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Anna B. Laakmann
Lewis & Clark Law School

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THE HATCH-WAXMAN ACT'S SIDE EFFECTS: PRECAUTIONS FOR BIOSIMILARS

*Anna B. Laakmann**

The Drug Price Competition and Patent Term Restoration Act of 1984 (generally known as the Hatch-Waxman Act, or “Hatch-Waxman”) was designed to expedite regulatory approval of generic drugs while simultaneously preserving incentives for innovators to invest in the research and development of new drugs. While Hatch-Waxman has undoubtedly achieved its aim of creating a robust generic pharmaceuticals market, it has also produced several unanticipated consequences. Its changes to the federal regulatory scheme have yielded convoluted products liability rules, upsetting the conventional notion that the seller of a defective product is liable for harm caused by its intended use. In addition, its modifications to patent law have had the perverse effects of propagating patents of questionable value and encouraging potentially anti-competitive agreements between generic and brand name manufacturers.

Hatch-Waxman’s emergent repercussions are particularly salient in light of the recent passage of the Biologics Price Competition and Innovation Act (BPCIA). The BPCIA, enacted as part of the Patient Protection and Affordable Care Act of 2010, crafted a compromise between pioneer and follow-on biologics manufacturers patterned after Hatch-Waxman’s regulatory scheme for pharmaceuticals. This Article reviews Hatch-Waxman unintended effects, and suggests that they should serve as precautionary guideposts for implementation of the BPCIA. The FDA and lawmakers should heed these potential pitfalls and proactively confront unavoidable tradeoffs between safety, cost, and access to therapeutic biologics.

* Assistant Professor, Lewis & Clark Law School. J.D., Stanford University; M.D., University of Pennsylvania; B.A., Williams College. I wish to thank the staff of the *Loyola of Los Angeles Law Review* for their invitation to contribute to Volume 47’s symposium issue on emerging health law issues, and for their excellent editorial assistance.

TABLE OF CONTENTS

I. INTRODUCTION	919
II. PATIENT SAFETY CONCERNS	921
A. Bioequivalence and Generic Substitution.....	921
B. Labeling Requirements and the Duty to Warn	922
III. PATENT COMPLICATIONS	927
A. Evergreening and Inventing Around	927
B. Pay-for-Delay Settlements	930
IV. IMPLICATIONS FOR THE BIOLOGICS PRICE COMPETITION AND INNOVATION ACT	932
A. Defining Similarity and Interchangeability	933
B. Interplay Between Federal and State Regulation	935
C. Balancing Competition and Innovation	938
IV. CONCLUSION	941

I. INTRODUCTION

The Drug Price Competition and Patent Term Restoration Act of 1984 (generally known as the Hatch-Waxman Act, or “Hatch-Waxman”) structured a compromise between brand name and generic pharmaceutical manufacturers.¹ The legislative goal was to expedite the approval of generic drugs while simultaneously preserving sufficient incentives for innovators to invest in the research and development of new drugs.² Hatch-Waxman made several changes to patent law and the federal Food, Drug, and Cosmetic Act (FDCA). It authorized patent term extensions for innovative drugs to compensate for patent life lost during premarket review by the Food and Drug Administration (FDA)³ and created FDA-administered exclusivities for new products and indications.⁴ Hatch-Waxman also established an abbreviated new drug application (ANDA) pathway under which generic manufacturers may rely on FDA findings of safety and efficacy for brand name equivalents and avoid the expensive process of producing their own clinical trials data.⁵ In addition, it exempted from patent infringement the use of patented inventions for research intended to generate information for ANDA submission.⁶ Finally, it created a complex scheme whereby generic manufacturers can challenge the validity and scope of brand name manufacturers’ patents prior to bringing generic versions to market.⁷

Generic drug utilization has dramatically increased since

1. Pub. L. No. 98-417, § 101, 98 Stat. 1538, 1585 (1984) (codified as amended at 35 U.S.C. § 156 (2012)).

2. *Abbott Labs. v. Young*, 920 F.2d 984, 991 (D.C. Cir. 1990) (“The Act emerged from Congress’s efforts to balance two conflicting policy objectives: to induce brand name pharmaceutical firms to make the investments necessary to research and develop new drug products, while simultaneously enabling competitors to bring cheaper, generic copies of these drugs to market.”).

3. 35 U.S.C. § 156(c) (2006) (patent life is extended by a “time equal to the regulatory review period for the approved product”); *see id.* § 156(g)(6)(A) (capping the extension at five years).

4. 21 U.S.C. § 355(j)(5)(F)(ii) (2006) (five years of data exclusivity for FDA-approved new chemical entities (NCEs); *Id.* § 355(j)(5)(F)(iii) (three years of data exclusivity for FDA-approved new indications requiring submission of clinical data).

5. *Id.* § 355(j).

6. 35 U.S.C. § 271(e)(1).

7. 21 U.S.C. § 355(j)(5)(B).

Hatch-Waxman's enactment. In 2012, generics accounted for 84 percent of all U.S. prescriptions,⁸ compared to only 19 percent in 1984.⁹ This growth has stemmed in part from Hatch-Waxman's incentives for generic manufacturers to assert that brand name patents are either invalid or not infringed by generic versions.¹⁰ The passage in all fifty states of generic substitution laws, which enable pharmacists to fill prescriptions for brand name drugs with their generic copies, has further fueled widespread generic adoption.¹¹

While Hatch-Waxman has undoubtedly achieved its aim of producing a robust generic pharmaceuticals market, it has also created several unanticipated consequences. Its modifications to the federal regulatory scheme have produced convoluted products liability rules, upsetting the conventional notion that the seller of a defective product is liable for harm caused by its intended use.¹² Additionally, its provisions that are designed to encourage generic manufacturers to challenge unexpired patents have had the perverse effects of propagating patents of questionable value and encouraging potentially anti-competitive agreements between generic and brand name manufacturers.¹³

Hatch-Waxman's emergent repercussions are particularly salient in light of the recent passage of the Biologics Price Competition and Innovation Act (BPCIA). The BPCIA, enacted as part of the Patient Protection and Affordable Care Act of 2010, crafted a compromise between pioneer and follow-on biologics manufacturers patterned after Hatch-Waxman's regulatory scheme for pharmaceuticals.¹⁴

8. Elizabeth Richardson, *Health Policy Brief: Biosimilars*, HEALTH AFFAIRS, Oct. 10, 2013, at 2, available at http://www.healthaffairs.org/healthpolicybriefs/brief.php?brief_id=100.

9. Henry Grabowski et al., *Implementation of the Biosimilar Pathway: Economic and Policy Issues*, 41 SETON HALL L. REV. 511, 537 (2011).

10. C. Scott Hemphill & Bhaven N. Sampat, *When Do Generics Challenge Drug Patents?*, 8 J. EMPIRICAL LEGAL STUD. 613, 614 (2011) ("[T]he prevalence of challenges has risen dramatically over the past 25 years, placing them at the center of a vigorous debate about drug innovation and access."); C. Scott Hemphill, *Paying For Delay: Pharmaceutical Patent Settlement as a Regulatory Design Problem*, 81 N.Y.U. L. REV. 1553, 1567 (2006) (noting that nine of the ten best-selling drugs in 2000 attracted pre-expiration patent challenges).

