

FOLLOW-ON BIOLOGICS: PROTECTING CONSUMERS THROUGH STATE PHARMACY LAW IN LIGHT OF FDA ACTIONS

Stacey L. Worthy and John F. Kozak*

Introduction

In recent years, much attention has been given to the role that generic medications play in reducing health care costs.¹ Most prescription medicines are synthesized from traditional, small molecule chemical compounds.² They are easily replicated using well-known chemical processes.³ For decades, pharmaceutical companies have been making generic copies of these drugs after the patent protections for the original drug, also

* Stacey L. Worthy, Esq., associate attorney, DCBA Law & Policy. John F. Kozak, J.D., 2014, The Catholic University of America, Columbus School of Law; B.A., 2011, Washington and Lee University. The authors would like to thank Michael C. Barnes, Esq., for his conceptual and editing contributions to this Article.

¹ See, e.g., Toni Johnson, *The Debate Over Generic-Drug Trade*, COUNCIL ON FOREIGN REL. (Aug. 3, 2011), <http://www.cfr.org/drug-trafficking-and-control/debate-over-generic-drug-trade/p18055>.

² See LONZA, BUSINESS AWARENESS, SMALL MOLECULES ARE STILL BIG BUSINESS FOR THE PHARMACEUTICAL INDUSTRY 2 (2009), available at http://www.lonza.com/~media/Files/Business%20Awareness%20Articles/Small_Molecules.ashx; see also 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, 156 (2005) (noting that “the majority of drugs prescribed by physicians or bought over the counter contain a small molecule as the active therapeutic ingredient”).

³ See Steven A. Nash & Rebecca Workman, *A New Pathway for Follow-on Biologics*, 20 FED. CIR. B.J. 193, 195 (2010-11).

known as the “innovator” product, have expired.⁴ Generic small molecule drugs are generally available to patients at a much lower cost than the patented innovator product.⁵ To help lower prescription drug costs, all states have laws encouraging pharmacists to substitute generics for brand-name prescription medications, often without the prior consent of physicians.⁶ These “substitution” laws have proved effective in safely lowering prescription drug costs for small molecule drugs.⁷

During the “biotechnology revolution” of the 1980s, both new small molecule drugs, as well as new forms of protein-based medications were developed using DNA biotechnology.⁸ These drugs, called biologics, have proven effective at treating many forms of illness, from arthritis to cancer;⁹ however, they are expensive to develop and must be manufactured using tightly controlled processes for safety reasons.¹⁰

For instance, in the late 1990s, the U.S. manufacturer of

⁴ See *id.* at 197 (noting that the “approval of generic small-molecule drugs has been permitted for over twenty-five years”); see also Dudzinski, *supra* note 2, at 155-56 (describing the advancement and standardization of pharmaceutical chemistry following World War II).

⁵ See U.S. FED. TRADE COMM’N, EMERGING HEALTH CARE ISSUES: FOLLOW-ON BIOLOGIC DRUG COMPETITION: FED. TRADE COMM’N REPORT 12 (2009), available at <http://www.ftc.gov/sites/default/files/documents/reports/emerging-health-care-issues-follow-biologic-drug-competition-federal-trade-commission-report/p083901biologicsreport.pdf> [hereinafter FTC REPORT] (finding that prescribing small molecule generic drugs in place of the branded medication may provide consumers cost savings of between 25 and 80 percent, depending on the number of generics in the market).

⁶ See Thomas P. Christensen et al., *Drug Product Selection: Legal Issues*, 41 J. AM. PHARMACEUTICAL ASS’N 868, 869 (2001) (explaining that “[c]urrently, all U.S. states and territories have some form of drug product selection law allowing a pharmacist, under certain circumstances, to substitute a generic drug product when a physician has written a prescription for a brand product”).

⁷ See FTC REPORT, *supra* note 5, at 12-13.

⁸ See Sharon Begley, *As top court invalidates some gene patents, biotech has moved on*, REUTERS (June 13, 2013, 6:59 PM), <http://www.reuters.com/article/2013/06/13/usa-court-genes-industry-idUSL2N0EO1XK20130613>. According to the FDA, biotechnology is defined as “the application of biological systems and organisms to technical and industrial processes.” Frank E. Young, *Biotechnology: The View from the FDA*, 4.3 HEALTH MATRIX 10, 10 (1986).

⁹ See NAT’L PHYSICIANS BIOLOGICS WORKING GRP., ALLIANCE FOR PATIENT ACCESS, BIOLOGICS: A DIFFERENT CLASS OF MEDICATIONS THAT MAKES A DIFFERENCE FOR OUR PATIENTS 2 [hereinafter ALLIANCE FOR PATIENT ACCESS], available at http://gallery.mailchimp.com/c67da0b816e8460d454282be4/files/NPBWGWhitePaper_1Final.pdf.

¹⁰ See *id.* at 6.

erythropoietin¹¹ gave exclusive licensing rights to another manufacturer to produce the same drug in the European Union (“EU”).¹² The EU manufacturer used the same methodology to produce the drug, making only minor manufacturing changes.¹³ Yet, in reaction to the new EU version, multiple EU patients developed pure red cell aplasia, “a severe and life-threatening condition [in which] the bone marrow ceases to produce red blood cells.”¹⁴ As a result, several patients “died and others became permanently transfusion-dependent.”¹⁵ No such effects were observed in patients taking the U.S. version,¹⁶ highlighting the health and safety dangers that even small changes in biologics can cause.

Yet, biologics are generally more expensive than most traditional medications, leading many policy-makers in Congress and the U.S. Food and Drug Administration (“FDA”) to attempt to establish a “generic” market for biologics similar to the one that has been established for small molecule drugs.¹⁷ These “generic” biologics are often called “follow-on biologics” (“FOBs”) or “biosimilars.”¹⁸

The debate over FOBs has intensified in recent years as the biologics industry approaches a “patent cliff” with several of the leading biologics losing patent and exclusivity protections within the next six years.¹⁹ When these protections expire, other manufacturers can legally copy and market the existing products, potentially leading to uncompensated use of trade secrets and uncompensated takings under the Fifth Amendment of the U.S.

¹¹ Erythropoietin is a biologic drug that promotes red blood cell growth in those with anemia. See Bryan A. Liang & Timothy Mackey, *Emerging Patient Safety Issues Under Health Care Reform: Follow-On Biologics and Immunogenicity*, 7 THERAPEUTICS & CLINICAL RISK MGMT. 489, 490 (2011), available at <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3253755/pdf/tcrm-7-489.pdf>; see also GROUP HEALTH COOPERATIVE, ERYTHROPOIETIN (EPO) TREATMENT AND MONITORING GUIDELINE 2 (2010) (noting that erythropoietin “is a drug used to treat anemia”).

¹² Liang & Mackey, *supra* note 11, at 490.

¹³ *Id.*

¹⁴ *Id.*

¹⁵ *Id.*

¹⁶ *Id.*

¹⁷ See discussion *infra* Part I.E.

¹⁸ This Article uses these terms interchangeably.

¹⁹ Bruno Calo-Fernández & Juan Leonardo Martínez-Hurtado, *Biosimilars: Company Strategies to Capture Value from the Biologics Market*, 5 PHARMACEUTICALS 1393, 1394-95 (2012), available at <http://www.mdpi.com/1424-8247/5/12/1393>.

Constitution.²⁰ As such, manufacturers should challenge such uncompensated use of trade secrets and takings.²¹

Moreover, there are very important distinctions between FOBs and traditional, small molecule generics. Unlike small molecule drugs, biologics are virtually impossible to replicate,²² and the large-sized proteins, as well as the protein configuration, make biologics more likely to trigger an adverse immune response in patients, as exemplified with erythropoietin.²³ Despite these differences, recently enacted federal laws allow the FDA to approve FOBs that are “highly similar” to the original biologics drug, commonly called the reference product biologic (“RPB”), through an abbreviated approval pathway.²⁴ “Highly similar” implies that FOBs do not need to be identical.²⁵ Pursuant to recent FDA guidance interpreting such laws, this policy may result in the substitution of an FOB for a biologic without the prescribing physicians’ knowledge, placing the patient at risk for harm.²⁶ Therefore, the FDA’s recent guidance

²⁰ Bloomberg BNA, *More Than 900 Biologic Drugs, Vaccines Currently Under Development, PhRMA Says*, in LIFE SCIENCES LAW & IND. REPORT, BLOOMBERG BNA (Mar. 22, 2013) (noting that as of March 2013, at least 8 FOBs were currently being developed).

²¹ See generally ABBOTT LABS’ CITIZEN PETITION, FDA Docket No. FDA-2012-P-0317 (Apr. 2, 2012) [hereinafter ABBOTT LABS’ CITIZEN PETITION], available at <http://www.regulations.gov/#!documentDetail;D=FDA-2012-P-0317-0001>. This citizen petition is an example of a manufacturer challenging such uncompensated trade secrets and takings.

²² See FTC REPORT, *supra* note 5, at 5 (noting that “[c]urrent technology does not yet allow for the creation of an exact replica of a pioneer biologic drug product”); see also ALLIANCE FOR PATIENT ACCESS, *supra* note 9, at 3.

²³ Liang & Mackey, *supra* note 11, at 490.

²⁴ See Public Health Service Act (PHSA), 42 U.S.C.A. § 262(k) (West 2013).

²⁵ See *id.* § 262(i)(2).

²⁶ U.S. FOOD & DRUG ADMIN., DRAFT GUIDANCE FOR INDUSTRY ON BIOSIMILARS: QUESTIONS AND ANSWERS REGARDING IMPLEMENTATION OF THE BIOLOGICS PRICE COMPETITION AND INNOVATION ACT OF 2009 3 (2012) [hereinafter DRAFT BIOSIMILARS GUIDANCE], available at <http://www.fda.gov/downloads/Drugs/Guidances/UCM273001.pdf>. According to the FDA:

To meet the higher standard of ‘interchangeability,’ an applicant must provide sufficient information to demonstrate biosimilarity, and also to demonstrate that the biological product can be expected to produce the same clinical result as the reference product in any given patient and, if the biological product is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch (see section 351(k)(4) of the PHS Act).

Id.

should be challenged through citizen petitions or lawsuits because it interprets standards for approval too broadly and risks placing modest cost savings ahead of patient safety.

Additionally, states must step in and protect patients that potentially may use these FOBs, especially because of the high level of deference that federal agencies receive.²⁷ States must develop new statutory protections for patients that provide physicians, in conjunction with their patients (as opposed to pharmacists), the authority to decide whether interchangeable FOBs are appropriate substitutions for RPBs. The benefits of such state legislation outweigh the potential costs.

This Article argues that the FDA's approach conflicts with the constitutional protections of trade secrets and uncompensated takings. Additionally, the FDA's approach conflicts with federal laws designed to ensure the safety of biologics, presenting serious safety concerns. This Article concludes that, based on the FDA's lax interpretations, the duty falls to the states to enact proper legislation requiring prior authorization from a physician, and informed consent from the patient, before a pharmacist may substitute an FOB for the RPB.

To provide context, Part I of this Article outlines the current federal laws and regulations governing the approval of small molecule drugs and biologics. Part II discusses trade secret and Fifth Amendment takings jurisprudence, concluding that recent FDA actions have resulted in uncompensated use of trade secrets and uncompensated takings. Part III provides an overview of legal doctrines used to determine whether an agency's rules and policies are legally binding, as well as the level of deference such agency rules and policies receive. Part III also evaluates the FDA's recent guidance under the *Skidmore* doctrine,²⁸ and suggests that such guidance should be challenged as an overly broad interpretation of federal law. Part III concludes by recommending that the FDA look to European and Canadian

²⁷ See, e.g., *Chevron, U.S.A., Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837, 844 (1984); see also Elbert Lin & Brendan J. Morrissey, *No Notice, No Deference: Agency Deference after Christopher v. SmithKline Beecham Corp.*, BLOOMBERG LAW, <http://about.bloomberglaw.com/practitioner-contributions/no-notice-no-deference-agency-deference-after-christopher-v-smithkline-beecham-corp-by-elbert-lin-and-brendan-j-morrissey-wiley-rein-llp/> (last visited Apr. 21, 2014).

²⁸ *Skidmore v. Swift & Co.*, 323 U.S. 134, 139-40 (1944).

policies on biologics as guidance. In light of the FDA's recent missteps, this Article concludes by calling on state legislators to draft legislation that ensures physicians, and not pharmacists, take the leading role in determining whether a patient may be dispensed appropriate FOBs.

I. FDA Approval Processes of Small Molecule Drugs and Biologics

Federal legislators apparently used the approval processes for small molecule brand and generic drugs as models when they enacted such processes for biologics and FOBs.²⁹ Therefore, it is important to understand how each process works. Part I provides a simple overview of such processes as well as a brief explanation of patents and exclusivity.

A. Small Molecule Brand Drugs

Since the 1940s, pharmaceutical manufacturers have been replicating pure, chemically identical active ingredients for small molecule drugs.³⁰ Small molecule drugs are comprised of relatively simple chemical compounds that are replicable through chemical synthesis of organic or inorganic compounds.³¹ Today, small molecule drugs make up about 80 percent of the pharmaceutical market and include many of the best selling prescription drugs.³² Although major pharmaceutical companies have been increasingly investing in other types of innovations, such as biologics, small molecule drugs will continue to be a major focus and source of revenue for the foreseeable future.³³ Once a controlled manufacturing procedure has been established, these chemical processes can be consistently

²⁹ Charles Davis, Note, *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 Biologics Approval Process*, 81 GEO. WASH. L. REV. 1255, 1268, 1273 (2013).

³⁰ See Dudzinski, *supra* note 2, at 155-56.

³¹ *Small and large molecules: drugs on a chemical and biological basis*, BAYER HEALTHCARE PHARMACEUTICALS, <http://www.bayerpharma.com/en/research-and-development/technologies/small-and-large-molecules/index.php> (last visited Apr. 21, 2014).

³² See LONZA, *supra* note 2, at 2.

³³ See Maxx Chatsko, *Should Big Pharma Follow the Spin-off Trend?*, DAILY FINANCE (Feb. 17, 2013, 2:30 PM), <http://www.dailyfinance.com/2013/02/17/should-big-pharma-follow-the-spinoff-trend/>.

replicated to produce a chemically identical active ingredient.³⁴

The FDA regulates the production of small molecule brand and generic drugs.³⁵ Before a generic drug can be approved, an original “brand” product must already exist.³⁶ Under section 505 of the Food, Drug, and Cosmetics Act (“FDCA”),³⁷ a brand drug manufacturer must submit a New Drug Application (“NDA”) to the FDA and obtain certification that the new drug is “safe and effective.”³⁸ If the FDA approves the NDA, the new drug will have market exclusivity, in addition to any remaining patent protection.³⁹

B. Patents and Exclusivity

Patents and exclusivity serve a similar function through different means. The U.S. Patent and Trademark Office can grant a patent anytime during the development lifespan of a drug and such patent can encompass a wide range of rights protecting the intellectual property of the innovator.⁴⁰ Generally, a patent “exclude[s] others from making, using, offering for sale, or selling the invention”⁴¹ In exchange for these exclusive

³⁴ See Nash & Workman, *supra* note 3, at 195.

³⁵ See James J. Wheaton, *Generic Competition and Pharmaceutical Innovation: The Drug Price Competition and Patent Term Restoration Act of 1984*, 35 CATH. U. L. REV. 433, 439-41 (1986) (describing how the FDA initially permitted abbreviated applications for generic versions of drugs approved prior to 1962, but required all other generics to undergo the full, “new drug” approval process). Prior to 1962, the FDA’s treatment of generics was inconsistent, and, at times, the agency did not consider generics to be “new drugs” needing separate approval. See DONALD O. BEERS & KURT R. KARST, *GENERIC AND INNOVATOR DRUGS: A GUIDE TO FDA APPROVAL REQUIREMENTS* § 1.03[A] (8th ed. 2013) (describing the evolution of the FDA’s position on small molecule generic drugs).

³⁶ See U.S. FOOD & DRUG ADMIN., *Generic Drugs: Questions and Answers*, DRUGS, <http://www.fda.gov/drugs/resourcesforyou/consumers/questionsanswers/ucm100100.htm> (last updated Sept. 3, 2013).

³⁷ Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C.A. § 355 (West 2013).

³⁸ *Id.* at § 355(j)(2)(C).

³⁹ See 21 C.F.R. § 314.108(b)(2) (2014) (establishing a five year market exclusivity for newly approved drugs). The Hatch-Waxman Act also will extend the term of any unexpired patent by up to five years to compensate for patent protection time expended while the drug was being approved by the FDA. See 35 U.S.C.A. § 156 (West 2013); see also *Merck & Co. v. Kessler*, 80 F.3d 1543, 1547 (Fed. Cir. 1996) (describing the patent restoration provisions of Hatch-Waxman).

⁴⁰ U.S. FOOD & DRUG ADMIN., *Frequently Asked Questions on Patents and Exclusivity*, DRUGS, <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079031.htm> (last updated Dec. 5, 2012) [hereinafter FDA QUESTIONS ON PATENTS AND EXCLUSIVITY].

