

The Statutory and Regulatory Scheme*

I. The Drug Price Competition and Patent Term Restoration Act of 1984 (aka the Hatch-Waxman Act)

In 1984 the Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as the Hatch-Waxman Act, was passed into law.¹ The act was intended to “strike[] a balance between two potentially competing policy interests—inducing pioneering development of pharmaceutical formulations and methods and facilitating efficient transition to a market with low-cost, generic copies of those pioneering inventions at the close of a patent term.”²

The 1984 decision of the U.S. Court of Appeals for the Federal Circuit in *Roche Products v. Bolar Pharmaceutical*³ is often described as a catalyst for the passage of the Hatch-Waxman Act. The circumstances leading to the decision in *Bolar* and the passage of the Hatch-Waxman Act shortly thereafter, however, should be recognized as the culmination of many

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1. Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified at 21 U.S.C. §§ 355, 360cc; 35 U.S.C. §§ 156, 271), 21 U.S.C. 355(j)(2)(A), as amended by the Medicare Prescription Drug Improvement and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066 (2003) (collectively, the Hatch-Waxman Act).

2. See *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 601 F.3d 1359, 1360 (Fed. Cir. 2010) (citing *Andrx Pharms., Inc. v. Biovail Corp.*, 276 F.3d 1368, 1371 (Fed. Cir. 2002)), *rev'd on other grounds*, 132 S. Ct. 1670 (2012).

3. 733 F.2d 858 (Fed. Cir. 1984).

years of tension and shifting over how to best structure statutory incentives in the pharmaceutical industry.

Movement toward the Hatch-Waxman compromise developed over many years. Notably, in the late 1950s and early 1960s it became known that the use of thalidomide, a sedative frequently prescribed to pregnant women experiencing morning sickness, significantly increased the risk of birth defects. The thalidomide scare led to the 1962 amendments to the Federal Food, Drug, and Cosmetic Act (FDCA), which required all new drugs to be proven safe and effective prior to approval by the Food and Drug Administration (FDA).⁴ The new requirements were seen to discourage entry into the market by generic manufacturers.⁵ Meanwhile, branded pharmaceutical manufacturers pushed for additional protections against entry by generic manufacturers. In 1978, President Carter recommended patent term restoration for pharmaceuticals and any other products that required regulatory review, in order to compensate for the time lost to the review, by extending a patent's term.⁶ By 1983, debate over the Drug Price Competition Act raged in Congress.⁷ The 1984 *Bolar* decision served as an important event leading to the passage of the compromise Hatch-Waxman Act, because the *Bolar* decision highlighted the public policy tensions for the pharmaceutical industry that only Congress could properly address.

Roche Products, a brand-name pharmaceutical company, was the maker of Valium, the formulation for which was protected by patent. Prior to the expiration of Roche's patent on the formulation, generic manufacturer Bolar Pharmaceuticals tested the chemical formulation of Valium, to determine if Bolar's generic product was bioequivalent to Valium in order to have an FDA-approved generic ready to market upon the expiration of Roche's patent.⁸ The determination of generic bioequivalence to a previously approved drug was and is necessary to obtain FDA approval for a generic version of the drug.⁹

Roche brought a patent infringement suit against Bolar for this use of Roche's patented formulation, because a U.S. patent provides its owner

4. Pub. L. No. 87-781, 76 Stat. 780 (codified at 21 U.S.C. §§ 321, 331–32, 348, 351–53, 355, 357–60, 372, 374, 376, 381).

5. G.J. Mossinghoff, *Overview of the Hatch-Waxman Act and Its Impact on the Drug Development Process*, 54(2) FOOD DRUG L.J. 187 (1999).

6. *Id.* at 187.

7. *Bolar*, 733 F.2d 865 (citing Drug Price Competition Act of 1983, H.R. 3605, 98th Cong., 1st Sess. (1983) (amending 21 U.S.C. § 355(b) to allow faster marketing of new generic drugs equivalent to approved new drugs); Patent Term Restoration Act of 1983, S. 1306, 98th Cong., 1st Sess. (1983), S. CONG. REC. 6863 (daily ed. May 17, 1983), 26 Pat. Trademark & Copyright J. (BNA) 87–88 (May 26, 1983) (amending 35 U.S.C. § 155 to add to the patent grant a period of time equivalent to that lost due to regulatory delay)).

8. 733 F.2d at 860.

9. 21 U.S.C. § 355.

with the right to exclude not only the unauthorized sale of a product (or practicing of a method) covered by the patent, but even the making or using of a product (or the product of a method) that is patented. In response to the suit, Bolar argued that its use of Roche's patented formulation was not infringement, because it was permitted under the common law experimental use exception to the patent laws.

It was a principle of long standing in U.S. patent law that the otherwise-infringing production and/or use of a patented product for experimental, noncommercial uses, was permitted.¹⁰ Nevertheless, the Federal Circuit rejected the argument advanced by Bolar, and held that the experimental use exception did not apply because Bolar intended to sell its generic product in competition with Roche's Valium after patent expiration and, therefore, the experiments conducted by Bolar had a business purpose.¹¹

Bolar also pled the equities of a public policy that favors the availability of generic drugs immediately following patent expiration, therefore justifying the experimental use of the patented chemical.¹² Bolar argued that denying such use would effectively extend Roche's monopoly beyond the normal expiration of its patent. In rejecting this argument the court explained that such policy decisions should be made by Congress.¹³ In further deference to Congress on policy considerations, the court highlighted the public policy conflict between the goals of the Food and Drug Act and the Patent Act.¹⁴

Shortly after the *Bolar* decision, Congress passed the Hatch-Waxman Act, which, among many compromise elements, created a statutory exception to infringement for the use by a generic manufacturer of patented products in experiments for the purpose of obtaining FDA approval.¹⁵

II. Statutory Overview and Specific Amendments

A. General Compromise

As noted previously, the official title of the Hatch-Waxman Act is the Drug Price Competition and Patent Term Restoration Act of 1984. The "price competition" side of the act specifically authorizes and streamlines

10. *See, e.g.*, *Akro Agate Co. v Master Marble Co.*, 18 F. Supp. 305 (D.C. W. Va. 1937); *Northill Co. v Danforth*, 51 F. Supp. 928 (D.C. Cal. 1943); *Kaz Mfg. Co. v. Chesebrough-Pond's, Inc.*, 211 F. Supp. 815 (S.D.N.Y. 1962).

