and (3) “a clinical study or studies” sufficient to demonstrate the safety, purity, and potency of the product.⁷⁵ The use of the word “and” without an “or” qualifier suggests that applications must include all three types of studies. The statute’s description of the purpose behind each study supports this interpretation. There is, however, some ambiguity surrounding the number of studies required for each type. The statute states that there may be “a clinical study or studies,” but only uses the plural “studies” in reference to animal and analytic studies, which, read together, suggests that the application requires multiple animal and analytic studies to gain approval. However, regardless of the statute’s text, the elements necessary for an application’s approval are subject to the FDA’s broad authority.⁷⁶

¶22 The remaining four criteria are less ambiguous, at least textually. To meet the second BPCIA requirement, a § 262(k) biologic-license application must show that the biosimilar’s mechanism of action mirrors that of the reference product.⁷⁷ But because these mechanisms are often initially unknown, the extent of this requirement is limited to only what is identifiable. The third criterion requires the biosimilar and the reference product to

⁶⁷ Henry G. Grabowski, *Patents, Innovation, and Access to New Pharmaceuticals*, 5 J. INT’L ECON. L. 849, 852 (2002), available at <http://jiel.oxfordjournals.org/content/5/4/849.full.pdf+html>.

⁶⁸ *Id.* at 8–9.

⁶⁹ JOHNSON, *supra* note 2, at 8.

⁷⁰ *Id.* at 9.

⁷¹ 42 U.S.C. § 262 (i)(4) (2012).

⁷² *Id.* § 262(i)(3).

⁷³ *Id.* § 262(i)(2).

⁷⁴ *Id.* § 262(k)(2)(A)(i).

⁷⁵ *Id.* § 262(k)(2)(A)(i)(I).

⁷⁶ *Id.* § 262(k)(2)(A)(ii).

⁷⁷ *Id.* § 262(k)(2)(A)(i)(II).

be labeled with the same conditions of use.⁷⁸ The fourth requires that the biosimilar's dose, route of administration, and strength are the same as that of the reference product.⁷⁹ Lastly, the application must show that the facilities where the biosimilar product is manufactured, processed, packed, and held meet standards sufficient to assure that the product is safe, pure, and potent.⁸⁰

¶23 In addition, the application may include data indicating that it meets the elevated requirements for interchangeability.⁸¹ Unlike mere biosimilarity, an interchangeability designation provides for both an exclusivity period⁸² and automatic substitution for the reference product.⁸³ This requires not only a showing of biosimilarity, but also that the new drug can be expected to produce the same clinical result as the reference product.⁸⁴ Applicants must also demonstrate that any risks concerning safety or diminished efficacy are no greater than that of the reference product.⁸⁵ Notwithstanding these statutorily defined steps, the Secretary of Health and Human Services may nevertheless decide to waive any of the elements normally required for a § 262(k) biosimilar-license application at any time.⁸⁶

¶24 The original reference product receives extensive protection under the BPCIA. For instance, while § 262(k) applications can be submitted just four years after the approval of the reference product,⁸⁷ applications cannot be approved until a minimum of twelve years after the licensing of the reference product under § 262(a).⁸⁸ These rules do not apply, however, to licensure for a supplement to the original reference product or to approval of modifications made by the original manufacturer concerning dosage, route of administration, strength, or biological structure.⁸⁹

¶25 The BPCIA also protects the first interchangeable-biosimilar approved.⁹⁰ Under § 262(k)(6), no subsequent product may be deemed interchangeable until one of four possible conditions is met. Namely, if: (1) one year elapses from the first commercial marketing of the interchangeable;⁹¹ (2) eighteen months pass after the final decision in or dismissal of a patent infringement suit to prevent marketing of the interchangeable; (3) forty-two months pass after the initiation of an ongoing patent infringement litigation;⁹² or (4) eighteen months pass after the approval of the first interchangeable, assuming no one has filed an infringement suit.⁹³ Crucially, the last condition prevents interchangeable

⁷⁸ *Id.* § 262(k)(2)(A)(i)(III).