11. Wyeth, Inc. v. Weeks, 2014 WL 4055813, at *16 (Ala. Aug. 15, 2014).

12. See *infra* Part II.A.

13. See *infra* Parts III.A and III.B.

14. Patient Protection and Affordable Care Act (PPACA), Pub. L. No. 111-148, § 7001-03, 124 Stat. 119, 804-21 (2010) [hereinafter BPCIA]. Biologics are animal-based large molecules typically regulated under the Public Service Act, which contained no provision for an abbreviated approval pathway prior to passage of the BPCIA. See 42 U.S.C.A § 262 (2012); Grabowski et al., *supra* note 9, at 512-17.

This Article highlights the policy problems spawned by Hatch-Waxman and anticipates the challenges that lie ahead with the advent of biosimilars.¹⁵

II. PATIENT SAFETY CONCERNS

A. Bioequivalence and Generic Substitution

In order to use Hatch-Waxman's ANDA pathway, a generic drug manufacturer must show that its product contains the same active ingredient(s) as the brand name drug; has the same route of administration, dosage form, and strength; and is "bioequivalent."¹⁶ Bioequivalence is established by showing that the rate and extent of absorption of the generic drug into the patient's bloodstream is within 80 percent to 125 percent of that of the brand name drug.¹⁷ If a generic drug is "therapeutically equivalent" to its brand name counterpart, states may permit pharmacists to substitute the generic for the brand name drug without authorization from the prescribing physician.¹⁸ Therapeutic equivalents "can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling."¹⁹ All fifty states have enacted laws that either allow or mandate generic substitution.²⁰ Pharmacies are encouraged to substitute generics for brand name drugs, since they commonly receive higher dispensing fees for

15. A "biosimilar" is a biologic molecule that closely resembles a biologic product that has already been approved by the FDA. The BPCIA authorizes the FDA to approve a biosimilar through a streamlined process if there are "no clinically meaningful differences . . . in terms of safety, purity, and potency" between the reference product and the biosimilar. 42 U.S.C. §262(i)(2). *See infra* Part IV.A.

16. Janet Freilich, *The Paradox of Legal Equivalents and Scientific Equivalence: Reconciling Patent Law's Doctrine of Equivalents with the FDA's Bioequivalence Requirement*, 66 SMU L. REV. 59, 70 (2013).

17. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES FOR ORALLY ADMINISTERED DRUG PRODUCTS—GENERIC CONSIDERATIONS 20 (2003), available at <http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070124.pdf>.

18. Grabowski et al., *supra* note 9, at 524.

19. FOOD & DRUG ADMIN., APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS vii (2012) [hereinafter Orange Book], available at <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm071436.pdf>.

20. David R. Holmes et al., *American College of Cardiology Foundation and American Heart Association 2011 Health Policy Statement on Therapeutic Interchange and Substitution*, 58 J. AM. C. CARDIOLOGY 1287, 1305–07 (2011).

selling generics than for selling brand name equivalents.²¹

Although this practice helps to reduce healthcare costs, it also raises safety concerns.²² Contrary to popular perception, generic drugs are rarely identical to their brand name counterparts.²³ Generics must contain the same active ingredients as brand name drugs, but the FDA permits generic companies to use different inactive ingredients.²⁴ “High variability” drugs have absorption rates that differ considerably from patient to patient, and small differences in the formulations of generic and brand name versions may yield clinically significant effects.²⁵ Generic substitution can pose safety hazards even in cases that do not involve high variability drugs. For example, case evidence suggests that some patients with epilepsy suffer more frequent seizures following substitution of brand name antiepileptic agents with generic versions.²⁶ Concerns that switching between pioneer and generic equivalents could adversely affect patients have led some states to exempt certain classes of drugs from state substitution laws.²⁷

B. Labeling Requirements and the Duty to Warn

Hatch-Waxman’s expedited approval pathway has created thorny regulatory and tort issues with regard to dangers that are discovered after generic versions of a brand name drug have entered

21. HENRY GRABOWSKI, COMPETITION BETWEEN GENERIC AND BRANDED DRUGS, PHARMACEUTICAL INNOVATION: INCENTIVES, COMPETITION, AND COST-BENEFIT ANALYSIS IN INTERNATIONAL PERSPECTIVE 153, 156 (Frank A. Sloan & Chee-Ruey Hsieh eds., 2007).

22. See Peter Meredith, *Bioequivalence and Other Unresolved Issues in Generic Drug Substitution*, 25 CLINICAL THERAPEUTICS 2875, 2875–76 (2003).

23. Freilich, *supra* note 16, at 61; Melinda Beck, *Inexact Copies: How Generics Differ from Brand Names*, WALL ST. J., Apr. 22, 2008, at D1 (reporting that an FDA review found that generic Wellbutrin XL reached its maximum blood concentration in about half the time as the brand name version, but dismissing this difference as clinically insignificant).

24. Freilich, *supra* note 16, at 81.

25. *Id.* at 72 (noting that the pharmacokinetic parameters of generic and brand name “high variability” drugs may differ by more than 10 percent).

26. M.J. Berg et al., *Generic Substitution in the Treatment of Epilepsy: Case Evidence of Breakthrough Seizures*, 71 NEUROLOGY 525, 525–30 (2008). See also R. Talati et al., *Efficacy and Safety of Innovator Versus Generic Drugs in Patients With Epilepsy: A Systematic Review*, 32 PHARMACOTHERAPY 314 (2012) (concluding, based on limited data, that innovator and generic antiepileptic agents are equally safe and effective, but that switching from one version to the other may be associated with more hospitalizations and longer hospital stays).

27. See, e.g., *Abbott Labs. v. Mylan Pharms., Inc.*, 15 So. 3d 642, 645–46, 656–57 (Fla. Dist. Ct. App. 2009); Jonathan D. Rockoff, *Cost of Medicine Could Increase: Brand-Name Drugmakers Target Generic Prescriptions*, BALT. SUN, June 17, 2008, at 1A (noting recent laws passed in Tennessee and Utah that prohibit the substitution of antiepileptic agents).

the market. FDA approval is not a guarantee of safety and efficacy, as risks frequently are identified only after widespread use in the general patient population.²⁸ To bolster patient safety, the FDA mandates post-market surveillance and compels manufacturers to establish risk mitigation and evaluation strategies.²⁹ The agency may require drug sponsors to perform additional clinical studies in order to investigate risks that are discovered after FDA approval.³⁰ It also may prescribe labeling changes if it becomes aware of new information that must be included in the product's labeling.³¹

FDA labeling regulations impose different post-market obligations on brand name and generic manufacturers. These differences proved crucial in a series of Supreme Court decisions considering the preemptive effects of federal regulatory law on state tort claims alleging that drug manufacturers inadequately warned of risks that arose after market approval. In 2009, the Court held in *Wyeth v. Levine*³² that federal law did not preempt a claim against a brand name drug manufacturer asserting that the label contained an inadequate warning about the risks of a particular method of administration.³³ The Court reasoned that because manufacturers do not need FDA preapproval to strengthen the warnings on their labels, and there was no evidence that the FDA would have prohibited Wyeth from making such a labeling change, it was not impossible for Wyeth to satisfy both federal regulatory and state tort duties.³⁴

But two years later, in *PLIVA v. Mensing*,³⁵ the Court held that federal law did preempt a failure-to-warn claim against a generic drug manufacturer.³⁶ The Court explained that the FDA requires that a generic drug's warning always be the same as that on the label of its brand name reference product; therefore, a generic manufacturer

28. Anna B. Laakmann, *Collapsing the Distinction Between Experimentation and Treatment in the Regulation of New Drugs*, 62 ALA L. REV. 305, 327–29 (2011); Lars Noah, *Informed Consent and the Elusive Dichotomy Between Standard and Experimental Therapy*, 28 AM. J.L. & MED. 361, 394 (2002) (“The issuance of a product license does not magically transform an investigational medical technology into one that has matured fully and requires no additional scrutiny.”).