11. 733 F.2d at 863.

12. *Id.* at 863–64.

13. *Id.* at 864–65.

14. *Id.*

15. *See* § 271(e)(1).

the process of generic entry through the establishment of the Abbreviated New Drug Application (ANDA). This part of the act is unusual in that it is more prohibitive than enabling of the actions of the FDA. Specifically, it prohibits the FDA from doing more than asking for bioavailability studies from the ANDA filer.¹⁶

On the “restoration” side, the act provides a set of “exclusivity” incentives for patented drug manufacturers to engage in new development and testing in exchange for longer periods of market exclusivity, that is, an FDA promise to delay the review or approval of a competing drug.

The act also establishes the framework for addressing patent protection disputes implicated by a rival generic manufacturer’s attempt to obtain FDA approval. The framework requires that the generic ANDA filer include one of the following four certifications with its application: (1) that the drug has not been patented; (2) that the patent has already expired; (3) that the generic drug will not go on the market until after the known expiration of nonexpired patent(s); or (4) that the patent is not infringed or is invalid. These certifications are frequently referred to as the paragraphs I, II, III, and IV certifications, respectively. Paragraph IV certifications create jurisdiction for a patent dispute between the generic ANDA filer and the patented drug manufacturer to be resolved in a federal district court in the United States.

Despite the absence of actual sales of the accused infringing product in ANDA cases, the U.S. Federal Circuit Court of Appeals has affirmed the existence of specific personal jurisdiction over ANDA filers.¹⁷ Whether an ANDA file may be subject to venue in a particular court, however, is a separate matter. In *TC Heartland LLC v. Kraft Foods Grp. Brands LLC*,¹⁸ the U.S. Supreme Court corrected a misperception regarding the patent venue statute, when it explained that the patent venue statute did not intend to make venue co-extensive with personal jurisdiction.¹⁹ The patent venue statute provides that “[a]ny civil action for patent infringement may be brought in the judicial district where the defendant resides, or where the defendant has committed acts of infringement and has a regular and

16. H.R. REP. NO. 98-857, pt. 1, at 72 (1984).

17. In its affirmance, the Federal Circuit explained that ANDA filings “are tightly tied, in purpose and planned effect, to the deliberate making of sales [within a state of the United States] . . . and the suit is about whether that in-State activity will infringe valid patents.” *Acorda Therapeutics, Inc. v. Mylan Pharm., Inc.*, 817 F.3d 755, 760 (Fed. Cir. 2016). The court further noted that jurisdictional considerations in ANDA litigations are “distinctive” in view of the prospective focus on “whether, if a particular drug were put on the market, it would infringe the relevant patent.” *Id.* at 760.

18. *TC Heartland LLC v. Kraft Foods Grp. Brands LLC*, 137 S. Ct. 1514 (2017).

19. *Id.* at 1514–15.

established place of business.”²⁰ The Supreme Court concluded that a domestic corporation “resides” only in its state of incorporation for purposes of the patent venue statute. In view of this clarification, courts have determined that an ANDA filer may only be subject to venue where the ANDA defendant has a regular and established place of business or in its state of incorporation.²¹

B. Legislative Foundation and Subsequent Amendments

The ANDA framework created by the Hatch-Waxman Act was built upon a foundation of laws, beginning with the Pure Food and Drug Act of 1906 (also known as the Wiley Act), which created the FDA.²² The Wiley Act was replaced by the Federal Food, Drug, and Cosmetic Act of 1938 (FD&C Act),²³ which was passed in response to the problem of a legally marketed toxic elixir killing 107 people.²⁴ Title 21 of the U.S. Code codifies the FD&C Act and its many amendments. The FDA identifies over two dozen significant amendments to the FD&C Act since 1980, including the Hatch-Waxman Act in 1984.²⁵

The Hatch-Waxman Act itself has been augmented by subsequent legislation. Notable augmentations include the Prescription Drug User Fee Act (PDUFA) first enacted by Congress in 1992 and reauthorized every five years (through various statutes passed in 1997, 2002, 2007, 2012, and 2017),²⁶ as well as the Generic Drug User Fee Amendments (GDUFA) of 2012 and 2017.²⁷ PDUFA, GDUFA, and similar fee collection provisions authorize the FDA to collect more substantial fees from applicants requesting FDA approval for new drugs, generic drugs, biologic compounds, biosimilar compounds, and medical devices, in order to better fund, and therefore enhance and expedite, the FDA’s regulatory review processes. The Biologics Price Competition and Innovation Act of 2009

20. 28 U.S.C. § 1400(b).

21. *See, e.g.,* Bristol-Myers Squibb Co. v. Aurobindo Pharma USA Inc., No. 17-374-LPS, 2018 U.S. Dist. LEXIS 179154, at *7 (D. Del. Oct. 18, 2018) (finding the facts of record “insufficient to pierce the corporate veil or render one entity the alter ego of the other,” in order to impute venue to a nonresident corporate entity).

22. Pub. L. No. 59-384.

23. Pub. L. No. 75-717.

24. FDA, Regulatory Information, <https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/hatch-waxman-letters> (last accessed Dec. 4, 2019).

25. FDA, Regulatory Procedures Manual, Chapter 2—FDA Authority, 2-2 Selected Amendments to the Federal Food, Drug, and Cosmetic Act, at 4-10, <https://www.fda.gov/media/77516/download> (last accessed Dec. 4, 2019) (last visited Apr. 17, 2019).

26. Pub. L. No. 102-571 (PDUFA of 1992); Pub. L. No. 105-115 (PDUFA II of 1997); Pub. L. No. 107-188 (PDUFA III of 2002); Pub. L. No. 110-85 (PDUFA IV of 2007); Pub. L. No. 112-144 (PDUFA V of 2012); Pub. L. No. 115-52 (PDUFA VI of 2017).

27. GDUFA II and PDUFA VI were passed as part of the Food and Drug Administration Reauthorization Act (FDARA) of 2017, Pub. L. No. 115-52.