⁴¹ See 35 U.S.C.A. § 154(a)(1) (West 2013); see also *United States v. Line Material Co.*, 333 U.S. 287, 308 (1948) (noting that patent protection “excludes all except its

rights, the patent applicant must disclose to the public the “best mode . . . of carrying out the invention.”⁴² To be eligible to receive patent protection, the invention must be useful, novel, and non-obvious.⁴³ Patents for new drugs and biologics are usually granted for a 20-year term from the date of filing, after which those exclusive rights expire.⁴⁴

“Exclusivity” is the statutory marketing rights that the FDA grants upon final approval of a drug.⁴⁵ Exclusivity gives the manufacturer the ability to sell its product without any competition for a limited time.⁴⁶ The FDA has explained that “[s]ome drugs have both patent and exclusivity protection[s,] while others have just one or none.”⁴⁷ This exclusivity period may or may not overlap with the patent.⁴⁸ In contrast to a patent application, obtaining exclusivity does not require that an innovator publish its invention or secret process, and thus may be more attractive than patents if the innovation is unlikely to be independently replicated and can be securely protected from disclosure.⁴⁹ Even if the manufacturer decides to disclose its

owner from the use of the protected process or product”).

⁴² 35 U.S.C.A. § 112(a) (West 2013).

⁴³ See *Graham v. John Deere Co. of Kan. City*, 383 U.S. 1, 14 (1966).

⁴⁴ See 35 U.S.C.A. § 154(a)(2) (West 2013).

⁴⁵ See FDA QUESTIONS ON PATENTS AND EXCLUSIVITY, *supra* note 40. Some commentators have described the BPCIA exclusivity as “data exclusivity” because competition is prevented by not allowing a follow-on to reference the innovator for a period of time. See John A. Vernon et al., *Exploration of Potential Economics of Follow-on Biologics and Implications for Data Exclusivity Periods for Biologics*, 16 B.U. J. SCI. & TECH. L. 55 (2010). Exclusivity protections in Hatch-Waxman governing small molecule drugs are often referred to as “marketing exclusivity” since it prohibits other manufacturers from marketing and selling a generic version during that period. See D. Christopher Ohly & Sailesh K. Patel, *Evergreening Biologics*, 8 J. OF GENERIC MEDICINES 132, 133 (2011); see also Brian Bouggy, Note, *Follow-On Biologics Legislation: Striking a Balance between Innovation and Affordability*, 7 IND. HEALTH L. REV. 367, 378-80 (2010) (describing exclusivity and distinguishing between data and market exclusivity).

⁴⁶ Unlike a patent, which is a positive grant of certain rights, exclusivity operates as a de facto monopoly resulting from the FDA’s refusal to approve any new products. See Yaniv Heled, *Patents vs. Statutory Exclusivities in Biological Pharmaceuticals—Do We Really Need Both?*, 18 MICH. TELECOMM. & TCH. L. REV. 419, 430 (2012). Compared to the relatively successful tactic of filing a patent infringement lawsuit, any challenge to the FDA’s inaction on a new drug approval or the FDA’s interpretation of the exclusivity requirement is likely to be unsuccessful. *Id.* at 431-32 (citing *Heckler v. Cheney*, 470 U.S. 821, 831 (1985) and *Chevron, U.S.A., Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837, 842-44 (1984)).

⁴⁷ FDA QUESTIONS ON PATENTS AND EXCLUSIVITY, *supra* note 40.

⁴⁸ *Id.*

⁴⁹ See *Trade-Secret versus Patent Protection*, FOUND. FOR BIOTECHNOLOGY AWARENESS &

product information through the patent process, it still has exclusivity for the statutory period.⁵⁰

The 1984 Hatch-Waxman Act contains exclusivity provisions for small molecule drugs.⁵¹ This Act represents a compromise between brand and generic drugs manufacturers. Brand drugs receive exclusivity periods to compensate innovators for patent-protected time lost during product development and the FDA approval process, while generic drugs receive an abbreviated generic approval pathway to shorten the approval process.⁵² These exclusivity periods apply to any new drugs registered under the FDCA.⁵³ This means an innovator will have at least five years to exclusively market and sell the new drug from the date of approval, even if the remaining patent protection is shorter.⁵⁴ In many cases, however, the remaining patent life of 20 years may extend beyond the exclusivity period. Market or regulatory forces may also delay the introduction of generic drugs.⁵⁵ For instance, the Federal Trade Commission (“FTC”) has cited studies showing that, although a brand drugs exclusivity is limited to five years, most generic drugs do not make it to market until about 11 to 13 years after the reference products are approved.⁵⁶

EDUC., http://www.fbae.org/2009/FBAE/website/biotechnology-and-ipr_trade-secret.html (last visited Apr. 21, 2014); see discussion *infra* Part II.A.

⁵⁰ See 35 U.S.C.A. § 154(a)(2) (West 2013).

⁵¹ Drug Price Competition and Patent Term Restoration (Hatch-Waxman) Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified as amended in scattered sections of 21 U.S.C.). Prior to Hatch-Waxman, most generic drugs were required to submit a “new drug application.” See *United States v. Generix Drug Corp.*, 460 U.S. 453, 457-61 (1983) (holding that a generic version of a drug is still a “new drug” under the FDCA).

⁵² See *Bristol-Myers Squibb Co. v. Royce Labs., Inc.*, 69 F.3d 1130, 1133-34 (Fed. Cir. 1995) (noting that Hatch-Waxman represented Congress’ attempt “to strike a ‘careful balance between the policies of fostering the availability of generic drugs and of providing sufficient incentives for research on breakthrough drugs’”; see also Krista Hessler Carver et al., *An Unofficial Legislative History of the Biologics Price Competition and Innovation Act of 2009*, 65 FOOD & DRUG L.J. 671, 676-77 (2010).

⁵³ See 21 C.F.R. § 314.108(b)(2) (2014). Presumably, these exclusivity provisions apply to any biologic product that was approved under the FDCA. See 35 U.S.C.A. § 154(a)(2) (West 2013).

⁵⁴ See 21 C.F.R. § 314.108(b)(2); see also Matthew J. Seamon, *Antitrust and the Biopharmaceutical Industry: Lessons from Hatch-Waxman and an Early Evaluation of the Biologics Price Competition and Innovation Act of 2009*, 34 NOVA L. REV. 629, 636 (2010) (noting that some drugs may not have any patent protection by the time the FDA approves the NDA).

⁵⁵ See FTC REPORT, *supra* note 5, at ii-v.

⁵⁶ *Id.* at 40. Hatch-Waxman also gives the first approved generic version 180 day exclusivity before other generic competitors can be marketed. See *Alphapharm Pty Ltd. v. Thompson*, 330 F. Supp. 2d 1, 2 (D.D.C. 2004).

C. *Small Molecule Generic Drugs*

Generic small molecule medications must still be individually approved under federal law even though they contain a previously approved active ingredient.⁵⁷ Currently, several abbreviated pathways exist under the FDCA that allow generic drug manufacturers to seek approval without submitting a full NDA.⁵⁸ These statutes took their current form with the passage of the Hatch-Waxman Act in 1984.⁵⁹ First, the “abbreviated new drug application” (“ANDA”) pathway, found under section 505(j) of FDCA, permits duplicate, generic versions of small molecule drugs to be approved without full reports from clinical trials or studies.⁶⁰ Additionally, the FDCA section 505(b)(2) pathway allows for similar, but not identical, generic versions to be approved using an abbreviated application.⁶¹ Both generic approval pathways, to some degree, rely on information generated by the manufacturer of the FDA-approved brand drug, also known as the reference product sponsor.⁶²

1. *ANDA Pathway to FDA Approval*

To prove that a drug is safe and effective under the 505(j) ANDA process, the drug manufacturer must prove that the generic version has the same active ingredients, the same route of administration, and the same dosage, form, and strength as the innovator product.⁶³ Currently, ANDA applicants must use a

⁵⁷ See *United States v. Generix Drug Corp.*, 460 U.S. 453, 459-60 (1983) (holding that “drug” under the FDCA includes both the active and inactive ingredients).

⁵⁸ See Tam Q. Dinh, *Potential Pathways for Abbreviated Approval of Generic Biologics Under Existing Law and Proposed Reforms to the Law*, 62 FOOD & DRUG L.J. 77, 78 (2007); 21 U.S.C.A. § 355(b)(2) (West 2013); 21 U.S.C.A. § 355(j) (West 2013).

⁵⁹ The current FDA generic pathway took its current form from a 1984 law commonly referred to as the Hatch-Waxman Act. See *Drug Price Competition and Patent Term Restoration (Hatch-Waxman) Act of 1984*, Pub. L. No. 98-417, 98 Stat. 1585 (codified as amended in scattered sections of 21 U.S.C.).

⁶⁰ 21 U.S.C.A. § 355(j) (West 2013).

⁶¹ See U.S. FOOD & DRUG ADMIN., DRAFT GUIDANCE FOR INDUSTRY: APPLICATIONS COVERED BY SECTION 505(B)(2) 1-2 (1999), available at <http://www.fda.gov/downloads/Drugs/Guidances/ucm079345.pdf> [hereinafter FDA GUIDANCE ON 505(B)(2) APPLICATIONS].

⁶² See discussion *infra* Part I.C.

⁶³ 21 U.S.C.A. § 355(j) (West 2013). However, in July 2013, the FDA announced that it may permit generic drug makers to make changes to their safety labels. See Katie Thomas, *F.D.A. Rule Could Open Generic Drug Makers to Suits*, N.Y. TIMES, July 3, 2013,

label identical to the FDA-approved reference product, even if the generic manufacturer is aware of dangerous side effects not on that label.⁶⁴ As an additional requirement, the generic drugs must be between 80 to 125 percent as effective as the innovator product in order to be considered “bioequivalent”⁶⁵ under the law.⁶⁶

Given that small molecule drugs are relatively simple chemical compounds, exact replication of the active ingredient is usually achievable.⁶⁷ The FDA claims that most generics fall well within certain statistical parameters for bioequivalence.⁶⁸ If the ANDA requirements are satisfied, the applicant may rely “solely on the previous finding of safety and effectiveness” for the reference product, and the generic drug will be considered the “therapeutic equivalent” to the brand product.⁶⁹ To find

<http://www.nytimes.com/2013/07/04/business/fda-rule-could-open-generic-drug-makers-to-suits.html>.

⁶⁴ See *Mut. Pharm. Co. v. Bartlett*, 133 S. Ct. 2466, 2470-71 (2013).

⁶⁵ The FDA defines bioequivalence as:

[T]he absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. Where there is an intentional difference in rate (e.g., in certain extended release dosage forms), certain pharmaceutical equivalents or alternatives may be considered bioequivalent if there is no significant difference in the extent to which the active ingredient or moiety from each product becomes available at the site of drug action. This applies only if the difference in the rate at which the active ingredient or moiety becomes available at the site of drug action is intentional and is reflected in the proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.

21 C.F.R. § 320.1(e).

⁶⁶ See 21 U.S.C.A. § 355(j)(2)(A)(iv) (West 2013); 21 C.F.R. § 320.1; see also Michelle Hottinger & Bryan A. Liang, *Deficiencies of the FDA in Evaluating Generic Formulations: Addressing Narrow Therapeutic Index Drugs*, 38 AM. J. L. & MED. 667, 671-72 (2012), available at <http://hlaw.ucsd.edu/people/documents/Hottinger-Liang.pdf> (describing bioequivalence ratios).

⁶⁷ See Nash & Workman, *supra* note 3, at 195.

⁶⁸ See U.S. FOOD & DRUG ADMIN., *Facts about Generic Drugs*, DRUGS, http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/ucm167991.htm#_ftnref2 (last updated Sept. 19, 2012) [hereinafter *Facts about Generic Drugs*]. The FDA cites a recent study that the average difference in absorption rate is 3.5 percent in a generic-brand name comparison. It claims that this difference is similar to the difference between different batches of the same brand drugs. *Id.*

⁶⁹ See U.S. FOOD & DRUG ADMIN., U.S. DEP’T OF HEALTH & HUMAN SERVS., RESPONSE TO CITIZEN PETITIONS, FDA DOCKET NOS. 2001P-0323/CP1 & C5, 2002P-

bioequivalence, the FDA essentially requires the ANDA applicant to prove that the active ingredient is chemically identical to the reference product's active ingredient.⁷⁰ Variations in bioequivalence in small molecule drugs are usually caused by small differences in formulation or inactive ingredients that, in most cases, do not pose significant health or safety concerns.⁷¹ In all states, pharmacists may substitute generic drugs for therapeutically equivalent brand drugs.⁷²

Although the FDA has provided guidelines regarding determinations of bioequivalence for small molecule generics, case studies report widespread anecdotal evidence of adverse effects on patients who have switched to generic versions of certain "narrow therapeutic index" drugs.⁷³ This class of drugs has an especially small range between the recommended "therapeutic" dosage and a "toxic" dosage, and even slight variations normally found between most generics and brand drugs can have an adverse effect on the patient.⁷⁴ The

0447/CP1, AND 2003P-0408/CP1 14, 32-33 (Oct. 14, 2003), *available at* <http://www.fda.gov/ohrms/dockets/dockets/04p0231/04p-0231-c000001-Exhibit-29-vol4.pdf> [hereinafter FDA RESPONSE TO OCTOBER 2003 CITIZEN PETITIONS].

⁷⁰ See Kathleen R. Kelleher, Note, *FDA Approval of Generic Biologics: Finding a Regulatory Pathway*, 14 MICH. TELECOMM. & TECH. L. REV. 245, 249 (2007) (explaining that "[w]hile the FDA originally interpreted 'sameness' rather leniently, the term is now generally interpreted to require absolute chemical identity" to the reference product's active ingredient).

⁷¹ See *Facts about Generic Drugs*, *supra* note 68.

⁷² See *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567, 2583 (2011) (Sotomayor, J., dissenting).

⁷³ Hottinger & Liang, *supra* note 66, at 669-70, 677-78 (noting that although these adverse reactions to switching to generics have not been consistently proved controlled, double-blind studies, the prevalence of adverse affects in case studies merits adopting stricter bioequivalence ranges for certain generic drugs including antiepileptics, anticoagulants, and antidepressants). The "narrow therapeutic index drug products," or "narrow therapeutic range drug products," as they are referred to by the FDA, are defined as products "containing certain drug substances subject to therapeutic drug concentration or pharmacodynamic monitoring, and/or where product labeling indicates a narrow therapeutic range designation." U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES FOR ORALLY ADMINISTERED DRUG PRODUCTS—GENERAL CONSIDERATIONS 20 (2003), *available at* <http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070124.pdf>.

⁷⁴ Hottinger & Liang, *supra* note 66, at 669-70, 676-77. For instance, a report released in 2011 by Johns Hopkins researchers found that generic anti-epilepsy drugs are different enough from brand formulations that they may not be effective, particularly if patients switch between two generic drugs. See Press Release, *Variation in Make-Up of Generic Epilepsy Drugs Can Lead to Dosing Problems*, JOHN HOPKINS MED. INST. (June 30, 2011), http://www.hopkinsmedicine.org/news/media/releases/variation_in_make_up_of_gen

substitution of FOBs for innovator products presents similar safety concerns because even slight variations, which are inherent in most FOBs, may trigger adverse immune responses in patients.⁷⁵

2. *FDCA Section 505(b)(2) Pathway to Approval*

Section 505(b)(2) is the FDCA approval pathway for drugs that are similar to, but not identical “duplicates” of the reference product.⁷⁶ Unlike the ANDA process, the 505(b)(2) pathway does not require a statistical showing of bioequivalence.⁷⁷ However, the exact scope of section 505(b)(2) has been a source of confusion over the years.⁷⁸ The FDA attempted to clarify the issue in 2003, by stating that 505(b)(2) applications may be used for drugs with “substantial differences” from the reference product, but only if such differences are supported by supplemental “safety and effectiveness information.”⁷⁹ The applicant may rely on the FDA’s finding of the reference product’s safety and efficacy to the extent that the generic can be considered identical to such product.⁸⁰ Thus, under section 505(b)(2), the generic applicant must submit its own studies and may also rely, in part, on the FDA’s prior findings regarding the reference product’s safety and efficacy.⁸¹ The applicant may also rely on data found in published literature.⁸²

D. *Biologics*

Biologics are pharmaceutical products that are

eric_epilepsy_drugs_can_lead_to_dosing_problems.

⁷⁵ See Liang & Mackey, *supra* note 11, at 491.

⁷⁶ FDA GUIDANCE ON 505(B)(2) APPLICATIONS, *supra* note 61, at 2.

⁷⁷ See Dudzinski, *supra* note 2, at 213-16.

⁷⁸ See generally Dudzinski, *supra* note 2, at 196-220.

⁷⁹ FDA RESPONSE TO OCTOBER 2003 CITIZEN PETITIONS, *supra* note 69, at 3 (attempting to clarify some ambiguity in the 505(b)(2) process). Significant differences often include changes to dosage formulation, dosing regimen, Rx/OTC switch, new molecular entity, strength, route of administration, new combination product, bioequivalence, and change in active ingredient. See FDA GUIDANCE ON 505(B)(2) APPLICATIONS, *supra* note 61, at 4-5.

⁸⁰ FDA RESPONSE TO OCTOBER 2003 CITIZEN PETITIONS, *supra* note 69, at 3.

⁸¹ *Id.* at 9. An applicant who relies solely on the FDA’s prior findings for the reference product should proceed under the section 505(j) ANDA process. *Id.* at 7.

