Hatch-Waxman Turns 30: Do We Need a Re-Designed Approach for the Modern Era?

Aaron S. Kesselheim
Harvard Medical School

Jonathan J. Darrow
Harvard Medical School

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Hatch-Waxman Turns 30: Do We Need a Re-Designed Approach for the Modern Era?

Aaron S. Kesselheim & Jonathan J. Darrow

Abstract:
In 1984, Congress passed the Hatch-Waxman Act, which catalyzed the creation of the modern generic drug industry. Generic drugs today account for eighty-four percent of all prescriptions dispensed, but less than twenty percent of drug costs. Despite this success, numerous problems in the generic drug market have emerged. Some involve the deliberate manipulation of the Hatch-Waxman system, while others have arisen more unexpectedly, such as the Supreme Court’s 2011 decision in *Pliva v. Mensing* that could undermine consumer confidence in generic drugs. We discuss these emerging challenges and propose updates to the Hatch-Waxman Act to continue support for the timely emergence of safe generic drugs.
# Table of Contents

**Table of Contents**

**Introduction** ........................................................................................................................................... 295

## I. The Hatch-Waxman Act: Background and Regulatory Framework

- A. Background and Origins of the Hatch-Waxman Act ................................................................. 297
- B. Bioequivalence Pathway for Generic Drugs ............................................................................... 301
- C. Generic Challenges to Brand-Name Market Exclusivity ......................................................... 302
- D. Competition-Free Periods for Innovative Drug Approvals ..................................................... 305
- E. Extensions of Brand-Name Market Exclusivity ........................................................................ 305
- F. Summary ..................................................................................................................................... 307

## II. The Hatch-Waxman Legacy

- A. Innovation by Brand-Name Drug Manufacturers ..................................................................... 307
- B. Use of Generic Drugs .................................................................................................................. 309
- C. Impact on Patient Outcomes and Healthcare Spending .......................................................... 314
- D. Summary ..................................................................................................................................... 319

## III. Thirty Years After Hatch-Waxman: Current and Emerging Challenges

- A. Limits or Delays to Generic Drug Availability Under Hatch-Waxman .................................. 319
  1. Patent Accumulation .................................................................................................................. 320
  2. Reverse Payment Paragraph IV Challenge Settlements (“Pay for Delay”) ............................ 328
  3. Authorized Generics .................................................................................................................. 333
  4. Dose Form or Other Changes in the Listed Drug ...................................................................... 336
  5. Refusal to Provide Material for Purpose of Establishing Bioequivalence ............................... 340
- B. Ensuring Continued Safety of Generic Drugs ....................................................................... 342

## V. Conclusion........................................................................................................................................ 345
INTRODUCTION

The last major piece of legislation that revolutionized the U.S. prescription drug market was Drug Price Competition and Patent Term Restoration Act of 1984, which is more commonly known as the Hatch-Waxman Act. Observing a pharmaceutical marketplace dominated by expensive brand-name drugs despite their patent protection having lapsed, while also hearing complaints from brand-name manufacturers about the rising costs of innovative drug development, legislators constructed the Hatch-Waxman Act to give brand-name pharmaceutical manufacturers additional incentives to develop new drugs. At the same time, the Hatch-Waxman Act reduced drug prices for unpatented drugs by facilitating regulatory approval of low-cost, high-quality generic prescription drugs. Generic drugs are therapeutically equivalent to brand-name products made by first-entry or pioneer manufacturers. The factors defining therapeutic equivalence include both pharmaceutical equivalence and bioequivalence.

By nearly every measure, the Hatch-Waxman Act has been remarkably impactful. In 2012, generic drugs made up about eighty-four percent of all U.S. prescriptions dispensed. Generic drugs are available in nearly every therapeutic class, have become the standard of care for many common diseases, and are less expensive in the United States than in most other countries. The success of generics translates into improved medication adherence and dramatically reduced healthcare costs—more than a trillion dollars in the past decade, according to the Government Accountability Office. At the same time, Hatch-

3. See, e.g., Mark Metzke, Increasing Follow-on Biologics Competition with a New Biologics Act, 39 AIPLA Q.J. 357, 371 (2011) (“From a utilitarian standpoint, the Hatch-Waxman Act worked.”). But see Jeremy A. Greene, Generic: The Unbranding of Modern Medicine 88 (2014) (arguing that “a single piece of legislation signed into law in 1984 did not create the modern generic drug industry . . . By the time the Hatch-Waxman Act was passed in 1984, the existence of such an industry was no longer really in question, as it had been in the beginning of the 1960s”).
6. William H. Shrank et al., The Implications of Choice: Prescribing Generic or Preferred Pharmaceuticals Improves Medication Adherence for Chronic Conditions, 166 ARCH. INTERN. MED. 332, 335 (2006) [hereinafter The Implications of Choice] (finding that the proportion of days covered, a measure of adherence was 12.6% greater for patients initiated on generic versus non-preferred medications).
Waxman was also a boon to the brand-name drug industry by providing market exclusivity extensions, which translated into billions of dollars in additional revenue. Since Hatch-Waxman, transformative drugs brought to market based in part on investment by brand-name drug companies have offered advances in clinical care for infectious diseases like HIV, cardiovascular disease, and rheumatologic disease, as well as for numerous hereditary genetic disorders.

Thirty years later, however, the Hatch-Waxman Act has in some corners of the prescription drug marketplace become a victim of its own success. Numerous issues now affect patient access to generic drugs and prevent the generic drug industry from having an even more substantial effect on U.S. healthcare spending. Some of these issues, like business deals between brand-name and generic manufacturers that serve to delay the introduction of bioequivalent generic drugs, were spawned by the provisions of the Hatch-Waxman Act itself. Other such issues were barely contemplated in the early 1980s when the statute was designed, such as authorized generics, which emerged as a viable variation on the concept of a generic drug only after traditional generic manufacturers demonstrated the success of their business model under the Hatch-Waxman Act and the resulting generic drug approval system advanced at the Food and Drug Administration (FDA).

In light of the Hatch-Waxman Act’s thirtieth anniversary in September 2014, we sought to review the generic drug approval system. While the structure of the legislation may have been appropriate in the context of the pharmaceutical market in the late 1970s and early 1980s, a substantially different drug market in the twenty-first century presents challenges that may not be readily addressed under the current regulatory regime. Part I of this Article reviews the background and origins of the Hatch-Waxman Act and explains the balanced incentive system it created. Part II examines the beneficial legacy of the Hatch-Waxman Act. Part III synthesizes criticisms and potential problems that have been created or become evident over the past thirty years and identifies areas for potential legislative amendment. Part IV concludes by summarizing the key areas that could form the basis for reconsideration of the 1984 legislation: delays to generic drug availability, tactics that reduce access to or raise the costs of generic drugs, and oversight of evolving knowledge about safe and effective prescribing of generic drugs.


I. THE HATCH-WAXMAN ACT: BACKGROUND AND REGULATORY FRAMEWORK

A. Background and Origins of the Hatch-Waxman Act

The Hatch-Waxman Act had its origins in policymakers' dissatisfaction with the regulation of prescription drugs that hindered the ability of generic manufacturers to market low-cost copies of brand-name drugs. Prior to 1984, the most significant federal legislation affecting the pharmaceutical market was the 1962 Kefauver-Harris Amendments to the Food, Drug, and Cosmetic Act (FDCA). The Kefauver-Harris Amendments gave the FDA the power to require pharmaceutical manufacturers to prove that their drugs were safe and efficacious before the drugs could be sold. Premarket clinical (i.e., human) trials of the drugs were needed to provide this proof of safety and efficacy. Following this piece of legislation, in 1963 the FDA issued regulations requiring manufacturers to file investigational new drug (IND) applications before commencing clinical trials. In these rules, the FDA laid out the expected progression of pre-approval clinical trials, starting with Phase 1 trials, usually in a small number of healthy volunteers, to determine a safe dosage range. The next step was Phase 2 dose-determining studies in a limited number of patients with the disease intended to be treated that also could provide some initial efficacy data. The final stage in the pre-approval clinical trial process was larger Phase 3 studies, which were described as adequate and well-controlled investigations providing efficacy and safety data sufficient for approval.

Pursuant to the FDCA, the submission of a New Drug Application (NDA) was the final step following a successful clinical trial process. An NDA demonstrated the clinical circumstances in which a manufacturer's drug appeared to be both useful and sufficiently safe, and generally included reports of clinical trials, as well as pharmacologic, preclinical, and other data compiled during a drug's development. The FDA reviews the NDA to determine if there is "a lack of substantial evidence that the drug will have the effect it purports or is represented to have... or [the drug's] labeling is false or misleading in any particular." The statute also defines "substantial evidence" as "evidence consisting of adequate and well-controlled investigations, including clinical investigations... [showing] the drug will have the effect it... is represented to have." Thus, to have a drug approved by the FDA, a manufacturer needs to

12. § 355(d).
13. Id.
show it is both safe and efficacious in clinical trials. Moreover, because "adequate and well-controlled investigations" was written in the plural form, the FDA interpreted the statute to prefer at least two separate comparative clinical trials, which usually were performed as Phase 3 trials.\(^\text{14}\)

By requiring the FDA to make an affirmative approval decision on an NDA before a new prescription drug could be marketed, the Kefauver-Harris Amendments thrust the FDA into a gatekeeper role in verifying how a prescription drug worked.\(^\text{15}\) After the Amendments, it took substantial resources for a drug company to sell a new prescription drug because developing a new drug and completing the clinical trials necessary for FDA approval were expensive endeavors.\(^\text{16}\) Importantly, however, these responsibilities applied equally to brand-name and generic manufacturers that were attempting to market copies of post-1962 brand-name drugs after the expiration of the brand-name manufacturer's essential patents on the underlying active ingredient.\(^\text{17}\) In most other industries, patent expiration means that competitors can join the market and prices can fall, but generic manufacturers seeking to enter the pharmaceutical marketplace with products for which the patent on the underlying active ingredient had expired generally also had to conduct clinical trials to receive approval from the FDA.\(^\text{18}\) There were no provisions in the Kefauver-Harris Amendments allowing expedited approval of drugs that were the same as products already approved by the FDA. Instead, new clinical trials had to be conducted even for generic drugs.\(^\text{19}\) Prior to 1962, approval costs had not been as substantial of an issue, since no drugs were required to affirmatively prove safety and efficacy prior to FDA approval. While the FDA created an abbreviated new

\(^{\text{14.}}\) Warner-Lambert Co. v. Heckler, 787 F.2d 147, 151 (3d Cir. 1986). The FDA did not view the two-trial requirement rigidly, and subsequent amendments codified FDA practice to require only one trial in certain circumstances.

\(^{\text{15.}}\) Significant Dates in U.S. Food and Drug Law History, FOOD & DRUG ADMIN., http://www.fda.gov/AboutFDA/WhatWeDo/History/Milestones/ucm128305.htm (last visited Apr. 12, 2015).


\(^{\text{19.}}\) In 1978, the FDA started a "paper NDA" process to allow approval of generic copies of new drugs introduced post-1962 based on published literature alone, but adequate literature able to support a paper NDA was available for only a fraction of post-1962 drugs, so the impact of the paper NDA process was extremely limited.
HATCH-WAXMAN TURNS 30

drug application (ANDA) process in 1970 to handle “similar and related” products that came on the market between 1938 and 1962, the absence of a legal pathway for generics after 1962 dramatically raised the costs required to bring generic copies of post-1962 drugs to market. Since generic drugs were at least the second entrant into the market and would not be able to command the same high prices as original brand-name drugs, market economics also reduced the incentive for manufacturers to create generic drugs.

On the eve of the Hatch-Waxman Act, another substantial barrier to FDA approval of generic drugs emerged and threatened to make entry into the market even more difficult—the application of the experimental use defense to patent liability infringement in the pharmaceutical space. In the 1960s and 1970s, it was common practice for generic companies to experiment with brand-name drugs before patent expiration in anticipation of FDA review. This experimentation process allowed drug companies to prepare a dossier of trials showing that their generic versions of the brand-name product were bioequivalent, or reached similar blood concentration levels and generally worked the same way in the human body. However, this changed in Roche Products, Inc. v. Bolar Pharmaceutical Co., in which the newly created Court of Appeals for the Federal Circuit was asked to decide whether generic companies could conduct testing on patented products solely for the purpose of seeking FDA approval to make a generic copy. The controversy arose in the context of a generic version of flurazepam (Dalmene), a widely prescribed anxiolytic and sleeping pill. Before the expiration of the patent on the active ingredient, Bolar, a generic manufacturer, obtained a batch of the drug and began conducting basic pharmacologic tests on it to prepare for its own NDA. Roche, the brand-name manufacturer of Dalmane, sued to enjoin Bolar from using its patented product for any purpose whatsoever during the life of the patent. The Federal Circuit agreed with Roche, holding that pre-expiration testing of patent-protected brand-

20. Frank, supra note 18, at 1993-94.
23. See Engelberg, supra note 2, at 396 (“[T]he weight of judicial authority and common industry belief and practice supported the view that it was not an act of patent infringement to make or use a patented drug solely for the purpose of seeking approval to market a generic copy of the patented drug.”).
25. Id. at 860; see also Pfizer, Inc. v. Int'l Rectifier Corp., 545 F. Supp. 486 (C.D. Cal. 1980) (rejecting as improper the use within the United States of patented doxycycline tablets without authorization of the patent holder, in order to gain FDA approval).
name drugs was not covered under any experimental use defense to liability for infringement because of the substantial commercial implications of Bolar’s actions. The court held it to be an act of patent infringement for a generic drug manufacturer to perform tests on a patented product during the patent period where those tests might lead to FDA approval. A generic company could not even begin the preclinical and clinical process needed for FDA approval of its own version before all of the relevant patents on the brand-name drug expired. Roche v. Bolar served to effectively extend product exclusivity periods and threatened to dampen the market for generic products even further.