(BPCIA)²⁸ “borrow[s] from . . . the Hatch-Waxman Act’s process for use of an Abbreviated New Drug Application (ANDA), rather than a full New Drug Application, to obtain approval of generic versions of previously approved drugs.”²⁹ The BPCIA establishes an abbreviated FDA regulatory-approval process—as compared to the full Biologics License Application process—for “biosimilars,” biological products that are shown to be biosimilar to a “reference product” already approved by the FDA.³⁰ Like PDUFA and GDUFA, the Biosimilar User Fee Amendments (BsUFA) of 2012 and 2017 authorize the FDA to assess and collect fees for biosimilar biological products.³¹ Also significant is the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA),³² which included the Access to Affordable Pharmaceuticals Act (AAPA) that resolved certain ambiguities, attempted to close perceived loopholes, and codified important court rulings on the original Hatch-Waxman scheme. Other notable legislation involving this framework includes the Orphan Drug Act of 1983,³³ the Best Pharmaceuticals for Children Act of 2002 (BPCA),³⁴ and the Food and Drug Administration Amendments Act of 2007,³⁵ which included the Best Pharmaceuticals for Children Act of 2007.³⁶

These legislative amendments are incorporated in the following general description of the Hatch-Waxman statutory scheme, often referred to as the ANDA statutes.

While not part of the ANDA statutory framework, one significant legislative development impacting all types of patent litigation, including ANDA, is the Leahy-Smith America Invents Act (AIA).³⁷ The AIA, among many policy and procedural changes to the U.S. patent system, implemented a new administrative procedure, known as *inter partes* review (IPR), through which a challenger may seek to invalidate an adversary’s patent in a focused proceeding before the U.S. Patent and Trademark Office’s (USPTO) Patent Trial and Appeals Board (PTAB). PTAB proceedings offer patent challengers an opportunity to invalidate one or more claims of an adversary’s patent in a proceeding that is typically faster and less expensive than traditional patent litigation in federal district court. Moreover, the burden of persuasion is lower in IPRs (preponderance of the

28. Pub. L. No. 111-148.

29. *See Sandoz Inc. v. Amgen Inc.*, 773 F.3d 1274, 1276 (Fed. Cir. 2014).

30. *See* 42 U.S.C. § 262(k).

31. Pub. L. No. 108-173 (BsUFA I); Pub. L. No. 115-52 (BsUFA II) (hereinafter MMA).

32. MMA.

33. Pub. L. No. 97-414.

34. Pub. L. No. 107-109.

35. Pub. L. No. 110-85.

36. Pub. L. No. 110-85, 121 Stat. 823.

37. Pub. L. No. 112-29.

evidence) than in district court litigation where the patent is presumed valid³⁸ and, therefore, only invalidated upon a showing of clear and convincing evidence. Statistical comparisons, as might be expected, show a generally high invalidation rate in IPR proceedings as compared to district court litigation, where Orange Book–listed patents were shown to have a lower invalidation rate in IPRs as compared to all other technology areas.³⁹ This backdrop, coupled with the steep cost to petition for and institute an IPR,⁴⁰ and the potential to be estopped for raising similar invalidity defenses during district court litigation, deter many accused infringers from IPR.

III. Statutory Balancing: Incentives to Patentees and Generics

As referenced previously, the Hatch-Waxman Act was designed to strike a balance between the patent exclusivity rights of patented drug developers and the right of the public to purchase less-expensive generic drugs. New Drug Application (NDA) filers benefit by receiving legislative compensation for administrative delays caused by the FDA review process. This compensation is granted by extending the patent term of the NDA filer covering the patented drug.

A. New Drug Application Filers

1. Patent Term Extension and Exclusivity

a. Extension Based on FDA Review

The Hatch-Waxman Act specifies that the term of a patent covering NDA inventions can be extended to make up for patent life lost during the

38. See 35 U.S.C. § 282.

39. The USPTO-published Orange Book–listed Patent Study (Mar. 2018) reveals that, for FDA-approved drug patents challenged in AIA trials, 46 percent of all PTAB final written decisions find no claims patentable, while 66 percent of PTAB final written decisions for all other technologies find no claims patentable. See https://www.uspto.gov/sites/default/files/documents/chat_with_the_chief_march_2018.pdf (last visited May 2, 2019) at p. 45. By comparison, a comprehensive study of patent litigation in the U.S. federal court system reveals a patent invalidation rate of 42.6 percent in district court litigation. John R. Allison, Mark A. Lemley, & David L. Schwartz, *Our Divided Patent System*, 82 U. CHI. L. REV. 1073–154 (2015), Stanford Public Law Working Paper No. 2510004, Chicago-Kent College of Law Research Paper No. 2014-28, at p. 1100, available at https://papers.ssrn.com/sol3/Delivery.cfm/SSRN_ID2666709_code32215.pdf?abstractid=2510004&mirid=1 (last updated Feb. 9, 2016).

40. See USPTO, USPTO Fee Schedule, <http://www.uspto.gov/learning-and-resources/fees-and-payment/uspto-fee-schedule#PTAB%20Fees> (last visited May 2, 2019).

approval process for the patented drug.⁴¹ The patent-term-extension provisions of the Hatch-Waxman Act provide an extension of up to five years for drugs, medical devices, and food additives that have premarket delays caused by administrative and regulatory evaluations. The rationale for patent extension is that the lengthy approval process under the FDCA affects the useful life of an NDA filer's patent term because the new drug cannot be marketed until after completion of FDA review.

NDA patents that qualify for term extension include those claiming products, methods of manufacturing, and methods of use for human and veterinary drugs, medical devices, and food additives. The patent must be issued prior to FDA approval for the patent to be eligible for term extension. In addition, the patent must not have been extended for another reason. Further, the regulatory approval must be the first such approval for a commercial use of the product.

The USPTO and the FDA jointly administer the patent-term-extension provisions of the Hatch-Waxman Act. The FDA identifies the period of extension by calculating the period of regulatory review of the drug product. Two periods of regulatory review are included in the calculation. According to 35 U.S.C. § 156 (g)(1)(B), subsections (i) and (ii), there are two relevant regulatory review periods—the “testing phase” and the “approval phase.” These two regulatory phases correspond to the Investigational New Drug (IND) application period and the NDA review period, respectively.⁴²

The Federal Circuit has interpreted 35 U.S.C. § 156 as entitling patentees to patent term extensions for a single approved product, but not for all potential products covered by the patent claims.⁴³ The statute states that the grant of a patent extension is both patent-specific and product-specific. Accordingly, only one extension may be granted for each patent and only one patent extension is granted per active ingredient, even if multiple patents claim the ingredient. Further, the extension is specific to a single NDA, that is, only one extension is permitted, even if other

41. See 35 U.S.C. § 156. This “extension” of patent term related to FDA review should not be confused with patent term “adjustment” (PTA) under 35 U.S.C. § 154(b) whereby an adjustment will be calculated and patent term added for delays in the prosecution of a patent application because of untimely action by the USPTO. An Orange Book-listed patent may obtain the benefit of both an extension under § 156 and PTA adjustment under § 154. For PTA, the Federal Circuit has clarified that “the USPTO may not count as applicant delay a period of time during which there was no action that the applicant could take to conclude prosecution of the patent.” *Supernus Pharm., Inc. v. Iancu*, 913 F.3d 1351, 1358 (Fed. Cir. 2019).