29. 21 U.S.C. § 355-1(a)(1)–(2) (2012).

30. *Id.* § 355(o)(3).

31. *Id.* § 355(o)(4).

32. 555 U.S. 555 (2009).

33. *Id.*

34. *Id.* at 570–73.

35. 131 S. Ct. 2567 (2011).

36. *Id.*

would violate federal law if it unilaterally made changes to strengthen its warning.³⁷ Thus, unlike brand name manufacturers, it would be impossible for generic manufacturers to comply with both federal sameness requirements and state tort duties mandating warnings that are stronger than those listed in the FDA-approved generic label.³⁸

In 2013, the Supreme Court extended the scope of generic manufacturers' protection from tort liability by holding that federal law also preempted claims that generic drugs were defectively designed.³⁹ The Court reasoned that federal regulations forbade a generic manufacturer both from changing the chemical composition of its drug's active ingredients and from independently revising its warning label; therefore, impossibility preemption applied.⁴⁰ The Court rejected the plaintiff's argument that the generic manufacturer could have complied with both federal regulatory and state tort law by simply withdrawing its product from the market.⁴¹

Can patients who are harmed by generic drugs sue the manufacturer of the *brand name* reference product? The majority of courts that have grappled with this question have adopted the Fourth Circuit's reasoning in *Foster v. American Home Products Corp.*⁴² to conclude that they cannot.⁴³ In *Foster*, the plaintiffs' daughter died after taking a generic form of the brand name drug Phenergan.⁴⁴ They sued the manufacturer of Phenergan, asserting negligent misrepresentation and strict liability.⁴⁵ The federal district court dismissed the strict liability claim because the brand name firm had not manufactured the product that had allegedly caused the injury.⁴⁶ The district court allowed the negligence claim to proceed, but the Fourth Circuit reversed this decision.⁴⁷ Applying Maryland law, the appeals court reasoned that the brand name manufacturer did not owe

37. *Id.* at 2574–75.

38. *Id.* at 2577–78.

39. *Mut. Pharm. Co., Inc. v. Bartlett*, 133 S. Ct. 2466 (2013).

40. *Id.* at 2473–77.

41. *Id.* at 2478 (rejecting the First Circuit's "stop-selling rationale" for why impossibility preemption should not apply).

42. *Foster v. Am. Home Prods. Corp.*, 29 F.3d 165 (4th Cir. 1994).

43. *Mensing v. Wyeth, Inc.*, 588 F.3d 603, 613 (8th Cir. 2009) (noting that the "overwhelming majority" of courts considering the issue have followed *Foster*).

44. *Foster*, 29 F.3d at 166.

45. *Id.* at 167.

46. *Id.* at 166–67.

47. *Id.* at 171–72.

a duty to the user of a generic version of its drug, even if it was foreseeable to the brand name manufacturer that statements contained in its label could result in injury to the generic user.⁴⁸

*Conte v. Wyeth*⁴⁹ is a notable exception to the prevailing view that a person who is harmed by a generic drug cannot assert a negligent misrepresentation claim against the brand name manufacturer.⁵⁰ The California Court of Appeals reasoned that brand name firms owe a duty to all persons whose physicians foreseeably rely on the information contained in their product labels, including those who take generic versions of the prescribed drug.⁵¹ Citing FDA bioequivalence requirements and state substitution laws, the court concluded that it was foreseeable as a matter of law that a prescription for a generic version of Wyeth's drug Reglan would be filled in reliance on the information disclosed in Reglan's label.⁵² The court rejected Wyeth's argument that it is unfair to hold brand name manufacturers liable for injuries caused by their generic competitors' drugs, given that innovators bear the costly burden of generating information for FDA approval "while generic manufacturers merely 'rid[e their] coattails.'"⁵³

Although *Conte* represents the minority view,⁵⁴ the Supreme Court's recent preemption jurisprudence might compel more courts to entertain negligent misrepresentation claims against brand name manufacturers for harms caused by generic drugs. Since compliance with FDA sameness requirements essentially immunizes generic

48. *Id.* at 171.

49. 168 Cal. App. 4th 89 (2008).

50. *Id.* at 94–95.

51. *Id.*

52. *Id.* at 105 ("In California, as in most states, pharmacists have long been authorized by statute to fill prescriptions for name-brand drugs with their generic equivalents unless the prescribing physician expressly forbids such a substitution [I]t is also eminently foreseeable that a physician might prescribe generic metoclopramide in reliance on Wyeth's representations about Reglan.").

53. *Id.* at 109.

54. Two other courts have followed *Conte*. See *Kellogg v. Wyeth*, 762 F. Supp. 2d 694 (D. Vt. 2010) (holding that a brand name manufacturer had a duty to use due care in disseminating information about its drug and that a genuine issue of material fact existed as to whether the plaintiff's physicians relied upon information provided by the brand name manufacturer when they prescribed generic versions of the drug); *Wyeth, Inc. v. Weeks*, 2014 WL 4055813, at *16 (Ala. Aug. 15, 2014) (rejecting *Foster's* holding that a plaintiff harmed by a generic drug is barred from asserting a tort claim against the brand name manufacturer and noting that "[t]he *Foster* court's finding that manufacturers of generic drugs are responsible for the representations they make in their labeling regarding their products is flawed based on the 'sameness' requirement discussed in *PLIVA*").

manufacturers from tort liability,⁵⁵ the brand name manufacturer may be the only possible defendant that can be sued by a patient harmed by a generic drug. Courts that wish to ensure that such plaintiffs have a viable avenue of relief might be inclined to adopt *Conte's* view of innovator liability. Such an approach would advance compensatory goals, but could further dampen the incentives to create new drugs and thus reduce overall patient welfare.

In November 2013, the FDA proposed a rule that would mitigate the differential impact of the Supreme Court's preemption jurisprudence on tort claims against brand name and generic manufacturers.⁵⁶ The proposed rule would permit ANDA holders, like brand name manufacturers, to change their labels in response to new risk information without obtaining FDA preapproval.⁵⁷ Impossibility preemption presumably would no longer apply to claims against generic manufacturers if the FDA were to authorize generic firms to unilaterally update their labels in response to newly discovered harms. But the patient protection and victim compensation objectives furthered by such changes would come at a steep price. Generic manufacturers are able to offer low-cost drugs precisely because they are not obligated to generate, aggregate, and analyze safety and efficacy data about their products, as innovators are required to do.⁵⁸ If federal regulations and tort law were to change in ways that compel generic manufacturers to do more in the post-market phase, the cost to sell generic pharmaceuticals would increase and drug prices would correspondingly rise. Moreover, the benefits of uniformity might be lost if the warnings on generic labels

55. Generic manufacturers may still be held liable for failing to timely update their drug labels in response to labeling changes made by the brand name reference product sponsor. *See, e.g., In re Fosamax Products Liab. Litig.*, 965 F. Supp. 2d 413, 416–19 (S.D.N.Y. 2013) (holding that “failure to update” claims against the Generic Defendants were not preempted).

56. *See* Supplemental Applications Proposing Labeling Changes For Approved Drugs and Biological Products, 78 Fed. Reg. 67985-02 (proposed Nov. 13, 2013) (to be codified at 21 C.F.R. pt. 314 and 601).

57. *Id.* *See also* Katie Thomas, *Label Updates May Be Allowed For Generics*, N.Y. TIMES, Nov. 8, 2013, http://www.nytimes.com/2013/11/09/business/fda-proposes-letting-generic-drug-companies-alter-labels.html?_r=0 (including a statement by a representative of the trade group for the generics industry questioning whether the FDA has statutory authority to promulgate this regulation).