⁷⁹ *Id.* § 262(k)(2)(A)(i)(IV).

⁸⁰ *Id.* § 262(k)(2)(A)(i)(V).

⁸¹ *Id.* § 262(k)(2)(B).

⁸² *Id.* § 262(k)(6).

⁸³ Sara Margolis, Note, *Destined for Failure? An Analysis of the Biologics Price Competition and Innovation Act of 2009*, 2013 COLUM. BUS. L. REV. 209, 227 (2013).

⁸⁴ *Id.* § 262(k)(4)(A).

⁸⁵ *Id.* § 262(k)(4)(B).

⁸⁶ *Id.* § 262(k)(2)(A)(ii).

⁸⁷ *Id.* § 262(k)(7)(B).

⁸⁸ *Id.* § 262(k)(7)(A).

⁸⁹ *Id.* § 262(k)(7)(C). This assumes there is no change to safety, purity, or potency of the reference product, which only applies if there is a change to the actual structure, not in the former case where the change is to method of use. *Id.*

⁹⁰ *Id.* § 262(k)(6).

⁹¹ *Id.* § 262(k)(6)(A).

⁹² *Id.* § 262(k)(6)(C)(i).

⁹³ *Id.* § 262(k)(6)(C)(ii).

license holders from strategically using their licenses to preclude other companies from entering the market.

¶26 Yet the majority of biopharmaceutical firms are unlikely to find § 262(k)(6) particularly useful. Rather than applying to the biosimilar classification, § 262(k)(6) exclusively applies to interchangeable follow-ons, which experts anticipate will be an incredibly difficult designation to obtain.⁹⁴ For instance, the FDA could require extensive crossover trials, which often deter patient participation, or limit interchangeability designations to only those biologics that current technology can be used to demonstrate sameness.⁹⁵ Ultimately, and regardless of the FDA’s eventual process determination, the likelihood of § 262(k)(6) having a significant impact seems slight.

2. Patent Infringement Issues

¶27 As previously alluded to, the BPCIA provides a complicated system for resolving patent disputes between follow-on and reference-product producers.⁹⁶ The first step, known as the patent-exchange step, requires the biosimilar manufacturer and the reference-product manufacturer to share information.⁹⁷ After applying for a § 262(k) license, the applicant must deliver a copy of the application to the reference-product manufacturer,⁹⁸ and, in exchange, the reference-product manufacturer must give the applicant a copy of all relevant patents that might be infringed, referred to as a “Paragraph 3 list.”⁹⁹ If the Paragraph 3 list does not include a relevant patent, the reference-drug manufacturer cannot later sue for that patent.¹⁰⁰ The applicant then submits a rebuttal Paragraph 3 list of its own relevant patents, as well as a claim-by-claim analysis of the reference-product manufacturer’s list wherein the applicant explains how it is not infringing.¹⁰¹ The last step of the information exchange requires the reference-product manufacturer to rebut the applicant’s rebuttal, explaining how the patents at issue are indeed likely to be infringed.¹⁰²

¶28 Importantly, this information exchange is a completely private interaction between the affected parties, subject to strict confidentiality requirements.¹⁰³ In contrast, the Hatch-Waxman Act establishes procedures requiring public disclosure of patents, which, in turn, are included in the Approved Drug Products with Therapeutic Equivalence Evaluations, referred to as the “Orange Book.”¹⁰⁴ But because there are no public disclosure

⁹⁴ Margolis, *supra* note 83, at 227.

⁹⁵ *Id.*

⁹⁶ 42 U.S.C. § 262(l).

⁹⁷ *Id.* § 262(l)(1).

⁹⁸ *Id.* § 262(l)(1)(B)(i); see also 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).

⁹⁹ 42 U.S.C. § 262(l)(3)(A). The name “Paragraph 3 list” is taken from its relevant statutory portion in subsection (l).

¹⁰⁰ *Id.* § 262(l)(7).

¹⁰¹ *Id.* § 262(l)(3)(B).