42. See 35 U.S.C. §§ 156(g)(1)(B)(i)–(ii), 21 C.F.R. § 60.22; 37 C.F.R. § 1.775 (b).

43. See, e.g., *Merck & Co. v. Kessler*, 80 F.3d 1543, 1547 (Fed. Cir. 1996) (“the restoration period of the patent does not extend to all products protected by the patent but only to the product on which the extension was based”).

approved NDAs for alternative indications had additional administrative delays. Additionally, the Federal Circuit has also clarified that patent term extensions under 35 U.S.C. § 156 are only intended for patented inventions that are subject to FDA premarket approval.⁴⁴

b. “New Data” Exclusivity

The Hatch-Waxman Act and other subsequent acts incentivize drug companies to discover and test drugs by offering periods of exclusivity.

i. New Chemical Entity

Five-year exclusivity for new chemical entity with a novel “active moiety”

The Hatch-Waxman Act also created another type of competition-protection for NDA approvals of new chemical entities (NCE). Under the act, once an NDA covering an NCE is approved, for five years no submission by another party may be made to the FDA of any request for approval of that NCE either alone or in combination with other active molecules. Thus, greater than five years of exclusivity is effectively possible. An application for approval of that NCE by another party may be submitted after four years, if the application is made with a certification of patent invalidity or noninfringement.

The five-year exclusivity applies only to novel chemical entities. The NCE that must not have been previously approved is the “active moiety.”⁴⁵ The FDA has described an “active moiety” as “the part of the drug that makes the drug work the way it does.”⁴⁶ The regulations promulgated by the FDA define “active moiety” as, “the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.”⁴⁷

This narrow interpretation of the statutory term “active ingredient” was adopted to avoid overcompensating drug makers who had made “minor variations of previously approved chemical compounds.”⁴⁸ However, the statute does not expressly limit “active ingredients” eligible for NCE exclusivity to “active moieties.” Before the FDA officially adopted the narrow definition of “active ingredient,” the District of Columbia district

44. *Proveris Scientific Corp. v. Innovasystems, Inc.*, 536 F.3d 1256, 1265 (Fed. Cir. 2008).

45. 21 C.F.R. § 314.108.

46. 64 Fed. Reg. 47,719, 47,721 (Sept. 1, 1999).

47. *See* 21 C.F.R. § 314.108(a).

48. 54 Fed. Reg. 28,872, 28,898 (July 10, 1989).

court rejected the “active moiety” restriction as contrary to the plain meaning of the statute. However, the D.C. Circuit vacated the ruling of the district court and remanded the question to the FDA for further consideration.⁴⁹ Moreover, the Federal Circuit has since held that the interpretation “active moiety” by the USPTO was incorrect, and that the phrase “active ingredient” is unambiguous in the statute.⁵⁰ In 2010, the D.C. Circuit approved FDA’s defining of NCE under the statute, finding reasonable “[t]he FDA’s . . . view that drug derivatives containing non-ester covalent bonds are, on the whole, distinct from other types of derivative drugs such that the former are uniquely deserving of “new chemical entity” status and the resulting five-year exclusivity.”⁵¹

ii. Three-Year New Clinical Investigation Exclusivity

Three-year exclusivity for applicants conducting “essential” new clinical investigations on previously approved active ingredients

The Hatch-Waxman Act also includes a three-year period of exclusivity for a drug product that contains an active ingredient that has been previously approved, when the application contains reports of “new clinical investigations” conducted or sponsored by the applicant that were essential to approval of the application. For example, if the applicant provides support showing changes in an approved drug product that affect its active ingredient(s), strength, dosage form, route of administration or conditions of use, then the applicant may be granted exclusivity if new clinical investigations were essential for approval of the application containing those changes.⁵²

The FDA interprets the term “new clinical investigations” to mean safety or efficacy studies in humans. Bioavailability studies do not qualify.⁵³ Although the statute requires that the studies be “new,” the regulations require only that the studies be “new” to the FDA; the studies should not have been previously relied upon to support either the safety or efficacy of a drug.⁵⁴ Further, the new clinical investigations must have been conducted or sponsored by the NDA applicant or holder, who must ordinarily have contributed at least 50 percent of the study’s cost.⁵⁵ Finally, the new studies must be essential to the approval by the FDA of the application.

49. See *Abbott Labs. v. Young*, 691 F. Supp. 462 (D.D.C. 1988), *vacated and remanded*, 920 F.2d 984 (D.C. Cir. 1990).

50. *PhotoCure ASA v. Kappos*, 603 F.3d 1372 (Fed. Cir. 2010).

51. *Actavis Elizabeth LLC v. U.S. Food & Drug Admin.*, 625 F.3d 760, 766 (D.C. Cir. 2010).

52. 21 U.S.C. § 355(j)(5)(F)(iii), (iv); 21 C.F.R. § 314.108(a).

53. See 21 U.S.C. § 355(j)(5)(F)(iii), (iv); 21 C.F.R. § 314.108(a).

54. See 21 C.F.R. § 314.108(a) (2006).

55. *Id.*

This aspect can be disputed because opinions can differ on whether data is “essential” to the application or merely “confirmatory” of previously submitted studies.⁵⁶

While a generic manufacturer may submit an ANDA during the three-year new clinical investigation exclusivity period, the FDA is prohibited from approving the application. In addition, the three-year exclusivity only covers the indication(s) approved in the supplemental NDA approval. Consequently, a generic manufacturer may seek and obtain approval for other indications not covered by the exclusivity period, that is, the exclusivity covered indications are “carved out” of the ANDA filers’ application.⁵⁷ The FDA is deemed to have been delegated the authority to “fill in statutory gaps,” including the ability to determine what constitutes a “supplement” to a drug application and the requirements thereof.⁵⁸

iii. Orphan Drug Exclusivity

Seven-year exclusivity for drugs treating or preventing rare but serious diseases (aka “orphan drugs”)

The Orphan Drug Act was enacted to encourage drug manufacturers to develop drugs for rare but serious diseases.⁵⁹ The FDA will designate a drug candidate as an “orphan drug” after review of the “sponsor’s” request. The request must describe the rare disease or condition for which the drug is being investigated, explain why the drug is thought to have potential for treating or preventing the disease, and provide documentation that the disease is “rare.”