⁸² FDA GUIDANCE ON 505(B)(2) APPLICATIONS, *supra* note 61, at 2.

manufactured inside a living organism, such as a plant or animal cell.⁸³ The newest and most profitable biologics are usually proteins that are produced using recombinant DNA technology.⁸⁴ These recombinant DNA techniques were first developed in the 1970s and 1980s and involve splicing and altering the DNA structure of organisms, such as bacteria, in order to transform them into protein producing “factories.”⁸⁵ Unlike small molecule chemical drugs, these proteins are extremely complex and particularly sensitive to changes in the manufacturing process.⁸⁶ The molecular structure of a biologic is usually 100 to 1,000 times larger than traditional, small molecule drugs.⁸⁷ As a result of this complexity, the FDA has recognized that “generic” or follow-on versions of biologic products “are unlikely to be shown to be structurally identical to a reference product.”⁸⁸ In other words,

⁸³ See *How do Drugs and Biologics Differ?*, BIOTECHNOLOGY INDUS. ORG. (Nov. 20, 2010), <http://www.bio.org/articles/how-do-drugs-and-biologics-differ>. Under federal law, a “biological product” is “a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings.” 42 U.S.C.A. § 262(i)(1) (West 2013).

⁸⁴ U.S. FOOD & DRUG ADMIN., DRAFT GUIDANCE FOR INDUSTRY: QUALITY CONSIDERATION IN DEMONSTRATING BIOSIMILARITY TO A REFERENCE PROTEIN PRODUCT 2 (2012), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf> [hereinafter FDA DRAFT QUALITY GUIDANCE]; see also Dudzinski, *supra* note 2, at 143-44. Early biologic products were crude forms of vaccines and antibody serums harvested from infected animals. See Linda Bren, *The Road to the Biotech Revolution - Highlights of 100 Years of Biologics Regulation*, FDA CONSUMER MAGAZINE (2006), available at <http://www.fda.gov/AboutFDA/WhatWeDo/History/FOrgsHistory/CBER/ucm135758.htm> (describing how incidents in the early 20th Century involving tainted, animal-derived biologics led Congress to pass the first legislation regulating biologics and vaccines in 1902).

⁸⁵ See Dudzinski, *supra* note 2, at 160-61. Although the modern biologics industry started in the United States, Asian nations such as India, China, and Korea recently have taken advantage of lower costs and greater government support to develop their indigenous biopharmaceutical industries. See Stanton J. Lovenworth, *The New Biosimilar Era: The Basics, the Landscape, and the Future*, in LIFE SCIENCES LAW & IND. REPORT, BLOOMBERG BNA 11 (Sept. 21, 2012). Leading U.S. innovators and biosimilar developers, eager to tap these huge markets, have been seeking joint-ventures with many Asian companies. *Id.*

⁸⁶ See ALLIANCE FOR PATIENT ACCESS, *supra* note 9, at 3-4 (noting that biologics are generally 100 to 1,000 times larger than conventional, small molecule drugs).

⁸⁷ See *id.*

⁸⁸ U.S. FOOD & DRUG ADMIN., DRAFT GUIDANCE FOR INDUSTRY: SCIENTIFIC CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY TO A REFERENCE PRODUCT 4 (2012), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf> [hereinafter FDA DRAFT SCIENTIFIC GUIDANCE].

whereas generic small molecule drugs and their reference products are “the same,” FOBs and their RPBs are “highly similar.”

Moreover, the FDA has found that “even minor structural differences . . . can significantly affect a protein’s safety, purity, and/or potency”⁸⁹ The large size of the molecules makes biologics more likely to trigger an immune response in a patient than a traditional, small molecule chemical drug.⁹⁰ Most biologics are administered through injections or intravenously, but many can be administered by patients at home.⁹¹

1. *Approval of Biologics*

Unlike small molecule drugs, which are approved under the FDCA, the FDA approves most biologics under section 351 of the Public Health Services Act (“PHSA”).⁹² Compared to the FDCA, the PHSA gives the FDA greater regulatory control over the manufacturing processes that are especially critical in the production of biologics.⁹³ Manufacturers submit a Biologic License Application (“BLA”) to the FDA for approval of their biologics.⁹⁴ The applicant must submit information regarding

⁸⁹ *Id.*

⁹⁰ AMGEN COMMENT ON FDA QUESTIONS AND ANSWERS REGARDING THE BPCIA, FDA Docket No. FDA-2011-D-0611 4 (Apr. 16, 2012), *available at* http://www.pharmamedtechbi.com/~media/Supporting%20Documents/The%20Pink%20Sheet/74/18/Amgen_comments.pdf (“specific structural features of a molecule that cause immunogenicity are largely unknown”).

⁹¹ *See* Nat’l Patient Org., *Testimony of Lawrence A. LaMotte: Concerns with HB 1315, IMMUNE DEFICIENCY FOUND.* (Mar. 11, 2013), *available at* <http://primaryimmune.org/idf-advocacy-center/idf-advocacy-center-activity/?aid=7576&sa=1>.

⁹² *See* 42 U.S.C. § 262; *see* Blank v. United States, 400 F.2d 302, 303 (5th Cir. 1968) (noting that the “predecessor of § 262 . . . sought to regulate the manufacture and sale of certain substances of animal origin . . . [t]he purity of [which] is of far more importance than is the purity of ordinary drugs . . .”). Numerous government agencies have been involved in the regulation of biologic drugs over the past century, including the Treasury, the National Institutes of Health, and finally the FDA. *See* Edward L. Korwek, *What Are Biologics? A Comparative Legislative, Regulatory and Scientific Analysis*, 62 FOOD & DRUG L.J. 257, 260-61 (2007).

⁹³ FDA QUESTIONS ON PATENTS AND EXCLUSIVITY, *supra* note 40.

⁹⁴ *See* 42 U.S.C.A. § 262(a) (2013). The BLA process allows the FDA to supervise the production of the biologic product. *Id.* Production facilities are inspected by the FDA during the BLA application process and at least once every two years after the BLA is granted. *See* 21 C.F.R. § 600.21 (2013). The inspector may inspect production and storage facilities, collect samples of products and ingredients, question staff, and observe the production process. *See* 21 C.F.R. § 600.22 (2013).

both the drug and the manufacturing process as part of the BLA,⁹⁵ and the FDA will approve the BLA if the manufacturer proves that both the biologic product and the manufacturing process are “safe, pure, and potent.”⁹⁶ The FDA has defined “safety” as “the relative freedom from harmful effect . . .” to persons taking the drug.⁹⁷ “Purity” is defined as the “relative freedom from extraneous matter in the finished product, whether or not harmful to the recipient or deleterious to the product.”⁹⁸ Potency is “interpreted to mean the specific ability or capacity of the product, as indicated by . . . tests or . . . clinical data . . . to effect a given result.”⁹⁹ These are not quantified or measurable standards. Instead, they are general definitions applied by the FDA on a case-by-case basis.¹⁰⁰

2. *Exclusivity*

To help address the uncertainty surrounding biologics, Congress passed the Biologics Price Competition and Innovation Act of 2009 (“BPCIA”) as part of health care reform under the Patient Protection and Affordable Care Act (“ACA”).¹⁰¹ The BPCIA contains a 12-year exclusivity period for the innovator product approved under the PHSA, during which time the FDA will not approve an FOB that references such innovator

⁹⁵ See 21 C.F.R. § 601.2 (2013). The FDA’s labeling requirements for PHSA biologics are the same as for drugs regulated under the FDCA. See 21 C.F.R. § 201.56 (2013). Although the labeling regulation addresses both classes of products at the same time, the FDA believes that both the FDCA and the PHSA independently give the FDA statutory authority to promulgate labeling regulations. See Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3964-65 (Jan. 24, 2006) (codified at 21 C.F.R. pts. 201, 314, and 601).

⁹⁶ See 42 U.S.C.A. § 262(a)(2)(C)(i) (2013).

⁹⁷ 21 C.F.R. § 600.3(p) (2013).

⁹⁸ 21 C.F.R. § 600.3(r) (2013).

⁹⁹ 21 C.F.R. § 600.3(s) (2013).

¹⁰⁰ See *Berlex Labs., Inc. v. FDA*, 942 F. Supp. 19, 25 (D.D.C. 1996) (noting that the regulations “set out definitions [prescribing the standards of safety, purity and potency, which] guide FDA’s case-by-case determinations”); The FDA follows a detailed approval procedure outlined in guidance for staff and industry. See generally U.S. FOOD & DRUG ADMIN., GUIDANCE FOR REVIEW STAFF AND INDUSTRY: GOOD REVIEW MANAGEMENT PRINCIPLES AND PRACTICES FOR PDUFA PRODUCTS (2005), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079748.pdf>.

¹⁰¹ See JOHN R. THOMAS, CONG. RESEARCH SER., FOLLOW-ON BIOLOGICS: THE LAW AND INTELLECTUAL PROPERTY ISSUES 1 (Jan. 15, 2014), available at <http://www.fas.org/sgp/crs/misc/R41483.pdf>.

product.¹⁰² These relatively lengthy exclusivity protections may actually be more useful to innovators than a patent due to legal uncertainty surrounding biologic patent law.¹⁰³ Furthermore, FOB sponsors may not even submit their applications to the FDA for at least four years after the innovator receives approval.¹⁰⁴ To address concerns that innovators could make small changes to their product to further extend the exclusivity, a practice known as “evergreening,”¹⁰⁵ the law states that an additional 12 years of exclusivity will not be granted to the innovator for supplemental applications or subsequent applications that make minor changes to their products.¹⁰⁶

E. *Follow-on Biologics*

Given the complexity of biologics and the fact that they are not easily replicable, Congress recognized that the ANDA and 505(b)(2) pathways used for generic, small molecule drugs were inappropriate for FOBs.¹⁰⁷ Instead, Congress created a separate,

¹⁰² 42 U.S.C.A. § 262(k)(7)(A).

¹⁰³ See Heled, *supra* note 46, at 456-61 (noting that it is unclear whether an FOB could be similar enough to the reference product to take advantage of the abbreviated approval process while also being different enough to circumvent the RPB’s patent protections); see also Janet Freilich, *Patent Infringement in the Context of Follow-On Biologics*, 16 STAN. TECH. L. REV. 9, 23 (2012).

¹⁰⁴ 42 U.S.C.A. § 262(k)(7)(B).

¹⁰⁵ See Glyn Moody, *Indian Supreme Court Rejects Trivial ‘Evergreening’ Of Pharma Patents*, TECHDIRT (Apr. 1, 2013, 3:13 PM), <https://www.techdirt.com/articles/20130401/09233022536/indian-supreme-court-rejects-evergreening-pharma-patents.shtml> (describing the process of “evergreening” as “making small changes to a drug, often about to come off patent, in order to gain a new patent that extends its manufacturer’s control over it”).

¹⁰⁶ 42 U.S.C.A. § 262(k)(7)(C). It is unclear, however, exactly which factors the FDA will consider to determine if a modified product is worthy of a new 12 year exclusivity period. See BIOTECHNOLOGY INDUSTRY ORG., RE: DOCKET NO. FDA-2011-D-0611: DRAFT GUIDANCE FOR INDUSTRY ON BIOSIMILARS: QUESTIONS AND ANSWERS REGARDING IMPLEMENTATION OF THE BIOLOGICS PRICE COMPETITION AND INNOVATION ACT OF 2009, at 12 (Apr. 16, 2012), available at <http://www.bio.org/sites/default/files/2012-04-16%20Biosimilars%20Q&A%20-%20FINAL.pdf> [hereinafter BIOTECHNOLOGY INDUSTRY ORG. COMMENTS ON FDA DRAFT GUIDANCE] (commenting that the FDA “should address the factors to be considered in determining whether a change in safety, purity, or potency, such that a subsequent BLA would be eligible for 12-year exclusivity of its own”).

¹⁰⁷ See David M. Dudzinski & Aaron S. Kesselheim, *Scientific and Legal Viability of Follow-on Protein Drugs*, 358 N. ENG. J. OF MED. 843, 844-45 (2008), available at <http://amcp.org/WorkArea/DownloadAsset.aspx?id=11665>. The FDA has long maintained, as a legal matter, that biologic products are, with the exception of different

abbreviated approval pathway for FOBs under the BPCIA, which is found in section 351(k) of the PHSA.¹⁰⁸ Thus, the PHSA, like the FDCA, now contains licensing procedures for both RPBs and FOBs.¹⁰⁹ An FOB using the PHSA section 351(k) abbreviated pathway must be evaluated against an RPB with an FDA-approved BLA.¹¹⁰ FOBs can either be approved as “biosimilar” or “interchangeable” with the RPB.¹¹¹

An FOB is considered “biosimilar” if it “is *highly similar* to the [RPB] notwithstanding minor differences in clinically inactive components,” rather than identical, as is required for small molecule brand and generic drugs.¹¹² Moreover, “biosimilarity” requires that “there are no clinically meaningful differences between the biological product and the [RPB] in terms of the safety, purity, and potency of the product.”¹¹³ Similar to the ANDA process used for small molecule generics, section 351(k)’s

approval procedures, subject to both FDCA and PHSA requirements. *Id.* However, due to “historical vagaries” in the laws, the FDA approved several early recombinant protein biologics under the FDCA’s NDA process, and as a consequence, the FDA has recently approved certain FOBs under the 505(b)(2) pathway since these FOBs reference “well-understood” FDCA-approved biologics. *Id.* at 844-45; *see also* DEP’T OF HEALTH & HUMAN SERVICES, RE: DOCKET NOS. 2004P-0231/CPI AND SUP1, 2003P-0176/CPI AND EMCL, 2004P-0171/CPI, AND 2004N-0355, at 3 (May 30, 2006), *available at* <http://www.fda.gov/ohrms/dockets/dockets/04P0231/04P-0231-pdn0001.pdf> [hereinafter RESPONSE TO CITIZEN’S PETITION CONCERNING OMNITROPE].

For instance, in 2006, the FDA approved an FOB of a FDCA-approved biologic human growth hormone under 505(b)(2). *See* RESPONSE TO CITIZEN’S PETITION CONCERNING OMNITROPE, *supra* note 107, at 52 (explaining the FDA’s approval of the 505(b)(2) application for Omnitrope, a human growth hormone). The FDA, responding to court pressure, explicitly stated that it only approved the 505(b)(2) applications because of the historical anomaly. *Id.* at 42. The agency stated that the 505(b)(2) or the ANDA application would not necessarily be used for more complex biologic proteins or any BLAs whose reference products was approved under the PHSA. *Id.* at 3-4; *see also* Sandoz, Inc. v. Leavitt, 427 F. Supp. 2d 29, 38-39 (D.D.C. 2006) (requiring the FDA to either approve or deny the follow-on biologic Omnitrope’s application under the 505(b)(2) process).

¹⁰⁸ *See* 42 U.S.C.A. § 262.

¹⁰⁹ *See* 42 U.S.C.A. § 262(a). The law envisions that section 351 of the PHSA will be the sole pathway for RPB and FOB applications, but there is a 10-year transition period during which some RPB and FOB applications will be permitted under section 505 of the FDCA if a brand drug in the “same class” has already been approved under section 505 of the FDCA. *See* Patient Protection and Affordable Care Act, Pub. L. No. 111-148, § 7002(e), 124 Stat. 119, 817 (2010) (uncodified). After 10 years, any drug approved under section 505 FDCA will be “deemed” to have been approved under section 351 of the PHSA. *See* § 7001(e), 124 Stat., at 817.

¹¹⁰ 42 U.S.C.A. § 262(k).

¹¹¹ *Id.*

¹¹² *Id.* § 262(i)(2)(A).

¹¹³ *Id.* § 262(i)(2)(b).

abbreviated BLA process relieves the FOB applicant of the expense needed to prove *de novo* that its product is safe, pure, and potent. If the FOB is deemed “highly similar” to the RPB, the FDA will rely on its prior approval of the RPB’s application to prove the safety, purity, and potency of the FOB.¹¹⁴

Biosimilarity can be proved using data derived from analytical studies, animal studies, and clinical studies that “demonstrate safety, purity, and potency in 1 or more appropriate conditions of use for which the [RPB] is licensed and intended to be used and for which licensure is sought for the biological product.”¹¹⁵ In other words, clinical trials may be used but are not required if analytical or animal studies are adequately used, even though an FOB may result in immunogenicity, as explained below.¹¹⁶

In addition, the follow-on product must also be used for the same condition or conditions as the RPB, and must use the same route of administration, dosage form, and strength as the RPB.¹¹⁷ The application can be supplemented with any publicly available information regarding the FDA’s prior determination that the RPB was safe, pure, and effective.¹¹⁸

If an FOB meets the higher standard of “interchangeability,” then under federal law it may be considered a substitute for the RPB.¹¹⁹ An FOB will be considered “interchangeable” under section 351 if it meets the “biosimilar” requirements and, in addition, “can be expected to produce the *same* clinical result as the reference product in *any* given patient.”¹²⁰ Additionally, for products that are administered more than once to a patient, the statute requires that the “risk in terms of safety or diminished efficacy of alternating or switching between use of the [FOB] and

¹¹⁴ *Id.* § 262(k)(2)(A)(iii)(I). The follow-on application must include publicly available information regarding the FDA’s prior determination that the reference product, as per section 351(a) requirements for innovator biologic applicants, was safe, pure and effective. *Id.*

¹¹⁵ *Id.* § 262(k)(2)(A)(i)(I)(cc).

¹¹⁶ See discussion *infra* Part III.C.1.

¹¹⁷ 42 U.S.C. § 262(k)(2)(A)(i)(IV).

¹¹⁸ *Id.* § 262(k)(2)(iii)(I); see also ABBOTT LABS’ CITIZEN PETITION, *supra* note 21, at 17 (an explanation of the constitutional argument challenging that such data is “publicly” available).

¹¹⁹ *Id.* § 262(i)(3).