58. Emily Michiko Morris, *The Myth of Generic Pharmaceutical Competition Under the Hatch-Waxman Act*, 22 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 245, 266, 281 (2011) (noting that, unlike generic manufacturers, brand name manufacturers provide education, safety and efficacy data, and other social benefits).

were no longer required at all times to be identical to those of brand name drugs. Variations in the warning labels for brand name and generic versions of a drug would undermine the concept of a truly generic market. This could hamper the operation of state substitution laws, create patient and prescriber confusion, and exacerbate safety concerns.

III. PATENT COMPLICATIONS

A. *Evergreening and Inventing Around*

Manufacturers of new chemical entities (NCEs) list the patents covering their products in an FDA compendium commonly known as the Orange Book.⁵⁹ Generic manufacturers filing ANDAs must certify either: (i) that the NCE they wish to imitate is not covered by a patent; (ii) that any such listed patents have expired; (iii) that any such listed patents will have expired by the time the generic plans to enter the market; or (iv) that any such listed patents are invalid, not infringed by the generic product, or both.⁶⁰ These elections, known as paragraph I, II, III, and IV certifications respectively, give both the FDA and the brand name manufacturer notice of the ANDA applicant's intent.⁶¹ The first ANDA applicant to file a paragraph IV certification is eligible to receive 180 days of market exclusivity as the only generic manufacturer of the reference drug.⁶²

In patent infringement cases that arise from a paragraph IV certification, courts must consider the legal relevance of the generic manufacturer's assertion to the FDA that its product is bioequivalent to the brand name version. In *Abbott Laboratories v. Sandoz, Inc.*,⁶³ the Federal Circuit explained that bioequivalency and patent infringement are two distinct concepts. While bioequivalency is a medical and regulatory matter for the FDA, patent infringement is a legal issue that turns on comparative analysis of the claim elements and the accused product.⁶⁴ The upshot is that a generic drug can be

59. Hemphill & Sampat, *supra* note 10, at 618.

60. 21 U.S.C. § 355(j)(2)(A)(vii) (2006).

61. Gerald J. Mossinghoff, *Overview of the Hatch-Waxman Act and Its Impact on the Drug Development Process*, 54 FOOD & DRUG L.J. 187, 189–90 (1999).

62. 21 U.S.C. § 355(j)(5)(B)(iv) (2006).

63. 566 F.3d 1282, 1296–98 (Fed. Cir. 2009).

64. *Id.* at 1298 (“Bioequivalency is a regulatory and medical concern aimed at establishing that two compounds are effectively the same for pharmaceutical purposes. In contrast, equivalency for purposes of patent infringement requires an element-by-element comparison of

bioequivalent but not infringing. This means that some generic drugs can enter the market prior to the expiration of a valid patent covering a brand name drug.⁶⁵

Patentees who sue generic manufacturers must show either literal infringement or infringement under the doctrine of equivalents (DOE).⁶⁶ Literal infringement requires a showing that the accused product incorporates each and every element of the patent claim.⁶⁷ Absent literal infringement, patentees may successfully establish infringement under the DOE if the accused product “performs the same function, in substantially the same way, to achieve substantially the same result” as the patented invention.⁶⁸ Equivalence must be assessed on an element-by-element basis, rather than by comparing the claimed invention and the accused product holistically.⁶⁹ This element-by-element approach aims to preserve claims’ boundary-defining function and to avoid unduly enlarging the scope of the patent.⁷⁰

Hatch-Waxman’s patent provisions have engendered a complex game of cat and mouse between pioneer and generic manufacturers. Generic versions of brand name drugs may enter the market when patents covering the reference product’s active ingredients expire or are invalidated.⁷¹ But pioneer firms typically develop patent portfolios for their commercial products that cover more than the active ingredients.⁷² Through a process known as “evergreening,” brand name manufacturers obtain secondary patents on incremental improvements to their products and then add those patents to the Orange Book listing for their licensed drugs.⁷³ In addition to core

the patent claim and the accused product, requiring not only equivalent function but also equivalent way and result.”)

65. See *id.* (“‘If bioequivalency meant per se infringement, no alternative to a patented medicine could ever be offered to the public during the life of a patent.’” (quoting Abbott Labs. v. Sandoz, Inc., 486 F. Supp. 2d 767, 776 (N.D.Ill.2007))).

66. Harry Surden, *Efficient Uncertainty in Patent Interpretation*, 68 WASH. & LEE L. REV. 1737, 1762–63 (2011).

67. *Id.* at 1773–74.

68. Dawn Equip. Co. v. Ky. Farms Inc., 140 F.3d 1009, 1016 (Fed. Cir. 1998).

69. Warner-Jenkinson Co. v. Hilton Davis Chem. Co., 520 U.S. 17, 40 (1997).

70. See Surden, *supra* note 66, at 1773–74.

71. Lara J. Glasgow, *Stretching the Limits of Intellectual Property Rights: Has the Pharmaceutical Industry Gone Too Far?*, 41 IDEA 227, 231–32 (2001).

72. Gideon Parchomovskiy & R. Polk Wagner, *Patent Portfolios*, 154 U. PA. L. REV. 1, 5–6, 16–17 (2005).

73. Freilich, *supra* note 16, at 104.

patents covering the active ingredients, brand name manufacturers retain peripheral patents covering purity, stability, formulation, chemical synthesis, and methods of use.⁷⁴ The number of sequential pharmaceutical patents has skyrocketed since the passage of Hatch-Waxman.⁷⁵ This reflects a strategic response by brand name manufacturers to counteract the effects of robust generic competition resulting from its enactment.

In order to avoid these weaker follow-on patents, generic companies frequently seek to introduce products that differ slightly from the brand name versions.⁷⁶ Patent infringement cases involving peripheral patents often turn on whether the generic manufacturer has distinguished its product enough to avoid infringement under the DOE.⁷⁷ ANDA applicants are thus motivated to modify their products as much as they can without running afoul of the FDA's sameness requirements.⁷⁸ Contrary to their depiction as copycats that simply manufacture identical versions of brand name drugs and sell them at lower prices, generic manufacturers are thus encouraged by an amalgam of regulatory and patent hurdles to engage in their own forms of innovation.⁷⁹ While such innovation by generic manufacturers can yield social benefits, it also exacerbates patient safety concerns.⁸⁰ For example, generic manufacturers might deliberately increase levels of impurities in their products in order to avoid infringement.⁸¹ Since safety is not a relevant consideration in patent infringement cases, generic manufacturers have perverse

74. *Id.* at 103.

75. Hemphill & Sampat, *supra* note 10, at 619–20.

76. Freilich, *supra* note 16, at 61–62.

77. *See id.* at 103 (explaining that DOE cases typically involve peripheral patents, as core patents frequently expire before the brand name drug gets to market).

78. *Id.* at 80 (noting that this set of incentives creates a paradox whereby “patent law requires generic companies to innovate a certain distance from the bounds of the patent, but FDA regulations require generic companies to remain close to the brand name product”).

79. *Id.* at 107.

80. The safety of generic pharmaceuticals is a particular concern in light of the Supreme Court's decisions in *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567, 2569 (2011) (holding that failure-to-warn claims against generic manufacturers under state tort law were preempted by federal labeling regulations) and *Mutual Pharmaceutical Co., Inc. v. Bartlett*, 133 S. Ct. 2466, 2470 (2013) (holding that design defect claims against generic manufacturers under state tort law were preempted by federal law).