The Orphan Drug Act prohibits the FDA from approving another application for approval for such drug for such disease or condition for seven years from the date on which the FDA approves the NDA for the designated orphan drug.⁶⁰ In contrast to Hatch-Waxman exclusivities, the Orphan Drug Act bars approval of subsequent NDAs. However, the FDA has strictly construed the statutory phrase, “for such disease or condition” as limiting exclusivity to applications that seek approval for treating the same disease or condition that the orphan designation was made. Consequently, a competitor can obtain approval for the drug to be used in the treatment of other diseases or conditions. Further, while the statute does not indicate when a subsequent drug is the same as an exclusive orphan drug, FDA regulations, however, state that drugs are similar if they have

56. See *Upjohn Co. v. Kessler*, 938 F. Supp. 439 (W.D. Mich. 1996).

57. 21 C.F.R. § 314.94(a)(8)(iv).

58. *AstraZeneca Pharm. LP v. Food & Drug Admin.*, 713 F.3d 1134, 1140 (D.C. Cir. 2013).

59. See 21 U.S.C. §§ 360aa–360cc.

60. See *id.*

the same “active moiety” (for small molecules) or “contain[] the same principal molecular structural features” (for large molecules like proteins or nucleic acids).⁶¹ The FDA, however, will not deem a subsequent drug as the “same” as an approved orphan drug, even if it is structurally the same, if the latter drug is “clinically superior” or provides a “significant therapeutic advantage.”⁶²

iv. Pediatric Exclusivity

Six-month exclusivity, based on remaining patent life or data exclusivity protection, for pediatric studies on the safety, effectiveness, and conditions of use of approved drugs

Congress created an incentive for drug makers to determine the safety, effectiveness, and conditions of use of their drug products in children by enacting the Best Pharmaceuticals for Children Act of 2002.⁶³ Pediatric exclusivity is obtained by submitting the results of pediatric studies and the FDA’s acceptance of those studies. Typically, the FDA makes a written request for an NDA holder sponsor and study the pediatric use of its approved drug product. The written request will identify the “indication” of the drug that the FDA wants studied, the population to be studied, and the period for completion of the studies.⁶⁴ In 2007 the Best Pharmaceuticals for Children Act was amended to clarify that the FDA’s written request may include more than one indication, which may be “on-label” or “off-label”⁶⁵ and may include nonclinical studies.⁶⁶ Other changes implemented through the BPCA of 2007 include: (1) the requirement that an applicant submit a report of all adverse events with its final pediatric study report; (2) the requirement that final exclusivity determination based on new written requests be made within 180 days of a response to the written request; (3) the restriction of exclusivity only to applicants with at least nine months of data exclusivity or patent protection remaining at the time of determination; and (4) the prioritization of FDA review of applications submitted in response to a written request. In addition, under the BPCA of 2007, a sponsor must submit its application (or supplement) for pediatric exclusivity 15 months prior to expiration of adult exclusivity.

61. 21 C.F.R. § 316.3(b)(13)(ii).

62. *Id.* § 316.3(b)(3).

63. 21 U.S.C. § 355a.

64. *Id.* § 355a(c).

65. Regarding “off-label” uses, it has been notably held that “the government cannot prosecute pharmaceutical manufacturers and their representatives under the FDCA for speech promoting the lawful, off-label use of an FDA-approved drug.” *United States v. Caronia*, 703 F.3d 149, 169 (2d Cir. 2012).

66. Best Pharmaceuticals for Children Act of 2007, Pub. L. No. 110-85.

The BPCAs benefit manufacturers who conduct pediatric studies by providing an additional six-month extension of FDA exclusivity, based on existing patent life or data exclusivity, to which the manufacturer is already entitled. It is important to note that the manufacturer must have at least nine months of existing patent term or data exclusivity remaining for which “pediatric exclusivity” can attach. If not, then “pediatric exclusivity” provides it no additional term-extension benefit. Pediatric exclusivity does not actually extend the patent term, as many courts have misstated, but rather it extends by six months a bar to approval by the FDA of a generic version of the drug. Unlike other data-based exclusivities, the scope of the pediatric extension is not limited to the particular drug product that was the subject of the pediatric studies. The FDA interprets the extension as applying to all drug products, in all dosage forms, that contain the same “active moiety” that was present in the product that was studied for pediatric use.

2. Artificial “Act of Infringement” Based on ANDA Filing

Patent suit standing before generic launch: 35 U.S.C. § 271(e)(2) deems ANDA filing and certification an act of “infringement” against the listed patents (aka “artificial infringement”)

a. 35 U.S.C. § 271(e)(2)

The Hatch-Waxman Act was enacted to encourage patent owners and prospective generic drug makers to identify and resolve patent disputes before a generic product reaches the market. The act also established a new procedure for resolving patent infringement issues prior to patent expiration. Prior to the enactment of the Hatch-Waxman Act, generic manufacturers were obligated to notify patent owners respecting possible infringement and patent owners were given the right to litigate their claims of patent infringement prior to the time the generic drug is put on the market. However, this procedure also created a conundrum for adjudicating potential infringement claims, since in the premarket stage, the generic manufacturer does not sell the patented invention. Further, the Hatch-Waxman Act “safe harbor” immunizes the generic manufacturer from infringement for the use of the patented product in studies directed to FDA approval.⁶⁷ Accordingly, if the patentee attempted to sue the generic manufacturer for infringement prior to product launch, justiciability issues would arise because there has not been an actual act of infringement, and the patentee would lack standing to sue in federal court.

67. 35 U.S.C. § 271(e)(1).