Even though the FDA worked to promote availability of generic entry for post-1962 drugs, by the late 1970s there were few substitutable generic drugs on the market. About 150 brand-name drugs lacked generic versions despite being off-patent, and generics accounted for only nineteen percent of all prescriptions. In one study, only two of the top thirteen drugs between 1976 and 1982 were found to have had generic entry within one year of patent expiration. As explained in more detail below, this created problems for patients and public health outcomes. Naturally, patients benefit from the introduction of new brand-name drugs, if those drugs offer substantial advantages in patient care. However, patients also benefit from the low-cost generic drug market that is intended to emerge after the brand-name drug patents expire. The high cost of brand-name drugs can lead to reduced patient adherence to essential drug regimens and to adverse patient outcomes from excessive spending on healthcare products. The healthcare system also benefits from reasonable drug price competition, which permits payors to cover a greater range of healthcare interventions with the same

28. See supra note 19 for discussion of the paper NDA process.
investment of resources.

It was in this environment that the Hatch-Waxman Act came into force. The Hatch-Waxman Act was a combination of two separate pieces of legislation that sought to bolster both the brand-name and generic drug industries.\(^{32}\) The Act was intended to make low-cost generics more widely available while simultaneously maintaining adequate incentives for innovation.\(^{33}\) To do so, it contained provisions in four major subcategories: (1) creation of a separate abbreviated FDA approval pathway for generic drugs proven to be pharmaceutically equivalent and bioequivalent to their brand-name counterparts; (2) a system to adjudicate generic manufacturers’ challenges to brand-name drug manufacturers’ market exclusivity; (3) assurance of competition-free periods for innovative drug approvals; and (4) extensions of brand-name market exclusivity. Each is discussed in turn.

**B. Bioequivalence Pathway for Generic Drugs**

Title I of the Act established a formalized and expedited system for approval of generic drug products to ensure a vibrant competitive market and lower prices after the brand-name market exclusivity period ended.\(^{34}\) This system was the ANDA pathway, which allowed a generic manufacturer to seek FDA approval by submitting proof that the generic drug was both pharmaceutically equivalent and bioequivalent to the brand-name version.\(^{35}\) The statute implemented this pathway by permitting applicants to “file with the Secretary an abbreviated application for the approval of a new drug” and specified that such an abbreviated application need only make a few certifications with respect to the drug product. First, the applicant must demonstrate that the conditions of use recommended in the labeling for the new drug are the same as those for a drug already approved by the FDA as safe and effective.\(^{36}\) Second, the applicant must provide “information to show that the other active ingredients of the new drug are the same as the active ingredients of the listed drug,” that the “route of administration, the dosage

\(^{32}\) Mossinghoff, supra note 29, at 188.

\(^{33}\) Engelberg, supra note 2, at 389 (noting that it was “an unprecedented attempt to achieve two seemingly contradictory objectives, namely, 1) to make lower-costing generic copies of approved drugs more widely available and 2) to assure that there were adequate incentives to invest in the development of new drugs”).


form, and the strength of the new drug are the same as those of the listed drug," and that the drug is "bioequivalent to the listed drug." Finally, the applicant must certify that the labeling is the same. The government is enjoined from requiring additional scientific information. Taken together, the criteria for pharmaceutical equivalence and bioequivalence define therapeutic equivalence.

The FDA promulgated regulations permitting bioequivalence to be established based on several approaches, the principal one of which became blood level crossover studies typically done in healthy male volunteers. Bioequivalence measures drawn from these studies included time until maximum serum (or plasma) concentration of the drug (C<sub>max</sub>) is reached, or the area under a curve (AUC) defined by serum concentration as a function of time. The FDA defined bioequivalence as sufficient demonstration that the ninety percent confidence intervals for the ratio of pioneer-to-generic AUC and C<sub>max</sub> fall within an acceptance interval of 0.80-1.25 (known as the "-20%/+25% rule"). A bioequivalent generic drug, therefore, was required to provide an acceptably equivalent amount of the drug into the patient’s blood stream over an equivalent period of time.

The ANDA bioequivalence process permitted approval of generic drugs scientifically proven to work similarly well to their brand-name versions without subjecting those generic drugs to the same clinical trial requirements already completed by the brand-name manufacturer. If the generic manufacturer could show pharmaceutical equivalence and bioequivalence, additional Phase II and Phase III clinical trials would not be necessary. Generic manufacturers could thus focus on making their drugs as inexpensively and high-quality as possible. Avoiding the costs of these clinical tests was intended to lead to lower drug prices for consumers and for government payors.

C. Generic Challenges to Brand-Name Market Exclusivity

In addition to the drug product-related certification required of generic drug manufacturers in Title I, the Hatch-Waxman Act required a legal certification

regarding the status of the patents protecting the brand-name drug. A manufacturer seeking to market a generic drug needed to certify to the FDA one of the following: that no patents existed (Paragraph I); that previous relevant patents were expired (Paragraph II); that they would wait until currently in-force patents expired to market their versions (Paragraph III); or that their versions did not infringe these patents or that the patents were invalid. The final option, contained in the fourth paragraph of the relevant section of the statute, became known as a "Paragraph IV" certification.

To assist generic drug manufacturers in identifying patents that claimed the brand-name drug, or its uses, the FDA required brand-name manufacturers to list in the book of Approved Drug Products with Therapeutic Equivalence Evaluations—also known as the Orange Book—all relevant patents protecting their products. The Orange Book, first published in 1978, is a compendium of FDA-approved products available for generic substitution. The two regulatory criteria for listing a patent in the Orange Book are: (1) that the patent claim an approved drug, its formulation, or a method of using the drug; and (2) that the claim can be reasonably asserted in patent infringement litigation.

When a generic manufacturer makes a Paragraph IV certification, it is required to provide notice to the brand-name manufacturer. An ANDA submission containing such a certification would be deemed an act of patent infringement by the statute, and the brand-name company would be given forty-five days to initiate a lawsuit for alleged infringement. The brand-name manufacturer’s lawsuit would generate an automatic thirty-month stay during which the FDA could not approve the generic product, in order to allow some time for the legal process to operate. If patent litigation was not yet complete after thirty months, generic companies were eligible to obtain final FDA approval


47. Id. The Orange Book was named for its orange cover, which was chosen because the publication date of the first print edition in 1980 was around the time of Halloween. See Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book): About the Orange Book, FOOD & DRUG ADMIN. (Feb. 2015), www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm.

48. Submission of Patent Information, 21 C.F.R. § 314.53(b) (2014). One category of patents that are not listable in the Orange Book, for example, is patents covering methods of manufacture.

49. Id. at § 314.52.


and launch at risk. The Act afforded a six-month period of market exclusivity to the first generic manufacturer to certify that the Orange Book-listed brand-name manufacturer’s patents were invalid or not infringed. Prices during that period would remain higher than they would be in an openly competitive market with multiple generic competitors, incentivizing generic manufacturers to assume the legal fees and risks of challenging brand-name manufacturers’ patents.

The goal of creating the Paragraph IV challenge process was to provide a mechanism through which generic manufacturers could challenge weak patents. The pathway was necessary because brand-name drugs were (and are) rarely the subject of a single patent on their underlying active ingredient. Rather, after a successful molecule has been developed, brand-name drug manufacturers often obtain numerous secondary patents on peripheral aspects of the product, such as its coating, salt forms, alternative crystalline structures, and metabolites. These secondary patents, sometimes issued years after the original molecule’s discovery, can extend the effective market exclusivity of the drug beyond the life of the first patent. Yet these secondary patented structures may not add to the efficacy or safety of the original drug. Moreover, the patents themselves are more likely to be invalid as lacking novelty or for being obvious improvements on prior patented structures. Generic manufacturers seeking to make bioequivalent versions of the underlying active ingredient could also more easily design around secondary patents. Thus, there was a strong public policy rationale for building a system through which generic manufacturers could challenge these patents and obtain permission to market their approved generic versions as soon as possible after expiration of the underlying active ingredient’s patent. Deputizing generic manufacturers to break through the thicket of secondary patents surrounding the original patented molecule would reduce inappropriate or excessive extensions in market exclusivity by the brand-name manufacturer.

52. Id.
D. Competition-Free Periods for Innovative Drug Approvals

As it created a process for abbreviated approval of generic drugs, the Hatch-Waxman Act provided assurance that brand-name manufacturers of innovative products or uses of drugs would enjoy guaranteed minimum periods of exclusivity. The legislation mandated that the ANDA process for new molecular entities (NMEs) would not be allowed to start until five years after FDA approval of the NME. This guaranteed any manufacturer, even without a patent, at least five years to earn revenues to recoup research and development (R&D) costs and obtain monopoly profits. A successful application for a new use or a new formulation (e.g., immediate to modified delayed or extended release) of a previously approved drug based on original clinical investigations would receive three years of market exclusivity.

Because of the thirty-month stay on Paragraph IV certifications, most NMEs—unless they were not covered by a patent—would be expected to receive a minimum of seven-and-a-half years of market exclusivity. However, the Act also superseded Roche v. Bolar, allowing generic manufacturers to experiment with brand-name manufacturers’ drugs to test their bioequivalent versions before expiration of the patent so that ANDAs could be prepared and submitted to the FDA without additional delay.

E. Extensions of Brand-Name Market Exclusivity

Title II of the Hatch-Waxman Act provided additional incentives for brand-name drug manufacturers, who had argued that the 1962 Kefauver-Harris

58. 21 U.S.C. § 355(j)(5)(F)(ii) (2012). If the ANDA application contains a Paragraph IV certification, this period is shortened to four years, but the thirty-month stay is extended so as to ensure that 7.5 years elapses from the date of approval. Id.
60. § 355 (j)(5)(F)(iii).
61. § 355 (j)(5)(F)(ii) (extending the 30-month period “by such amount of time (if any) which is required for seven and one-half years to have elapsed from the date of approval of the subsection (b) application”). Exclusivity could terminate prior to the conclusion of the 30-month period “if before the expiration of such period the district court decides that the patent is invalid or not infringed,” or, if the district court finds infringement, “the date on which the court of appeals decides that the patent is invalid or not infringed.” § 355(j)(5)(B)(ii).
Amendments unfairly shortened their effective exclusivity periods by requiring a lengthy process of clinical testing and FDA review. The seventeen-year patent term in effect in 1984 began at the time the patent was granted, which could occur years prior to FDA approval. In cases in which development and approval took especially long, brand-name manufacturers might find that little or no patent term remained by the time the FDA approved the drug for marketing.

The Hatch-Waxman Act addressed this issue by granting brand-name companies “patent term restoration,” or additional time that would be added to the seventeen-year patent term to compensate the patent holder for a portion of the patent term that was lost during the clinical testing phases and FDA review period. For any first approval of a product subject to a regulatory review period, the extension applied to any patents that claimed products, methods of using the products, or methods of manufacturing the products as long as the patents were still in force at the time of the extension application and had not been extended before. If more than one patent were asserted as applying to a given drug product, only one patent’s term could be extended. The period of patent term extension was calculated by adding one half of the time from the filing of the IND to the filing of the NDA to the full time during which the FDA had reviewed the NDA. Since some of the lost marketing time results from necessary development effort rather than government delay, the extension was capped at five years, and overall could not extend patent expiration past fourteen years from the date of the drug’s FDA approval. The time extensions did not include time before the issuance of the patent or periods in which the patent holder did not act with “due diligence . . . in seeking FDA approval.”

64. The patent term now ends twenty years from the date of filing, 35 U.S.C. § 154(a) (2012), creating an even greater lag between when the patent “clock” begins to run and FDA approval.
65. The issue was also addressed by the enactment of the Prescription Drug User Fee Act of 1992 (PDUFA), Pub. L. No. 102-571, 106 Stat. 4491, which authorized the FDA to collect “user fees” from pharmaceutical manufacturers. These fees allowed the FDA to hire more employees, which reduced the time needed for the FDA to review new drug applications. See Jonathan J. Darrow et al., New FDA Breakthrough Drug Category: Implications for Patients, 370 NEW ENG. J. MED. 1252, 1253 (2014).
67. § 156(c)(4).
68. § 156(c)(2).
69. § 156(c)(3) & (g)(6).
70. A due diligence limitation could only be invoked by special petition from another party filed within 180 days of the publication of the patent term extension determination. The FDA has never received a petition charging lack of due diligence. Small Business Assistance: Frequently Asked Questions on the Patent Term Restoration Program, FOOD & DRUG ADMIN., http://www.fda.gov/drugs/developmentapprovalprocess/smallbusinessassistance/ucm069959.htm
HATCH-WAXMAN TURNS 30

F. Summary

Title II of the Hatch-Waxman Act provided additional incentives for brand-name drug manufacturers, who had argued that the 1962 Kefauver-Harris Amendments unfairly shortened their effective exclusivity periods by requiring a lengthy process of clinical testing and FDA review. The seventeen-year patent term in effect in 1984 began at the time the patent was granted, which could occur years prior to FDA approval. In cases in which development and approval took especially long, brand-name manufacturers might find that little or no patent term remained by the time the FDA approved the drug for marketing.

II. THE HATCH-WAXMAN LEGACY

In the years after the Hatch-Waxman Act, hundreds of new generic drugs were approved via the bioequivalence ANDA pathway. For seventeen major drugs with patents expiring between 1990 and 1993, fourteen had generic entry in just over one month following patent expiration. State-level "Drug Product Selection" (DPS) laws aided in the widespread use of these generics. In this section, we discuss the various contributors to the legacy of the Hatch-Waxman Act.

A. Innovation by Brand-Name Drug Manufacturers

There have been no direct studies of the success of the Hatch-Waxman Act with respect to brand-name drug innovation, which was one of the two primary goals of the legislation. Studies investigating the patent terms of new prescription drugs before and after the legislation show an effect on lengthening market exclusivity, as intended. One study found that after passage of the Hatch-Waxman...
Waxman Act, the market exclusivity period for brand-name drugs introduced between 1990 and 1995 was 11.7 years as a result of the patent term restoration process, compared to 8.1 years for drugs approved between 1980 and 1984. More recent studies have generally been consistent with the earlier studies, finding that actual average pharmaceutical market exclusivity periods (i.e., the time between approval and first generic entry) are approximately twelve years.