81. *E.g.*, *Sunovion Pharm., Inc. v. Teva Pharm. USA, Inc.*, 731 F.3d 1271 (Fed. Cir. 2013); *Pozen Inc. v. Par Pharm. Inc.*, 800 F. Supp. 2d 789, 809–12 (E.D. Tex. 2011); *see also* *EKR Therapeutics, Inc. v. Sun Pharm. Indus.*, 633 F. Supp. 2d 187 (D.N.J. 2009) (offering another example of harm that may result when generics deliberately manufacture drugs that differ from their brand name counterparts).

incentives to expose patients to unnecessary risks.⁸²

B. Pay-for-Delay Settlements

Hatch-Waxman created an incentive for generic manufacturers to challenge unexpired drug patents by authorizing 180 days of exclusivity for the first ANDA applicant to file a paragraph IV certification.⁸³ This 180-day period could be worth several hundred million dollars to an ANDA applicant that successfully challenges patents covering the reference product.⁸⁴ The FDA may not approve any other generic version of the innovator's drug until the exclusivity period expires. Since the first paragraph IV filer would be the only generic manufacturer of the drug during this time, it can expect to share duopoly profits with the brand name firm.⁸⁵ Importantly, only the *first* generic firm to file a paragraph IV certification is entitled to receive this lucrative bounty.⁸⁶ If multiple generic manufacturers file on the same day, they are entitled to share the exclusivity period.⁸⁷

Brand name manufacturers have adapted to this regulatory scheme by negotiating "pay-for-delay" settlements with paragraph IV filers. Under the terms of these settlements, the generic firm concedes the validity of the innovator's patents and agrees not to market a competing drug. In exchange, the brand name manufacturer pays the generic firm cash or other consideration.⁸⁸

While such deals are presumably optimal for the settling parties, they can produce negative externalities by undermining Hatch-Waxman's pro-competition objectives. When the first paragraph IV filer takes litigation to completion and successfully invalidates the innovator's patent, it opens the door to robust generic competition

82. Freilich, *supra* note 16, at 109–10 ("It would be better to craft laws that avoid giving generic companies perverse incentives to make products less safe.").

83. 21 U.S.C. § 355(j)(5)(B)(iv) (2012).

84. Hemphill, *supra* note 10, at 1579.

85. *Id.* at 1590.

86. *Id.* at 1560; *see* 21 U.S.C. § 355(j)(5)(D)(iii) (stating that upon the first ANDA applicant's forfeiture, no other applicants are eligible for the exclusivity period).

87. *F.T.C. v. Actavis*, 133 S. Ct. 2223, 2246 (2013) (Roberts, C.J., dissenting) (citing amicus brief stating that the yearly average number of first-day generic applications between 2002 and 2008 never dropped below three).

88. *See, e.g., id.* at 2229 (majority opinion) (explaining the terms of a pay-for-delay settlement whereby the manufacturer of name brand AndroGel paid several million dollars to paragraph IV filers in exchange for their agreement to refrain from bringing generic versions to market).

upon expiration of the 180-day exclusivity period.⁸⁹ Settlement short-circuits this process. If the first paragraph IV filer refrains from challenging the innovator's patents in exchange for cash or in-kind compensation, other generic manufacturers (who are not eligible for generic exclusivity) might elect to wait until patent expiration before filing their own ANDAs. Pay-for-delay settlements thereby reduce consumer surplus by extending the period during which the innovator enjoys freedom from competition and associated monopoly prices.⁹⁰

The Federal Trade Commission (FTC) has long insisted that such reverse payment settlement agreements violate antitrust law and has challenged numerous agreements as unreasonable restraints of trade.⁹¹ Noting that courts have differed in their application of the antitrust laws to Hatch-Waxman-related patent settlements, the Supreme Court recently considered the issue in *Federal Trade Commission v. Actavis, Inc.*⁹² The Court declined to set a categorical rule that such agreements are presumptively unlawful, but held that the FTC should have the opportunity to challenge pay-for-delay agreements on a case-by-case basis under the "rule of reason."⁹³ It reasoned that such settlements are an unintended by-product of "Hatch-Waxman's unique regulatory framework"⁹⁴ and run counter to the statute's sponsors' policy goals.⁹⁵

The ramifications of the Supreme Court's *Actavis* decision are unclear. On one hand, increased FTC scrutiny of reverse payment settlements could benefit consumers by spurring generic

89. See *Hemphill*, *supra* note 10, at 1567.

90. *Id.* at 1572–73 (noting that economic modeling shows that consumer welfare is reduced, on average, if the paragraph IV filer enters into a pay-for-delay settlement rather than seeing patent litigation to completion).

91. Duff Wilson, *F.T.C. Criticizes Agreements That Delay Generic Drugs*, N.Y. TIMES, Sept. 1, 2011, at B2; see also Editorial, *The "Pay for Delay" Rap*, WALL ST. J., Oct. 5, 2010, at A22 (stating that FTC Chairman Jon Leibowitz "has been conducting his campaign with evangelical zeal").

92. 133 S. Ct. at 2230 (2013) (observing that some lower courts found such settlements to be presumptively lawful while others had found them to be presumptively unlawful).

93. *Id.* at 2236–37.

94. *Id.* at 2235.

95. *Id.* at 2234 (citing 148 Cong. Rec. 14437 (2002); 146 Cong. Rec. 144 (2000) ("([R]emarks of Sen. Hatch) ('It was and is very clear that the [Hatch-Waxman Act] was not designed to allow deals between brand and generic companies to delay competition') . . . (remarks of Rep. Waxman) (introducing bill to deter companies from 'strick[ing] collusive agreements to trade multimillion dollar payoffs by the brand company for delays in the introduction of lower cost, generic alternatives').").

manufacturers to pursue patent challenges rather than agreeing to delay market entry.⁹⁶ On the other hand, greater FTC oversight might discourage ANDA applicants from filing paragraph IV challenges in the first place, which could have the overall effect of extending the life of brand name manufacturers' patent protection.⁹⁷ In any event, antitrust litigation will be one of Hatch-Waxman's lingering side effects for the indefinite future.

IV. IMPLICATIONS FOR THE BIOLOGICS PRICE COMPETITION AND INNOVATION ACT

The BPCIA created an abbreviated approval pathway for follow-on biologics modeled after Hatch-Waxman's scheme for generic drugs. The statute authorizes the FDA to approve a biosimilar upon expiration of a twelve-year data exclusivity period for the corresponding pioneer biologic.⁹⁸ The biosimilar applicant may rely on the FDA's prior approval of the pioneer's biologic if there are "no clinically meaningful differences . . . in terms of safety, purity, and potency" between the pioneer's reference product and the biosimilar.⁹⁹ If the FDA finds that a biosimilar is sufficiently similar to be "interchangeable" with the reference product, the biosimilar may be substituted for the reference product without the intervention of the prescribing health care provider.¹⁰⁰ The first biosimilar found to be interchangeable is entitled to an exclusive marketing period during which no other product may be deemed interchangeable with the same reference product.¹⁰¹ The BPCIA also contains a complex

96. *See id.* ("Continued litigation, if it results in patent invalidation or a finding of noninfringement, could cost the patentee \$500 million in lost revenues, a sum that then would flow in large part to consumers in the form of lower prices.").

97. *Id.* at 2247 (Roberts, J., dissenting) ("The irony of all this is that the majority's decision may very well discourage generics from challenging pharmaceutical patents in the first place Taking the prospect of settlements off the table—or limiting settlements to an earlier entry date for the generic, which may still be many years in the future—puts a damper on the generic's expected value going into litigation, and decreases its incentives to sue in the first place.").