¹²⁰ *Id.* § 262(k)(4)(A)(ii).

the reference product is not greater than the risk of using the reference product” for more than one administration.¹²¹ In draft guidance, the FDA has stated that it will use the “totality-of-the-evidence approach” to evaluate the applications and will decide what specific supporting data and clinical trials are required on a product-specific basis.¹²²

II. *The FDA Failed to Protect Innovator Investments: Trade Secret and Constitutional Takings*

The FDA’s push to aggressively promote an abbreviated pathway for FOBs may violate trade secret laws as well as the U.S. Constitution.¹²³ Innovative biologic manufacturers have invested billions of dollars into the research and development of life-saving treatments,¹²⁴ in exchange for “. . . the exclusive right to reap the benefits of their efforts[, which] compensates them for the costs of innovation, the risk of failure and the potential liability that can arise if the product proves defective.”¹²⁵ An increasing portion of recent biotechnology developments has come from smaller companies whose investments in new biologic medications and technologies expose them to serious financial risks.¹²⁶ If courts and policymakers fail to protect these substantial investments, innovators will be less likely to develop new products to treat challenging diseases.¹²⁷

¹²¹ *Id.* § 262(k)(4)(B).

¹²² FDA DRAFT SCIENTIFIC GUIDANCE, *supra* note 88, at 8.

¹²³ *See generally* ABBOTT LABS’ CITIZEN PETITION, *supra* note 21.

¹²⁴ ABBOTT LABS’ CITIZEN PETITION, *supra* note 21, at 1-2 (noting that the reference product sponsor has “invested massive amounts of capital, which studies show often surpasses more than a billion dollars). It has been estimated that an innovator will spend about \$1.31 billion to bring a typical biologic drug to market. *See* FTC REPORT, *supra* note 5, at A-2-A-3.

¹²⁵ *G.S. Rasmussen & Assocs. v. Kalitta Flying Servs.*, 958 F.2d 896, 900 (9th Cir. 1992).

¹²⁶ *See* Erwin A. Blackstone & Joseph P. Fuhr, Jr., *The Future of Competition in the Biologics Market*, 31 TEMP. J. SCI. TECH. & ENVTL. L. 1, 29 (2012).

¹²⁷ Gregory Dolin, *Exclusivity without Patents: The New Frontier of FDA Regulation for Genetic Materials*, 98 IOWA L. REV. 1399, 1406 (2012-2013) (noting that innovators will be less likely to invest “time, money, and energy” without adequate legal protections); *see also* RICHARD A. SAMP & CORY L. ANDREWS, COMMENTS OF THE WASHINGTON LEGAL FOUNDATION TO THE FOOD AND DRUG ADMINISTRATION DEP’T OF HEALTH & HUMAN SERVICES, CONCERNING CITIZEN PETITION BY ABBOTT LABORATORIES REGARDING BIOSIMILAR APPLICATIONS THAT CITE BIOLOGICAL PRODUCTS FOR WHICH THE BLA WAS SUBMITTED TO FDA BEFORE MARCH 23, 2010, at 4 (Feb. 13, 2013) (noting that “[i]f FDA determines that it is free to ignore its past promises of confidentiality to BLA applicants,

As a result, the FDA must clarify the extent to which innovator trade secrets will be used to evaluate a 351(k) application and ensure that such use does not violate federal or state trade secret laws. Additionally, the FDA's current willingness to evaluate 351(k) applications for FOBs approved prior to the enactment of the BPCIA can be considered a "regulatory taking" under the Fifth Amendment to the U.S. Constitution.¹²⁸ Such a taking will be unconstitutional if, as in this case, the government does not provide "just compensation" to the RPB developer.¹²⁹

A. *Biologics' BLA Information is a Trade Secret*

Trade secrets are protected by both state and federal laws, but are defined and established by state law.¹³⁰ Most states and the District of Columbia have codified their trade secret common law doctrines by adopting the Uniform Trade Secrets Act ("UTSA").¹³¹ For example, under the Maryland Trade Secrets Act, a "trade secret" is any information that:

- (1) [d]erives independent economic value, actual or potential, from not being generally known to, and not being readily ascertainable by proper means by, other persons who can obtain economic value from its disclosure or use; and (2) [i]s the subject of efforts that are reasonable under the circumstances to maintain its secrecy.¹³²

Echoing the general state law requirements, FDA regulations

businesses subject to government regulation will be less willing in the future to spend the massive sums necessary to develop innovative and life-saving products") [hereinafter WASH. LEGAL FOUND. CONCERNING ABBOTT CITIZEN PETITION].

¹²⁸ See U.S. CONST. amend V; see generally *Penn. Cent. Transp. Co. v. New York City*, 438 U.S. 104 (1978).

¹²⁹ See U.S. CONST. amend. V.

¹³⁰ See 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, 288 (2011) (discussing how trade secrets are distinct from federal patent protections for innovators who publish their inventions in exchange for a fixed period of exclusive rights).

¹³¹ See Bradley Chambers, *Texas Joins 47 Other States to Adopt the Uniform Trade Secrets Act*, JD SUPRA BUSINESS ADVISOR (June 1, 2013), <http://www.jdsupra.com/legalnews/texas-joins-47-other-states-to-adopt-the-81706/>. New York and Massachusetts are the only states that have yet to adopt some form of the USTA. *Id.*

¹³² See *LeJeune v. Coin Acceptors, Inc.*, 849 A.2d 451, 462 (Md. 2003).

define a “trade secret” as 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.”¹³³ The FDA uses a six-factor test to evaluate the value of the innovation and the efforts to maintain secrecy:

- (1) The extent to which the identity of the ingredient is known outside petitioner’s business;
- (2) The extent to which the identity of the ingredient is known by employees and others involved in petitioner’s business;
- (3) The extent of measures taken by the petitioner to guard the secrecy of the information;
- (4) The value of the information about the identity of the claimed trade secret ingredient to the petitioner and to its competitors;
- (5) The amount of effort or money expended by petitioner in developing the ingredient; and
- (6) The ease or difficulty with which the identity of the ingredient could be properly acquired or duplicated by others.¹³⁴

Information submitted to the FDA in a full 351(a) BLA application regarding a biologic’s manufacturing process and clinical and analytical data are “trade secrets” under state and federal law.¹³⁵ Information submitted by the RPB manufacturer has “economic value” because it helps the manufacturer receive a license to do what it would otherwise not be permitted to do, namely, produce and sell a biologic drug.¹³⁶

¹³³ 21 C.F.R. § 20.61(a); *see* *Zotos Int’l, Inc. v. Young*, 830 F.2d 350, 352 (D.C. Cir. 1987).

¹³⁴ *See Zotos*, 830 F.2d at 352.

¹³⁵ WASH. LEGAL FOUND. CONCERNING ABBOTT CITIZEN PETITION, *supra* note 127, at 8. Even though some of the data or the manufacturing process can be considered “intangible,” it is still considered a trade secret in which the innovator has a property interest. *See Pharm. Care. Mgmt. Ass’n v. Rowe*, 307 F. Supp. 2d 164, 177 (D. Me. 2004).

¹³⁶ *See G.S. Rasmussen & Assocs. v. Kalitta Flying Servs.*, 958 F.2d 896, 900-901 (9th Cir. 1992) (noting that the “time, money and effort [the inventor] devoted to obtaining his [license] would largely be wasted but for the fact that they generated the data necessary to satisfy the requirements of the [federal law]”); *see also* ABBOTT LABS’ CITIZEN

Manufacturers also use reasonable efforts to maintain secrecy. Unlike patented innovations, which are protected by publicly filing an application with the government and can be copied from publicly available information after expiration, trade secrets are maintained using internal precautions and controls designed to keep the information “secret” in perpetuity.¹³⁷ Moreover, compared to small molecule drugs produced using relatively common chemistry techniques, biologics’ trade secret concerns are generally more acute given that they are the product of exceedingly complex manufacturing processes that innovators want to keep secret.¹³⁸ The secrecy requirement is also satisfied because biologic manufacturers aggressively protect this information throughout the drug development and approval process¹³⁹ and only disclose it to FDA officials who are legally prohibited from disclosing such information.¹⁴⁰ The Federal Trade Secrets Act imposes criminal penalties on federal agents or employees who disclose confidential information or trade secrets in violation of federal law or agency regulations.¹⁴¹

Given that the information submitted in an innovator’s BLA application is a “trade secret,” the FDA’s “use” of that information is subject to restrictions under state and federal law.¹⁴²

PETITION, *supra* note 21, at 4, n.7 (citing *Webb v. Dep’t of Health & Human Servs.*, 696 F.2d 101,103 (D.C. Cir. 1982), which notes that “[i]f a manufacturer’s competitor could obtain all the data in the manufacturer’s NDA, it could utilize them in its own NDA without incurring the time, labor, risk, and expense involved in developing them independently”).

¹³⁷ See, e.g., *Network Telecomm., Inc. v. Boor-Crepeau*, 790 P.2d 901, 902 (Colo. App. 1990) (noting that precautions do not need to be particularly expensive and can include measures such as requiring employees to sign confidentiality agreements, controlling plant access, and limiting access to a “need-to-know” basis); see also Epstein, *supra* note 130, at 287.

¹³⁸ See D’vorah Graeser, *Industry Voices: Biosimilars and trade secrets*, FIERCE BIOTECH (Oct. 24, 2012), http://www.fiercebiotech.com/story/industry-voices-biosimilars-and-trade-secrets/2012-10-24?utm_source=rss&utm_medium=rss.

¹³⁹ ABBOTT LABS’ CITIZEN PETITION, *supra* note 21, at 4-5.

¹⁴⁰ See *Webb*, 696 F.2d at 103 (noting that “disclosure of NDA data is further discouraged by the existence of criminal sanctions for FDA officials who release trade secrets without the submitter’s consent[,]” and that such sanctions are “contained in both the Food, Drug, and Cosmetic Act and the [Federal] Trade Secrets Act”).

¹⁴¹ See 18 U.S.C.A. § 1905. There have, however, been instances where the FDA has inadvertently or negligently disclosed trade secret data during the drug approval process. See, e.g., *Jerome Stevens Pharms., Inc. v. FDA*, 402 F.3d 1249, 1251 (D.C. Cir. 2005) (describing how the FDA posted trade secrets related to a company’s drug manufacturing process on the agency’s website for five months).

¹⁴² *Syngenta Crop Protection, Inc. v. Helliker*, 42 Cal. Rptr. 191, 218 (Cal. Ct. App.

Additionally, the demonstration of the reference drug's "safety, purity, and potency" is itself a trade secret given that the FDA assigns this designation based on the commercially valuable and secret information that the RPB's sponsor submits.¹⁴³

B. Government's Use of Innovators' Trade Secrets to Approve Abbreviated FOB Applications is a Misappropriation

The 351(k) application process allows FOB manufacturers to submit data showing that their products are "biosimilar" to an already approved RPB.¹⁴⁴ This abbreviated pathway exists for FOBs because the innovator has already proved the safety, purity, and potency of the RPB.¹⁴⁵ This 351(k) application (and the ANDA and 505(b)(2) applications for that matter) is designed to relieve the FOB manufacturer from the time and expense of proving *de novo* that its FOB product is safe, pure, and potent—the applicant merely needs to prove that the FOB is highly similar to a product that is already approved as safe, pure, and potent.¹⁴⁶ Thus, but for the innovator's efforts to gain approval for the RPB, the FDA would not be able to approve the FOB application using the abbreviated pathway.¹⁴⁷

Courts have recognized that use of innovator data to approve an FOB product constitutes a "use" of trade secrets.¹⁴⁸ In an analogous regulatory licensing case, a California court examined a state agency's approval of a new pesticide.¹⁴⁹ The agency based its decision, in part, on the fact that the agency had previously approved another product using the same active ingredient.¹⁵⁰ The court found that the government "relieve[d] a current

2006) (describing how the government's "use" of a trade secret can be considered a "misappropriation" of that information, at least in California, where the California Civil Code defines "misappropriation" to include the "use of a trade secret of another without express or implied consent").

¹⁴³ ABBOTT LABS' CITIZEN PETITION, *supra* note 21, at 16-19.

¹⁴⁴ 42 U.S.C.A. § 262(k).

¹⁴⁵ ABBOTT LABS' CITIZEN PETITION, *supra* note 21, at 15.

¹⁴⁶ *Id.*

¹⁴⁷ *G.S. Rasmussen & Assocs. v. Kalitta Flying Servs.*, 958 F.2d 896, 903 (9th Cir. 1992) (noting that "[w]ithout Rasmussen's efforts, the [federal approval license] Kalitta relied on simply would not exist").

¹⁴⁸ ABBOTT LABS' CITIZEN PETITION, *supra* note 21, at 15.

¹⁴⁹ *See Syngenta Crop Protection, Inc. v. Helliker*, 42 Cal. Rptr. 191, 196-97 (Cal. Ct. App. 2006).

¹⁵⁰ *Id.* at 197.

applicant of the expense of producing or otherwise acquiring similar data and “use[d]” the data to the benefit of the current applicant.”¹⁵¹ The court found that this “use” could be a misappropriation of trade secrets under state law even if the agency had only “passively” considered the original applicant’s information when approving the new product.¹⁵² Because the government is using the innovator’s data to approve an FOB, the FDA must either ensure that the innovator is compensated or refrain from using the data.¹⁵³

C. Using BLA Information Submitted Prior to the BPCIA is a Fifth Amendment Taking of Innovator Data

The Fifth Amendment of the U.S. Constitution prohibits the government from “taking” private property without “just compensation.”¹⁵⁴ The Fifth Amendment’s Takings Clause was “designed to bar Government from forcing some people alone to bear public burdens which, in all fairness and justice, should be borne by the public as a whole.”¹⁵⁵ Generally, the courts have recognized three variations of takings: *per se*, regulatory, and land use exactions.¹⁵⁶

Regulatory takings are the most relevant to the issue of FOB applications. The U.S. Supreme Court, in the landmark *Penn Central* case, identified three factors that can be used to evaluate a regulatory taking: (1) the economic impact on the affected private party, (2) the “extent to which the regulation has interfered with distinct investment-backed expectations” of the private party, and (3) the general nature of the government action.¹⁵⁷ This is a nuanced, context-specific inquiry, and any one

¹⁵¹ *Id.* at 218.

¹⁵² *Id.*

¹⁵³ See *Ruckelshaus v. Monsanto Co.*, 467 U.S. 986, 1011, n.15 (1984) (explaining that “the value of a trade secret lies in the competitive advantage it gives its owner over competitors. Thus, it is the fact that operation of the data-consideration or data-disclosure provisions will allow a competitor to register more easily its product or to use the disclosed data to improve its own technology that may constitute a taking”); see also U.S. CONST. amend. V (stating that the government must compensate takings of private property).

¹⁵⁴ U.S. CONST. amend. V.

¹⁵⁵ *Armstrong v. United States*, 364 U.S. 40, 49 (1960).

¹⁵⁶ See *ABBOTT LABS’ CITIZEN PETITION*, *supra* note 21, at 10, n.26.

¹⁵⁷ *Penn. Cent. Transp. Co. v. New York City*, 438 U.S. 104, 124 (1978).

factor can be dispositive.¹⁵⁸

In *Ruckelshaus v. Monsanto Co.*, the Supreme Court explored the issue of constitutional takings in government licensing applications—specifically, the licensing of “follow-on” pesticides.¹⁵⁹ In 1972, Congress was concerned with the safety of pesticides and enacted legislation to transform a statute imposing labeling requirements into a comprehensive regulatory regime.¹⁶⁰ The enhanced federal laws required manufacturers to submit to the EPA data and studies regarding the safety and environmental impact of their products as part of a registration process.¹⁶¹ The new law allowed manufacturers to designate certain information about their products as “trade secrets.”¹⁶² The law also included a process, somewhat analogous to an ANDA, whereby the EPA could “consider data submitted by one applicant for registration in support of another application pertaining to a similar chemical.”¹⁶³ The law, however, operated as a mandatory licensing scheme, and the EPA could only approve follow-on products if the sponsor compensated the reference product manufacturer.¹⁶⁴

In addition, data designated as a “trade secret” by the innovator manufacturer could not be used at all without its permission.¹⁶⁵ The law was later amended in 1978 to remove the trade secret protections and allowed the EPA to consider all data submitted in the innovator application to approve the follow-on.¹⁶⁶ Monsanto was a pesticide manufacturer that submitted a full application during the time period (1972-1978) when the EPA had ensured that any trade secrets would be protected and

¹⁵⁸ See *Maine Educ. Ass'n Benefits Trust v. Cioppa*, 695 F.3d 145, 153 (1st Cir. 2012) (explaining that the *Penn Central* factors are “[d]esigned to facilitate a careful examination and weighing of all the relevant circumstances”); *Philip Morris v. Reilly*, 312 F.3d 24, 36 (1st Cir. 2002) (noting that “in some regulatory takings cases, one factor is frequently dispositive”).

¹⁵⁹ See generally *Ruckelshaus v. Monsanto Co.*, 467 U.S. 986, 990 (1984).

¹⁶⁰ *Id.* at 991.

¹⁶¹ *Id.* at 992-93.

¹⁶² *Id.* at 992. The scope of this definition was subject to intense litigation before the law was amended again. See, e.g., *Chevron Chem. Corp. v. Costle*, 443 F. Supp. 1024 (N.D. Cal. 1978).

¹⁶³ *Ruckelshaus*, 467 U.S. at 992.

¹⁶⁴ *Id.*

¹⁶⁵ *Id.* at 993.