Other studies have looked at the number of new drug introductions. Since the Hatch-Waxman Act was enacted, the number of new drugs approved each year has generally reflected the continued upward trend that has characterized the market since the 1950s. Studies have also shown an increase in the average R&D expenditures per drug approval. According to one report, pharmaceutical R&D spending has increased by nine percent annually in real terms. There does not appear to be a relationship between the cost of innovative drug R&D and the Hatch-Waxman Act.

By contrast, there may be a relationship between the existence of vigorous and timely generic competition and brand-name manufacturers’ willingness to invest in innovative drug development. Low-cost generic drugs advance innovation in the pharmaceutical marketplace by forcing innovator


77. See Bernard Munos, Lessons from 60 Years of Pharmaceutical Innovation, 8 NATURE REVIEWS: DRUG DISCOVERY 959, 959 (2009); see also Jonathan J. Dartow & Aaron S. Kesselheim, Trends in Drug Development and Approval, 1987-2013, 370 NEW ENG. J. MED. 639 (2014). The number of new molecular entities (NMEs) approved during the twenty years following Hatch-Waxman (1985-2004; 602 NMEs) was 79% greater than during the twenty years prior to Hatch Wxan (1965-1984; 336 NMEs). Id.

78. See, e.g., Fabio Pammolli et al., The Productivity Crisis in Pharmaceutical R&D, 10 NATURE REVIEWS: DRUG DISCOVERY 428, 428 (2011) (noting that “although investment in pharmaceutical research and development (R&D) has increased substantially in this time, the lack of a corresponding increase in the output in terms of new drugs being approved indicates that therapeutic innovation has become more challenging”); Jack W. Scannell et al., Diagnosing the Decline in Pharmaceutical R&D Efficiency, 11 NATURE REVIEWS: DRUG DISCOVERY 191, 191 (2012).

pharmaceutical companies to develop new products that will contribute to the next generation of therapies and medical progress, rather than simply re-investing in their current drug product lines. \footnote{Graham and Higgins studied 308 pharmaceutical companies with one FDA-approved product between 1985 and 2001 and found that loss of market exclusivity protection was the “most important predictor” of the arrival of a new product and the number of new product introductions. They concluded that pharmaceutical companies act strategically with respect to new product introductions, timing the introduction according to when exclusivity is expiring on their other products and in particular “targeting the three-year window around the loss of exclusivity to introduce new products.”} Thus, data show that the Hatch-Waxman Act increased market exclusivity periods for brand-name drugs, but there is no clear evidence that these longer periods had any impact on rates of brand-name drug innovation. Circumstantial evidence suggests that the vigorous generic substitution market organized by the legislation may help provide a stimulus for brand-name drug innovation. Further, many new products are not genuinely innovative and there has been much consolidation in the pioneer industry with consequent reduction in pipelines for new drug development.

\textbf{B. Use of Generic Drugs}

While the relationship between the passage of the Hatch-Waxman Act and brand-name drug innovation has not been firmly established, the legislation indisputably helped galvanize increases in the overall dispensing of generic drugs in the United States. The less expensive Hatch-Waxman ANDA regulatory approval process was a major factor in allowing generic drugs to reach the market expeditiously and with less up-front investment. As a consequence, generic drugs could be offered at substantially lower prices than their

\footnote{See United States v. Aluminum Co. of Am., 148 F.2d 416, 427 (2d Cir. 1945) (“Many people believe that possession of unchallenged economic power deadens initiative, discourages thrift and depresses energy; that immunity from competition is a narcotic, and rivalry is a stimulant, to industrial progress; that the spur of constant stress is necessary to counteract an inevitable disposition to let well enough alone.”). See generally Kenneth J. Arrow, Economic Welfare and the Allocation of Resources for Invention, in Essays in the Theory of Risk-Bearing 144, 157 (3d ed. 1976) (declaring “the incentive to invent is less under monopolistic than under competitive conditions”); Joseph E. Stiglitz, Economic Foundations of Intellectual Property Rights, 57 Duke L.J. 1693, 1696 (2008) (arguing that that an excessively strong intellectual property regime can impede innovation).}
corresponding brand-name products, which quickly reduced drug costs for patients and payors. One study showed a more than five-fold increase in the percentage of brand-name prescriptions being filled with generics from 1980 to 1989.\textsuperscript{82} By 2002, the Federal Trade Commission (FTC) could confidently state that “[b]eyond any doubt, Hatch-Waxman has increased generic drug entry,” noting that the generic drug prescription fill rate had increased to forty-seven percent.\textsuperscript{84} Based on market and other incentives, generic usage continued to increase dramatically to sixty percent in 2005, seventy-four percent in 2009\textsuperscript{85} and eighty-four percent in 2012.\textsuperscript{86}

In addition to spurring the creation of a competitive market with numerous generic drug entrants after patent expiration, the Hatch-Waxman Act successfully created a pathway that stimulated generic drug manufacturers to initiate lawsuits challenging existing brand-name drug patents. Generic manufacturer-led Paragraph IV challenges as a fraction of contributions to all new generic drug approvals increased from two percent in the 1980s to approximately twenty percent by 2000.\textsuperscript{87} As the statute intended, studies have shown that Paragraph IV challenges commonly addressed secondary patents covering peripheral components of the drug, rather than the patent on the underlying active ingredient.\textsuperscript{88} Indeed, these same studies show that the patents subject to Paragraph IV challenges also tended to be lower “quality,” defined as being in retrospect much more likely to have been improperly granted by the United

\begin{itemize}
  \item \textsuperscript{82} See generally How Increased Competition from Generic Drugs has Affected Prices and Returns in the Pharmaceutical Industry, CONG. BUDGET OFF. (1998), http://www.cbo.gov/sites/default/files/cbofiles/ftpdocs/6xx/doc655/pharm.pdf (explaining the impact of generic drugs on brand-name drug revenues).
  \item \textsuperscript{83} Caves et al., supra note 30, at 7 (“[G]eneric substitution for brand-written multisource prescriptions is relatively infrequent, confined to 29 percent of these prescriptions in 1989 . . . [as compared to] 5 percent of brand-written multisource prescriptions in 1980.”).
  \item \textsuperscript{84} Generic Drug Entry Prior to Patent Expiration, supra note 45, at i.
  \item \textsuperscript{85} Ernst R. Berndt & Murray Aitken, Brand Loyalty, Generic Entry and Price Competition in Pharmaceuticals in the Quarter Century After the Waxman-Hatch Legislation, 18 INT'L J. ECON. BUS. 177, 181 fig.2, 183 tbl.1, 186 (2011).
  \item \textsuperscript{86} Thomas, supra note 4, at A1. IMS is a leading provider of data regarding drug prices and sales. See also All Together Now: Liberalisation and the Quest for Scale are Pushing Generic-Drug Firms to Merge, ECONOMIST, July 24, 2008 (“Generics make up nearly two-thirds of the American drugs market by volume, but only thirteen percent by value.”).
  \item \textsuperscript{87} Generic Drug Entry Prior to Patent Expiration, supra note 45, at 10 (“According to the data provided by the FDA, during the 1980s (1984-89), only 2 percent of ANDAs contained paragraph IV certifications. This share increased to approximately 12 percent for the 1990s, and it has increased substantially in the last few years: from 1998-2000, approximately 20 percent of ANDAs contained paragraph IV certifications.”).
  \item \textsuperscript{88} C. Scott Hemphill & Bhaven N. Sampat, When Do Generics Challenge Drug Patents? , 8 J. EMPIRICAL LEGAL STUD. 613 (2011).  
\end{itemize}
In the late 1970s and early 1980s, the growth of DPS laws in each of the fifty states bolstered the impact of the Hatch-Waxman Act’s generic approval and challenge pathways in helping set an environment in which generic competition for brand-name drugs could flourish after their market exclusivity terms expired. For much of the early twentieth century, generic drug manufacturers were less reputable and many physicians and pharmacists worried about the safety of drugs made by these companies. By the 1960s, nearly every state had “anti-substitution laws” that required pharmacists to fill physicians’ prescriptions exactly as written and not to substitute a similarly named product made by a different manufacturer. Generic drugs, because of these barriers, did not present an effective competitive alternative to brand-name drugs, even when they were therapeutically equivalent.

However, after the Kefauver-Harris Amendments introduced assurance of safety and efficacy for new products, many states started repealing their anti-substitution statutes, replacing them with laws that allowed prescriptions to be filled with FDA-approved generic drugs. If the FDA certified a generic drug as safe and efficacious for its intended use, there was no clinical or public health reason to prevent it from being substituted at the pharmacy for a prescription written for a bioequivalent brand-name drug. The publication of the Orange Book contributed to the increase in demand for generic drugs occasioned by the repeal

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89. Id.
of anti-substitution laws and the enactment of DPS laws. With its central listing of all FDA-approved generic products, the Orange Book allowed healthcare decision makers to easily determine which generic products were both bioequivalent and pharmaceutically equivalent (meaning they had the same dosage strength and form, e.g., tablet to tablet, capsule to capsule), to the reference-listed brand-name drug. A key purpose of developing this list of bioequivalent drugs was to make drugs products “sufficiently interchangeable so that price can be a major factor in their selection.”

By the mid-1980s, all fifty states had repealed their anti-substitution laws and replaced them with laws encouraging substitution, at the level of the pharmacy, of less-expensive generic drugs approved by the FDA as being pharmaceutically equivalent and bioequivalent to the brand-name version. Some state boards of pharmacy adopted mandatory generic substitution laws. These required pharmacists to substitute a less-expensive generic for a brand-name medication unless the prescriber specified that only the brand-name drug should be dispensed. More permissive DPS laws enacted in other states give pharmacists more discretion by allowing, but not requiring, pharmacists to substitute less-expensive generics. In addition, some states require patient consent before substitution of a generic, while other states do not.

The new state DPS laws allowed the Hatch-Waxman Act generic drug approval pathway to flourish because of the unique relationship of the patient, physician, and pharmacist.

97. See Substitution Laws, supra note 96.
99. Id. One of the goals of the Orange Book was to create a list of therapeutically equivalent drugs, and it was believed that “publication of the List will lend to increased consumer awareness of less expensive therapeutically equivalent prescription drug products.” Therapeutically Equivalent Drugs, 45 Fed. Reg. 72,582, 72,583 (Oct. 31, 1980) (codified at 21 C.F.R. pt. 20). This “increased awareness should stimulate greater consumer demand for less expensive therapeutic equivalents, and physicians and pharmacists should be influenced to respond to that demand by prescribing and dispensing such less expensive drug products.” Id.
102. Shrank et al., supra note 96, at 1384.
103. Id.
104. Other policies, such as the introduction of tiered formularies by insurance companies, have also incentivized the use of generic medicines. See, e.g., Haiden A. Huskamp et al., The Effect of Incentive-Based Formularies on Prescription-Drug Utilization and Spending, 349 NEW ENG. J. MED. 2224, 2231 (2003) (“[A] sizeable minority of patients did change to less expensive tier-1 [i.e. generic] or tier-2 [i.e. preferred non-generic] alternatives [following implementation of a three-tier formulary] . . .”).
prescriber, and payor in the pharmaceutical marketplace: the physician writes the prescription for the medication, the pharmacist dispenses and sells the medication (provided it has the same non-proprietary name), and the patient (or patient’s insurer) pays for the medication. The separation of the prescription-writing act from the prescription-paying act caused a disconnect between medication use and payment in ways that hindered or prevented effective price competition. In 1979, an FTC report observed, “the forces of competition do not work well in a market where the consumer who pays does not choose and the physician who chooses does not pay.” 105 The FTC report lamented the ability of FDA-approved therapeutically equivalent products to lead to reduced prices because physicians were not involved in paying for drugs and were largely unaware of drug prices. Physicians’ lack of awareness of drug prices and spending by patients on drugs persists to the present day. 106 Importantly, as the 1979 FTC report recognized, the price disconnect could be bridged by the pharmacist. 107 The report noted that pharmacists

have both the power and the incentive to respond to lower prices. That is the role envisioned for the drug product selection laws: to transfer some of this power to pharmacists. Consumers are the ones most interested in a lower price, and pharmacists must respond to consumer demand because of direct competition with other pharmacies on prescription prices. 108

With the Hatch-Waxman Act, the number of AB-rated 109 generic versions of


108. Masson & Steiner, supra note 105, at 7.

109. “Multisource drug products listed under the same heading (i.e., identical active
reference brand-name products listed in the Orange Book grew as more generic manufacturers took advantage of the ANDA bioequivalence pathway and, later, Paragraph IV challenges. The state DPS laws helped lead to rapid uptake of bioequivalent generic drugs in practice without the time and expense needed to encourage physicians to change their prescribing practices. After the relevant brand-name manufacturers’ exclusivity periods expired, generic manufacturers could compete purely on the basis of price, leading to rapid consumer savings.  

Indeed, early studies showed rapid improvement in consumer access to generic drugs. Shortly after the Hatch-Waxman Act came into effect, the end of a brand-name drug’s market exclusivity period became synonymous with the manufacturer’s loss of revenue and the onset of significant generic price competition for that drug. As a result of the Hatch-Waxman Act and pro-substitution DPS laws in each state supporting automatic substitution by the pharmacist, generic drugs generally now sell for between twenty and seventy percent of the original price of the drug and take up to ninety percent of the brand’s sales within a year after generic entry.  

C. Impact on Patient Outcomes and Healthcare Spending  

Since the Hatch-Waxman Act, studies and substantial clinical experience
have supported the bioequivalence standard as a means of ensuring the efficacy and safety of generic drugs for patients. Patients who receive a generic drug have experienced the same beneficial clinical outcomes and risks of side effects as patients taking brand-name drugs. On a pharmacologic level, a review by the FDA of bioequivalence studies conducted between 1996 and 2007 found that the average difference in bioequivalence measures between generic and innovator products was about four percent, and that in nearly ninety-eight percent of the bioequivalence studies, the pharmacodynamics (i.e., the effect of the drug in the human body) of the generic product differed from that of the innovator product by less than ten percent. The FDA standard for bioequivalence requires that the bioequivalence measures be within 80-125%, a standard that also applies to the variability between lots of branded drugs. This review therefore demonstrated that generics were produced at a level of pharmaceutical quality consistently well within FDA standards.