98. 42 U.S.C. § 262(k)(7)(A) (2012). An additional six months of exclusivity is available for the reference innovative biologic if pediatric study requirements are met. *Id.* § 262 (m)(2). The innovator cannot extend the exclusivity period by making minor changes to its product and filing a supplemental or subsequent application. *See id.* § 262(k)(7)(C) (listing modifications for which the exclusivity period does not apply).

99. *Id.* § 262(i)(2).

100. *Id.* § 262(i)(3).

101. *Id.* § 262(k)(6). Exclusivity extends until the earliest of: one year after the first commercial marketing of the first-approved interchangeable biosimilar; eighteen months after a final court decision or the dismissal of a patent infringement suit against the first interchangeable

set of patent-related provisions that require private information exchanges among the biosimilar applicant, the reference product sponsor, and patent holders.¹⁰²

A. *Defining Similarity and Interchangeability*

The BPCIA gives the FDA broad discretion to determine biosimilarity and interchangeability. Evidence to support biosimilarity may include analytical, animal-based, and clinical studies, but the FDA may waive the need for these data in any given case.¹⁰³ The FDA has authority to designate a biosimilar interchangeable if it finds that the biosimilar “can be expected to produce the same clinical result as the reference product in any given patient,” and repeated administration of the drug will not reduce its efficacy or increase its toxicity beyond what is expected from the reference biologic.¹⁰⁴

The agency faces a daunting task in making these determinations because biologics typically are more complex molecules than small-molecule chemical drugs. They are produced using biological processes rather than chemical syntheses, which means that small manufacturing deviations can significantly alter a product’s safety and efficacy.¹⁰⁵ While generic small-molecule drugs sometimes manifest unexpected clinical effects,¹⁰⁶ biosimilars present an exceedingly more complicated set of scientific considerations.¹⁰⁷ One particular danger that may result from subtle differences between seemingly interchangeable biologics is increased immunogenicity, which occurs when a patient’s immune system

biosimilar; forty-two months after the approval of the first interchangeable biologic if patent litigation is still ongoing; or eighteen months after the approval of the first interchangeable biosimilar if the applicant has not been sued. *Id.*

102. *Id.* § 262(l).

103. *Id.* § 262(k)(2)(A).

104. *Id.* U.S.C. § 262(k)(4)(A).

105. Henry Grabowski et al., *The Market for Follow-on Biologics: How Will it Evolve?*, 25 HEALTH AFFS. 1291, 1291–1301 (2006).

106. *See supra* Part II.A.

107. *Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States: Hearing Before the H. Subcommittee on Health and H. Comm. on Energy and Commerce*, 110th Cong. 22 (2007) (statement of Janet Woodcock, M.D., Deputy Comm’r, Chief Medical Officer, FDA), available at <http://www.fda.gov/NewsEvents/Testimony/ucm154017.htm> (noting that the idea of sameness used in the generic small-molecule approval process usually will not be appropriate in the biologics context).

develops antibodies to protein-based drugs.¹⁰⁸

The FDA's limited experience reviewing the safety and efficacy of follow-on protein products presages the issues that it will face under the BPCIA. Section 505(b)(2) of the FDCA permits an applicant to file a new drug application that relies on clinical investigations that were not sponsored by the applicant and for which the applicant lacks a right of reference or use.¹⁰⁹ This provision authorizes streamlined review of products that do not meet the sameness requirements for generic drug approval and thus cannot be approved through the ANDA pathway.¹¹⁰ The FDA has used the section 505(b)(2) provision to approve some second-generation biologics, including recombinant versions of human growth hormone and the enzyme hyaluronidase.¹¹¹ In these cases, the agency required the applicant to generate its own clinical data in addition to relying on publicly available information.¹¹² Notably, while the FDA has approved several follow-on protein products, the agency has never found one to be therapeutically equivalent to (and thus substitutable with) a reference product.¹¹³

The amount of evidence that the FDA requires to establish similarity and interchangeability will dictate the contours of the biosimilars market.¹¹⁴ These determinations implicate inevitable cost-quality tradeoffs. The more robust the data to support safety and efficacy, the more confidence patients, physicians, and payers will

108. Trevor Woodage, *Blinded by (a Lack of) Science: Limitations in Determining Therapeutic Equivalence of Follow-On Biologics and Barriers to Their Approval and Commercialization*, 9 STAN. TECH. L. REV. 1, 6 (2012); see also Robert N. Sahr, *The Biologics Price Competition and Innovation Act: Innovation Must Come Before Price Competition*, B.C. INTELL. PROP. & TECH. F., 2009, at 3 (describing how a biosimilar erythropoietin drug sold in Europe triggered an unexpected immune response in patients that exacerbated their preexisting anemia).

109. 21 U.S.C. § 355(b)(2)(2012).

110. 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, 679 (2010).

111. *Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States: Hearing Before the H. Subcommittee on Health and H. Comm. on Energy and Commerce*, supra note 107. The FDA used the ANDA provisions to approve a generic version of the hormone Pergonal in 1997. Carver et al., supra note 110, at 685–86. Although this approval withstood a legal challenge when the D.C. Circuit deferred to the FDA's decision, the agency has not since approved an ANDA for a therapeutic protein product. *Id.* at 686.

112. *Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States: Hearing Before the H. Subcommittee on Health and H. Comm. on Energy and Commerce*, supra note 107.

113. *Id.*

114. *Id.*

have in biosimilar drugs and the wider their adoption will be.¹¹⁵ But data generation is expensive, and if the bar for approval is set high, the envisioned cost savings from a biosimilars market will fail to materialize.¹¹⁶

Undoubtedly, biosimilars producers will face much higher start-up and manufacturing costs than generic drug companies.¹¹⁷ Firms may be unwilling or unable to obtain interchangeability status, given current uncertainty about applicable standards and the feasibility of achieving them.¹¹⁸ If a biosimilar is not deemed interchangeable, its manufacturer will need to advertise to promote its use, which will further drive up costs and prices.¹¹⁹ In sum, scientific and regulatory complexity will likely prevent biosimilars from causing the same downward price pressure on the biologics market that generic drugs exerted on the pharmaceuticals market following Hatch-Waxman's passage. The amount of price competition that does result will be a function of the FDA's willingness to permit the free exchange of related, but not identical biologics.¹²⁰

B. Interplay Between Federal and State Regulation

Along with federal regulators, state lawmakers face cost and safety tradeoffs in considering the substitutability of biosimilars.¹²¹ Existing state statutes regulating generic drug substitution are

115. Grabowski et al., *supra* note 9, at 517.

116. *See id.* at 522 (citing cost estimates for developing complex biosimilars of \$100 to \$150 million, compared to \$1 to \$2 million for completing bioequivalence studies for generic drugs); Jason Kanter & Robin Feldman, *Understanding and Incentivizing Biosimilars*, 64 HASTINGS L.J. 57, 80 (2012) (noting that empirical data on the impact of generic entry on drug prices suggests that consumers will not obtain significant cost savings unless multiple biosimilars are developed to compete with the same brand name biologic).

117. Grabowski et al., *supra* note 9, at 538–39.

118. In 2005, the European Union passed legislation that adopted the concept of a “similar biological medicinal product.” *What You Need to Know About Biosimilar Medicinal Products*, European Commission, (2013), available at http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/biosimilars_report_en.pdf. Each member country may set its own rules regarding substitution of biosimilars. Currently no country authorizes the substitution of biologics made by different manufacturers and some EU Member States have expressly banned this practice. *Possibility of Substitution of Biosimilars in Europe*, GENERICS AND BIOSIMILARS INITIATIVE (June 14, 2013), <http://gabionline.net/reports/possibility-of-substitution-of-biosimilars-in-Europe>.