¹⁶⁶ *Id.* at 994-97.

would not be used to approve similar products.¹⁶⁷ When the EPA later, under the post-1978 law, tried to use this information to approve a similar pesticide for a different pesticide manufacturer, Monsanto sued, claiming a Fifth Amendment taking.¹⁶⁸

Applying the *Penn Central* factors, the Supreme Court held that Monsanto had a reasonable “investment-backed expectation” that its trade secrets would not be used to approve competing products when it submitted its data under the 1972-1978 law.¹⁶⁹ The Supreme Court decided that any government disclosure or use of the data to approve a follow-on pesticide would interfere with this economic expectation and, therefore, would be an uncompensated taking under the Fifth Amendment.¹⁷⁰ In contrast, the Court stated that the EPA’s use of data submitted after the 1978 amendments (that abolished many of the data protections) would not be a taking because, after the amendment, innovators no longer had a reasonable economic expectation that the data they submitted would not be used to approve competing products.¹⁷¹

Like the pesticide manufacturer, biologic innovators submitting data and trade secrets to the FDA prior to the establishment of the abbreviated pathway in 2009, therefore, had a reasonable economic “investment-backed expectation” that their data would not be used to approve competing products.¹⁷² As discussed above, generics and FOBs are very different products, and the existence of an abbreviated pathway for generics would not place biologic manufacturers that had innovator products approved under the PHSA on notice that their data would be used in a similar way.¹⁷³ Even prior to the Hatch-Waxman amendments, the FDA, at times, had allowed traditional generics to be approved through an abbreviated

¹⁶⁷ *Id.* at 1010-11.

¹⁶⁸ *Ruckelshaus*, 467 U.S. at 1011.

¹⁶⁹ *Id.* at 1010-11.

¹⁷⁰ *See id.* at 1011.

¹⁷¹ *Id.* at 1013.

¹⁷² ABBOTT LABS’ CITIZEN PETITION, *supra* note 21, at 21.

¹⁷³ *Id.*; Supporters of Abbott noted that the legal uncertainty surrounding the pre-Hatch-Waxman small molecule generic approval process would not have given innovators a basis for a reasonable expectation that their data would not be used. *See* WASH. LEGAL FOUND. CONCERNING ABBOTT CITIZEN PETITION, *supra* note 127, at 21-22.

approval process.¹⁷⁴ Generally, such abbreviated approval procedures were not used for FOBs of PHSA-approved biologics.¹⁷⁵ Moreover, Congress specifically excluded biologics when it enacted the Hatch-Waxman amendments.¹⁷⁶

To avoid violating the Constitution, the FDA should not use any data from innovators submitted prior to the BPCIA's enactment in 2009 to approve FOB products. Congress did not provide for any compensation or licensing scheme, which means that any use of innovator data submitted prior to 2009 is an unconstitutional taking.¹⁷⁷ The FDA is not permitted to take actions that create a class of constitutional taking claimants.¹⁷⁸ The Supreme Court has repeatedly noted that when courts try to interpret the intent of Congress, “. . . constitutionally doubtful constructions should be avoided where possible.”¹⁷⁹

As a policy matter, the FDA must recognize that innovators, not FOB manufacturers, should take on the most risk to develop these life-saving drugs. The FOB manufacturer makes its investment in a proven product, but the innovator has no such assurance when committing billions of dollars to develop a RPB.¹⁸⁰ In order to incentivize further innovation, biologic developers need to have assurances that the government will recognize and protect their “investment-backed expectations.”¹⁸¹ Without some level of certainty about how the government will treat their trade secrets over the decades-long development and

¹⁷⁴ See Nathan A. Beaver & Kelly A. Hoffman, *Final Word: Omnitrope's Approval: What Does it Mean For Other Generics?*, 19 *BIOPHARM INTERNATIONAL* 8 (Aug. 1, 2006), available at <http://www.biopharminternational.com/biopharm/Article/Final-Word-Omnitropes-Approval-What-Does-It-Mean-F/ArticleStandard/Article/detail/361018> (discussing Omnitrope and 502(b)(2)).

¹⁷⁵ *Id.*

¹⁷⁶ Dudzinski & Kesselheim, *supra* note 107, at 844-45; see also *Lucas v. S.C. Coastal Council*, 505 U.S. 1003, 1031 (1992) (noting that longstanding government policy or practices affecting similarly situated parties can serve as a reasonable basis for an investment-backed expectation, even in the absence of an explicit government pronouncement on the particular issue).

¹⁷⁷ See U.S. CONST. amend. V.

¹⁷⁸ See *Nat'l Mining Ass'n v. Kempthorne*, 512 F.3d 702, 711 (D.C. Cir. 2008) (noting that the “canon of constitutional avoidance trumps *Chevron* deference”); see also *Bell Atl. Tel. Cos. v. FCC*, 24 F.3d 1441, 1445 (D.C. Cir. 1994).

¹⁷⁹ See *Jones v. United States*, 529 U.S. 848, 851 (2000).

¹⁸⁰ FTC REPORT, *supra* note 5, at A-2-A-3 (noting that it costs around \$1.3 billion dollars to develop a RPB).

¹⁸¹ See WASH. LEGAL FOUND. CONCERNING ABBOTT CITIZEN PETITION, *supra* note 127, at 4.

application process, it will be impossible for investors to make reasoned investment choices that are essential to fostering a world-class, innovative biologics market that satisfies the needs of patients.¹⁸²

III. Impermissible Interpretations of the BPCIA

The FDA recently promulgated guidelines interpreting the BPCIA and the approval process of FOBs.¹⁸³ This Article contends that the FDA's interpretation was too lax and should not be given deference. In order to make that determination, Part III analyzes whether such guidelines are legally or non-legally binding and the extent of deference such guidelines should receive. It then discusses the reasons for which the guidelines are impermissibly lax.

A. Tests for Determining Whether a Rule is Legally Binding and What Level of Deference it Should Receive

Administrative agencies often interpret statutes in three ways: through legislative rules, interpretive rules, and policy statements.¹⁸⁴ Legislative rules are rules that an agency "promulgate[s] pursuant to statutory law-making authority and in accordance with the statutory procedures for making rules," such as notice and comment procedures, and carry the force of law.¹⁸⁵ Interpretive rules are non-legislative rules interpreting statutes or regulations that agencies promulgate without such authority and are therefore not legally binding.¹⁸⁶ Examples of interpretive rules include agency manuals, guidelines, and memoranda.¹⁸⁷ Policy statements are pronouncements outside of the legislative-rule framework that do not interpret statutory or regulatory language and are also not legally binding.¹⁸⁸

¹⁸² *Id.*

¹⁸³ See Cooley LLP, *Draft Biosimilars Guidance Released by Food and Drug Administration* (Feb. 16, 2012), available at <http://www.cooley.com/showalert.aspx?Show=66122>.

¹⁸⁴ Thomas J. Fraser, Note, *Interpretive Rules: Can the Amount of Deference Accorded Them Offer Insight into the Procedural Inquiry?*, 90 B.U.L. REV. 1303, 1303 (2010).

¹⁸⁵ *Id.* at 1308.

¹⁸⁶ *Id.*

¹⁸⁷ *Id.*

¹⁸⁸ *Id.*

In determining whether a rule is legislative, interpretive, or policy, courts apply one of two tests: the legal effects test or the *American Mining* test.¹⁸⁹ When distinguishing between a legislative rule and a policy statement, the legal effects test as articulated in *Pacific Gas & Electric Co. v. Federal Power Commission*,¹⁹⁰ is used.¹⁹¹ The legal effects test examines whether the agency limited its discretion in future adjudications when it promulgated the rule, looking to the agency's manifested intent to treat the rule as binding or nonbinding.¹⁹² The critical distinction between a substantive rule and a policy statement is "the different practical effect that these two types of pronouncements have in subsequent administrative proceedings."¹⁹³

When distinguishing between a legislative rule and an interpretive rule, the *American Mining* test is used.¹⁹⁴ The test requires a court to consider the following factors:

- (1) Whether in the absence of the rule there would not be an adequate legislative basis for enforcement action or other agency action to confer benefits or ensure the performance of duties;
- (2) Whether the agency has published the rule in the Code of Federal Regulations;
- (3) Whether the agency has explicitly invoked its general legislative authority; or
- (4) Whether the rule effectively amends a prior legislative rule.¹⁹⁵

However, subsequent court decisions have modified the test, eliminating the second prong – whether the agency published the rule in the Code of Federal Regulations.¹⁹⁶ Courts have also

¹⁸⁹ See *Syncor Int'l Corp. v. Shalala*, 127 F.3d 90, 93-94 (D.C. Cir. 1997).

¹⁹⁰ *Pacific Gas & Elec. Co. v. Fed. Power Comm'n*, 506 F.2d 33 (D.C. Cir. 1974).

¹⁹¹ See *Shalala*, 127 F.3d at 93-94. The court in *Syncor* distinguished between the rules and policy statements.

¹⁹² *Pacific Gas & Elec.*, 506 F.2d at 38.

¹⁹³ *Id.*

¹⁹⁴ See *Shalala*, 127 F.3d at 93-94.

¹⁹⁵ See, e.g., *Am. Mining Cong. v. Mine Safety & Health Admin.*, 995 F.2d 1106, 1112 (D.C. Cir. 1993).

¹⁹⁶ *Health Ins. Ass'n of Am., Inc. v. Shalala*, 23 F.3d 412, 423 (D.C. Cir. 1994) (finding that publication of a rule in the Code of Federal Regulations is nothing more than a "snippet of evidence of agency intent").

revised the fourth prong. Instead of looking at whether the rule amends a prior *legislative* rule, courts now look to whether the rule amends a prior *interpretive* rule.¹⁹⁷

After deciding whether a rule is binding or not, the court then determines what level of deference to give to the agency's interpretation.¹⁹⁸ Courts apply either the *Chevron* "two-step" test or the *Skidmore* test.¹⁹⁹ Applying the *Chevron* test, courts first determine whether the statute is ambiguous by examining the plain language of the statute.²⁰⁰ If the statute is found to be unambiguous, the court applies the law itself, regardless of the agency's interpretation.²⁰¹ But if the reviewing court finds that the language of the statute is ambiguous, the court must uphold the agency's reasonable interpretation of the law and may not substitute its judgment for that of the agency.²⁰² The *Chevron* test applies when determining the level of deference to give an agency regarding a legislative rule.²⁰³

In contrast, courts apply the *Skidmore* test when determining the level of deference to give an agency regarding an interpretive rule or policy statement.²⁰⁴ In *U.S. v. Mead*, the Supreme Court revived *Skidmore v. Swift & Co.* and articulated a lesser degree of deference as "respect" for a well-reasoned agency action.²⁰⁵ The *Skidmore* test states: "The weight of [the administrator's] judgment in a particular case will depend upon the thoroughness evident in its consideration, the validity of its reasoning, its consistency with earlier and later pronouncements, and all those factors which give it power to persuade, if lacking power to control."²⁰⁶

In contrast to *Chevron*, a reviewing court applying *Skidmore* deference may substitute its own reasoning for an agency's reasoning if the court determines that the agency did not have

¹⁹⁷ *Paralyzed Veterans of Am. v. D.C. Arena L.P.*, 117 F.3d 579, 586 (D.C. Cir. 1997).

¹⁹⁸ *Fraser*, *supra* note 184, at 1308.

¹⁹⁹ *Id.* at 1319-20.

²⁰⁰ *Chevron, U.S.A., Inc. v. NRDC, Inc.*, 467 U.S. 837, 842-44 (1984).

²⁰¹ *Id.*

²⁰² *Id.*

²⁰³ *United States v. Mead Corp.*, 533 U.S. 218, 226-27 (2001).

²⁰⁴ *Id.* at 232.

²⁰⁵ *Id.* at 227-28; *but see Christensen v. Harris Cnty.*, 529 U.S. 576, 587 (2000) (declining to give "respect" to an "unpersuasive" agency opinion letter).

²⁰⁶ *Skidmore v. Swift & Co.*, 323 U.S. 134, 140 (1944).

the best interpretation of the statute.²⁰⁷ In other words, *Skidmore* deference shifts control over the statute's interpretation from the agency to the courts.²⁰⁸

B. FDA Guidelines, as Interpretive Laws, Should Receive Skidmore Deference

When Congress passed the BPCIA, after allowing for public participation, it authorized the FDA to issue "guidance" on general and specific requirements regarding follow-on biologics.²⁰⁹ In February 2012, the FDA issued various draft guidance, including *Guidance for Industry, Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009* ("Biosimilars Guidance").²¹⁰ The FDA developed the Biosimilars Guidance to implement the BPCIA, and it addresses a broad range of issues, including the quality and scientific considerations in demonstrating biosimilarity.²¹¹

After a period of notice and comment, the FDA issued the Biosimilars Guidance, which describes the FDA's current interpretations of certain statutory requirements in the BPCIA.²¹² Since its issuance, the question remains whether such Guidance is a legislative or interpretive rule. Making such a determination requires the application of the four-part *American Mining* test.

Under the first prong, in the absence of the Biosimilars Guidance, there would still be an adequate legislative basis for enforcement actions or other agency action to confer benefits or ensure the performance of duties. The FDA presumably could not apply the regulations in any enforcement action against an applicant because the Guidance explicitly states that even final guidance does not "bind the FDA or the public" or "establish legally enforceable responsibilities."²¹³ The Guidance only

²⁰⁷ K.M. Lewis, Note, *Informal Guidance and the FDA*, 66 FOOD & DRUG L.J. 507, 529 (2011).

²⁰⁸ *Id.* (noting that *Skidmore* gives courts, rather than the agency, the power to interpret ambiguous provisions of regulatory statutes).

²⁰⁹ 42 U.S.C.A. § 262(k)(8)(a) (2012).

²¹⁰ See generally DRAFT BIOSIMILARS GUIDANCE, *supra* note 26.

²¹¹ *Id.* at 1-2.

²¹² *Id.* at 1.

²¹³ *Id.* at 2; see also *Mada-Luna v. Fitzpatrick*, 813 F.2d 1006, 1013 (9th Cir. 1987) (noting that agency action does not carry the force of law because it does not limit

purports to represent the FDA's "current thinking" on the topic and does not invoke any legislative authority from the enabling statute.²¹⁴

Although the Biosimilars Guidance does appear in the Federal Register, this prong of the *American Mining* test is no longer relevant, as stated above. More importantly, pursuant to the third prong, the Biosimilars Guidance explicitly has not invoked its general legislative authority.²¹⁵ The Biosimilars Guidance states that it does "not establish legally enforceable responsibilities," and should instead be viewed as a recommendation.²¹⁶

Finally, under the forth prong, the Biosimilars Guidance does not effectively amend a prior legislative rule, interpretive or otherwise. Therefore, the Biosimilars Guidance should be viewed as a non-binding, interpretive rule because it interprets the BPCIA but explicitly does not carry the force of law. As such, the Biosimilars Guidance should be given *Skidmore* deference. This means that if a party were to challenge it as an improper rule, the court would not be required to defer to the agency's interpretation of the BPCIA.

C. FDA Guidance on Biosimilarity and Interchangeability is Impermissibly Lax

As a threshold matter, the FDA acknowledged that current scientific understanding of biologics is insufficient to determine interchangeability, noting that "[a]t this time, it would be difficult as a scientific matter for a prospective biosimilar applicant to establish interchangeability in an original 351(k) application."²¹⁷

To date, the FDA has not provided any specific guidance regarding the types of data or findings needed to prove interchangeability. Industry observers noted that the issue of interchangeability will remain a "theoretical concept" until the FDA acquires the scientific knowledge to issue more specific

agency discretion).

²¹⁴ See DRAFT BIOSIMILARS GUIDANCE, *supra* note 26, at 2.

²¹⁵ See generally *id.*

²¹⁶ *Id.* at 2.

²¹⁷ *Id.* at 11.

guidance on the issue.²¹⁸ Although the FDA declined to provide substantive, technical guidance on interchangeability, the agency did, in general terms, provide a preview of the types of differences that could be tolerated between “interchangeable” products.²¹⁹ Additionally, it is far from certain that a court would directly review the FDA’s Biosimilars Guidance unless the agency instituted an enforcement action against a manufacturer that was not in compliance with the Guidance²²⁰—an action the FDA has indicated it cannot take.²²¹ Some courts, however, have looked to the practical impact of guidance documents and found them reviewable.²²²

Applying *Skidmore*, a court may decline to uphold an agency’s unpersuasive interpretation or policy statement.²²³ Upon heightened scrutiny, the FDA’s Guidance on biosimilarity and interchangeability conflicts with the BPCIA’s safety, purity, and potency standard that underpins the purpose and context of the PHSA biologics application process. Moreover, such Guidance does not comport with the clear statutory standard that the interchangeable products must produce the “same clinical result [as the RPB] in any given patient.”²²⁴

1. *Different Delivery Device or Container*

The FDA draft Guidance leaves open the possibility that a

²¹⁸ ARNOLD & PORTER LLP, FDA’S DRAFT BIOSIMILARS GUIDANCE DOCUMENTS: OVERVIEW AND IMPLICATIONS 5 (Feb. 2012), available at http://www.arnoldporter.com/resources/documents/Advisory%20FDA%E2%80%99s_Draft_Biosimilars_Guidance_Documents_Overview_and_Implications.pdf; see also LOVENWORTH, *supra* note 85.

²¹⁹ ARNOLD & PORTER, *supra* note 218, at 2.

²²⁰ See, e.g., *Colwell v. HHS*, 558 F.3d 1112, 1128 (9th Cir. 2009) (holding that a determination of the legal status of an HHS “Policy Guidance” was “unripe” for judicial review because the agency had not used the guidance against the plaintiff).

²²¹ See DRAFT BIOSIMILARS GUIDANCE, *supra* note 26, at 1-2 (Guidance does not establish legally enforceable responsibilities).