The Hatch-Waxman Act overcomes this issue by making the filing of an ANDA an act of “artificial infringement” that satisfies the Article III case or controversy requirements and gives the patentee standing to file suit against the generic manufacturer. Thus, the artificial act of infringement accomplished by filing an ANDA application serves “to create case or controversy jurisdiction to enable a court to promptly resolve’ a dispute concerning an infringement that will happen in the future.”⁶⁸ The Hatch-Waxman Act amended the basic infringement section of the Patent Act, 35 U.S.C. § 271, to add subsection (e), which provides in pertinent part:

It shall be an act of infringement to submit—

...

an application under Section 505(j) of the [Food, Drug, and Cosmetic Act] or described in Section 505(b)(2) of such act for a drug claimed in a patent or the use of which is claimed in a patent . . .

if the purpose of such submission is to obtain approval under such Act to engage in the commercial manufacture, use, or sale of a drug . . . claimed in a patent or the use of which is claimed in a patent before the expiration of such patent.⁶⁹

b. “Orange Book” Listing

Patents covering NDA drug must have been listed in FDA’s “Orange Book”

The Hatch-Waxman Act requires that an NDA applicant or holder list patent rights applicable to a drug in an official FDA publication titled Approved Drug Products with Therapeutic Equivalence Evaluations, more commonly called the Orange Book owing to its original orange-colored cover. The Orange Book lists all commercial drug products approved for safety and effectiveness in the United States together with patents relevant to the active drug substances as well as drug formulations, inert ingredients and uses.⁷⁰ The Orange Book is published annually with quarterly supplements, and is accessible on the FDA’s website in an electronic

68. Bayer AG v. Elan Pharm. Res. Corp., 212 F.3d 1241, 1249 (Fed. Cir. 2000) (quoting Glaxo, Inc. v. Novopharm, Ltd., 110 F.3d 1562, 1569 (Fed. Cir. 1997)).

69. 35 U.S.C. § 271(e).

70. 21 U.S.C. § 355(b)(1), (j)(7).

version that is updated daily to provide all newly listed patents and newly approved generic drugs.⁷¹

Submission of a patent for Orange Book listing is the responsibility of the patent owner. The Hatch-Waxman Act specifies two types of patents that can be listed in the Orange Book: any patent that (1) “claims the drug for which the applicant submitted the application” or (2) that “claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug.”⁷² FDA regulations require a description of any method-of-use patent, known as a “use code.”⁷³ Thus, the typical types of patents listed in the Orange Book are compound claims, formulations, and methods of use or treatment claims. Patents claiming a manufacturing process, packaging, metabolites, and intermediates are not eligible for Orange Book listing.⁷⁴

c. Orange Book “Delisting” Counterclaim

The MMA permits a generic manufacturer who has been sued under 35 U.S.C. § 271(e)(2) to assert a counterclaim seeking an order requiring the NDA drug manufacturer/patent owner to correct or delete patents listed in the Orange Book listing.⁷⁵ The generic manufacturer may assert that either the listed patent does not claim the drug for which the application was approved, or does not claim an approved method of using the drug.⁷⁶ This section does not provide an independent cause of action, and no damages are available under such a counterclaim.

d. Paragraph IV Certification

Infringement under 35 U.S.C. § 271(e)(2) is triggered based on the ANDA filer’s “certification” that the listed patents are not infringed or are invalid (aka “paragraph IV certification”)

When an ANDA is filed, the ANDA applicant must certify to the FDA that for each patent applicable to the patented drug, the proposed generic drug would not infringe the patent because, the ANDA filer will not market the

71. FDA, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, <http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm> (last visited Dec. 4, 2019).

72. 21 U.S.C. § 355(b)(1)(G).

73. See 21 C.F.R. §§ 314.53(c)(2)(ii)(P)(3), (e); Caraco Pharm. Labs., Ltd. v. Novo Nordisk A/S, 132 S. Ct. 1670, 1672 (2012).

74. 21 C.F.R. § 314.53(b)(1).

75. 21 U.S.C. § 355(j)(5)(C)(ii).

76. The ANDA filer may bring a counterclaim to challenge a brand’s inaccurate or overbroad use code. Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd., 601 F.3d 1359, 1361 (Fed. Cir. 2010) 132 S. Ct. 1670, 1688 (2012).

generic drug until after the applicable patents expire,⁷⁷ or the patent is believed to be invalid or will not be infringed by the manufacture, use, or sale of the drug for which the ANDA applicant seeks approval.⁷⁸ The certification of invalidity or noninfringement is commonly called a “paragraph IV certification.” Once issued, the patent owner and/or NDA holder are given notice by the generic applicant that an ANDA has been filed with a paragraph IV certification. The paragraph IV certification constitutes the only required notice to the patent owner that an ANDA has been filed by someone seeking to market before patent expiration. The required notice sent to a patented drug manufacturer following a generic manufacturer’s paragraph IV certification must explain in detail the legal and factual reasons why the patent is believed to be invalid or not infringed.⁷⁹ However, the ANDA application itself is not required to include any details beyond the labeling and certification elements listed in 21 U.S.C. § 355(j)(2)(A).⁸⁰

e. Method-of-Use Statement and “Carve Outs”

Where an ANDA filer seeks approval for a use that is outside the scope of a method-of-use patent listed for the drug, the ANDA filer must submit a “method of use” statement to this effect.⁸¹ It is not an act of infringement to submit an ANDA for marketing approval of drug for a use when neither the drug nor that use is covered by an existing patent, and the patent at issue is for a use not approved under the NDA.⁸²

The ANDA filer may attempt to “carve out” any mention of the patented method of use from the proposed label for the generic drug.⁸³ Unlike paragraph III or IV certifications, the filing of a “method of use” or “section viii” statement will not by itself delay approval of an ANDA.⁸⁴

77. 21 U.S.C. § 355(j)(2)(A)(vii)(III).

78. *Id.* § 355(j)(2)(A)(vii)(IV).

79. *Id.* § 355(j)(2)(B). As noted previously in section III(B), patent validity may also be challenged through an USPTO administrative proceeding called IPR. It is within the discretion of the federal district court in which the ANDA litigation is pending to decide whether to stay the district court case pending the outcome of the IPR. In many instances, however, ANDA litigation is not stayed over concerns that this may cause the case to extend well past the 30-month automatic stay of FDA approval, which is addressed in more detail in section III(A)(3).

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

81. 21 U.S.C. § 355(j)(2)(A)(viii).

82. *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1362 (Fed. Cir. 2003).

83. *See* 21 C.F.R. § 314.92(a)(1); *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 132 S. Ct. 1670, 1688 (2012).