Thus, as approved, generic drugs have produced the same clinical effects for patients as their brand-name counterparts. No prospective randomized controlled trials comparing brand-name and AB-rated generic drugs have shown any clinically significant variations in outcomes between brand-name and generic drugs. Two systematic reviews of studies comparing clinical outcomes from the use of brand-name and generic drugs in all types of cardiovascular disease and for epilepsy found no evidence of worse clinical outcomes from the use of generic drugs for these conditions. Other well-controlled studies of individual


115. Barbara M. Davit et al., Comparing Generic and Innovator Drugs: A Review of 12 Years of Bioequivalence Data from the United States Food and Drug Administration, 43 ANNALS PHARMACOTHERAPY 1583, 1588 (2009).


117. Aaron S. Kesselheim et al., The Clinical Equivalence of Generic and Brand-Name Drugs Used in Cardiovascular Disease: A Systematic Review and Meta-Analysis, 300 JAMA 2514, 2524 (2009) (concluding that “generic and brand-name cardiovascular drugs are similar in nearly all clinical outcomes”).

118. Id. at 2514.

drugs or drug classes have also concluded that generic substitution does not exacerbate disease or increase drug-related adverse events.

The increased availability of therapeutically equivalent generic drugs approved via the Hatch-Waxman ANDA pathway has had an important and positive effect on patient care. Low-cost generic drugs have been shown to promote adherence to medication regimens, enhance access to drugs for lower-income patients, and reduce financial strain caused by illness. With these improvements, more patients experience the benefits from essential prescription drug therapies, which translates into better patient health outcomes. Medication non-adherence, which occurs when patients do not take medications as prescribed by their healthcare providers, is a key public health issue. A study of patients with hypertension, hyperlipidemia, and diabetes found that one in four patients failed to adhere to their medication regimen. Non-adherence has been linked to adverse health effects including stroke in hypertensive patients, higher viral load in patients with HIV, and hospitalization and mortality in patients with heart failure. Overall, approximately 125,000 lives are lost annually from non-adherence. The cost to the U.S. healthcare system may exceed $100 billion per year due to complications that could have been prevented.

120. Scott T. Devine et al., Acute Epilepsy Exacerbations in Patients Switched Between A-Rated Anti-Epileptic Drugs, 26 CURRENT MED. RES. & OPINION 455, 463 (2010).
122. The Implications of Choice, supra note 6, at 335.
123. See Yuting Zhang et al., Access to and Use of $4 Generic Programs in Medicare, 27 J. GEN. INTERNAL MED. 1251, 1256 (2012) (noting that only 16.3% used a $4 program in 2007).
125. See Gagne et al., supra note 31, at 405.
128. Ashley A. Fitzgerald et al., Impact of Medication Nonadherence on Mortality in Heart Failure, 17 J. CARDIAC FAILURE 664, 668 (2011); Marcia McDonnell Holstad et al., Adherence, Sexual Risk, and Viral Load in HIV-Infected Women Prescribed Antiretroviral Therapy, 25 AIDS PATIENT CARE & STDs 431, 437 (2011); Paul Muntner et al., Low Medication Adherence and the Incidence of Stroke Symptoms Among Individuals with Hypertension: The REGARDS Study, 13 J. CLINICAL HYPERTENSION 479, 484 (2011) (concluding that “a graded association was present between worse medication adherence and a higher risk for developing new stroke symptoms”).
if patients had taken their medications as prescribed.\textsuperscript{130}

One of the key contributors to medication non-adherence is the high cost of prescription drugs.\textsuperscript{131} In one survey, one-third of elderly patients reported not filling a prescription or taking a reduced dose as a result of the drug’s high out-of-pocket costs.\textsuperscript{132} By contrast, generic drugs’ lower prices promote patient adherence to essential medications.\textsuperscript{133} This can be particularly important for patients with limited income and public insurance programs with constrained budgets. Thus, increasing availability of generic drugs has contributed to substantial improvements in public health outcomes.

The increased availability of generic drugs also has financial benefits for United States taxpayers. As healthcare costs rise, the cost of medications purchased by government programs becomes an important health policy issue.\textsuperscript{134} Within Medicaid—the federal- and state-funded healthcare insurance program for the poor—an annual spending on prescription drugs increased from $22.3 billion in 2007 to $25.4 billion in 2009. This accounted for 6.6 percent of total Medicaid spending on all services during those years and ten percent of total prescription drug spending in the United States.\textsuperscript{135} High spending on healthcare can be damaging to the economy,\textsuperscript{136} and as a result of high costs, payors have cut benefits or increased co-payments, and public insurers have raised their thresholds for eligibility.\textsuperscript{137} Reducing drug costs thus allows the benefits of all healthcare services to be spread more widely throughout society.\textsuperscript{138} The

\textsuperscript{130} Osterberg & Blaschke, supra note 126, at 488.
\textsuperscript{131} See Dana P. Goldman et al., Prescription Drug Cost Sharing: Associations with Medication and Medical Utilization and Spending and Health, 298 JAMA 61, 65 (2007); Osterberg & Blaschke, supra note 126, at 491 tbl.2.
\textsuperscript{133} The Implications of Choice, supra note 6, at 335.
\textsuperscript{134} Kelly Kennedy, States Scramble to Drive Down Medicaid Drug Costs, USA TODAY, Aug. 12, 2013, http://www.usatoday.com/story/news/politics/2013/08/11/medicaid-drug-benefit/2636891/ (“The increase in spending for Medicaid, the federal-state health care program for low-income Americans, has bedeviled states for decades.”).
\textsuperscript{135} Medicaid Payment for Outpatient Prescription Drugs, KAISER FAM. FOUND. 1 fig.1 (2011), http://kaiserfamilyfoundation.files.wordpress.com/2013/01/1609-04.pdf.
availability of bioequivalent generic drugs and state DPS laws have reduced pharmaceutical spending and helped rein in healthcare costs. Indeed, in 2012, pharmaceutical spending fell one percent, the first decrease in nearly two decades, a trend attributed to more widespread generic drug availability.

C. Impact on Patient Outcomes and Healthcare Spending

Since the Hatch-Waxman Act, studies and substantial clinical experience have supported the bioequivalence standard as a means of ensuring the efficacy and safety of generic drugs for patients. Patients who receive a generic drug have experienced the same beneficial clinical outcomes and risks of side effects as patients taking brand-name drugs. On a pharmacologic level, a review by the FDA of bioequivalence studies conducted between 1996 and 2007 found that the average difference in bioequivalence measures between generic and innovator products was about four percent, and that in nearly ninety-eight percent of the bioequivalence studies, the pharmacodynamics (i.e., the effect of the drug in the human body) of the generic product differed from that of the innovator product by less than ten percent. The FDA standard for bioequivalence requires that the bioequivalence measures be within 80-125%, a standard that also applies to the variability between lots of branded drugs. This review therefore demonstrated that generics were produced at a level of pharmaceutical quality consistently well within FDA standards.

140. Thomas, supra note 4. It is notable that generic drug usage has increased from nineteen percent to eighty-four percent in the thirty years since the Hatch-Waxman Act, yet overall drug spending largely increased steadily over the same period. Explanations for this trend include an aging of the population, greater use of pharmaceuticals in medical care, and higher prices over time for brand-name prescription drugs. See Panos Kanavos et al., Higher U.S. Branded Drug Prices and Spending Compared to Other Countries May Stem Partly from Quick Uptake of New Drugs, 32 Health Aff. 753, 756-57 (2013); Glen T. Schumock et al., National Trends in Prescription Drug Expenditures and Projections for 2014, 71 Am. J. Health Sys. Pharmacy 482, 483 (2014).
142. Barbara M. Davit et al., Comparing Generic and Innovator Drugs: A Review of 12 Years of Bioequivalence Data from the United States Food and Drug Administration, 43 Annals Pharmacotherapy 1583, 1588 (2009).
143. 21 C.F.R. § 210.3(b)(2) & (10) (2014); Process Validation, supra note 116, at 6; Letter from Roger L. Williams to Carmen A. Catizone, supra note 116, at 2-4.
HATCH-WAXMAN TURNS 30

D. Summary

In the past thirty years, the Hatch-Waxman Act has directly contributed to a revolution in the United States therapeutic marketplace from an environment in the early 1980s in which most prescriptions were filled by brand-name drugs to the present day when most prescriptions are filled are by generic drugs. Pro-substitution DPS laws have led to numerous health, social, and economic benefits to U.S. patients and the healthcare system. The impact of this major shift in the generic marketplace on brand-name drug innovation is less clear. While the Hatch-Waxman Act led to longer market exclusivity periods for brand-name drugs, the rate of increase in the number of NMEs approved per year has not measurably changed since the legislation, while the cost of drug development has increased.

III. THIRTY YEARS AFTER HATCH-WAXMAN: CURRENT AND EMERGING CHALLENGES

Despite revolutionary changes in the generic drug market since the Hatch-Waxman Act, the past decade has seen a number of challenges arise that threaten the continued success of the generic drug market. First, despite the systems set up by the Hatch-Waxman Act, market entry of generic drugs has been delayed beyond the point at which they should have been available. This has reduced drug availability and increased unnecessary spending by patients and payors. Delay strategies have been growing in type and scope and can generally be traced to unintended consequences of the legislation or features of the Hatch-Waxman Act that were sensible thirty years ago but have no place in the modern prescription drug market. A second major challenge involves the Supreme Court’s recent interpretation of the Hatch-Waxman Act in a way that limits the liability of generic drug companies when patients are harmed by their drugs, which may disincentivize future generic drug use. We review these challenges to the Hatch-Waxman regime in turn and assess whether changes to the legislation are necessary to address these shortcomings.

A. Limits or Delays to Generic Drug Availability Under Hatch-Waxman

In this section, we detail how Hatch-Waxman generic drug approval pathway has evolved in certain ways to support inappropriate extensions in market exclusivity of brand-name drugs.

1. Patent Accumulation

The patent-related provisions of the Hatch-Waxman Act provide one mechanism for delaying the availability of generic drugs. Pharmaceutical manufacturers had long relied on patents to protect the intellectual property in their products, given the relative ease with which small-molecule pharmaceutical products can be reverse-engineered. The Hatch-Waxman Act set a floor of five years of guaranteed market exclusivity for all new molecules. Following this five-year period, any additional brand-name drug exclusivity was to be determined by reference to relevant patents that covered the pharmaceutical product, which under the terms of the Hatch-Waxman Act had to be listed in the Orange Book.\(^{145}\)Expiration of these Orange Book-listed patents marks the initiation of the competitive generic drug market, and it is these patents that are the primary subjects of the Paragraph IV challenge process.

Patents listed in the Orange Book by the brand-name manufacturer provide automatic thirty-month extensions of the guaranteed market exclusivity period if they are challenged through the Paragraph IV litigation process. This thirty-month stay effectively increases the guaranteed minimum market exclusivity period for every new drug that lists patents in the Orange Book from five years to seven years and six months.\(^{146}\)Importantly, this thirty-month stay is available no matter how weak the patent is or how peripheral the protected feature is to the underlying active ingredient, product, or use.\(^{147}\)For example, in the case of the proton-pump inhibitor omeprazole (Prilosec), used to treat gastroesophageal reflux disease, the Orange Book-listed patents covering the coating of the pill served as the basis for litigation between the brand-name manufacturer and generic competitors seeking to enter the market.\(^{148}\)Generic competition emerged only after litigation revealed that the coating by one of the potential generic entrants did not infringe the brand-name product’s coating patent. By enabling companies to obtain an automatic thirty-month stay even for secondary patents associated with pharmaceutical products, Hatch-Waxman rewarded brand-name pharmaceutical manufacturers for seeking such patents.

The centrality of patents to the Hatch-Waxman Act’s balancing of brand-name and generic drug availability has had numerous consequences for the pharmaceutical market. Chief among these is that the Act reinforced the pursuit


\(^{147}\)As explained below, it is possible this thirty-month stay could terminate early if patent litigation is resolved prior to the end of the thirty-month period. See supra note 61.

\(^{148}\)See, e.g., In re Omeprazole Patent Litig., 536 F.3d 1361 (Fed. Cir. 2008).
of multiple secondary patents, on features such as small changes to formulation, variation in the inactive salt component, or other crystalline structures. Since the early 1980s, there has been substantial growth in the overall number of patents covering pharmaceutical products. Experts have noted that, for example, "the number of patents per new drug has increased dramatically" since the early 1980s.149 From 1992 to 2012, the combined number of patents granted in classes 424 and 514 (both listed as "Drug, Bio-Affecting and Body Treating Composition") increased 256 percent—from 3,596 to 9,210.150 It is not uncommon for marketed drugs to be covered by dozens of unique patents,151 although only a small fraction of these are listed in the Orange Book.152 For example, a patent map of the HIV protease inhibitors ritonavir and lopinavir—which are marketed together in the United States as a fixed-dose combination product called Kaletra for treatment of HIV infection—found 108 patents and patent applications, all but two of which covered secondary chemical structures or processes for manufacturing the pill.153

As the overall number of patents relating to pharmaceutical products has increased, so has the number of Orange Book-listed patents. The total number of Orange Book-listed patents increased by approximately 300 percent from 1992 to 2012.154 One review found that the number of patents per drug listed in the Orange Book increased over time from around 1.9 in a cohort of drugs approved between 1985-87 to nearly 3.9 in a comparable 2000-02 cohort.155 Blockbuster drugs tended to have the highest numbers of patents listed in the Orange Book, with an average of over five per drug. Another group of authors examined the 1,261 Orange Book-listed patents related to 528 NMEs approved by the FDA from 1988 to 2005.156 Of the 432 drugs that were protected by at least one patent, about two-thirds were protected by claims for the chemical compound, meaning that over a third of patented drugs had no chemical compound claims at all.