¹⁰² *Id.* § 262(l)(3)(C).

¹⁰³ *Id.* § 262(l)(1)(C).

¹⁰⁴ 21 C.F.R. § 314.53(e) (2009); see *Approved Drug Product with Therapeutic Equivalence Evaluations (Orange Book)*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm> (last updated Jan. 22, 2015).

requirements for biologic drugs, no equivalent record exists. This distinction is critical. Unlike traditional generic-drug manufacturers, follow-on biologic manufacturers cannot determine what patents they might be accidentally infringing in the course of designing their products.¹⁰⁵

¶29 Following the patent-exchange step, the BPCIA requires a good-faith negotiation over which patents, if any, will be subject to an action for patent infringement.¹⁰⁶ If the parties are unable to agree, the “Paragraph 5” patent-resolution provisions trigger.¹⁰⁷ In that case, the applicant must notify the reference-product manufacturer of the number of patents it believes might be subject to an infringement suit, thereby setting a ceiling for how many patents the reference-product manufacturer may list.¹⁰⁸ Within five days of this submission, both parties provide a Paragraph 5 list detailing the specific patents each believe may be infringed,¹⁰⁹ thus forming the basis of the infringement suit.

¶30 Only after the patent-exchange and patent-resolution processes end can litigation begin.¹¹⁰ The reference-product manufacturer can sue for any relevant patents no more than thirty days after the parties reach agreement under Paragraph 4,¹¹¹ or, if the parties were unable to agree on a patent list, thirty days after the parties exchanged Paragraph 5 lists.¹¹² Within thirty days of receiving the complaint, the § 262(k) applicant must notify the office of the Secretary of Health and Human Services and provide a copy of the complaint,¹¹³ which the Secretary uses to publish a relevant notice in the Federal Register.¹¹⁴ Unlike the Hatch-Waxman Act, there is no provision for an automatic stay of approval once a patent litigation is filed.¹¹⁵

¶31 After this initial litigation process, the applicant must inform the reference-product manufacturer 180 days prior to when the applicant intends to begin marketing the product,¹¹⁶ which allows the reference-product manufacturer to seek a preliminary injunction.¹¹⁷ Importantly, because courts must still determine validity, infringement, and enforcement issues for those patents on the Paragraph 3 list not included on the Paragraph 5 list,¹¹⁸ this notice provision, in essence, ensures that manufacturers maintain the right to sue for patents not included on the Paragraph 5 list.¹¹⁹ Similarly, should the applicant fail to comply with certain statutory requirements, the reference-product manufacturer may seek declaratory judgment for any patent on its Paragraph 3 list at any time.¹²⁰

¹⁰⁵ Charles Davis, *Take Two and Call Congress in the Morning: How the Biologics Price Competition and Innovation Act May Fail to Prevent Systemic Abuses in the Follow-On Biologic Approval Process*, 81 GEO. WASH. L. REV. 1255, 1282 (2013).

¹⁰⁶ 42 U.S.C. § 262(l)(4)(A).

¹⁰⁷ *Id.* § 262(l)(4)(B).

¹⁰⁸ *Id.* § 262(l)(5)(A).

¹⁰⁹ *Id.* §§ 262(l)(5)(B)(i)(I)–(II). Much like with Paragraph 3 lists, the term “Paragraph 5 list” is derived from its place in subsection (l). *Id.*

¹¹⁰ *Id.* § 262(l)(6).

¹¹¹ *Id.* § 262(l)(6)(A).

¹¹² *Id.* § 262(l)(6)(B).

¹¹³ *Id.* § 262(l)(6)(C)(i).

¹¹⁴ *Id.* § 262(l)(6)(C)(ii).

¹¹⁵ Davis, *supra* note 105, at 1277.

¹¹⁶ *Id.* § 262(l)(8)(A).

¹¹⁷ *Id.* § 262(l)(8)(B).