²²² See, e.g., *Gen. Electric Co. v. EPA*, 290 F.3d 377, 380-81 (D.C. Cir. 2002) (finding EPA guidance reviewable because it was essentially binding to both the applicants and the agency “on its face”); Nina A. Mendelson, *Regulatory Beneficiaries and Informal Agency Policymaking*, 92 CORNELL L. REV. 397, 411 (2007) (noting that courts will sometimes look to the practical binding effect of the guidance in order to decide whether the document is ripe for review).

²²³ See, e.g., *Christensen v. Harris Cnty.*, 529 U.S. 576, 587-88 (2000) (denying *Chervon* deference to a Labor Department opinion letter and holding that the letter was an unpersuasive interpretation of the statute).

²²⁴ 42 U.S.C.A. § 262(k)(4)(A)(ii) (2012).

biosimilar, or even an interchangeable FOB, could be permitted to use a different delivery device or container system than the RPB. This possibility is seemingly contrary to the PHSA, which requires follow-ons to have the same route of administration.²²⁵ For example, the FDA stated that it may consider an FOB with an auto-injector syringe device biosimilar to a RPB sold in vial packaging that is administered using a manual syringe.²²⁶ The FDA would consider two such products to have the same “route of administration” and “dosage form” since they are both injectable.²²⁷ The FDA notes, however, that “appropriate studies” would be needed to confirm that the new delivery device met the section 351(k) biosimilar requirements.²²⁸ In addition, the FDA left open the possibility that an FOB using a different delivery device or container could be considered interchangeable with the RPB.²²⁹ The FDA noted, however, that additional considerations, including performance studies or modified usage instructions, might be required to satisfy this higher standard of interchangeability.²³⁰

It is important to note, however, that biologics are so complex that changes in packaging may alter the patient’s response to the product.²³¹ Even slight manufacturing changes can greatly affect the biological composition of biologics and

²²⁵ DRAFT BIOSIMILARS GUIDANCE, *supra* note 26, at 5-6.

²²⁶ *Id.* at 5.

²²⁷ *Id.* The FDA classifies products using over 100 different “route of administration” classifications ranging from nasal, to intravenous, to intraspinal. See U.S. FOOD & DRUG ADMIN., *Route of Administration*, DRUGS, <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/DataStandardsManualmonographs/ucm071667.htm> (last updated Apr. 30, 2009). The FDA has described “dosage form” as the “way of identifying the drug in its physical form.” See U.S. FOOD & DRUG ADMIN., *Dosage Form*, DRUGS, <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/DataStandardsManualmonographs/ucm071666.htm> (last updated Apr. 30, 2009). In determining dosage form, the FDA examines such factors as, “(1) physical appearance of the drug product, (2) physical form of the drug product prior to dispensing to the patient, (3) the way the product is administered, (4) frequency of dosing, and (5) how pharmacists and other health professionals might recognize and handle the product.” *Id.*

²²⁸ DRAFT BIOSIMILARS GUIDANCE, *supra* note 26, at 5.

²²⁹ *Id.* at 5-6.

²³⁰ *Id.* at 5.

²³¹ See Bryan A. Liang, *Regulating Follow-On Biologics*, 44 HARV. J. ON LEGIS. 363, 377-78, 385 (2007) (noting that even “seemingly minor changes in a biologic can have a tremendous clinical impact”).

FOBs, and, subsequently, their safety and efficacy in patients.²³² For instance, “[d]ifferences in protein configurations may occur because of the environmental conditions in which a biologic is manufactured and will have correspondingly different effects on individuals.”²³³

Immunogenicity is an example of a major safety concern associated with differences between products.²³⁴ Immunogenicity is a patient’s adverse reaction in which the body perceives a biologic to be a foreign microorganism or virus, stimulating an immune response in the human body and prompting the formation of antibodies that may affect human health.²³⁵ In the case of the biologic erythropoietin, immunogenicity proved fatal for several patients that died of pure red cell aplasia after taking a form of the biologic that caused a severe antibody reaction. Researchers attributed this reaction to a modification in the type of rubber used in the stopper on the product packaging.²³⁶ Like many biologics, the immunogenicity of the erythropoietin was not well understood, and after the patient deaths, it took about four years and over \$100 million dollars to determine the cause of the problem.²³⁷

The erythropoietin case demonstrates that minor manufacturing and packaging changes could compromise patient safety and may even violate the statutory requirement that interchangeable products produce the same clinical results in any patient.²³⁸ Presumably, these sorts of minor, yet potentially harmful variances would be inevitable when multiple manufacturers produce and package a biologic or FOB product using different delivery devices.

²³² See Jeanne Yang, Note, *A Pathway to Follow-On Biologics*, 3 HASTINGS SCI. & TECH. L.J. 217, 225 (2011).

²³³ *Id.*

²³⁴ *Id.*

²³⁵ See Donna M. Gitter, *Informed by the European Union Experience: What the United States Can Anticipate and Learn from the European Union’s Regulatory Approach to Biosimilars*, 41 SETON HALL L. REV. 559, 561 (2011); see also Ingrid Kaldre, Note, *The Future of Generic Biologics: Should the United States “Follow-On” the European Pathway?*, 2008 DUKE L. & TECH. REV. 9, ¶3 (2008).

²³⁶ See Liang, *supra* note 231, 377-78.

²³⁷ See Donna M. Gitter, *Innovators and Imitators: An Analysis of Proposed Legislation Implementing an Abbreviated Approval Pathway for Follow-On Biologics in the United States*, 35 FLA. ST. U. L. REV. 555, 605-606 (2008).

²³⁸ See 42 U.S.C.A. § 262(k)(4)(A)(ii) (2012).

As a general legal matter, to permit FOB manufacturers to intentionally make their product different from the RPB would frustrate the BPCIA's purpose and introduce unnecessary risk.²³⁹ Therefore, if *Skidmore* deference is applied, the FDA Guidance should not be given strong deference, and courts should rule that the Guidance is not the best interpretation of the statute.

In light of the statutory context and the threat to patient safety, the FDA should not certify FOBs as biosimilar or interchangeable with RPBs that use different delivery systems, devices, or packaging components because such changes may result in “clinically meaningful differences . . . in terms of safety, purity, and potency” due to their complex structures, sensitivity to the manufacturing process, and tendency toward immunogenicity.²⁴⁰

2. *FOBs With Fewer Uses than the Reference Products*

According to the Biosimilars Guidance, the FDA may also approve as biosimilar or interchangeable, FOB products that have fewer routes of administration, fewer presentations, or fewer conditions of use than the RPB, contrary to the PHSA.²⁴¹

²³⁹ JANSSEN RESEARCH & DEVELOPMENT, LLC, RE: DOCKET NO. FDA-2011-D-0611: DRAFT GUIDANCE FOR INDUSTRY ON BIOSIMILARS: QUESTIONS AND ANSWERS REGARDING IMPLEMENTATION OF THE BIOLOGICS PRICE COMPETITION AND INNOVATION ACT OF 2009; 77 FED. REG. 8885 (FEB. 15, 2012), at 10 (Apr. 16, 2012), *available at* http://www.pharmamedtechbi.com/~media/Supporting%20Documents/The%20Pink%20Sheet/74/18/Janssen_comments.pdf [hereinafter JANSSEN RESEARCH COMMENTS ON FDA DRAFT GUIDANCE] (urging the FDA to take the position that readily avoidable differences not be allowed in a section 351(k) application because intentional and avoidable differences from the reference product introduce additional and unnecessary safety risks); *see also* PHRMA, RE: DOCKET NO. FDA-2011-D-0611: DRAFT GUIDANCE FOR INDUSTRY ON BIOSIMILARS: QUESTIONS AND ANSWERS REGARDING IMPLEMENTATION OF THE BIOLOGICS PRICE COMPETITION AND INNOVATION ACT OF 2009; 77 FED. REG. 8885 (FEB. 15, 2012), at 7 (Apr. 16, 2012), *available at* <http://www.pharmamedtechbi.com/~media/Supporting%20Documents/The%20Pink%20Sheet/74/17/PhRMAQAcomments.pdf> [hereinafter PHRMA COMMENTS ON BDA DRAFT GUIDANCE] (urging the FDA to recognize that the potential for increased risk to patients and the statutory intent requires that “applicants refrain, whenever possible, from deliberately modifying controllable product design elements”); *see also* Dolan v. U.S.P.S., 546 U.S. 481, 486 (2006) (noting that statutes must be interpreted in a manner consistent with their “purpose and context”).

²⁴⁰ Gitter, *supra* note 235, at 565.

²⁴¹ DRAFT BIOSIMILARS GUIDANCE, *supra* note 26, at 6-7. In medical terminology, “presentation” is a patient’s symptom or group of symptoms. *See* MERRIAM-WEBSTER, MEDICAL DICTIONARY, *Presentation*, *available at* <http://www.merriam-webster.com/medlineplus/presentation> (last visited Apr. 23, 2014).

Labeling FOBs with a limited subset of uses as interchangeable with the RPB, which is approved for additional uses, may result in additional threats of harm to patients.

First, physicians, pharmacists, and patients would presumably make the logical inference that an “interchangeable” product could be used for all the same uses as the RPB, and not just a subset of uses. A pharmacist, for example, might unknowingly substitute an “interchangeable” FOB for a RPB when the use or presentation is not among the FOB’s limited subset of uses or presentations. Such a substitution would not properly treat the patient’s ailments in the same manner as the RPB.

Furthermore, as a legal matter, it may be impossible to establish, without clinical trials, that a product licensed only for a subset of uses meets the statutory requirement that it produce the “*same* clinical result” as the RPB as required by the PHSA. If the FOB were truly producing the “same” results in the human body as the RPB, as required by the plain language of the statute, then it is unclear why the FOB could not be approved for all uses identical to those of the RPB.²⁴² Therefore, approving such FOBs as interchangeable conflicts with the statutory requirement that an interchangeable product “produce the *same* clinical result . . . in *any* given patient.”²⁴³

3. *FOBs with Different Subsets of Uses or Delivery Methods Should Not be Approved as RPBs*

Alternatively, FOB manufacturers may try to have their products approved as a RPB rather than follow-ons if their products have a different subset of uses or different delivery methods. The FDA should not approve such applications as RPBs under 351(a) of the BPCIA. Such an alternative approach risks creating a loophole whereby an FOB could avoid the 351(k) exclusivity provisions by masquerading as a “new” product under 351(k). Failure to prevent this sort of action could also encourage companies to modify their products to a point where they are considered “new,” creating an unsafe environment in

²⁴² See *Conn. Nat’l Bank v. Germain*, 503 U.S. 249, 253-54 (1992) (noting that “courts must presume that a legislature says in a statute what it means and means in a statute what it says there”).

²⁴³ 42 U.S.C.A. § 262(k)(4) (2012).

which companies are constantly tweaking highly sensitive products.²⁴⁴

The PHSa does not allow 351(a) applications to implicitly reference another product.²⁴⁵ Allowing a “functionally biosimilar” FOB to proceed as a new BLA under 351(a), instead of as an FOB under 351(k), impermissibly renders 351(k) superfluous.²⁴⁶ In addition, the inconsistent treatment of these biologics could be considered “arbitrary and capricious”²⁴⁷ under § 706 of the Administrative Procedure Act if the FDA effectively permitted a product to proceed under more than one pathway.²⁴⁸ Failure to maintain the integrity of the pathways undermines the exclusivity protections of the BPCIA, which was implemented by Congress to promote life-saving innovation and protect the substantial investment of the innovator.²⁴⁹

Thus, the FDA’s Guidance on biosimilarity and interchangeability does not align with the purpose of the BPCIA, which is to ensure safe and effective FOB products. If the FDA attempts to classify FOBs with different delivery devices or containers, fewer uses, or different subsets of uses or delivery methods than the RPBs, as biosimilar or interchangeable, a court reviewing the Guidance under *Skidmore* should overturn such guidelines because the reasoning and application conflict with the statute.²⁵⁰

²⁴⁴ PHRMA COMMENTS ON BDA DRAFT GUIDANCE, *supra* note 239, at 7 (recognizing that this loophole may create safety problems for patients); *see also* U.S. FOOD & DRUG ADMIN., ABBOTT LABS Q&A COMMENTS, FDA Docket Nos. FDA-2011-D-0602, FDA-2011-D-0605, and FDA-2-11-D-0611, at 10-12 (Apr. 16, 2011) [hereinafter ABBOTT LABS COMMENTS], *available at* <http://www.pharmamedtechbi.com/~media/Supporting%20Documents/The%20Pink%20Sheet/74/18/Abbottcomments.pdf>.

²⁴⁵ ABBOTT LABS COMMENTS, *supra* note 244, at 9.

²⁴⁶ *See* Freytag v. Comm’r, 501 U.S. 868, 877 (1991) (explaining that “[o]ur cases consistently have expressed ‘a deep reluctance to interpret a statutory provision so as to render superfluous other provisions in the same enactment’”).

²⁴⁷ 5 U.S.C.A. § 706(2)(A) (2012). A reviewing court may deem an agency action to be “arbitrary and capricious” if the agency failed to consider all the relevant factors when making the decision or made a clear error of judgment. *See, e.g.*, Motor Vehicle Mfrs. Ass’n. v. State Farm Mut. Auto. Ins. Co., 463 U.S. 29, 43 (1983); Citizens to Preserve Overton Park, Inc. v. Volpe, 401 U.S. 402, 416 (1971).

²⁴⁸ PHRMA COMMENTS ON BDA DRAFT GUIDANCE, *supra* note 239, at 11.

²⁴⁹ ABBOTT LABS COMMENTS, *supra* note 244, at 10; *see also* Carver et al., *supra* note 52, at 764.

²⁵⁰ Dolan v. U.S.P.S., 546 U.S. 481, 486 (2006) (noting that statutes must be interpreted in a manner consistent with their “purpose and context”).

D. *International Regulatory Schemes*

For an example of effective FOB policy that protects patient safety, the FDA should look to Europe's biologics regulatory scheme. As expressed by the European Medicines Agency ("EMA"),²⁵¹ the European approach to FOBs is premised on the assumption that, given the complexity of biologics, the small molecule generic approach is "scientifically not appropriate" for FOBs.²⁵² EMA guidelines state that an FOB must be "similar" to the RPB in terms of "quality, safety, and efficacy."²⁵³ Unlike the FDA Guidelines for biosimilarity status, the EMA guidance envisions that clinical studies will be necessary to prove similarity.²⁵⁴ In Europe, studies conducted by the FOB sponsor to evaluate the similarity of immune responses may, in some cases, be more extensive than the initial studies conducted by the RPB developer to prove safety.²⁵⁵ Since 2006, the EMA has only approved 12 FOBs as biosimilar.²⁵⁶

The EMA guidelines do not address the possibility that any FOB be deemed "interchangeable" to the RPB.²⁵⁷ Instead, EMA states that decisions regarding interchangeability and automatic

²⁵¹ The EMA approves drugs using a centralized procedure that is binding on European Union member states. See European Medicines Agency, *Central authorisation of medicines*, http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000109.jsp&mid=WC0b01ac0580028a47 (last visited on Apr. 23, 2014) [hereinafter European Medicines Agency]. EMA is only responsible for approving certain classes of drugs, including "medicines derived from biotechnology processes" and medicines used to treat "HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, and viral diseases." *Id.* Member nations have their own procedures for approving medicines falling outside the scope of EMA's authority. Prior to a rebranding in 2009, EMA was abbreviated as "EMEA" in reference to the agency's former title, the European Agency for the Evaluation of Medicinal Products. See *EMEA becomes EMA*, PM LIVE (Dec. 14, 2009), http://www.pmlive.com/pharma_news/emea_becomes_ema_197492.

²⁵² See *Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues 4*, EUROPEAN MEDICINES AGENCY (Feb. 22, 2006), available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003953.pdf [hereinafter *Guidelines by European Medicines Agency*]. These biologic guidelines are binding on all European Union member states.

²⁵³ *Guidelines by European Medicines Agency*, *supra* note 252, at 3.

²⁵⁴ Lovenworth, *supra* note 85, at 10. In addition, it has been noted that European post-market surveillance and reporting are generally more rigorous than in the U.S. *Id.*

²⁵⁵ See Kaldre, *supra* note 235, at 9.

²⁵⁶ See Bronwyn Mixer, *European Panel Recommends Approval of Two Biosimilar Versions of Remicade*, LIFE SCIENCES LAW & INDUST. REPORT (June 28, 2013) (noting that several other products are advancing through the approval process).

²⁵⁷ *Id.*

substitution must be made on a national level.²⁵⁸ Yet, as of 2013, no European nation has permitted pharmacist substitutions of FOBs.²⁵⁹ France and Spain have passed legislation banning pharmacist substitution of FOBs without express approval from a physician, and it is believed that most other European countries are opposed to automatic pharmacist substitution for biologics.²⁶⁰

Additionally, in 2010, Canada's federal agency, Health Canada, recommended that the provinces and territories not permit automatic substitution of FOBs.²⁶¹ Starting with the recognition that FOBs "are not 'generic' biologics," Health Canada also reiterated its belief that physicians should be the ones to make decisions regarding interchangeability and substitution of biologics.²⁶²

The federal and state governments in the United States should look to the European and Canadian approach as a model for FOBs. These nations recognize that interchangeability for biologics is an exceedingly high standard.²⁶³ The European and Canadian approach recognizes that safety, not cost savings, should be the overarching concern when implementing a new

²⁵⁸ European Medicines Agency, *Q&A 31-43: Similar biological product applications, #43: Will my similar biological medicinal product be considered interchangeable with the reference medicinal product?*, http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000129.jsp&mid=WC0b01ac0580533e0f (last visited Apr. 23, 2014).