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149. Kapczynski et al., supra note 55, at *1.
152. Ruben Jacobo-Rubio et al., Pharmaceutical Patent Litigation: Measuring the Value of Generic Entry Rights and Brand Deterrence (June 2013) (unpublished manuscript) (on file with authors) (noting that the average branded drug product has five listed patents).
154. Jacobo-Rubio et al., supra note 152, at 13 fig.1.
155. Hemphill & Sampat, supra note 88, at 619 ("Drugs in the first cohort, approved between 1985 and 1987, have an average of 1.9 patents per drug. In the final (2000 to 2002) cohort, the mean slightly more than doubles to 3.9 patents per drug.").
156. Kapczynski et al., supra note 55, at *2-3.
Eighty-one percent were protected by formulation claims, eighty-three percent by method-of-use claims, and fifty-one percent by claims relating to alternative structures of the product including polymorphs, isomers, prodrugs, esters, and salts. On average these secondary patents were more likely to be found listed in high-sales drugs, and had expiration dates that were six to seven years after the expiration date of the last expiring chemical compound patent.

The growth of secondary pharmaceutical patents, as well as Orange Book patent listings, slows approval of generic drugs and raises the cost of market entry. Prospective generic entrants must expend effort evaluating the thicket of patents surrounding a particular drug product to determine which of them may serve as potential barriers to entry. Some patents can delay competitors and force generic manufacturers to design around certain features of the drug product. In addition, the brand-name manufacturer may make slight changes to the marketed molecule or obtain one or more secondary patents on the slightly altered molecule or its formulation, which has implications for the bioequivalence testing process that the generic manufacturer needs to pursue. Since these patents are generally all issued in the years following the patent on the underlying active ingredient, they can help to extend the market dominance of the brand manufacturer, which can introduce slightly modified products that delay or reduce competition without contributing substantial new therapeutic benefit.\(^5\)\(^7\) For example, the anti-cancer drug imatinib (Gleevec) has been protected by two key patents: the initial patent dating back to 1993, which covers the basic active ingredient (imatinib); and a subsequent patent (dating back to 1998) that covers the product as formulated and marketed for use by patients (the beta crystalline form of imatinib mesylate). The 1993 patent is for the active ingredient, while the 1998 patent is for the end-formulated version as sold.\(^5\)\(^8\) There is no evidence that the beta crystalline form provides relevant clinical improvement over the original version, but it does offer the possibility of extended market exclusivity. In the case of Kaletra, Abbott’s secondary patents nominally extend its exclusivity from 2016 to 2028 and beyond in the United States,\(^5\)\(^9\) although some empirical work suggests that weak, late-expiring patents are the most likely to be challenged and subsequently overturned.\(^1\)\(^6\) Though it may be possible to market the older

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159. Amin & Kesselheim, supra note 153, at 2290.
version of Kaletra once its patent and regulatory exclusivities expire in 2020,161 it is likely that these older versions would not be considered interchangeable with the current formulation of the drug. A generic manufacturer would therefore need to separately market their drug product, cutting into prospective cost-savings. Instead of serving as a means to prevent generic substitution, an improved formulation of the listed drug should ideally lead to the removal of the predicate version and should occur in a timely way based on public health considerations.

Of course, it is difficult to parse the impact of Hatch-Waxman from general patenting trends over the past three decades, including the overall rise in the annual number of patents issued in the United States. Other laws such as the 1980 Bayh-Dole Act,162 which encouraged university patenting, may also have played a role in the proliferation of drug patents. The total number of United States patents issued (excluding design patents and plant patents) increased dramatically from 1981 to 2014—from 65,771 to 300,678—an increase of 357 percent.163 While the number of pharmaceutical patents has certainly increased, it is difficult to say whether pharmaceutical innovation has increased equally (or at all) in magnitude. It is even more difficult to determine whether this innovation, however significant from a technical perspective, has been translated into the types of therapeutic advances that matter to patients. What can be said with greater certainty is that many of the patents protecting pharmaceuticals are “weak” (i.e., likely to be found invalid if challenged in court), that the cost of proving patent invalidity is high, and that these weak patents delay generic entry. One study found that generic firms prevailed in seventy-eight (forty-nine percent) of 159 Paragraph IV cases that were litigated to decision,164 a figure that climbs to seventy-six percent if settlements (which conclude about half of all Paragraph IV challenges) are included.165 A 2012 study found that more than fifty percent of Paragraph IV lawsuits involved disputes over secondary patents, rather than

164. Jacobo-Rubio et al., supra note 152, at 15 tbl.1; see also Generic Drug Entry Prior to Patent Expiration, supra note 45, at 16 (finding that generic applicants prevailed in twenty-two (73%) of thirty cases in which a court had resolved the drug patent dispute).
those covering the drug compound.\textsuperscript{166} Patent litigation can nevertheless be lengthy and expensive, costing the generic applicant as much as $10 million.\textsuperscript{167} One study found the average time to a district court decision was 2.3 years, with an additional 1.2 years to reach an appellate court decision.\textsuperscript{168} The average cost of patent litigation may be $4.5 million per party or more.\textsuperscript{169}

Reforms to patent law or alterations to the Hatch-Waxman Act can counteract excessive and wasteful accumulation of low-value pharmaceutical patents. Some have advocated raising the obviousness, novelty, or utility standards, in order to make pharmaceutical patents more difficult to obtain.\textsuperscript{170} In 2007, the U.S. Supreme Court revisited the obviousness criterion in its case of \textit{KSR v. Teleflex},\textsuperscript{171} setting down a new higher standard for determining obviousness of combinations of two pieces of existing technologies. Societal concern over low-value patents is also reflected in the growing trend among other countries to statutorily raise the bar for obtaining pharmaceutical patents. While current U.S. practice evaluates the appropriateness of pharmaceutical patent applications by focusing primarily on molecular form—asking whether the particular crystalline structure sought to be protected is sufficiently different from a previously described structure—other countries have developed pharmaceutical-specific patent laws that explicitly tie novelty and non-obviousness to the effectiveness of the drug. India, for example, has refined its law to prevent patents on drug products created through minor modifications to previously existing products that do not demonstrate enhanced efficacy.\textsuperscript{172}

A second avenue of patent reform that could address the problem of low-value secondary drug patents would be to facilitate patent challenges after they are granted. For example, some have proposed streamlining post-grant opposition

\textsuperscript{166} Jacobo-Rubio et al., \textit{supra} note 152, at 7.
\textsuperscript{168} Jacobo-Rubio et al., \textit{supra} note 152, at 14.
\textsuperscript{169} Hemphill, \textit{supra} note 54, at 1574 & n.89 (citing AM. INTELLECTUAL PROP. LAW ASS’N, REPORT OF THE ECONOMIC SURVEY 2005, at 22 (2005)) (median expenses on patent litigation with more than $25 million at risk is $4.5 million). The outcomes of pharmaceutical patent cases can implicate far more than $25 million, so even $4.5 million may be a conservative estimate.
\textsuperscript{172} See Rahul Rajkumar & Aaron S. Kesselheim, \textit{Balancing Access and Innovation: India’s Supreme Court Rules on Imatinib}, 310 JAMA 263, 263 (2013).
HATCH-WAXMAN TURNS 30

procedures in order to both encourage and reduce the cost of challenges to weak patents.\textsuperscript{173} In general, this approach may be preferable if the percentage of patents that are subject to litigation or licensing is low, because it defers costly examination and limits it to those patents that matter most. Placing yet greater emphasis on post-grant oppositions would continue a trend Congress started in 1980 and significantly expanded in 1999 and 2011.\textsuperscript{174} The 2011 Leahy-Smith America Invents Act established new post-grant opposition proceedings through which third parties could challenge the existence of a patent by submitting additional information bearing on patentability of the claimed invention to the USPTO.\textsuperscript{175} The presumption of patent validity does not apply in these proceedings.\textsuperscript{176} This is in contrast to ordinary judicial proceedings in which a patent is presumed valid and the challenger must prove invalidity by clear and convincing evidence.\textsuperscript{177} Post-grant opposition proceedings have the potential for weeding out bad pharmaceutical patents without the protracted time and cost of litigation, though the America Invents Act only permits the broadest type of post-grant opposition proceedings for nine months after issuance of the patent.\textsuperscript{178}

While patent reform proposals have merit and are consistent with current trends, U.S. lawmakers have been resistant to making market-specific exclusions or changes to patent law. Proposals to change the statutory definition of criteria such as novelty or non-obviousness across the board would be politically challenging. Therefore, a more viable approach could be to revisit the Hatch-Waxman Act and adjust the patent-listing process. For example, the Hatch-Waxman Act could be amended such that the listing of a patent in the Orange Book automatically reopened a post-grant review window of nine months, which would make it symmetric with the America Invents Act.\textsuperscript{179} At that point, the patent's invalidity could be administratively reconsidered by the USPTO based on details offered by the generic manufacturers or other interested parties.


\textsuperscript{176} See 35 U.S.C. § 316(e) (2012) ("Evidentiary Standards. In an inter partes review . . . the petitioner shall have the burden of proving a proposition of unpatentability by a preponderance of the evidence.").


\textsuperscript{179} Id.
Resolving patent disputes outside of judicial proceedings would increase efficiency. Indeed, the 180-day generic exclusivity period was originally inserted into the Hatch-Waxman Act because of the concern that the patent challenge and litigation process may be too time-consuming and costly for many generic manufacturers without some sort of bonus.\textsuperscript{180} Streamlining the patent-challenge process by adopting the USPTO-based pathway for administrative reconsideration of the patent would reduce the need to grant the generic manufacturer 180 days of market exclusivity. The goal of such a pathway would be to reduce the number of weak secondary patents that now populate the Orange Book without the need for a costly—and time-intensive—litigation process that necessarily involves a thirty-month extension of guaranteed exclusivity.\textsuperscript{172} If challenging potentially invalid patents could be made less costly, incentivizing the generic manufacturer with a 180-day period of higher prices would become less necessary. Hence, robust generic competition could begin immediately after expiration of any remaining patents. In addition, by minimizing the cost of challenging weak patents, expanded post-grant review could reduce the overall risk of anticompetitive settlements.

More radically, the Hatch-Waxman Act could be altered to permit listing of only original drug compound patents in the Orange Book, as opposed to other drug formulations or methods of use. This avenue would reduce the market impact of all secondary patents, whether strong or weak.\textsuperscript{181} One positive outcome would be to reduce uncertainty. Brand-name manufacturers would bear less risk of weak patents being invalidated during the regulatory exclusivity period. Generic manufacturers would have a clear date on which they could enter the market at a lower risk.\textsuperscript{182} Although secondary patents might still be asserted at

\begin{itemize}
  \item \textsuperscript{180} See Janssen Pharmaceutica, N.V. v. Apotex, Inc., 540 F.3d 1353, 1361 (Fed. Cir. 2008) ("The 180-day exclusivity period is important to generic pharmaceutical companies as it promotes patent challenges by enabling a generic company a period to recover its investment in [challenges to Orange Book listed patents].").
  \item \textsuperscript{181} This proposed solution draws a bright line, which makes it easier to implement, but also risks reducing the incentives for incremental innovations on drug products that actually do lead to improved clinical benefits. For example, if a different crystalline structure of a drug is discovered after approval that improves its bioavailability or potency in a clinically meaningful way, the patent covering this new formulation would not qualify, reducing the drug company's motivation to identify such better-acting compounds. But real-life examples of this sequence of events occurring are relatively rare. Most examples of incremental or follow-on innovations in the pharmaceutical market that are clinically meaningful involve major alterations in a drug's chemical structure that allow it to be taken less often (e.g., once instead of multiple times per day as in the case of metoprolol and extended release metoprolol), or that isolate the more active isomer (e.g., omeprazole and esomeprazole). Changes of this sort are typically filed as under their own NDAs, so our proposal would not affect incentives to innovate these products.
\end{itemize}
any point prior to expiration, the threat of thirty-month stays would largely be eliminated, in part because, as indicated above, most Paragraph IV challenges are brought against secondary patents. The reduction in the number of Paragraph IV challenges would also reduce the prevalence of 180-day generic exclusivity periods. Transaction costs arising from litigation and patent searching might decline as incentives to file for patent term extensions and obtain thirty-month stays become less important.\textsuperscript{183}

Since the combination of five-year data exclusivity and the thirty-month stays arising from Paragraph IV challenges essentially provide pioneer manufacturers with 7.5 years of guaranteed market exclusivity, this proposal threatens to reduce that number to closer to five years.\textsuperscript{184} Five years of exclusivity is often sufficient time for most brand-name manufacturers to earn back their investment on a drug and earn a substantial profit. In the case of sofosbuvir (Sovaldi), the transformative oral antiviral agent to treat hepatitis C virus, the brand-name manufacturer paid $11 billion for the small company making the drug at a late stage, and earned back that investment in the first year the drug was on the market. However, not all drugs have the immediate success of sofosbuvir.\textsuperscript{185} Thus, it might be necessary to assure brand-name drug manufacturers that they will benefit from slightly longer market exclusivity periods, since most new drugs will not be brought to market until six to ten years after the original patent on their underlying active ingredient is granted.\textsuperscript{186} A two-

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\textsuperscript{183} In the field of taxation, the use of the standard deduction serves a similar role by encouraging the substitution of numerous small, high-transaction-cost deductions with a single, low-transaction-cost standard deduction. These small, high-transaction-cost deductions are analogous to the numerous secondary patents that could be replaced by a lengthened regulatory exclusivity period.

\textsuperscript{184} Under Hatch-Waxman, a generic drug manufacturer’s application cannot be filed until five years have passed. This means that an application to market a generic drug must await review by the FDA’s Office of Generic Drugs. Delays at the FDA due to lack of resources have caused a backlog and, as a result, the application review process can take more than three years. The backlog at the Office of Generic Drugs has shortened considerably since 2012, when the FDA Safety and Innovation Act created a generic drug user fee system to enhance FDA resources for generic drug application reviews. So even without the Paragraph IV challenge process, the actual exclusivity period for most products will likely remain between 6 and 8 years.