¹¹⁸ *Id.*

¹¹⁹ *Id.* § 262(l)(8)(C). Both sides must cooperate with discovery as needed. *Id.*

¹²⁰ *Id.* § 262(l)(9)(B). The BPCIA imposes punishment for noncompliance during the information-exchange process. For example, if the § 262(k) applicant fails to provide its application to the reference-

III. FORECASTING THE IMPACT OF THE BPCIA ON BIOLOGIC DRUG PRICES

¶32 Fundamentally, Congress enacted the BPCIA to decrease biologic drugs prices for consumers without stifling biotech research and innovation.¹²¹ Whether the BPCIA will fulfill these goals is unknown. It is simply too soon to tell. But perhaps, comparing the BPCIA to the legislation it was modeled after—the Hatch-Waxman Act—provides some guidance. Stated simply, the Hatch-Waxman Act has been hugely successful in reducing the price of drugs. Generally, the first generic to enter the market costs about 25% less than the branded drug, and after multiple generic drugs enter the market, prices often drop up to 80% from their peak. Because of these decreased prices, more Americans in need have access to beneficial medication. As a result, generic drugs now represent roughly 70% of total pharmaceutical prescriptions.¹²² Thus at first blush, it is unsurprising that Congress modeled the BPCIA after the Hatch-Waxman Act.

¶33 But the BPCIA is unlikely to meet these high expectations. Compared to the Hatch-Waxman Act, various obstacles stand in the way of the BPCIA similarly reducing drug prices. First, biologics are inherently more expensive to manufacture, increasing barriers to entry and thus reducing competition and its corresponding impact on drug prices. Second, the BPCIA imposes long exclusivity periods for both the reference drug and the first interchangeable biosimilar, again hindering new firms from competing effectively. Lastly, the BPCIA's interchangeability standards allowing for automatic substitution, the primary driver of price reductions, are difficult to meet.

A. *Biosimilar Drugs Are Significantly More Expensive to Develop Than Chemical Generics*

¶34 Biopharmaceuticals are inherently more costly to develop than chemical drugs. Further, they are difficult to manufacture in quantity, require precise manufacturing processes, and involve exorbitant start-up costs, such as the estimated \$200 to \$400 million required just to build the initial manufacturing plant.¹²³ As a result, the production of a new biologic drug generally requires an investment of approximately \$1.2 billion.¹²⁴ In other words, developing a new biopharmaceutical drug costs double the estimated \$802 million required to develop a new chemical drug.¹²⁵

¶35 This cost difference is even greater when comparing biosimilars to generics. For instance, in Europe the cost of bringing a biosimilar to market ranges from \$75 to \$250 million,¹²⁶ and requires between eight and ten years to develop.¹²⁷ On the other hand,

product manufacturer upon completion, it may be sued for declaratory judgment of infringement at any time for any patent. *Id.* § 262(l)(9)(C).

¹²¹ See Epstein, *supra* note 3, at 286.

¹²² *Id.* at 223.

¹²³ See SCHACHT & THOMAS, *supra* note 8, at 21–22.

¹²⁴ Grabowski et al., *supra* note 52.

¹²⁵ SCHACHT & THOMAS, *supra* note 8, at 22.

¹²⁶ Mark McCamish & Gillian Woollett, *Worldwide Experience with Biosimilar Development*, 3 MABS 209, 211 (2011), available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3092622/pdf/mabs0302_0209.pdf.

¹²⁷ 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-key-success-factors>.

standard chemical-drug generics require only a few years and \$1 to \$2 million to develop, a mere fraction of its biologic counterpart.¹²⁸

¶36 There are two primary reasons for these high manufacturing costs: scientific challenges specific to biologic production and more burdensome data requirements. First, it is simply more difficult to make the sort of large molecules characteristic of biologic drugs. Virtually every aspect of production must be meticulously controlled and monitored to generate a useable product,¹²⁹ with even minor temperature changes potentially ruining an entire batch of biopharmaceuticals.¹³⁰ The medium of production and storage conditions are also essential to the final product.¹³¹ Impurities can arise from nearly any change in the manufacturing process,¹³² and because this process takes more time than that for chemical drugs, sometimes lasting up to nine months per batch, the likelihood of an impurity corrupting the batch increases.¹³³ All of this is without accounting for the costs of materials, which are often 20 to 100 times more expensive than for conventional chemical drugs.¹³⁴ Perhaps the biggest obstacle, however, is the cost of building, equipping, and qualifying the manufacturing plant, which generally costs between \$250 million and \$1 billion.¹³⁵