119. Richardson, *supra* note 8, at 4.

120. *See generally id.* (discussing the interchangeability of biosimilars and how that will affect pricing).

121. Kanter & Feldman, *supra* note 116, 73–74.

inapplicable to biosimilars.¹²² For example, section 4073 of the California Business and Professions Code permits substitution of drugs with the “same active chemical ingredients,” a restrictive standard that interchangeable biosimilars will be unable to meet.¹²³ In anticipation of FDA guidance on interchangeability standards, several states are considering legislation governing biosimilar substitution.¹²⁴ Pioneers, follow-on developers, pharmacist associations, health insurers, and other interested parties are intensely lobbying state officials on proposed legislation.¹²⁵ The principal contested issue is whether pharmacists will be required to notify patients and prescribing physicians before substituting a pioneer’s biologic with an interchangeable biosimilar.¹²⁶

In contrast to existing generic drug substitution laws, most of the draft bills require physician notification when a pharmacist substitutes a brand name biologic with an interchangeable biosimilar.¹²⁷ As of October 2013, only five such bills had passed, and none had been signed into law.¹²⁸ Three of the bills include sunset provisions that are likely to expire before the FDA approves the first biosimilar.¹²⁹ California Governor Jerry Brown vetoed a bill that would have required prescriber notification of biosimilar substitution, concluding that it was premature to enact state legislation before the FDA established interchangeability standards.¹³⁰ The state-level battle between pioneers and biosimilar firms will likely escalate as the FDA specifies the hurdles that must be cleared to attain interchangeable status.

Additional contentious issues relate to the identification and labeling of biosimilars.¹³¹ A key unresolved question is whether

122. *Id.* at 74.

123. *Id.* at 74 (explaining why state generic substitution laws must be adapted for biosimilars).

124. Richardson, *supra* note 8, at 4.

125. *See id.*

126. Kurt R. Karst, *The Biosimilars State Legislation Scorecard*, FDA LAW BLOG (Sep. 4, 2013), http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2013/09/biosimilars-state-legislation-scorecard.html.

127. Richardson, *supra* note 8, at 4.

128. *Id.*

129. *Id.*

130. Letter from Edmund G. Brown Jr., Cal. State Governor, to the Members of the California State Senate (Oct. 12, 2013), *available at* http://www.gphaonline.org/media/cms/SB_598_2013_Veto_Message.pdf.

131. *See* U.S. DEP’T OF HEALTH & HUMAN SERVS., FOOD & DRUG ADMIN., DOCKET NO. FDA-2010-N-0477, APPROVAL PATHWAY FOR BIOSIMILAR AND INTERCHANGEABLE

interchangeable biosimilars, like generic drugs, will receive the same official (i.e., non-trademarked) name as their reference products. Pioneer firms have argued that interchangeable biosimilars should have unique names, which would enhance patient safety by facilitating adverse event monitoring.¹³² Biosimilar firms and pharmacist associations counter that unique names could lead to duplicative prescribing of highly similar products and would create unnecessary consumer and prescriber confusion.¹³³

A bipartisan group of U.S. Senators recently sent a letter to the FDA noting: “In crafting the BPCIA, the intent of Congress was to create a safe and competitive marketplace for biosimilars, akin to the marketplace for generic drugs.”¹³⁴ The letter expressed concern that requiring different names for biosimilars would undermine that goal by discouraging substitution and inflating healthcare costs.¹³⁵ Yet, the FDA must strike a delicate balance between fostering competition between comparable biologics and ensuring that patients, physicians, and payers have clear and accurate information that enables them to make informed choices. Patient safety concerns might dictate unique names and distinctive labeling for some biosimilars.

The FDA faces additional policy decisions regarding the regulation of risk information acquired after biosimilars enter the market. The BPCIA states that biosimilar manufacturers must comply with FDA post-market requirements.¹³⁶ But it remains to be seen how the FDA will formulate risk evaluation and mitigation strategies for biosimilars. If the agency treats biosimilars like generic

BIOLOGICAL PRODUCTS; PUBLIC HEARING; REQUEST FOR COMMENTS 64–101 (2010) (noting the need to distinguish among the reference product, related biological products that have not been shown to be biosimilar, biosimilar products, and interchangeable products).

132. Richardson, *supra* note 8, at 4.

133. *Id.* The Generic Pharmaceutical Association recently filed a citizen’s petition with the FDA requesting that all biosimilars approved by the FDA use the international non-proprietary name (INN) of their reference products because by definition biosimilars have no clinically meaningful differences. *Generic Industry Calls on FDA to Uphold Consistent, Proven International Standard for Biosimilar Naming*, GENERIC PHARM. ASS’N (Sept. 19, 2013), <http://www.gphaonline.org/gpha-media/press/generic-industry-calls-on-fda-to-uphold-consistent-proven-international-standard-for-biosimilar-naming>.

134. Ed Silverman, *Senators to FDA: Has Biosimilar Naming Policy Changed?*, PHARMALIVE (Oct. 23, 2013), <http://www.pharmalive.com/senators-to-fda-has-biosimiliar-naming-policy-changed>.

135. *Id.*

136. 42 U.S.C. § 262(a)(2)(D).

drugs and stresses the need for sameness between innovative and follow-on biologics with respect to both product composition and labeling, the agency may be reluctant to impose individualized requirements on biosimilars manufacturers. On the other hand, real differences among brand name and follow-on protein products might compel a more tailored regulatory approach. The more particularized the regulation of biosimilars firms, the farther the industry will stray from a “generic” market for biologics.

Federal labeling requirements will determine the viability of products liability claims against biosimilar manufacturers. If the FDA permits biosimilar producers to unilaterally change their labels in response to risk information discovered after market approval, then federal law would not preempt state tort claims.¹³⁷ However, if the FDA compels biosimilars firms to maintain warnings that are identical to those of interchangeable brand name biologics, then impossibility preemption presumably would foreclose failure-to-warn claims.¹³⁸ Patients who take biosimilars would enjoy lower up-front costs but at the risk of uncompensated harm.¹³⁹

C. Balancing Competition and Innovation

Hatch-Waxman’s unintended effects on competition and innovation highlight potential pitfalls that could emerge under the biosimilars regime.¹⁴⁰ Unlike generic drug firms, the first biosimilar manufacturer to successfully challenge an innovator’s patent does not receive a 180-day exclusivity period.¹⁴¹ Hence, we may not see the same type of pay-for-delay settlements that arose in response to Hatch-Waxman. However, the first biosimilar deemed to be interchangeable with a reference product enjoys a period of exclusivity whose length depends on when the biosimilar enters the market and whether the biosimilar manufacturer is sued for patent infringement.¹⁴² In addition, biosimilars applicants must disclose

137. *See supra* Part II.B.

138. *Id.*

139. *See Morris, supra* note 58, at 281 (discussing how generic drugs are cheaper than the name brand drug).

140. *See supra* Part II.

141. Grabowski et al., *supra* note 9, at 515.

142. 42 U.S.C. § 262(k)(6) (2012). Exclusivity extends until the earliest of: one year after the first commercial marketing of the first-approved interchangeable biosimilar; eighteen months after a final court decision or the dismissal of a suit against the first interchangeable biosimilar; forty-two months after the approval of the first interchangeable biologic if patent litigation is still

confidential information to reference product sponsors and patent holders for the purpose of identifying patent infringement claims and anticipating litigation.¹⁴³ These BPCIA provisions create opportunities for strategic behavior among pioneers and follow-on developers.