\textsuperscript{185} For example, one economist has estimated that the overall break-even point for a “representative portfolio” of approved biologic drugs is approximately 12.9 years, although the estimate includes assumptions highly favorable to originator biotechnology companies, such as $1.2 billion in capitalized research and development costs. See Henry Grabowski et al., \textit{Data Exclusivity for Biologics}, 10 NATURE REVIEWS: DRUG DISCOVERY 15, 15-16 (2011).

or three-year longer guaranteed exclusivity period would not necessarily delay generic entry for many drugs already protected by the original patent on the underlying active ingredient, since FDA exclusivity periods (other than six-month pediatric exclusivities) run concurrently with the patent period.

2. Reverse Payment Paragraph IV Challenge Settlements ("Pay for Delay")

Few aspects of Hatch-Waxman have generated as much controversy or confusion as the settlement of patent litigation between brand-name and generic manufacturers. In general, nearly all civil lawsuits are resolved by settlement—more than ninety-eight percent, according to some estimates—although this figure can vary substantially by type of litigation. Settlement is a more amicable means of resolving disputes that not only reduces litigation expenses, but can also resolve issues more quickly and reduce the burden on the judiciary.

Naturally, litigation that arises in the Hatch-Waxman context may culminate in settlement when a potential generic competitor challenges a brand-name manufacturer’s Orange Book-listed patent. These settlements may result from reasoned decision-making on behalf of the parties, taking into account the risks of litigation, the strengths of the patents being challenged, and other aspects of the market. However, they have become a source of controversy in recent years in cases with arguably anticompetitive settlement terms. Of particular concern...
are settlements that include substantial payments from a brand-name manufacturer to a potential generic competitor, with the generic manufacturer agreeing to drop its challenge or to introduce its generic only at (or close to) the original patent’s expiration date. In such cases, the generic manufacturer appears to be accepting a short-term guaranteed payment instead of pursuing the challenge envisioned under the Hatch-Waxman Act, while the brand-name manufacturer appears to be propping up potentially weak or invalid patents by providing a large enough payment to generic manufacturers to fend off their challenges. Settlements with these terms have been called “reverse payment” (or, more pejoratively, “pay-for-delay” settlements), because unlike most patent settlements in which the alleged infringer agrees to pay a reasonable royalty to end litigation, payments in the Hatch-Waxman context run from brand-name manufacturer to the prospective generic competitor. 189

Commentators have often viewed the delay in generic competition that may accompany such settlements (hence the term “pay-for-delay”) as running counter to the intent of Hatch-Waxman, which provides the 180-day exclusivity bounty for the purpose of motivating patent challenges that lead to earlier generic entry. 190 Numerous commentators 191 and legislators 192 have expressed concern

189. See FTC v. Actavis, 133 S. Ct. 2223, 2235 (2013) (“[W]here only one party owns a patent, it is virtually unheard of outside of pharmaceuticals for that party to pay an accused infringer to settle the lawsuit.”).

190. In addition to the use of authorized generics to diminish the value of the 180-day bounty, brand-name companies in the 1990s simply declined to bring suit against the Paragraph IV filer, thus depriving it of the trigger for 180-day exclusivity. This practice ended with Mova Pharmaceutical Corp. v. Shalala, 140 F.3d 1060 (D.C. Cir. 1998), which held that the first Paragraph IV ANDA filer was entitled to 180-day exclusivity even if it was not sued.

with reverse payment settlements, although a number have also defended them as legitimate. The FTC, an independent, bipartisan agency with a declared possibility of shared monopoly profits creates an incentive to settle; (3) patents confer are probabilistic rights (i.e., they may be invalid); and (4) consumer welfare losses from delay are large); Erica J. Hemphill Kraus, A Shift on Pay for Delay: Reopening Doors for Pharmaceutical Competition?, 367 NEW ENG. J. MED. 1681, 1683 (2012) ("[A]llowing these agreements frustrates the Act’s central precompetitive purpose . . . "); Pier Luigi Parcu & Maria Alessandra Rossi, Reverse Payment Settlements in the Pharmaceutical Sector: A European Perspective, 2 EUR. J. RISK REG. 260 (2011) ("[P]otential benefits associated with settlements are of an order of magnitude insufficient to outweigh the certain drawbacks . . . "); Carl Shapiro, Antitrust Limits to Patent Settlements, 34 RAND J. ECON. 391, 408 (2003) (arguing that “a naked cash payment flowing from the patentholder to the challenger (in excess of avoided litigation costs) is a clear signal that the settlement is likely to be anticompetitive” but acknowledging that other factors such as risk aversion and asymmetric information can come into play). Many other commentators have discussed reverse payments without taking a strong position in favor or against them. See, e.g., Henry N. Butler & Jeffrey Paul Jarosh, Policy Reversal on Reverse Payments: Why Courts Should Not Follow the New DOJ Position on Reverse-Payment Settlements of Pharmaceutical Patent Litigation, 96 IOWA L. REV. 57, 114 (2010) (recommending use of the rule of reason); John E. Lopatka, A Comment on the Antitrust Analysis of Reverse Payment Settlements: Through the Lens of the Hand Formula, 79 TUL. L. REV. 235, 264 (2004) (recommending use of the Hand formula); Amanda P. Reeves, Muddying the Settlement Waters: Open Questions and Unintended Consequences Following FTC v. Actavis, 28 ANTITRUST 9, 14 (Fall 2013) (explaining how companies and their attorneys should respond to Actavis); Miriam Shuchman, Delaying Generic Competition: Corporate Payoffs and the Future of Plavix, 355(13) NEW ENG. J. MED. 1297, 1297-1300 (2006) (summarizing several high profile pay-for-delay deals).


193. Hatch-Waxman Act: Reverse-Payment Settlements: FTC v. Actavis, 127 HARV. L. REV. 358, 367 (2013) ("[T]he Court should have prioritized judicial administrability by protecting settlement agreements within the scope of the relevant patent."); Daniel A. Crane, Per Se Illegality for Reverse Payment Settlements?, 61 ALA. L. REV. 575, 576 (2010) [hereinafter Per Se Illegality] (arguing that a ban on reverse payments would be futile because “creative lawyers are capable of crafting settlement agreements that have the same effects as the most pernicious reverse payment cases but would pass unscathed under a rule focusing on reverse payments”); Ronald W. Davis, Reverse Payment Settlements: A View into the Abyss, and a Modest Proposal, 21 ANTITRUST 26, 30 (Fall 2006) (arguing that if the patentee is more likely than not to prevail in litigation “then the patentee and the challenger should enjoy an unqualified right to agree to restrain trade”); Kevin McDonald, Hatch-Waxman Patent Settlements and Antitrust: On “Probabilistic” Patent Rights and False Positives, 17 ANTITRUST 68, 75 (Spring 2003) (approving of reverse payments “if the patent is valid and the exclusion of competition no broader than that inherent in the patent”); Stuart N. Senator & Rohit K. Singla, FTC v. Actavis: Antitrust Litigation over “Reverse-Payment” Pharmaceutical Patent Settlements, 22 COMPETITION: J. ANTITRUST & UNFAIR COMP. L. SEC. ST. B. CAL. 153, 163 (2013) (noting that under the Supreme Court’s reasoning in Actavis, “a reverse payment may be explained—that is, justified—based upon the value of the drug at issue”); Elizabeth Stanley, An Ounce of Prevention: Analysis of Drug Patent Settlements Under the Hatch-Waxman Act, 10 GEO. MASON L. REV. 345, 358 (2002) (expressing concern that too harsh a view of
mission to “protect consumers and promote competition,” has condemned reverse payment settlements since 1999. Both Senator Orrin Hatch and Representative Henry Waxman, the co-sponsors of the original 1984 Act, have spoken out against reverse payment settlements. Nonetheless, they have been popular, with a growing number of Paragraph IV cases settling with reverse payments or other terms. These terms invoke the specter of the brand-name manufacturer sharing its monopoly rents in return for a promise to discontinue challenging what may be a weak patent. Reflecting concern about possible consumer harm from anticompetitive settlement agreements, the Medicare Prescription Drug, Improvement, and Modernization Act (MMA) of 2003

settlements could adversely affect innovation).


196. 148 CONG. REC. 14,437 (2002) (statement 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.”); 146 CONG. REC. 18,774 (2000) (statement of Rep. Waxman) (introducing bill to deter companies from “strik[ing] collusive agreements to trade multimillion dollar payoffs by the brand company for delays in the introduction of lower cost, generic alternatives”); see also Brief for Representative Henry A. Waxman as Amicus Curiae Supporting Petitioner, at 2, FTC v. Watson Pharm. Inc., 113 S. Ct. 2223 (2013) (No. 12-416), 2013 WL 417736, at *2 (calling the shielding of reverse payment settlements from antitrust scrutiny “a significant obstacle to the fulfillment of the important public policies embodied in the Hatch-Waxman [Act]”).

197. See Shuchman, supra note 191, at 1297-1300 (discussing several such settlements).


199. Agreements Filed with the Federal Trade Commission Under the Medicare Prescription Drug, Improvement, and Modernization Act of 2003: Overview of Agreements Filed in FY 2012: A Report by the Bureau of Competition, FED. TRADE COMM’N, 1-2 (2013), https://www.ftc.gov/sites/default/files/documents/reports/agreements-filled-federal-trade-commission-under-medicare-prescription-drug-improvement-and/130117mmareport.pdf [hereinafter Overview of Agreements Filed in FY 2012]. The most recent year for which a report has been issued is 2012. Hatch-Waxman did not restrict the patents listed in the Orange Book to those covering the active ingredient itself. For purposes of Paragraph IV litigation, a patent on the underlying active ingredient is treated the same as a patent on a peripheral feature of the drug, such as its coating or heat stability, or a metabolite or other derivative crystalline structure. In addition, the FDA was not given authority to evaluate the patents listed by the brand-name company to determine their validity or relevance to the potential generic competitors.
requires that settlement agreements between Paragraph IV filers and brand-name companies be reported to the FTC.200

In 2013, the Supreme Court weighed in, holding in FTC v. Actavis that reverse payment settlement agreements can sometimes violate antitrust laws.201 The Court rejected the view of a growing number of U.S. Courts of Appeals that defendants would be immune from antitrust scrutiny so long as any anticompetitive effects of the settlement fell “within scope of the exclusionary potential of the patent,”202 noting that the patent at issue “may or may not be valid [and infringed].”203 The Court also disposed of the argument that patentees would find it too expensive to “buy off” other patent challengers by pointing out that if the first-to-file applicant forfeits its 180-day exclusivity right (which could occur following a reverse-payment settlement), no other generic can obtain it, dampening the likelihood of subsequent challenges.203 In holding that reverse payment settlements are subject to analysis under the rule of reason standard, the Court provided a useful guide to future cases, indicating that the excess of the reverse payment beyond what could be justified by litigation savings or other legitimate explanations could provide a workable surrogate for a patent’s weakness as well as insight into the ultimate question of antitrust violation. The Actavis case may slow the number of settlement agreements with reverse payments or other anticompetitive terms, or it may merely influence the content of those agreements; it is too early to tell. While a number of pending cases have been affected by the Actavis decision,204 its impact is not yet clear.

If reverse payment settlement agreements continue to prove problematic, a number of reforms could address this unintended consequence of the Hatch-Waxman Act. Currently, the FTC must be notified of reverse payment settlement agreements, but it does not prospectively approve or disapprove them as it does for proposed mergers under the Hart-Scott-Rodino Act.205 The absence of FTC approval means that brand-name and generic manufacturers may proceed

201. 133 S. Ct. 2223 (2013).
202. Id. at 2231.
203. Id. at 2229.
according to the terms of their agreements without waiting any particular period of time. They also need not negotiate with the FTC prior to entering into the settlement agreement. Legislative amendments to Hatch-Waxman might confer approval power to the FTC and impose a waiting period during which the FTC could evaluate a proposed settlement. The power to disapprove could help reduce or at least diminish the litigation burden on the FTC, as well as provide an opportunity to negotiate concessions with respect to the terms of any proposed settlement agreement. In addition, under the MMA amendments, failure to file with the FTC can result in civil penalties of up to $11,000 per day ($4 million per year). However, given that the forty potential reverse payment settlements filed with the FTC in 2012 concerned products that averaged $268 million in sales per year, these penalties may be too small. Finally, the MMA amendments to the Hatch-Waxman Act required filing of only settlement agreements between brand-name and Paragraph IV generic ANDA filers, but not those between brand-name and generic manufacturers that might later have filed a Paragraph IV challenge if not for an earlier agreement. Agreements entered into before the filing of Paragraph IV challenges might not be settlement agreements, but the FTC should be attentive to possible shifts in concerted practices that could result from stricter settlement agreement legislation and decisions.

3. Authorized Generics

In recent years, the rise of a new category of drugs called “authorized generics” has threatened the balance between brand-name drug exclusivity periods and generic drug competition established by the Hatch-Waxman Act. Authorized generics are products that are marketed as generics but sold by a brand-name manufacturer or its licensee. Because authorized generics administratively fall under the brand-name company’s original NDA approval, they can be introduced at the brand-name company’s discretion. In most cases, they are sold just prior to the beginning of the 180-day generic exclusivity period.
that occurs when the first traditional generic drug enters the market after a successful Paragraph IV challenge. As a result, authorized generics have been criticized as a deliberate attempt to undermine the incentive structure of Hatch-Waxman, as they disincentivize the initiation of Paragraph IV challenges against weak Orange Book-listed patents protecting brand-name products.210 The presence of an authorized generic reduces the potential profits available to generic manufacturers by introducing a competitor to the generic during the exclusivity period. A 2009 FTC Report confirmed that authorized generics reduce prices by increasing competition during the 180-day period.211 Average retail prices were found to be 4.2 percent lower if an authorized generic entered the market than if it did not.212 The Report also confirmed the concern that entry by an authorized generic “significantly decreases the revenues”213 of the first-filing generic manufacturer by approximately fifty percent.214

Brand-name manufacturers have hinted that consumers benefit from the lower drug prices that authorized generics offer during the 180-day duopoly period.215 However, such positive outcomes come at a significant cost if they deter generic manufacturers’ willingness to bring Paragraph IV challenges in the first place. There is not yet conclusive evidence as to whether authorized generics deter the initiation of Paragraph IV challenges.216 Some commentators have concluded that authorized generics are unlikely to have a significant deterrent effect. Indeed, Paragraph IV certifications have been frequent despite existing situations in which multiple generic manufacturers might enter the market, such as might result from same-day filings217 or filings that pertain to different doses


212. Id. at 6-7; see also Aaron Barkoff, PhRMA Study Finds Authorized Generics Lead to Lower Drug Prices, ORANGEBOOKBLOG (June 27, 2006), http://www.orangebookblog.com/2006/06/phrma_study_fin.html (“[W]ith an authorized generic on the market during the exclusivity period, discounts to brand medicines were greater—on average 15.8 percentage points greater—than instances when a generic company did not face competition from an authorized generic.”).