²⁵⁹ EUROPEAN COMM'N, WHAT YOU NEED TO KNOW ABOUT BIOSIMILAR MEDICINAL PRODUCTS 16 (2013), available at http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/biosimilars_report_en.pdf.

²⁶⁰ JOAN ROVIRA ET AL., THE IMPACT OF BIOSIMILARS' ENTRY IN THE EU MARKET 19 (ANDALUSIAN SCHOOL OF PUBLIC HEALTH 2011), available at http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/biosimilars_market_012011_en.pdf; see also IRENE KRÄMER, SUBSTITUTION OF BIOSIMILAR ANTIBODIES: COULD THERE BE UNINTENDED CONSEQUENCES?, ROCHE, available at http://www.roche.co.il/fmfiles/re7128001/Restricted_Area/Pharmacists/Files/Substitution_Could_There_Be_Unintended_Consequenses-Kraemer.pdf. Other nations, such as Italy and Sweden, have excluded biologics from their official pharmacist substitution list. *Id.* Some nations such as the United Kingdom and Austria do not allow any forms of generic substitution by pharmacists. *Id.*

²⁶¹ Dr. Elwyn Griffiths (Director General of Health Canada), *Interchangeability/Substitution of Subsequent Entry Biologics (SEBs)* (July 29, 2010), available at <http://safebiologics.org/pdf/Health-Canada-Letter.pdf>.

²⁶² *Id.* (explaining that "Health Canada does not support automatic substitution of [follow-on biologics] . . . and recommends that physicians make only well-informed decisions regarding therapeutic interchange").

²⁶³ See Lovenworth, *supra* note 85, at 10.

approval and distribution pathway for FOBs.²⁶⁴

IV. *State Laws Governing Pharmacist-Directed Substitution of Follow-on Biologics*

Generic small molecule drugs have provided significant cost savings over brand products.²⁶⁵ To encourage lower prescription drug costs, all 50 states have laws allowing, or in some cases, requiring pharmacists to substitute an available “therapeutically equivalent”²⁶⁶ generic version of a drug in place of the more costly brand product.²⁶⁷ In some states, the substitution of a generic medication is mandatory unless a physician explicitly directs that the brand product is medically necessary.²⁶⁸ In the remaining states, pharmacists have discretion to substitute a generic version.²⁶⁹ Generally, pharmacists are not required to notify the prescribing physician of the switch.²⁷⁰

Not all of these cost savings from generic substitution, however, are passed on to consumers. In an effort to reduce expenses, many private and government prescription drug insurance programs will only reimburse the patient for the cost of the generic prescription and not the brand drug.²⁷¹ Many states’

²⁶⁴ *See id.*

²⁶⁵ FTC REPORT, *supra* note 5, at 12 (cost savings is usually between 25 and 80 percent, depending on the number of generics in the market).

²⁶⁶ To determine which drugs may be substituted, some states reference the FDA’s “orange book” of “therapeutically equivalent” drugs, while other states have their own lists or requirements. *See* Jesse C. Vivian, *Generic-Substitution Laws*, U.S. PHARMACIST (June 19, 2008), <http://www.uspharmacist.com/content/c/9787/> (describing the various state laws regulating generic substitution by pharmacists). The guide commonly referred to as the “orange book” is the FDA publication titled, *Approved Drug Products with Therapeutic Equivalence Evaluations*. The guide contains a listing of all FDCA approved drugs as well as a listing of drugs determined to be “therapeutically equivalent” under section 505 of the FDCA. *See* U.S. Food and Drug Admin., *Orange Book Preface*, DRUGS, <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm> (last updated Mar. 14, 2014).

²⁶⁷ *See* PLIVA, Inc. v. Mensing, 131 S. Ct. 2567, 2583 (2011). Some states have their own definitions or lists of drugs that can be substituted, while others reference the FDA’s “orange book” listing of therapeutically equivalent drugs. *See* Vivian, *supra* note 266.

²⁶⁸ PLIVA, 131 S. Ct. at 2583.

²⁶⁹ *Id.* Some states allow the patient to insist on having the brand product dispensed. *Id.*

²⁷⁰ *See, e.g.*, IOWA CODE § 155A.32 (2009); MICH. COMP. LAWS § 333.17755 (2013); 28 PA. CODE § 25.53 (2013); R.I. GEN LAWS § 21-31-16.1 (2011).

²⁷¹ *See* Texas State Board of Pharmacy, *Generic Drugs*, WWW.TSPB.STATE.TX.US, <http://www.tsbp.state.tx.us/consumer/broch3.htm> (last visited Apr. 23, 2014).

Medicaid programs will reimburse the pharmacy with a higher dispensing fee if a generic is substituted.²⁷² For many popular small molecule prescription medications, the profit margins for pharmacies and distributors may be higher on generics than the brand products.²⁷³ In lieu of expensive marketing campaigns to foster product adoption, generic manufacturers often use the promise of higher profit margins for pharmacies and distributors as an incentive to encourage generic substitution.²⁷⁴ Significantly lower wholesale costs for generic drugs also encourage some large retailers to use promotions for deeply discounted generic drugs as part of a “loss leader” strategy, whereby, a retailer offers a deep discount on certain products in an effort to generate increased traffic in their stores.²⁷⁵ The retailers believe that any losses on the drug sales used to entice customers to patronize the pharmacy will be more than offset by profits from other purchases customers will make during their visits.²⁷⁶

These various stakeholders in the prescription drug industry have a major profit incentive to try and substitute generics for as many patients as possible.²⁷⁷ It is likely that similar tactics will be used to encourage substitution of follow-on biologics, resulting in potentially dangerous consequences for patient safety. This Article refutes the notion that state action is preempted and makes various suggestions for legislation.

A. *State Action is Permitted Under the Preemption Doctrine*

The FDA’s expansive interpretation of interchangeability

²⁷² KAISER FAMILY FOUNDATION, *Medicaid Benefits: Prescription Drugs*, KFF.ORG, <http://kff.org/medicaid/state-indicator/prescription-drugs/> (last visited Apr. 23, 2014) (listing state Medicaid prescription drug reimbursement requirements).

²⁷³ See Adam J. Fein, *What Free Generic Lipitor Says about Pharmacy’s Future*, DRUG CHANNELS (Mar. 14, 2013), <http://www.drugchannels.net/2013/03/what-free-generic-lipitor-says-about.html> (some generic drugs bring pharmacies twice the profit as the brand version).

²⁷⁴ See J.K. Wall, *Profits at center of biosimilars debate*, INDIANA BUS. J. (Mar. 18, 2013), <http://www.ibj.com/profits-at-center-of-biosimilars-debate/PARAMS/article/40243>. Major wholesale distributors also make around an 18 percent profit on generic drugs, compared to a mere two percent on brand versions. *Id.*

²⁷⁵ See David Sell, *Wegmans extends offer of free cholesterol Drug*, PHILIDELPHIA INQUIRER (Mar. 14, 2013), http://articles.philly.com/2013-03-14/business/37685352_1_lipitor-atorvastatin-generic-drugs.

²⁷⁶ *Id.*

²⁷⁷ See Fein, *supra* note 273.

proves that the federal legislative branch cannot be relied on to ensure that interchangeable products meet the statutory safety requirements of the BPCIA. Therefore, state action is necessary to protect patients. Intense state efforts are underway to craft new laws that specifically address pharmacist substitution of FOBs.²⁷⁸ Yet, several opponents of the effort to limit biologic substitutions argue that these state substitution laws are preempted by the language from section 351 of the PHSA, which provides that interchangeable biologics “may be substituted” by a pharmacist without the intervention of the physician.²⁷⁹ This reading of the statute, however, impermissibly resolves the ambiguity in favor of finding preemption, and is therefore incorrect.²⁸⁰

The preemption doctrine holds that federal law only preempts state law if the federal law contains “express” language overruling state law or to the extent that the laws conflict, whereby, following the state law constitutes a violation of federal law.²⁸¹ Moreover, when interpreting the meaning of statutory

²⁷⁸ See Joy Liu, *The Biosimilar Substitution Battle: Branded Biotech Wins in Virginia, North Dakota, and Utah*, in PHARMACEUTICAL LAW & INDUSTRY REPORT (Bloomberg BNA Apr. 19, 2013), [http://www.ropesgray.com/biographies/1/~media/Files/articles/2013/04/The-Biosimilar-Substitution-Battle.ashx](http://www.ropesgray.com/biographies/1/~/media/Files/articles/2013/04/The-Biosimilar-Substitution-Battle.ashx); see also Bronwyn Mixter, *Branded, Generic Drugmakers Spar Over State Biosimilars Legislation*, in PHARMACEUTICAL LAW & INDUSTRY REPORT (Bloomberg BNA Mar. 1, 2013).

²⁷⁹ See Kurt R. Karst, *Biosimilar Substitution: Battles are Brewing at the State Level*, FDA LAW BLOG (Jan. 17, 2013), http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2013/01/biosimilar-substitution-battles-are-brewing-at-the-state-level.html.

²⁸⁰ The U.S. Supreme Court has cautioned against interpreting ambiguous provisions of federal statutes to override established state authority. See, e.g., *United States v. Rodgers*, 461 U.S. 677, 706 (1984) (explaining that “[t]he word ‘may,’ when used in a statute, usually implies some degree of discretion”); *Rastelli v. Warden, Metro. Correctional Ctr.*, 782 F.2d 17, 23 (2d Cir. 1986) (interpreting the statute to recognize that “[t]he use of a permissive verb – ‘may review’ instead of ‘shall review’ – suggests a discretionary rather than mandatory” action); *Kentucky Commercial Mobile Radio Serv. Emergency Telecomms. Bd. v. TracFone Wireless, Inc.* 735 F. Supp. 2d 713, 730 (W.D. Ky. 2010) (noting that “[a]s a general rule, ‘may’ is given a permissive interpretation”). Courts, if faced with a clause with more than one plausible reading, will generally interpret the statute in a way that will not preempt state law. See, e.g., *Altria Grp. Inc. v. Good*, 555 U.S. 70, 77 (2008) (explaining that “when the text of a pre-emption clause is susceptible of more than one plausible reading, courts ordinarily ‘accept the reading that disfavors pre-emption’”).

²⁸¹ *Pacific Gas & Elec. Co. v. State Energy Res. Conservation & Dev. Comm’n*, 461 U.S. 190, 203-04 (1983) (noting that Congress can, if acting pursuant to its Constitutional authority, preempt state law “by stating so in express terms”). In addition, there are certain areas of the law where the federal interest deemed to have preempted the entire “field” of regulations. *Id.* However, despite the existence of some federal laws

provisions, courts assume that Congress used the recognized meaning of words and followed established rules of grammar.²⁸² Section 351 of the PHSA states that an interchangeable product “*may* be substituted for the reference product without the intervention of the health care provider who prescribed the reference product,”²⁸³ giving states the right to enact more restrictive legislation.²⁸⁴ This substitution provision in the BPCIA does not explicitly place any demand on states to change their laws, and a plain language reading of the statute rules out any finding of conflict preemption.²⁸⁵ If Congress intended to preempt existing state substitution laws and impose a mandatory directive on the states, it would have used the word “shall” and not the permissive term “may.”²⁸⁶ The term “may” does not make any mandatory demands on pharmacists that would compel them to act contrary to state law in order to comply with the federal law.²⁸⁷

Moreover, states have broad authority under their police

regulating prescription drugs, the states have broad authority to regulate practices impacting the health of their citizens. *See* *United States v. Lopez*, 514 U.S. 549, 594 (Thomas, J., concurring) (noting that “[t]hat the internal commerce of the States and the numerous state inspection, quarantine, and health laws had substantial effects on interstate commerce cannot be doubted. Nevertheless, they were not ‘surrendered to the general government’”); *see also* Michael C. Barnes & Gretchen Arndt, *The Best of Both Worlds: Applying Federal Commerce and State Police Powers To Reduce Prescription Drug Abuse*, 16 J. HEALTH CARE L. & POL’Y 272 (2013) (noting that both the federal government and the states regulate prescription drugs concurrently).

²⁸² *See* *United States v. Ron Pair Enters., Inc.*, 489 U.S. 235, 241 (1989) (interpreting a statute according to the natural meaning of words and the grammatical structure of phrases). *United States v. Goldenberg*, 168 U.S. 95, 102-03 (1897) (noting that the “primary and general rule of statutory construction is that the intent of the lawmaker is to be found in the language that he has used [and] [h]e is presumed to know the meaning of words and the rules of grammar”).

²⁸³ 42 U.S.C.A. § 262(i)(3).

²⁸⁴ State law governs generic substitution laws and the practice of pharmacy generally. *See, e.g.*, MD. CODE ANN., HEALTH OCC. § 12-504 (state generic substitution law); *see also* *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567, 2583 (2011) (noting that all states have laws governing generic drug substitution). The federal government regulates the approval of drugs for specific medical uses pursuant to the commerce clause. *See, e.g.*, *Medical Ctr. Pharm. v. Mukasey*, 536 F.3d 383, 394 (5th Cir. 2008) (recognizing that the FDA has authority to approve “new drugs” entering interstate commerce); *Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 67 (D.D.C. 1998) (noting that the FDA’s authority over prescription drugs is not plenary).

²⁸⁵ 42 U.S.C.A. § 262(i)(3).

²⁸⁶ *See, e.g.*, *Anderson v. Yungkau*, 329 U.S. 482, 485 (1947) (noting that statutes using the word “shall” impose mandatory demands, whereas statutes using the word “may” allow, but do not require, a specific action).

²⁸⁷ *Id.*

powers to regulate professional practice.²⁸⁸ States have traditionally regulated both the practices of pharmacy and medicine.²⁸⁹ In other cases involving pharmaceuticals, courts recognize that, in many cases, states can provide additional protections or rights that exceed those granted by federal law.²⁹⁰ The same reasoning applies when states choose, in the interests of patient safety, to prevent pharmacists from substituting biologic drugs without the consent of the patient's physician.²⁹¹

Thus, state substitution consent laws are valid because Congress has not unambiguously preempted state law, nor is there a clear conflict between the federal and state laws.²⁹² The substitution reference in the federal law merely reiterates for biologics what is already the status quo permitting state regulation for small molecule generic substitution.²⁹³ This is unsurprising because biologics law was, in large part, modeled on the Hatch-Waxman scheme, which does not preempt state substitution laws.²⁹⁴

B. Recommendations for State Legislation

Currently, five states — Virginia, Utah, Oregon, Florida, and North Dakota — have enacted FOB substitution laws, and as of August 2013, 12 states have proposed similar legislation.²⁹⁵ The

²⁸⁸ See, e.g., Barnes & Arndt, *supra* note 281 (noting that both the federal government and the states regulate prescription drugs concurrently). For example, courts have recognized that federal law does not restrict the ability of a physician to prescribe a legal drug for any purpose, regardless of whether the FDA has approved the drug for that specific use. See Wash. Legal Found. v. Henney, 202 F.3d 331, 333 (D.C. Cir. 2000) (approving of “off-label” prescriptions).

²⁸⁹ Letter from Michael O. Leavitt to Sen. Edward Kennedy (June 26, 2007) (on file with authors).

²⁹⁰ Cf. Wyeth v. Levine, 555 U.S. 555, 573-74 (2009) (rejecting an argument that the FDCA established both a “floor” and a “ceiling” regarding the adequacy of drug warning labels).

²⁹¹ See Abby Bernstein, *In debate over ‘biosimilars,’ patient safety should come first*, BALTIMORE SUN (May 22, 2013, 12:59 PM), <http://www.baltimoresun.com/news/opinion/oped/bs-ed-biosimilars-20130522,0,1560283.story>.

²⁹² See Arizona v. United States, 132 S. Ct. 2492, 2500-01 (2012).

²⁹³ See PLIVA, Inc. v. Mensing, 131 S. Ct. 2567, 2583 (2011) (Sotomayor, J., dissenting) (noting that states currently regulate the substitution of generic drugs).

²⁹⁴ See United States v. Novak, 476 F.3d 1041, 1051 (9th Cir. 2007) (assuming that when Congress enacts a new statute based on a prior statute, it intended the new law to be interpreted in the same way as the existing one).

²⁹⁵ States with proposed legislation include Arizona, Arkansas, California, Colorado, Illinois, Indiana, Maryland, Massachusetts, Mississippi, Pennsylvania, Texas, and

states that have enacted substitution legislation typically pull from federal law determinations of biosimilarity and interchangeability, making substitution permissible.²⁹⁶ For instance, on March 16, 2013, the Virginia General Assembly unanimously approved amendments to the state's generic substitution laws that directly addressed FOBs.²⁹⁷ The new Virginia law, like most other state biologic substitution laws, directly references the federal definitions and standards for biologics, biosimilarity, and interchangeability, making any federal determinations on drugs using those standards applicable to the state law.²⁹⁸ The Virginia law allows, but does not require, a pharmacist to substitute a biologic considered "interchangeable" under federal law for the prescribed brand RPB.²⁹⁹

Recognizing that FOBs require different substitution protocols than small-molecule generics, the state legislation should include several requirements. First, pharmacists should be required to obtain preapproval from the prescribing physicians before substituting an FOB for the RPB. Most of the current proposed and enacted legislation only requires pharmacists to notify the physicians *after* the substitution has already taken place. Under the Virginia law³⁰⁰ and a Maryland bill,³⁰¹ a pharmacist may wait as long as five business days (and possibly longer in some cases)³⁰² to notify the prescribing physician of a substitution. In the spring of 2013, North Dakota³⁰³ and Utah³⁰⁴ also enacted laws requiring post-substitution

Washington. CAL. PENSION & HEALTH BENEFITS COMM., CAL. PUB. EMPLOYEES' RET. SYS., AGENDA ITEM 5E (Aug. 2013), *available at* http://www.gphaonline.org/media/cms/CalPERS_SB598_Analysis.pdf. It should be noted that California's governor vetoed California's FOB substitution bill, SB 598, in October 2013 based on the urging of several dozen marketplace stakeholders. *See* Andrew Pollack, *Governor Vetoes Bill to Limit Use of Generic Drugs in California*, NY TIMES, Oct. 12, 2013, *available at* http://www.nytimes.com/2013/10/13/us/governor-vetoes-bill-to-limit-use-of-generic-drugs-in-california.html?_r=0.