Under the BPCIA, a biosimilar application can be filed four years after the license date of the reference product.¹⁴⁴ The filing of a biosimilar application triggers a series of mandatory information exchanges between the biosimilar applicant, the reference product sponsor, and patent holders.¹⁴⁵ Like an ANDA, the submission of a biosimilar application constitutes an artificial act of infringement on any patent covering the reference product.¹⁴⁶ Since the BPCIA does not contemplate the creation of an Orange Book for biologics, the parties must cooperate to identify whether a patent infringement claim could reasonably be asserted against the biosimilar applicant.¹⁴⁷ This requires the applicant to disclose confidential information to both the reference product sponsor and the owner of a patent exclusively licensed to the reference product sponsor.¹⁴⁸ The pioneer receives the benefit of the ability to litigate patent infringement issues before biosimilar market entry in exchange for the losses it incurs from the biosimilar applicant's use of its safety and potency data.¹⁴⁹

Since biosimilars will differ somewhat from their brand name counterparts, follow-on developers may be able to circumvent pioneers' patents.¹⁵⁰ Pioneer firms have noted that patent protection

ongoing; or eighteen months after the approval of the first interchangeable biosimilar if the applicant has not been sued. *Id.*

143. *Id.* § 262(l)(1).

144. *Id.* § 262(k)(7)(B).

145. *Id.* § 262(l).

146. 35 U.S.C. § 271(e)(2)(C) (2012).

147. *See id.* § 262(l)(7)(B) (2012).

148. 42 U.S.C. § 262(l)(7)(B) (2012).

149. 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, 319 (2011) ("The two parts of the statute (i.e., those provisions allowing the biosimilar applicant to rely on FDA's prior finding of safety, purity, and potency for the reference product and those provisions allowing the pioneer to enforce its patents prior to biosimilar market entry) are dependent on each other. Both are essential pieces of an elaborate statutory bargain.")

150. Bruce S. Manheim, Jr. et al., *'Follow-On Biologics': Ensuring Continued Innovation in the Biotechnology Industry*, 25 HEALTH AFFS. 394, 398–400 (2006) (noting that biologics patents are often narrower in scope than those covering small-molecule drugs and thus at greater risk of being successfully challenged or evaded).

is narrower for biologics than for pharmaceuticals, which enables imitators to more easily design around biologic patents.¹⁵¹ Hence, biosimilars manufacturers might have even more success than generic drug companies establishing that their products, though similar enough to piggy-back on FDA approval of the pioneer's product, are different enough to avoid patent infringement.¹⁵² Such efforts to produce follow-on biologics that circumvent pioneers' patent claims yet receive the benefits of abbreviated FDA review, could exacerbate patient safety concerns.

The twelve-year data-exclusivity period for novel biologics may partly insure pioneer manufacturers against the risk that their patents fail to ward off follow-on competition.¹⁵³ But if FDA-administered exclusivities prove to be insufficient incentives,¹⁵⁴ pioneer biologics manufacturers will be spurred to ramp up patent evergreening strategies in the same way that small-molecule pharmaceutical manufacturers responded to the competitive threats created by Hatch-Waxman.¹⁵⁵ This may lead to an increase in sequential biologics patents, which could be a drag on innovation.¹⁵⁶

A biosimilar manufacturer seeking to avoid a pioneer's twelve-year exclusivity period or wary of the information-forcing provisions of the BPCIA may prefer to file a full biologics license application (BLA) rather than pursue the streamlined approval pathway.¹⁵⁷ If the biosimilar manufacturer takes this approach, it

151. See BIOTECH. INDUS. ORG., A FOLLOW-ON BIOLOGICS REGIME WITHOUT STRONG DATA EXCLUSIVITY WILL STIFLE THE DEVELOPMENT OF NEW MEDICINES 2–3 (2007), available at http://www.bio.org/sites/default/files/FOBSData_exclusivity_20070926_0.pdf.

152. See Manheim et al., *supra* note 150, at 401; Vincent J. Roth, *Will FDA Data Exclusivity Make Biologic Patents Passe?*, 29 SANTA CLARA COMP. & HIGH TECH. L.J. 249, 276 (2012) (noting the “sweet spot” in which “a biologic is similar enough for accelerated approval, but not identical for purposes of patent infringement”).

153. Grabowski et al., *supra* note 9, at 551. See also Roth, *supra* note 152, at 252 (arguing that the BPCIA did not create new data exclusivity protection, but rather shortened what had been “continuous data exclusivity” to twelve years).

154. Henry Grabowski, *Follow-on Biologics: Data Exclusivity and the Balance Between Innovation and Competition*, 7 NAT. REV. DRUG DISCOVERY 479, 486 (2008) (concluding that a representative portfolio of new biologic candidates would be expected to recoup R&D costs between 12.9 and 16.2 years after launch). *But see* FED. TRADE COMM'N, EMERGING HEALTH CARE ISSUES: FOLLOW-ON BIOLOGIC DRUG COMPETITION iii–vi (2009), available at <http://www.ftc.gov/os/2009/06/P083901biologicsreport.pdf> (asserting that patents and early-mover competitive advantages should be sufficient incentives to encourage biologic innovation).

155. See *supra* Part II.B.

156. See Grabowski, *supra* note 9, at 551.

157. See Sandoz Will Steer Clear of U.S. Biosimilars Pathway, *Use Other Applications*, PINK SHEET, May 3, 2010, available at <http://www.pharmamedtechbi.com/publications/the-pink-sheet>

cannot rely on the FDA's prior approval of the pioneer's biologic and must generate its own data demonstrating its product's safety, purity, and potency.¹⁵⁸ But commentators have expressed concern that the FDA will enable biosimilars firms to enjoy the best of both worlds by approving "skinny BLAs."¹⁵⁹ The worry is that the FDA will accept a follow-on developer's application as a traditional BLA, even though the application lacks comprehensive clinical data and more closely resembles an abbreviated biosimilar application.¹⁶⁰ While not admitting it, the FDA could rely on its prior finding that the pioneer's biologic is safe, pure, and potent and allow the biosimilar applicant to market its product immediately, without the restraints delineated in the BPCIA.¹⁶¹ Such practice would raise constitutional concerns, as arguably it would amount to a taking of the pioneer's trade secrets without compensation.¹⁶² It also could upset the BPCIA's designed balance between competition and innovation.

IV. CONCLUSION

Though the Hatch-Waxman Act was enacted thirty years ago, several latent side effects have recently surfaced. These complications highlight unresolved tensions between the goals of promoting innovation, ensuring pharmaceutical quality, and stabilizing healthcare costs. Hatch-Waxman's focus on premarket drug approval left unanswered questions about the regulation of risks that arise after generics enter the market. In addition, its drafters failed to fully anticipate the complex set of incentives created by the Act's patent and exclusivity provisions. Hatch-Waxman's unintended consequences serve as precautionary guideposts for implementation of a biosimilars regulatory approval pathway. The FDA and lawmakers should heed these potential pitfalls and proactively confront unavoidable tradeoffs between safety, cost, and access to therapeutic biologics.

/72/018/sandoz-will-steer-clear-of-us-biosimilars-pathway-use-other-applications (reporting that some companies have indicated that they will opt not to use the biosimilars pathway in order to avoid the BPCIA's information-sharing provisions).

158. Epstein, *supra* note 149, at 325.

159. *Id.* at 325–26.

160. *Id.*

161. *Id.* at 326.

162. *Id.* at 326–27.