213. Authorized Generics, supra note 211, at 16.

214. Id. at 3.

215. Barkoff, supra note 212.


of the same drug.\textsuperscript{218} Notwithstanding the possibility of entry by authorized generics, the number of Paragraph IV challenges increased dramatically from 35 in 2001 to 242 in 2011,\textsuperscript{219} although it fell to 204 in 2012.\textsuperscript{220} That challenges are frequent despite the disincentive created by the introduction of authorized generics can be explained in part by the fact that Paragraph IV challenges can be averted only if \textit{all} generics are deterred from filing under Paragraph IV. Generic manufacturers, however, may each have different business risk tolerance levels, assessments of likely litigation outcome, or thresholds for required return-on-investment. Given this variation, all generic manufacturers are likely to be deterred only when the relevant patents are perceived to be relatively strong or when expected profits are relatively small.\textsuperscript{221}

While the impact of authorized generics on initiation of Paragraph IV challenges by generic manufacturers is not fully known, authorized generics do appear to exert a strong effect on reverse payment settlements. Indeed, in many reverse payment cases, major settlement terms include the brand-name manufacturer's promise either not to market an authorized generic or to allow the generic challenger to market the authorized generic.\textsuperscript{222} Thus, the existence of authorized generics as a key negotiating tool in reverse payment settlement cases potentiates the anticompetitive effects and public health complications of those agreements.

Despite their potential to suppress Paragraph IV filings and clear impact in providing a vehicle for settlements in reverse payment cases, authorized generics appear to be a permanent fixture of the pharmaceutical market. Recognizing the potential chilling effect of authorized generics, generic manufacturers have petitioned the FDA to prevent their sale during the 180-day exclusivity period.\textsuperscript{223} These petitions have not been successful, as the FDA does not have authority to

\begin{itemize}
\item \textsuperscript{218} Ernst R. Berndt et al., \textit{Authorized Generic Drugs, Price Competition, and Consumers' Welfare}, 26 \textit{Health Aff.} 790, 793 (2007).
\item \textsuperscript{220} Id.
\item \textsuperscript{221} Berndt et al., \textit{supra} note 218, at 794.
\item \textsuperscript{222} C. Scott Hemphill, \textit{An Aggregate Approach to Antitrust: Using Data and Rulemaking to Preserve Drug Competition}, 109 \textit{Colum. L. Rev.} 629 (2009).
\end{itemize}
challenge brand-name manufacturers’ actions with respect to drug pricing (as opposed to actions that change the formulation of the drugs being sold). Courts have affirmed the ability for authorized generics to compete with ANDA-approved generic products during the 180-day exclusivity period.\footnote{See, e.g., Teva Pharm. Indus. Ltd. v. FDA, 355 F. Supp. 2d 111 (D.D.C. 2004), aff’d sub nom. Teva Pharm. Indus. Ltd. v. Crawford, 410 F.3d 51 (D.C. Cir. 2005) (holding that Pfizer may sell its own authorized generic version of its epilepsy drug gabapentin (Neurontin) during a 180-day exclusivity period granted to Teva Pharmaceuticals).}

Further study on the use and prevalence of authorized generics would help determine whether the public health benefits arising from the decrement in price that they offer during the 180-day exclusivity period is outweighed by the risks that they pose to the efficient functioning of the Hatch-Waxman Paragraph IV challenge process. Even without such evidence, it is clear that their existence undermines the deliberately crafted incentive structure in the Hatch-Waxman Act that intends to reward generic manufacturers for challenging weak or invalid brand-name patents. Since the FDA will not be able to act on authorized generics without additional authority, Congress should consider amending the Act to prohibit the introduction of authorized generics until after the conclusion of the 180-day period.

\section*{4. Dose Form or Other Changes in the Listed Drug}

One central purpose of the Hatch-Waxman Act was to guarantee a sufficient exclusivity period to the innovator while facilitating generic entry at the end of the exclusivity period. The balance can be tipped in favor of the innovator by the brand-name manufacturer’s strategic introduction of a slightly modified form of the product just prior to patent expiration. A common strategy is to introduce the new version while the patent on the old version still prevents competition. Then, before the old patent expires, the brand-name manufacturer engages in intensive marketing to convince physicians to prescribe the new product. The push to switch can be reinforced by discontinuing promotion of the old product, or even taking it off the market altogether, thereby preventing substitution at the pharmacy counter.\footnote{Michael A. Carrier, \textit{A Real-World Analysis of Pharmaceutical Settlements: The Missing Dimension of Product Hopping}, 62 FLA. L. REV. 1009, 1021-29 (2010); Seth C. Silber & Kara Kuritz, \textit{Product Switching in the Pharmaceutical Industry: Ripe for Antitrust Scrutiny?}, 7 J. GENERIC MEDICINES 119 (2012) (“[T]he market for [the old] product may be greatly depleted.”).} While such dose formulation or other changes in the listed drug\footnote{This process is sometimes referred to by the derogatory term “product hopping” in the literature. \textit{See, e.g., Jessie Cheng, An Antitrust Analysis of Product Hopping in the Pharmaceutical Industry, 108 COLUM. L. REV. 1471 (2008); Mark Metzke, Targeting Enantiomer Product Hopping with a New “Obviousness” Standard, 14 UCLA J. L. & TECH. 1 (2010).} can generally only succeed if the market can be convinced that the new

\begin{thebibliography}{9}
\bibitem{}\textit{Yale Journal of Health Policy, Law, and Ethics, Vol. 15 \[2015\], Iss. 2, Art. 2\footnote{http://digitalcommons.law.yale.edu/yjhple/vol15/iss2/2}}
\end{thebibliography}
version is superior, marketing has long proven successful at making new drugs appear more desirable than justified by their therapeutic value.\textsuperscript{227} For example, in the case of the antibiotic doxycycline hyclate extended release (Doryx), which was available in a capsule and nearing the date of expected generic competition, the manufacturer introduced a tablet version at the same dosage strength and withdrew the capsule from the market.\textsuperscript{228}

To support a change, the original product may also be delisted from pharmaceutical pricing guides, which are used by insurers and hospitals to determine which drugs are available in which forms, and whether they are produced by brand-name or generic manufacturers. For example, in the case of the cholesterol-lowering drug fenofibrate (Tricor), Abbott moved from a 67mg capsule to a 54mg tablet and then to a 48mg tablet. Abbott successfully mitigated competition for more than five years before a coalition of generics manufacturers, retail pharmacies, and class action plaintiffs convinced a court that the manufacturer's behavior had likely violated antitrust laws.\textsuperscript{229}

Only after consumers become familiar with the new version will the patent expire and competition for the old product begin. By then, however, switching costs have already taken hold in the form of familiarity with the new product. If providers are writing prescriptions for the new drug, the generic version of the old drug cannot be automatically substituted because it will not be AB-rated vis-à-vis the new drug. Substitution of non-AB-rated generics, even if bioequivalent, is generally not permitted under state substitution regimes without express authorization from the prescriber. This means that the physician has to be contacted and the prescription rewritten in order for a generic drug to be dispensed.\textsuperscript{230} The strategy is comparable to predatory pricing in that it lures consumers with a price that is initially the lowest available. Soon thereafter, when generic competition emerges for the older product, it becomes more expensive than other options. This is different from predatory pricing insofar as consumers could switch a second time to the newly-introduced generic. But generic manufacturers do not engage in sufficient marketing of their products to

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\item \textsuperscript{227} See generally Jonathan J. Darrow, \textit{Pharmaceutical Gatekeepers}, 47 \textit{Ind. L. Rev.} 363 (2014) (explaining why patients, physicians, insurance companies, government regulators, and courts do not effectively screen out drugs with poor therapeutic value).
\item \textsuperscript{228} Brief for FTC as Amicus Curiae, Mylan Pharm. v. Warner Chilcott Pub. Ltd. Co., 2:12-cv-03824-PD (No. 12-3824) (E.D. Pa., Nov. 21, 2012).
\item \textsuperscript{229} Abbott Labs. v. Teva Pharm. USA, Inc., 432 F. Supp. 2d 408, 434 (D. Del. 2006) (denying a motion to dismiss).
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promote such a switchback, although there may be financial pressures from insurers or other payors once they become savvy to the stratagem and if the new version's use cannot be justified by additional benefits.

Dose formulation or other changes in the listed drug are distinct from similar strategies in other industries in that they can entitle the patent holder to a second thirty-month stay of generic competition if a Paragraph IV challenge is brought against the new product. In the 1990s, brand-name manufacturers began to obtain multiple thirty-month stays on a single product before Congress generally barred that practice with the MMA of 2003.\textsuperscript{231} The provisions of the MMA, however, do not extend to an altered dosage, dosage form, or method of administration, since those are considered to result in a "new drug," as is combining two existing drugs into a single dosage form or altering the proportions of those drugs as compared to an existing combination.\textsuperscript{232} A drug for which the labeling is revised to indicate use for a different disease—or for the same disease in a different part of the body—could also be considered a "new drug" under FDA regulations.\textsuperscript{233}

Even absent an additional thirty-month stay, a shift to a new version will create delay by forcing the generic manufacturer to submit a second ANDA for the new product.\textsuperscript{234} Under the 2012 Generic Drug User Fee goals, the FDA will seek to act on ninety percent of ANDAs within ten months by the year 2017.\textsuperscript{235} But reformulation and ANDA preparation time must be added to this figure. While it is possible for the generic firm to market its copy of the old product under its own brand and encourage doctors to prescribe it directly, this is not a role that generics are well-equipped to undertake. In cases in which the brand-name manufacturer voluntarily withdraws the original drug from the U.S. market, the ANDA applicant will have to petition the FDA for a determination that the


\textsuperscript{232} 21 C.F.R. § 310.3(h) (2014).

\textsuperscript{233} Id.; see also 21 C.F.R. § 314.92(a)(1) (2014) ("For determining the suitability of an abbreviated new drug application, the term 'same as' means identical in active ingredient(s), dosage form, strength, route of administration, and conditions of use . . . .")

\textsuperscript{234} In some cases, the generic applicant may submit an amendment or supplement, such as where the ANDA seeks approval for different strengths of the same listed drug. Questions and Answers, supra note 231, at 3.

drug was not withdrawn for safety or effectiveness reasons,236 which may result in delay237 or even litigation to sort out the issue.238

A number of commentators have taken a permissive view of changing dose formulations or other pharmaceutically relevant features of the listed drug, often on the theoretically plausible (but largely unsubstantiated) basis that new versions could possess advantages that their predecessors do not.239 One suggested that the practice be allowed so long as the old drug is left on the market or the new one offers significant improvement.240 Another went further, suggesting that the practice be deemed per se legal so long as a valid patent supports the new product.241 One pair of antitrust attorneys pointed out that this is merely one form of life-cycle management, which firms have undertaken for decades and which is a normal part of development and innovation.242 They note that, in practice, courts have tended to find violations of the antitrust laws only where consumers are coerced into a choice, such as where the old version is removed from the market.243

The patent laws are intended to lay the groundwork for vigorous competition after the expiration of the patent term, and patentable product changes are therefore expected to create a new period of exclusivity for the modified form. The Hatch-Waxman Act, however, grew out of a special need in the

236. E.g., 21 C.F.R. § 314.92(a)(1) (2014) ("If a listed drug has been voluntarily withdrawn... sale by its manufacturer, a person who wishes to submit an abbreviated new drug application for the drug shall comply with § 314.122."); 21 C.F.R. § 314.122(a) (2014) (requiring submission of a petition to determine whether listed drug was withdrawn for safety or effectiveness reasons).

237. See 21 C.F.R. § 314.93(e)(1)(v) (2014) (noting that the petition may be disapproved if the agency has not determined whether the voluntary withdrawal from sale is for safety or effectiveness reasons); Michael A. Carrier & Daryl Wander, Citizen Petitions: An Empirical Study, 34 CARDOZO L. REV. 249, 262-63 (2012) (discussing delays in the petition process that culminated in a 2007 law requiring the FDA to respond within 180 days).

238. Cumberland Pharm. Inc. v. FDA, 981 F. Supp. 2d 38 (D.D.C. 2013). Moreover, withdrawal of the older branded drug may lead the FDA to designate a generic company as the RLD holder, which one court has held subjects the generic company to failure-to-warn liability normally borne only by brand manufacturers. In re Reglan/Metoclopramide Litig., 81 A.3d 80, 96 (Pa. Super. Ct. 2013), appeal denied, 99 A.3d 926 (Pa. 2014).


241. Michelle L. Ethier, Permissible Product Hopping: Why a Per Se Legal Rule Barring Antitrust Liability is Necessary to Protect Future Innovation in the Pharmaceutical Industry, 3 AKRON INTELL. PROP. J. 323, 324 (2009). To obtain a new 30-month stay for the new drug, at least one Orange Book-listed patent must exist in order to create a basis for a Paragraph IV certification.