84. *AstraZeneca Pharm. LP v. Apotex Corp.*, 669 F.3d 1370, 1381 (Fed. Cir. 2012) (“[T]he Act permits generic manufacturers to file ANDAs directed to a subset of FDA-approved indications and even provides a mechanism for ANDA applicants to affirmatively carve out patented indications by submitting Section viii statements.”).

A generic manufacturer cannot infringe by filing an ANDA where the generic manufacturer's intended (and NDA approved) use of the drug is not covered by an existing patent, even if there are patents listed in the Orange Book that cover other uses for the drug.⁸⁵ Likewise, inducement to infringe can only be found where the patented drug manufacturer's patented use is FDA-approved.⁸⁶ When the proposed instructions on a generic label will, however, encourage users to practice the drug manufacturer's patented and FDA-approved method of use, a claim for inducement to infringement may be established.⁸⁷ But in the absence of knowledge of the patent or evidence that an instruction would inevitably lead to the patented use, no claim for inducement may be found.⁸⁸

f. Declaratory Judgment by ANDA Filer

Under MMA, if a patent/NDA holder does not sue the ANDA filer for patent infringement within 45 days of receiving notice of the ANDA filer's paragraph IV patent challenge, then the ANDA filer may bring a declaratory-judgment action for patent invalidity or noninfringement under the following conditions: (1) the 45-day period following notice of the ANDA filing has expired; (2) the ANDA filer was not sued for infringement within the 45-day period; and (3) the ANDA filer asserting noninfringement provided notice to the NDA holder/patent owner that included an offer of confidential access to the ANDA application.⁸⁹ While the offer of confidential access is necessary to trigger declaratory-judgment rights for the ANDA filer asserting noninfringement, it is not an otherwise mandatory obligation of the ANDA filer. The NDA holder/patent owner recipient of this confidential information may only use it to evaluate possible infringement by the ANDA filer of the patents over which a paragraph IV certification was made, and the ANDA filer may redact extraneous information from their disclosure.⁹⁰ The NDA holder/patent owner's disclaimer of a patent and the lack of tentative FDA approval of the ANDA do not preclude an ANDA challenger's action for declaratory judgment, where potential legal barriers continue to impede the challenger's path to market.⁹¹

3. The 30-Month Stay

Final FDA approval of generic is stayed for 30 months pending timely filed patent litigation.

85. Warner-Lambert Co. v. Apotex Corp., 316 F.3d 1348, 1362 (Fed. Cir. 2003).

86. Allergan, Inc. v. Alcon Labs., Inc., 324 F.3d 1322 (Fed. Cir. 2003).

87. AstraZeneca v. Apotex, 633 F.3d at 1060–61.

88. Takeda Pharm. U.S.A., Inc. v. West-Ward Pharm. Corp., 785 F.3d 625, 632–34 (Fed. Cir. 2015).

89. MMA § 1101(a)(2)(C); 21 U.S.C. § 355(j)(5)(C)(i)(I); 35 U.S.C. § 271(e)(5).

90. MMA § 1101(a)(2)(C); 21 U.S.C. § 355(j)(5)(C)(i)(III).

91. Apotex, Inc. v. Daiichi Sankyo, Inc., 781 F.3d 1356, 1362 (Fed. Cir. 2015).

a. Litigation within 45 Days of Notice

The 30-month stay applies only when a patent infringement suit is brought on an Orange Book-listed patent within 45 days of notice of ANDA filing

Once the ANDA paragraph IV certification is filed, a patent owner has 45 days to sue the generic ANDA filer. FDA rules provide that a 30-month statutory stay period begins to run when the patent owner receives notice from the ANDA filer that it has made a paragraph IV certification.⁹² The FDA begins the 45-day period on the date of receipt of the notice by the patent owner and NDA holder's mailroom. The FDA requires strict compliance with the 45-day period.⁹³ If the patent owner fails to respond to the ANDA filing challenge, the FDA may approve the ANDA "immediately" without regard to any unresolved patent or exclusivity issues. If, however, the patent owner sues, the FDA may not approve the ANDA for 30 months.⁹⁴ The 30-month stay is terminated if a district court determines that the patent is invalid or not infringed.⁹⁵ Moreover, a patent owner can sue the ANDA filer outside the 45-day period but the patent owner will not have the benefit of the 30-month statutory stay. In addition, the court has the power to modify the 30-month stay if a party is not reasonably cooperating in expeditiously processing the case, although this rarely occurs.⁹⁶

b. ANDA Filer Must Give Notice of ANDA Filing within 20 Days

Prior to the AAPA, an ANDA filer had no time limit in which to provide notice to the patent holder and NDA holder of a paragraph IV certification that triggers the patent/NDA holder's 45-day period to file the patent infringement suit to obtain the benefit of the automatic 30-month stay. Under the AAPA, the ANDA filer must now give notice to the patent holder and NDA holder within 20 days of receiving notice from the FDA that the ANDA application has been filed.⁹⁷

The AAPA also changes the notice obligations of the ANDA filer regarding filing application amendments or supplements. Prior FDA regulations did not require ANDA filers to give notice to the patent/NDA holder when

92. 21 U.S.C. § 355(j)(4)(B); 21 C.F.R. § 314.707(b)(3).

93. See *Mylan Labs. v. Thompson*, 332 F. Supp. 2d 106, 113, *aff'd*, 389 F.3d 1272 (D.C. Cir. 2004) (45-day time limit not expanded for unintentional error).

94. See *In re Ciprofloxacin Hydrochloride Antitrust Litig.*, 261 F. Supp. 2d 188, 195 n.8 (S.D.N.Y. 2003) (recognizing that a longer period resulted for NCE).

95. 21 U.S.C. § 355(j)(5)(b)(iii)(I).

96. *Id.* § 355(j)(5)(B)(iii). "Trial courts, thus, may shorten or extend the thirty-month statutory period based on the parties' uncooperative discovery practices before the court." *Eli Lilly & Co. v. Teva Pharm. USA, Inc.*, 557 F.3d 1346, 1350 (Fed. Cir. 2009) (citing *Allergan, Inc. v. Alcon Labs., Inc.*, 324 F.3d 1322, 1337 n.5 (Fed. Cir. 2003)).