²⁹⁶ *See* Va. HB 1422, 2013 Va. Legis. Serv. 412 (West) (amending VA. CODE ANN. §§ 54.1-3401, 54.1-3434.1, & 54.1-3457 and adding § 54.1-2408.04).

²⁹⁷ *Id.*

²⁹⁸ *Id.*

²⁹⁹ *Id.*

³⁰⁰ *Id.*

³⁰¹ SB 781, 433rd Sess. (Md. 2013).

³⁰² *See supra* note 296 about collaborative agreements in Virginia.

³⁰³ SB 2190, 63rd Assembly (N.D. 2013).

³⁰⁴ S.B. 78, 2013 Gen. Sess. (Utah 2013).

notification to the physician's office within 24 hours and three days, respectively. A similar Arizona bill requires notification within 72 hours.³⁰⁵ If passed, the Arizona bill would require notification to take the form of a mere notation in electronic medical records.³⁰⁶

Given the fact that FOBs can trigger adverse immune responses or other health problems, notifying a physician after the patient has ingested the drugs could fail to avert any adverse reaction.³⁰⁷ Furthermore, in some cases, it is possible that a physician could be unaware that a substitution has occurred, especially under proposed bills similar to the Arizona bill, which merely requires a pharmacist to enter information in a patient's electronic medical record, but does not require any other affirmative act to notify or alert the physician to the substitution.³⁰⁸ In such a case, it is possible that a substitution could go completely unnoticed by the prescribing physician until he or she next reviewed the patient's medical record, exposing the patient to an increased risk of an adverse reaction or diminished efficacy.³⁰⁹

In early 2013, the Indiana legislature considered a bill that would allow pharmacists to substitute interchangeable biologics, but only if physicians approved the substitution in advance by writing the words "may substitute" on the prescription.³¹⁰ Although the provision was not enacted in the spring of 2013, the Indiana House is expected to reconsider the matter after studying the issue further.³¹¹ Such an advance physician authorization

³⁰⁵ SB 1438, 51st Leg., 1st Reg. Sess. (Ariz. 2013).

³⁰⁶ *Id.*

³⁰⁷ See Testimony, Lawrence A. LaMotte, Vice President, Public Policy, Immune Deficiency Foundation, Testimony of Lawrence A. LaMotte on Indiana HB 1315 to Indiana Senate Health and Provider Services Committee (Mar. 11, 2013), available at <http://primaryimmune.org/idf-advocacy-center/idf-advocacy-center-activity/?aid=7576&sa=1> (testifying that failure to notify patients and physicians in advance of substitution will place patients with immune deficiencies at increased risk).

³⁰⁸ SB 1438, 51st Leg., 1st Reg. Sess. (Ariz. 2013) (noting that "[t]his [notification] requirement is satisfied if the substitution information is entered into an electronic system between prescribing medical practitioners and pharmacists, including electronic medical records").

³⁰⁹ *Id.* (requiring only a notification in electronic medical records).

³¹⁰ HB 1315, 118th Gen. Assembly, 1st Reg. Sess. (Ind. 2013), available at <http://www.in.gov/legislative/bills/2013/PDF/HB/HB1315.2.pdf>.

³¹¹ See BARNES & THORNBURG LLP, INDIANA LEGISLATIVE UPDATE: 118TH GENERAL ASSEMBLY 2-3 (2013), available at <http://www.indianacountycommissioners.org/assets/>

requirement should serve as a model for all states considering biologic substitution legislation to protect patients, and states with substitution laws already in place should amend such laws to match Indiana's language in order to prevent unnecessary risk to patients.³¹²

Specifically, these states should require pharmacists to obtain physician approval in advance of filling the prescription. Although some argue that such a requirement is overly burdensome,³¹³ most biologics are currently dispensed clinically or by mail-ordered pharmacy, and therefore, the burden to retail pharmacies should be small.

Second, to the extent that states do not implement optimal patient protections by requiring preauthorization from physicians, states must, at a minimum, require post-substitution notice and must not permit the substitution of biosimilar FOBs for RPBs. In such a case, substitution should only be permitted for FOBs that are deemed "interchangeable" and that are approved for the same delivery devices, containers, and number and subset of uses and delivery methods.

It is unacceptable to permit substitution for biosimilar FOBs because such medications are not required to go through clinical trials to demonstrate safety, purity, and potency.³¹⁴ Whereas, interchangeable FOBs must demonstrate, through *de novo* clinical trials, that substitutions from the RPB have no negative effect on safety and effectiveness, including as a result of immunogenicity, biosimilar FOBs do not.³¹⁵ As a result, the EU and many nations around the world have stated that substitution of biosimilar FOBs

docs/2013Legislative/indiana%20legislative%20update%20-%20week%2014.pdf.

³¹² Although the FDA does not exercise direct authority over state pharmacist substitution laws, the agency has indicated that it "believes that patients should not be switched from the innovator biological product to a follow-on biological product (or vice versa) without the express consent and advice of the patient's physician." See Letter from Frank Torti, Principal Deputy Commissioner and Chief Scientist, to Frank Pallone, Jr., Chairman, H. Comm. on Energy & Commerce (Sept. 18 2008), *available at* http://step.berkeley.edu/Journal_Club/paper2_110309.pdf.

³¹³ See GaBI Journal Editor, *US state legislation on biosimilars substitution*, 2 GENERICS & BIOSIMILARS INITIATIVE J. 155 (2013), *available at* <http://gabi-journal.net/us-state-legislation-on-biosimilars-substitution.html>.

³¹⁴ 42 U.S.C.A. § 262(k)(2)(A)(i)(I).

³¹⁵ Richard O. Dolinar & Michael S. Reilly, *The future of biologic therapy: a pathway forward for biosimilars*, 2 GENERICS & BIOSIMILARS INITIATIVE J. 36 (2013), *available at* <http://gabi-journal.net/the-future-of-biological-therapy-a-pathway-forward-for-biosimilars.html>.

is inappropriate.³¹⁶ Moreover, as discussed above, differences in delivery devices and subsets of uses can result in immunogenicity. Therefore, if an FOB is substituted for a RPB, patients and physicians can feel most assured that all reasonable efforts have been undertaken to assess the possible adverse effects on a patient, in terms of diminished safety or effectiveness, when the medication is deemed “interchangeable” and has been approved for the same delivery devices, containers, and number and subset of uses and delivery methods as the RPB.³¹⁷

Additionally, physicians must be able to prevent substitution. The prescribing physician is in the best position to evaluate a patient’s treatment history and options and must have a way to ensure that the patient receives the precise medication that such physician believes should be dispensed.³¹⁸ Therefore, even if states refuse to require pre-authorization, physicians must be able, and should be encouraged, to write phrases such as “dispense as written” or “brand medically necessary” on the prescription in order to control the dispensation of a RPB over an inappropriate FOB.³¹⁹ Under Virginia’s law, the pharmacist cannot substitute a drug if the prescribing physician indicates that the “brand is medically necessary.”³²⁰ Other states should follow Virginia’s lead.

Moreover, should a pharmacist wish to substitute an FOB for a RPB, the patient’s approval should be required as well. Often, patients with chronic medical conditions try multiple treatment regimens in order to manage their conditions and minimize side effects to the greatest extent possible. This places patients in a strong position to know, generally speaking, which treatment works in their unique circumstance.³²¹ By requiring patient approval, the patient has the opportunity to discuss past treatments with the pharmacist or physician in order to avoid any

³¹⁶ *Id.*

³¹⁷ See Biotechnology Industry Organization, *BIO Principles on Patient Safety in the Substitution of Biologic Products*, <http://www.bio.org/sites/default/files/BIO-Principles-on-Substitution.pdf> (last visited Apr. 14, 2014) [hereinafter *Bio Principles on Patient Safety*].

³¹⁸ *Id.*

³¹⁹ *Id.*

³²⁰ *Id.*

³²¹ *Id.*

potential future problems.³²² Moreover, Virginia's law states that a pharmacist may not substitute a drug if the patient insists on receiving the brand RPB.³²³ Therefore, if the patient were notified beforehand, he or she could make an informed decision, which the pharmacist must obey according to law.

Finally, pharmacists and physicians should keep records of the substitution. Many biologics that are used to treat chronic conditions change over time, making it important for a patient's treatment team to have a record that documents how and when a patient was treated with biologic therapies in order to provide insight should an adverse reaction occur.³²⁴ Such a step should not be burdensome given the fact that pharmacists already maintain similar records for Medicare patients and at the hospital pharmacy level, and most of the legislation under current consideration requires retail pharmacists to retain records of substitutions.³²⁵ However, the length of time that such records have to be kept varies from two to 10 years.³²⁶ Adverse reactions and disease evolutions, however, can happen over the span of several years. Therefore, states should require a minimum of a 10-year retention period, if not a permanent record.

C. *Threat to Patient Safety Outweighs Minimal Cost Savings*

In considering any new legislation affecting health care, it is important to engage in a cost-benefit analysis to examine the true impact on patient welfare.³²⁷ The costs of substituting FOBs for biologics are much higher than costs associated with substituting generic small molecule drugs for brand drugs, and will negate much of the desired cost savings associated with substitution.³²⁸ FOB substitutions pose a greater threat to patient safety than

³²² *Bio Principles on Patient Safety*, *supra* note 317.

³²³ *Id.*

³²⁴ *Id.*

³²⁵ See GaBI Journal Editor, *supra* note 313.

³²⁶ *Id.*

³²⁷ See Paula Tironi, *Pharmaceutical Pricing: A Review of Proposals to Improve Access and Affordability of Prescription Drugs*, 19 ANN. HEALTH L. 311, 314 (2010) (using a cost benefit analysis to evaluate choice of prescription drugs).

³²⁸ R. TERRY HISEY ET AL., DELOITTE, THE FOLLOW-ON BIOLOGICS MARKET: ENTER AT YOUR OWN RISK 4, 8 (2011), available at https://www.deloitte.com/assets/Dcom-Korea/Local%20Assets/Documents/Industry/LSHC/kr_LSHC_FollowBiologicsMarket_113011.pdf.

small molecule generic substitutions, and such substitutions do not yield the substantial cost savings observed in the small-molecule generic market.³²⁹ In contrast to 80 percent price reductions to consumers and payers found in well-developed, small molecule generic markets, manufacturers of FOBs are unlikely to discount their prices lower than 10 to 30 percent from the RPB.³³⁰ The FTC has also estimated that even after FOB entry, innovators are still expected to retain between 70 and 90 percent of the market share because of significant barriers to entry, including costs and expectations that many physicians will be reluctant to switch patients to FOBs.³³¹

Many factors contribute to the relatively high costs of FOBs, including increased approval expenses, intensive studies, and higher fixed manufacturing costs necessary to create these complex proteins.³³² In Europe, the cost of conducting the abbreviated clinical trial required for approval of an FOB was estimated at \$10-\$40 million, compared with \$1-\$2 million spent to prove “bioequivalence” for small molecule generics.³³³ For the most complex biologics, development costs to produce an FOB may exceed \$100 million.³³⁴ Even after development, costs for biologics are significantly higher, and researchers have estimated that fixed manufacturing and material costs for new and follow-on biologics may be up to 150 percent greater than the costs for traditional drugs.³³⁵

In the case of biologics, the very real risk of adverse reactions should trump the minimal cost savings that could result from pharmacist-directed substitution because adverse events are costly

³²⁹ See FTC REPORT, *supra* note 5; see also Vernon et al., *supra* note 45, at 67 (concluding that the cost savings for follow-on biologics will be much less than traditional generics).

³³⁰ FTC REPORT, *supra* note 5, at vi; see also THOMAS, *supra* note 101, at 17-18 (noting that some studies have found follow-on biologics will only sell for 10 percent to 20 percent less than the innovator product).

³³¹ FTC REPORT, *supra* note 5, at vi.

³³² See Henry Grabowski et al., *The Market for Follow-on Biologics: How Will It Evolve*, 25 HEALTH AFFAIRS 1291, 1293-94 (2006).

³³³ *Id.*

³³⁴ See Henry Grabowski, et al., *Follow-on Biologics: Implementation Challenges and Opportunities: Implementation of the Biosimilar Pathway: Economic and Policy Issues*, 41 SETON HALL L. REV. 511, 522 (2011) (noting that the most complex follow-on products may cost up to \$150 million and take over eight years to develop).

³³⁵ Vernon et al., *supra* note 45, at 66-67.

and negate any cost savings.³³⁶ The fact that many users of biologics are already in poor health further outweighs any speculative economic benefits.³³⁷ Substituting an FOB without prior approval of the physician could put patients in grave risk for a life-threatening immune reaction or diminished effectiveness of the treatment.³³⁸ Many patients administer biologic treatments to themselves at home, placing them at risk when they try FOBs for the first time — especially if they are alone.³³⁹ If a patient returns home from a pharmacy and immediately ingests his or her FOB medication, even the 24-hour post-substitution notice provisions in some of the draft state legislation would not give a physician enough warning to avert or quickly respond to a potentially deadly reaction.³⁴⁰ A mere 10 to 30 percent in consumer cost savings does not justify this risk to patient safety, even if the risk of an adverse reaction is relatively small.³⁴¹

The evaluation of this trade-off between cost savings and safety should be made as part of an informed, confidential conversation between the patient and his or her physician.³⁴²

³³⁶ See Liang, *supra* note 231, at 415.

³³⁷ See Liang, *supra* note 231, at 415 (arguing that when considering biologics legislation “policymakers should consider information gaps related to substantive policy issues, the vulnerability of the polity that must bear the risk of policy failure, and the degree of potential harm if the policy fails[,]” which in the case of biologics, means that “policymakers should err on the side of safety rather than the side of potential economic benefit”).

³³⁸ See Testimony, Lawrence A. LaMotte, Vice President, Public Policy, Immune Deficiency Foundation, Testimony of Lawrence A. LaMotte on Indiana HB 1315 to Indiana Senate Health and Provider Services Committee (Mar. 11, 2013), *available at* <http://primaryimmune.org/idf-advocacy-center/idf-advocacy-center-activity/?aid=7576&sa=1>.

³³⁹ *Id.* (noting that “standards of care for treatment of patients with primary immunodeficiency diseases which says that when an Ig therapy is changed, the new product must be infused under the supervision of a physician because of the greater probability of adverse reactions”).

³⁴⁰ *Id.*

³⁴¹ See Mark Geistfeld, *Reconciling Cost-Benefit Analysis with the Principle That Safety Matters More than Money*, 76 N.Y.U.L. REV. 114, 124 (2001) (arguing that policymakers should always give more weight to safety because “physical injury is more disruptive to the pursuit of one’s life plan than is the loss of money”).

³⁴² See Jacob S. Sherkow, *Purdue Pharma & Oxycontin: Regulatory Gamesmanship? A Debate*, THE CENTER FOR LAW AND BIOSCIENCES, STANFORD LAW SCHOOL (May 5, 2013), <http://blogs.law.stanford.edu/lawandbiosciences/2013/05/05/purdue-pharma-oxycontin-regulatory-gamesmanship-a-debate/> (arguing that “[s]ome risks [posed by generic drugs] are too great to allow the public to assume them on their own, in the interest of low prices”); *see also* Allan Tennant, *Generic Substitution*, NAT’L KIDNEY FED’N (Apr. 17, 2009), <http://www.kidney.org.uk/help/medical-information-from-the-nkf-/medical-info-main-switch-meds-/main-switch-meds-dda-generic-subs/> (arguing generic

Moreover, as noted above, the pharmacy will likely be rewarded financially if an FOB is substituted, creating the potential for dangerous conflicts of interest between the pharmacy's self interest and the patient's health and safety.³⁴³ As such, the cost-benefit analysis further affirms that physicians, in conjunction with their patients, are in the best position to determine whether to substitute an FOB for a biologic medication.

Conclusion

The FDA's recent Guidance on biosimilarity and interchangeability shows that the agency is willing to sacrifice patient safety and the protection of trade secrets in exchange for the possibility of minimal cost savings. As such, manufacturers may challenge FDA actions as uncompensated use of trade secrets and takings, and may also challenge the FDA's interpretation of the BPCIA in federal guidance documents. Moreover, the federal government's expansive interpretation of biosimilarity and interchangeability risks harm to patients when these determinations are applied under state laws, which allow pharmacists to substitute an FOB for a RPB. Therefore, state legislatures, in their role as the regulators of pharmacy and medicine, must adopt legislation that puts patient safety first. Although in some cases, interchangeable FOBs could be safely dispensed to patients, this decision should be the result of an informed, confidential conversation between the physician and the patient. If states enact FOB substitution legislation with the requirements suggested herein, patient safety will be properly prioritized.

substitution may adversely affect the doctor-patient relationship).

³⁴³ See Fein, *supra* note 273.