242. Silber & Kuritz, supra note 225, at 3.

243. Id.
pharmaceutical market stemming from the fact that the expiration of the patent period alone could not adequately promote generic competition due to the high transaction costs associated with pharmaceutical introductions. While the ANDA process reduces these costs substantially, costs remain high, both in terms of dollar value and months of delay. For this reason, changes in dose formulations or other similar changes in the listed drug should be viewed skeptically. This will ensure that generic drugs can freely compete at the expiration of both patent and regulatory exclusivity periods, and will thwart what the FTC recently described as techniques used to “game the regulatory structure” on the part of brand-name manufacturers. Courts, the FTC, and even the FDA should closely scrutinize practices for which the primary purpose is to frustrate generic competition as generic competition for that product nears. These practices include voluntarily withdrawing a brand-name drug for reasons other than safety or efficacy or changing the number of milligrams of active ingredient in a formulation in ways that do not correspond to therapeutic demands. While discerning a company’s “purpose” in taking some action may be difficult, timing can provide an important clue. In light of the dramatic success and increasing market share of generics, scrutiny by the FTC and courts rather than statutory amendment should be sufficient to effectuate the purposes of the Hatch-Waxman Act with respect to this business practice. Should trends reverse and a clear pattern of abuse go uncorrected by the courts, statutory amendment might be a better means of reform.

5. Refusal to Provide Material for Purpose of Establishing Bioequivalence

Unintended consequences of legislation are not limited to oddities like “reverse” payments, well-timed switching of the dose formulation, or slight changes to other pharmaceutically relevant components of the listed drug. Another strategy brand-name manufacturers recently used to protect their market share was to take deliberate steps to prevent generic firms from obtaining samples of their branded products to conduct the bioequivalence testing envisioned under the Hatch-Waxman Act. Although the FDA takes a flexible approach to the determination of bioequivalence, generic approval as an AB-rated bioequivalent drug generally requires comparative testing of the generic against the innovator drug.245 The acquisition of a certain amount of brand-name


245. See, e.g., Complaint at 9-10, Mylan Pharm. Inc. v. Celgene Corp., No. 2:14-cv-02094

340
product is therefore usually a prerequisite to generic approval.\textsuperscript{246}

However, over the past several years, the FTC has been investigating allegations by some generic manufacturers that brand-name firms are deliberately withholding access to their products for the purpose of preventing bioequivalence testing.\textsuperscript{247} In 2009, generic firms reported that Celgene refused to sell them samples of thalidomide (Thalomid), the infamous drug associated with birth defects in the 1950s, which was approved in 1998 and 2006 to treat leprosy and a form of cancer called multiple myeloma, respectively.\textsuperscript{248} Gilead has been accused of including provisions in its supply chain contracts that restrict the distribution of ambrisentan (Letairis), a pulmonary artery hypertension drug, to generic manufacturers.\textsuperscript{249} Similar practices were challenged in court under the antitrust laws against Actelion, the company that manufactures bosentan (Tracleer), another pulmonary artery hypertension product, and miglustat (Zavesca), a treatment for a form of the rare genetic deficiency Gaucher disease.\textsuperscript{250} The FTC filed an amicus brief supporting the position of the generic manufacturers,\textsuperscript{251} but the case recently settled with an undisclosed outcome.

There are sometimes legitimate safety reasons to restrict sales of patented

\textsuperscript{246} Even if the branded drug is covered by a patent, a special provision provides an exemption from patent infringement litigation for otherwise infringing uses that are “reasonably related to the development of information” for FDA approval, therefore allowing bioequivalence testing prior to patent expiration. 35 U.S.C. § 271(e)(1) (2012).


\textsuperscript{248} Katie Thomas, Game Plan Against Generics, N.Y. TIMES, Apr. 15, 2013, at B1.

\textsuperscript{249} Id.


\textsuperscript{251} Brief for FTC as Amicus Curiae, supra note 228, at 2.
pharmaceuticals. In 2007, the Food and Drug Administration Amendments Act (FDAAA) gave the FDA power to require drugs to be distributed through controlled channels as part of its Risk Evaluation and Mitigation Strategies (REMS) provision.\(^{252}\) Foreseeing the potential to use this provision to frustrate generic entry, Congress specifically prohibited companies from using REMS to “block or delay approval” of an ANDA.\(^{253}\) However, the legislation did not address restrictions on distribution unrelated to REMS, nor did it affirmatively require brand-name companies to sell their products to generics. Nevertheless, deliberate attempts to frustrate the operation of the Hatch-Waxman Act’s bioequivalence provisions are likely to be viewed skeptically by courts. If the judiciary does not restrain this tactic, amending the Hatch-Waxman Act to ensure access may be a reasonable solution. The FDA recently issued guidance intended to assist the generic industry in obtaining samples of brand products subject to restricted distribution systems.\(^{254}\) It is too early to determine whether this guidance will have any positive impact.

**B. Ensuring Continued Safety of Generic Drugs**

A second major challenge to the Hatch-Waxman regime involves interpretation of the statute by the Supreme Court in a way that fundamentally, if unintentionally, has altered the interchangeability of generics and brands. Both Hatch-Waxman and state generic substitution laws depend on the assumption that generic products are medically equivalent to their brand-name versions. As discussed above, decades of evidence demonstrate that the safety and efficacy profiles of generic and branded drugs are equivalent. In 2011, however, the Supreme Court held in *Pliva, Inc. v. Mensing* that patients injured by a generic drug could not bring suit against the manufacturer for failing to include an adequate warning on the label.\(^{255}\) This was because the FDA interpreted the Hatch-Waxman Act to require generic manufacturers to display a label that is the same as the brand name label at all times.\(^{256}\) The FDA’s goal may have been to

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ensure that the drugs were as interchangeable as possible. Because the Court found that the Hatch-Waxman Act did not provide a clear pathway for generic manufacturers to independently change their label, generic manufacturers could not be liable under state law for failing to change it. Brand-name drug manufacturers, by contrast, could be liable for failing to conform to their state-law duties to provide adequate labeling and update their labeling proactively, because the FDA had provided a pathway to do that under the FDCA.257

The practical impact of the Mensing holding, however, is a reduction in safety oversight for, and an increased threat to, the interchangeability of generic drugs. Post-Mensing, there is little incentive for generic manufacturers to undertake pharmacovigilance or other programs intended to promote learning about the adverse effects of generic drugs. In the past, serious new safety issues have been identified after generic versions of a drug become available. A recent review led by Public Citizen identified dozens of drugs that had black box warnings—the most prominent sort of warning that the FDA can impose on a product—added after the generic version of the product was available.258 But many of these new warnings have been identified fortuitously by government-funded observational research or years of litigation led by injured plaintiffs.259 If generic manufacturers are not subject to lawsuit by virtue of their label not being updated to reflect ongoing learning about safe use of a drug, then they have no incentive to lead the studies that might contribute to such learning and uncover late-arising safety hazards. Because only brand-name manufacturers bear this responsibility, active learning about prescription drugs under the Mensing regime essentially stops after generics hit the market and brand-name manufacturers’ market penetration drops precipitously (or they exit the market altogether).260

In addition to its negative effects on public health, Mensing gave patients reason to be wary of accepting low-cost generic drugs that were pharmaceutically and clinically equivalent: if they were injured by side effects that were inadequately described in the label, they would find it more difficult to obtain compensation from the manufacturer. Mensing also undermines interchangeability in a second, complementary fashion. After 2011, physicians

260. See Henry Grabowski et al., Recent Trends in Brand-Name and Generic Drug Competition, J. MED. ETHICS 1, 6 (2013) (After only a single year of generic competition, “brands retained an average of only 16%” of unit sales.); see also id. at 7 fig.4 (illustrating that both the speed and extent of market share loss to generic entrants has increased between 1999 and 2012).
deciding whether to prescribe brand-name or generic drugs for their patients now faced an ethical conundrum. Should they prescribe the generic (or allow substitution), on the basis that most patients will appreciate the lower price and that they have an ethical responsibility to be prudent stewards of healthcare resources, or should they prescribe the brand-name drug so as to preserve a patient’s ability to obtain compensation should injury result? Or, would the physician be obligated to make a case-by-case determination, taking into account factors such as the likelihood and magnitude of potential harm and the patient’s financial position, including insurance coverage? Even more disconcerting, Mensing questions the ethics of generic substitution laws, threatening to erode the prodigious gains in generic market share over the past thirty years. Mensing was met with stunned bewilderment in the press and elicited pleas for reform by commentators.

Recognizing the oddity created by the Mensing holding, the Supreme Court offered that “Congress and the FDA retain the authority to change the law and regulations if they so desire.” Lawmakers responded by introducing legislation, but it has not passed. The FDA also acted on the Supreme Court’s invitation, issuing proposed regulations in late 2013 that would permit ANDA holders to distribute revised product labeling that differs, temporarily, from the brand-name version’s labeling. However, a dispersed community of generic manufacturers may not be well positioned to monitor and respond to safety concerns. Even brand-name manufacturers channel resources away from pharmacovigilance of their products once the products go off-patent. A more promising approach would be to centralize the collection and analysis of safety data about generic drugs at the FDA, which would coordinate the creation of a consensus label. Injured plaintiffs could be compensated out of a fund generated from a small tax on generic drug sales, using the National Childhood Vaccine Injury Act’s provision for the establishment of a National Vaccine Injury Fund.

261. See e.g., Katie Thomas, Generic Drugs Prove Resistant to Damage Suits, N.Y. TIMES, Mar. 20, 2012, at A1.
264. Risk, Responsibility, and Generic Drugs, supra note 259, at 1679.
266. Risk, Responsibility, and Generic Drugs, supra note 259, at 1680.
Compensation Program as a model. These steps would help to ensure adequate patient warnings, provide compensation to injured plaintiffs, and, most importantly for present purposes, restore both medical equivalence and ethical equipoise to the choice between brand-name products and their generic equivalents.

V. CONCLUSION

In the robust generic drug market in the United States, generics make up a dominant and rising share of prescriptions, and generic prices are low in the United States when compared with prices in other developed countries. This success is attributable to a number of features of the Hatch-Waxman Act that facilitate and encourage the introduction of new generic drugs and help to promote price competition once those drugs are approved. The 180-day generic exclusivity period offered to the first generic to challenge a pharmaceutical patent creates a financial incentive to bring generic drugs to market as early as possible, and potentially clears away weak patents so that other generic firms can enter the market at the end of the exclusivity period. By statutorily deeming the act of filing with the FDA to constitute constructive patent infringement, the Paragraph IV system provides a means to obtain a judicial determination of patent validity at relatively low risk, avoiding the need to "bet the farm" by entering the market and risking treble damages for intentional infringement. The bioequivalence pathway created by the Hatch-Waxman Act allows generic firms to obtain approval by showing acceptable serum concentrations based on data from a few dozen subjects, avoiding the need to conduct duplicative and costly full-scale clinical trials of hundreds or even thousands of subjects. Finally, DPS laws facilitate the dispensing of the generic drugs that are approved, providing a needed element in a system where insurance might otherwise inappropriately dampen price competition. As a result, scores of generic drugs are widely available for as little as $4 for a thirty-day supply at stores such as Wal-Mart and Target, and dozens of new generics are approved each month.

269. Danzon & Furukawa, supra note 5, at 528.
270. See Medimmune, Inc. v. Genentech, Inc., 549 U.S. 118, 129 (2007) (noting the importance to potential defendants of being able to obtain judicial resolution of patent matters without having to "bet the farm" by actually infringing the patent and risking treble damages).
Despite this generally positive record of success, a number of challenges to the continued effectiveness of the Hatch-Waxman Act have emerged that require legislative, regulatory, or judicial attention. Some of these developments consist of the deliberate reactions of industry players that are attempting to maximize profitability within the constraints of the Hatch-Waxman Act, while others have been technological or legal developments that have threatened to render the Act less effective or less relevant. Much like taxpaying entities alter their behavior in response to new tax laws, players in the brand-name and generic drug industries have rationally responded to the Hatch-Waxman legislation in a number of ways that may not be socially productive. Such responses include: amassing large numbers of patents that can be used to trigger a thirty-month stay; using the threat of authorized generics as a potentially anti-competitive lever to settle Paragraph IV challenges; and hopping to new products without a substantial clinical justification in order to obtain additional thirty-month stays. At the same time, the Supreme Court decision in *Pliva v. Mensing* has called into question the future clinical and ethical interchangeability of generic and brand-name drugs.

With three decades of experience to guide the way, numerous policy refinements could address these challenges and thereby help to fulfill the Hatch-Waxman Act’s original purpose. Congress should consider amending the Act to prohibit the introduction of authorized generics during the 180-day period. Courts and the FTC should scrutinize attempts by brand-name firms to engage in formulation changes or to prevent generic companies from obtaining needed test products unless it can be shown that these actions have a genuine clinical justification. Clinical equivalence and ethical equipoise should be restored by abrogating *Pliva v. Mensing* either via legislation or regulation, and considering whether compensation for harms might better be provided by a government-funded program analogous to that available for vaccine injuries. Additional funding may be needed to educate patients and healthcare professionals regarding generic equivalence and to generate additional data in those areas where evidence of equivalence is not sufficiently robust.

The Hatch-Waxman Act has transformed the pharmaceutical marketplace

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272. Following *Mensing*, the FDA proposed regulations that would permit ANDA holders to revise their product labels such that they differ in certain respects, on a temporary basis, from the label in the RLD. See Supplemental Application Proposing Labeling Changes for Approved Drugs and Biological Products, 78 Fed. Reg. 67,985 (proposed Nov. 13, 2013) (to be codified at 21 C.F.R. pts. 314, 601). Although this would likely preserve the ability of patients to bring failure-to-warn claims against generic manufacturers and thereby help to restore clinical and ethical equipoise, the proposed regulation has been criticized for its potential to lead to reduced generic drug availability due to liability costs and uncertainties. See Erin M. Bosman et al., *FDA Proposed Rule in Flux?*, MORRISON & FoERSTER LLP (2015), http://www.mofo.com/~/media/Files/ClientAlert/2015/02/150218FDAProposedRule.pdf.
over the last thirty years, and its influence around the world will only increase as trade agreements are developed and similar legislation is enacted in other countries. The importance of the law to setting the appropriate balance between pioneering innovation and a vibrant generic drugs market warrants continued vigilance in light of evolving circumstances. With attention to the issues raised in this Article, modest reshaping of the law can help assure the continued success of the Hatch-Waxman Act for decades to come.