¶37 On top of the arduous manufacturing process, biosimilars will likely face additional data requirements relative to generics. Hatch-Waxman provides very specific data standards ANDAs must meet to show bioequivalence, which often suffice to gain FDA approval if met.¹³⁶ The BPCIA, by contrast, only states that the FDA shall require analytic, animal, and clinical studies, and provides no further guidance detailing what sort of similarity applicants must show.¹³⁷ Most likely, and lasting for the indefinite future, the FDA will determine this amorphous similarity requirement on a case-by-case basis, relying only on the relative state of knowledge about the reference product in question.¹³⁸

¶38 Given the immense costs associated with entering the biosimilar market, it is likely that only well-established companies with substantial extant resources will be able to do so at all.¹³⁹ Even then, as indicated by the FTC, it will likely only be for drugs with annual sales greater than \$250 million.¹⁴⁰ Consequently, only the most profitable biologics are likely to face biosimilar competition. In the end, because niche markets and less profitable drugs are unlikely to spur the same degree of competition, high prices will remain the norm for biologics generally.

¹²⁸ Grabowski, *supra* note 67, at 852.

¹²⁹ See, e.g., Jordan Paradise, *The Devil Is in the Details: Health-Care Reform, Biosimilars, and Implementation Challenges for the Food and Drug Administration*, 51 JURIMETRICS J. 279, 281 (2011).

¹³⁰ See *id.*

¹³¹ *Id.*

¹³² SCHACHT & THOMAS, *supra* note 8, at 24.

¹³³ *Id.*

¹³⁴ *Id.*

¹³⁵ FTC Report, *supra* note 14, at 14.

¹³⁶ 21 U.S.C. § 355(j)(2)(A) (2012) (“The Secretary may not require that an abbreviated application contain information in addition to that required by clauses (i) through (viii).”).

¹³⁷ See 42 U.S.C. § 262(k)(2)(A)(i); see also Grabowski et al., *supra* note 52, at 518–19.

¹³⁸ Grabowski et al., *supra* note 52, at 519.

¹³⁹ FTC Report, *supra* note 14, at 15.

¹⁴⁰ *Id.*

B. The BPCIA's Long Exclusivity Periods Will Hamper the Emergence of Multiple Biosimilars

¶39 The BPCIA creates separate exclusivity periods for both the reference product and the first interchangeable-biosimilar approved.¹⁴¹ The reference drug receives a firm twelve-year exclusivity period before the first biosimilar can be approved, including four years of data exclusivity in which § 262(k) biosimilar applications cannot be filed.¹⁴² The first interchangeable, by contrast, receives an exclusivity period ranging from twelve to forty-two months, depending on the litigation process and marketing strategy employed.¹⁴³ Regardless, both impose much higher barriers to entry for new biosimilars than anything found under the Hatch-Waxman Act.¹⁴⁴ For example, the Hatch-Waxman Act affords a five-year exclusivity period for new chemical drugs and a three-year exclusivity period for new chemical investigations (NCIs) of small-molecule drugs.¹⁴⁵ Those supporting the longer exclusivity period for biologics relative to chemical drugs argue that the high costs of producing biologics require greater incentives for innovation, thus justifying the more restrictive exclusivity provisions.¹⁴⁶ Regardless of the reasoning behind these provisions, longer exclusivity periods naturally cause prices to remain higher for longer, further detracting from the BPCIA's professed goals.

¶40 The interchangeable exclusivity period also conflicts with its Hatch-Waxman Act counterpart. For a variety of reasons, however, the BPCIA's exclusivity period might actually provide a better catalyst for competition, hastening the entry of additional drugs to the market. Hatch-Waxman only provides exclusivity for a period of 180 days following an applicant's first commercial marketing efforts of the generic drug.¹⁴⁷ A first applicant is defined (somewhat obscurely) as "an applicant that, on the first day on which a substantially complete application . . . is submitted [to the FDA] for approval of a drug, submits a substantially complete application."¹⁴⁸ In other words, the first person to complete an ANDA gets 180 days of exclusivity dating from when she first begins marketing.

¶41 Though the Hatch-Waxman exclusivity period lasts only half as long as even the shortest potential exclusivity period under the BPCIA, initial loopholes allowed first applicants to game the system by preventing additional generics from entering the market.¹⁴⁹ Notably, Hatch-Waxman contained no tolling provision on the exclusivity period, extending 180 days after first marketing, regardless of when that actually occurred.

¹⁴¹ 42 U.S.C. §§ 262(k)(6)–(7).

¹⁴² *Id.* § 262(k)(7).

¹⁴³ *Id.* § 262(k)(6).

¹⁴⁴ 21 U.S.C. § 355(j)(2)(B)(iv). Hatch-Waxman establishes market exclusivity until 180 days after first commercial marketing of the first generic. There are also a number of forfeiture events specified in 21 U.S.C. § 355(j)(5)(D)(i) that result in loss of the exclusivity period. These forfeiture events primarily revolve around a variety of ways generic manufacturers could potentially prevent the exclusivity period from tolling, thus preventing any generics from entering the market. The forfeiture events were added by an amendment in 2003 in response to then-rampant abuse of the Hatch-Waxman system. *Id.*

¹⁴⁵ FTC Report, *supra* note 14, at 27.

¹⁴⁶ *Id.* at 25.

¹⁴⁷ 21 U.S.C. § 355(j)(5)(B)(iv)(I).

¹⁴⁸ *Id.* § 355(j)(5)(B)(iv)(II)(bb).

¹⁴⁹ *Valley Drug Co. v. Geneva Pharm., Inc.*, 344 F.3d 1294 (11th Cir. 2003). The Eleventh Circuit upheld an agreement between a pioneer manufacturer and the manufacturer of the first generic whereby the generic manufacturer agreed not to enter the market for a set period of time in exchange for a large payment from the pioneer manufacturer. *Id.*

Though the FDA initially required that generic-drug applicants defend a patent infringement claim successfully to be eligible for the 180-day exclusivity period, the U.S. District Court for the District of Columbia in *Mova Pharmaceutical Corp. v. Shalala* rejected this interpretation as plainly contrary to the statute as written.¹⁵⁰

¶42 Subsequently, the FDA began implementing the exclusivity provisions purely on a first-to-file basis, regardless of any other considerations.¹⁵¹ If the first applicant chose not to begin marketing, the 180-day exclusivity period never commenced, thus barring approval of any subsequent generics indefinitely.¹⁵² Because of this clear congressional oversight, first applicants began entering into settlements with pioneer drug companies whereby they agreed to refrain from entering the market in exchange for payments from the pioneer company.¹⁵³ Fortunately, Congress responded to these blatantly anticompetitive agreements by amending Hatch-Waxman to add a number of forfeiture events, which end the exclusivity period if triggered, thus deterring parties from entering into these arrangements.¹⁵⁴

¶43 The Hatch-Waxman loophole taught Congress a valuable lesson. Under the BPCIA, this type of anticompetitive behavior is impossible. For instance, should the first interchangeable choose to accept a payment in exchange for not entering the market, the exclusivity period simply runs for eighteen months before terminating.¹⁵⁵ While technically a party can block other biosimilars from entering the market for up to forty-two months, this requires there to be ongoing patent litigation, which inherently precludes the sort of reverse payments seen in the original Hatch-Waxman schemes.¹⁵⁶ Taking into account the exponentially higher costs biosimilar producers need to offset, Congress clearly learned from the mistakes it made when drafting Hatch-Waxman, thus providing a significantly superior interchangeable exclusivity period under the BPCIA.

C. *Interchangeability Is Unlikely to Be Utilized by the Majority of Biosimilars*

¶44 The FDA will approve an interchangeable designation if an applicant can show that, compared to the reference drug, the biosimilar will have the same clinical result in every patient and that it is as safe and efficacious.¹⁵⁷ This is, naturally, a more difficult classification to obtain than mere biosimilarity.¹⁵⁸ And while no formal regulations have yet been adopted, the FDA released draft guidance for biosimilarity determinations in February 2012.¹⁵⁹ The FDA's draft guidance recommends a stepwise methodology whereby a potential biosimilar must pass a series of tests to demonstrate biosimilarity,

¹⁵⁰ 955 F. Supp. 128, 131 (D.D.C. 1997), *aff'd*, 140 F.3d 1060 (D.C. Cir. 1998).

¹⁵¹ Natalie M. Derzko, *The Impact of Recent Reforms of the Hatch-Waxman Scheme on Orange Book Strategic Behavior and Pharmaceutical Innovation*, 45 IDEA 165, 195 (2005).

¹⁵² *Id.* at 196.

¹⁵³ *Id.* at 197.

¹⁵⁴ 21 U.S.C. § 355(j)(5)(D)(i)–(ii).

¹⁵⁵ 42 U.S.C. § 262(k)(6)(C)(ii).

¹⁵⁶ *Id.* § 262(k)(6)(C)(i).

¹⁵⁷ *Id.* § 262(k)(4).

¹⁵⁸ Margolis, *supra* note 83, at 227.

¹⁵⁹ *FDA Issues Draft Guidance on Biosimilar Product Development*, FOOD & DRUG ADMIN. (Feb. 9, 2012), <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm291232.htm>.

which the FDA will evaluate through applying a risk-based, totality-of-the-evidence approach.¹⁶⁰

¶45 But the standards for determining interchangeability are entirely unknown. The FDA has yet to issue even draft guidance regarding what will be required to determine that a biosimilar is interchangeable, but, judging from the FDA's own proclamations, the standards will likely be rigorous.¹⁶¹ For instance, the FDA may well require biosimilars to show "sameness" with the reference product under available tests to qualify as interchangeable.¹⁶² Alternatively, the FDA could mandate crossover trials, which require patients to switch between the reference product and the biosimilar during the course of a clinical trial.¹⁶³ These trials, however, are notoriously burdensome, causing many patients to refuse enrollment.¹⁶⁴

¶46 Moreover, the experiences of other countries with analogous biosimilar-interchangeable regulatory systems further indicate that those seeking interchangeable approval are likely facing an uphill battle. In the European Union, for example, the European Medicines Agency (EMA), serving in a role comparable to that of the FDA, has approved biosimilars of three different categories of biologic drugs, with three more likely to follow.¹⁶⁵ However, as of 2012, the EMA has not approved a single interchangeable.¹⁶⁶

¶47 The difficulty of obtaining interchangeable status is "likely to dampen how quickly a [follow-on biologic] manufacturer gains market share compared to generic drug entry."¹⁶⁷ In the traditional chemical-drug market, generic status normally results in automatic substitution by pharmacists without physician approval, allowing the generic to garner market share quickly at the brand-name drug's expense.¹⁶⁸ And as more generic drugs enter the market, the brand-name drug's market share continues to shrink, prompting further competition, all of which ultimately culminates in drastically lower prices for the consumer.¹⁶⁹ Each element of this chain of events is essential for reduced drug costs.

¶48 Biosimilars, however, need to qualify as interchangeable to get automatic substitution.¹⁷⁰ Dramatic price reductions become far less likely without automatic

¹⁶⁰ FOOD & DRUG ADMIN., SCIENTIFIC CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY TO A REFERENCE PRODUCT 7–8 (2012), *available at* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf>. The FDA specifically proposes beginning with an extensive structural and functional characterization of the proposed biosimilar and the reference product to determine what other studies are needed and any potentially important structural differences between the two products. *Id.* From there, the FDA recommends using animal testing to determine toxicity, followed by human testing. The totality-of-the-evidence approach is used afterwards to allow for approval in a case where the product is shown to have some differences from the reference product that are clinically insignificant. *Id.*

¹⁶¹ FOOD & DRUG ADMIN., BIOSIMILARS: QUESTIONS AND ANSWERS REGARDING IMPLEMENTATION OF THE BIOLOGICS PRICE COMPETITION AND INNOVATION ACT OF 2009 11–12 (2012), *available at* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf> (stating that the FDA is continuing to consider the information that will enable a determination of interchangeability). The FDA also notes that it would be "difficult as a scientific matter" to prove interchangeability given the statutory standards. *Id.*

¹⁶² Grabowski et al., *supra* note 52, at 519.

¹⁶³ *Id.* at 524.

¹⁶⁴ *Id.*

¹⁶⁵ *Id.* at 520–21.

¹⁶⁶ Blackstone & Fuhr, *supra* note 51, at 3.

¹⁶⁷ FTC Report, *supra* note 14, at 16.

¹⁶⁸ *Id.*

¹⁶⁹ *Id.*

¹⁷⁰ *Id.*

substitution. Because obtaining interchangeable status poses such difficulties, biosimilar manufacturers will have the additional burden of convincing physicians to prescribe the biosimilar in place of the reference drug, requiring significant marketing expenditures.¹⁷¹ Even with marketing, however, lingering uncertainties about differences between the biosimilar and the reference product will likely hamper sales, at least initially.¹⁷² Coupled with the fear of patients reacting differently to the biosimilar, few incentives exist for physicians to prescribe a new drug simply because it is cheaper.¹⁷³

¶49 Overall, commentators estimate follow-on biologics will achieve a 10%–30% market share.¹⁷⁴ Though this will likely decrease biologic drug prices, these slight cost reductions will pale in comparison to those resulting from traditional generic-drug market entry, which generally capture 80% of the market after introduction.¹⁷⁵ Europe's experience again supports these predictions, where biosimilars have caused prices to decrease in the range of only 25%–30%.¹⁷⁶

IV. CONCLUSION

¶50 For structural and legislative reasons, the BPCIA will likely fail to facilitate biosimilar market entry.¹⁷⁷ However, with respect to the long-term health of the biopharmaceutical industry, this failure may in fact be a blessing. Biotechnology remains one of the riskiest business ventures in the United States, with more than 90% of projects failing before reaching the market.¹⁷⁸ Even for the few biologics that do eventually make it to market, the task of recouping expenses remains daunting: a successful biologic typically requires a roughly \$1.2 billion investment over the course of 10–15 years.¹⁷⁹ If society wishes to see further investment in new and innovative biologic drugs, perhaps the most important factor is to ensure a sufficiently long period of market exclusivity, allowing companies to, at the very least, recoup expenditures.¹⁸⁰ Encouraging further biologic innovation thus seems *prima facie* incompatible with rapid biosimilar market entry.

¹⁷¹ Margolis, *supra* note 83, at 228.

¹⁷² FTC Report, *supra* note 14, at 16–17.

¹⁷³ *Id.*

¹⁷⁴ *Id.* at 19.

¹⁷⁵ Thomas Philipson, *Don't Be Fooled: Brand Drugs Cut Prices More than Generics*, FORBES (Feb. 3, 2014, 7:00 PM), <http://www.forbes.com/sites/tomasphilipson/2014/02/03/dont-be-fooled-brand-drugs-cut-prices-more-than-generics/>.

¹⁷⁶ Engelberg et al., *supra* note 62, at 1918.

¹⁷⁷ See *supra* Part III.

¹⁷⁸ See *supra* note 51.

¹⁷⁹ See *supra* notes 51 and 52.

¹⁸⁰ Derzko, *supra* note 151, at 253.