97. MMA § 1101(a)(1)(B); 21 U.S.C. § 355(j)(2)(B).

an application is amended to add an additional paragraph IV certification. Under the AAPA, however, the ANDA filer must give notice of a paragraph IV certification at the time of the amendment or supplement, regardless of whether the ANDA filer had provided a previous notice.⁹⁸

c. Timing of Final FDA Approval

Final FDA approval of generic occurs upon earliest of: expiration of last listed patent, final judgment, or expiration of 30-month stay

If the patentee sues the ANDA filer within the 45-day period, evaluation of the ANDA by the FDA will commence in its normal fashion, but final approval permitting market launch of the generic cannot be effective until the earlier of (1) the expiration of the Orange Book-listed patent(s); (2) a final judicial determination favorable to the ANDA applicant; or (3) expiration of the 30-month stay, unless the court determines that the patent owner has not been diligent in prosecuting the matter.⁹⁹ The typical period for evaluation and approval of an ANDA by the FDA is about 18 to 24 months.¹⁰⁰

If, prior to the expiration of the 30-month period, a federal district court invalidates the patent, or holds the patent not infringed, the ANDA approval date is the date of the final court decision.¹⁰¹ Importantly, a final decision is made by the Court of Appeals for the Federal Circuit. Thus, the legislative scheme permits litigation respecting validity and infringement to begin before FDA approval and allows the litigation to proceed simultaneously with the FDA's evaluation of the ANDA. The patent owner can litigate the patent issues before the generic copy reaches the market.¹⁰²

At the expiration of the 30-month period (or a shorter or longer period as a court may order), an ANDA filer that has received FDA approval may commence marketing immediately or it may delay such activities until the conclusion of the litigation. The Federal Circuit has affirmed the authority of the trial court to extend the 30-month stay based on perceived litigation delays caused by the generic manufacturer.¹⁰³ Even where an FDA-approved ANDA filer is free to begin marketing prior to the termination of the suit, it may still be subject to infringement damages if it ultimately loses the infringement suit (see *infra* section III.A.3.e, "At Risk" Launches).

98. Pub. L. No. 108-173 § 1101(c).

99. 21 U.S.C. § 355 (j)(5)(B)(iii).

100. *Bristol-Myers Squibb Co. v. Royce Labs.*, 69 F.3d 1130, 1131–32 (Fed. Cir.), *cert. denied*, 516 U.S. 1026 (1995).

101. 21 U.S.C. § 355 (j)(4)(BB)(iii)(I).

102. *See Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1569 (Fed. Cir. 1997).

103. *Eli Lilly & Co. v. Teva Pharm. USA, Inc.*, 557 F.3d 1346 (Fed. Cir. 2009).

Settlement of an ANDA litigation can also terminate the 30-month stay, since it eliminates the rationale for the stay, by providing the parties with an opportunity to resolve the patent challenge in court prior to FDA approval.

d. Changes to 30-Month Stay under 2003 Amendments

The most significant change brought by the AAPA is the limitation of only one statutorily prescribed automatic 30-month stay per product in ANDA litigation.¹⁰⁴ Prior to this change, the manufacturer/patent owner could obtain the benefit of an additional, automatic 30-month stay upon the later listing of an additional patent in the Orange Book for a product already subject to ANDA litigation, which required a new paragraph IV certification by the ANDA filer and a new ANDA litigation. Under the AAPA, however, an ANDA applicant need only make a certification as to those patents listed in the Orange Book at the time of the ANDA filing.

The AAPA also prevents an ANDA applicant from shortening the 30-month stay of approval by amending a previously filed ANDA to include a different drug, although ANDA amendments to include different strengths of the same drug are permitted.

Finally, the AAPA clarifies that the 30-month stay automatically terminates upon the entry of a district court judgment of patent invalidity or noninfringement. A patent invalidity or noninfringement ruling by the court of appeals following a district court determination of infringement terminates the stay upon the date of the court of appeals decision.

e. “At Risk” Launches

Post-stay launch by generic company may be “at risk” of damages liability to patent owner

The 30-month stay is not the only consideration that prevents the generic company from marketing the generic copy while the litigation is still pending. When the drug product in suit is an important one, a generic company could be financially destroyed by the patent infringement damages incurred for lost profits of a blockbuster drug.

In order for a company to collect infringement damages for a patent on an important drug, the company that is marketing the patented drug must also be the patent owner or have an exclusive license to the listed patent. A nonexclusive licensee of a patent does not have standing to sue for damages from infringement.¹⁰⁵ In contrast, a subsidiary corporation that owns

104. 21 U.S.C. § 355(j)(2), (5).

105. See *Ortho Pharm. Corp. v. Genetics Inst.*, 52 F.3d 1026, 1031 (Fed. Cir. 1995), cert. denied, 516 U.S. 907 (1995) (“A holder of such a nonexclusive license suffers no legal injury from infringement and, thus, has no standing to bring suit or even join in a suit with the patentee.”).

a patent, but does not market any product, has a patent infringement damages claim limited to a reasonable royalty. In addition, the obligation to pay a reasonable royalty is not likely to be a deterrent against a generic ANDA filer marketing “at risk” before the patent has been determined noninfringed or invalid. It also leaves the potentially enormous harm caused to the patent owner by an infringing generic drug launch beyond the reach of any effective legal remedy.

B. ANDA Filers

The Hatch-Waxman Act established several incentives for a drug manufacturer to file an ANDA for a generic drug, with the intention of meeting the policy goal of accelerating the introduction of generic drugs to the market. The statutory incentives to file an ANDA can be divided into three main categories:

1. Simplification of application requirements for an ANDA, as compared to the requirements for an NDA;
2. Broad-based immunity from patent infringement for the generic developer for activities related to the development and approval of the generic drug; and
3. Market exclusivity rights for the first ANDA filer making a paragraph IV certification, and risking a patent infringement action from the patent owner.

1. Abbreviated Process for Bioequivalence

Statute simplifies (abbreviates) FDA filing and approval requirements for new drugs that are therapeutically equivalent to a previously approved new drug

As its name indicates, the filing requirements for a generic drug under the ANDA scheme are simplified in comparison to the application process for the corresponding brand name drug. It is presumed that a generic drug will function in the same manner as the drug if the two drugs are identical. Thus, the major difference in application requirements for a drug and its generic is that the generic applicant is permitted to rely on the safety and efficacy testing data of the NDA drug application,¹⁰⁶ meaning the generic applicant is not required to submit new preclinical and clinical testing data in an ANDA.

In place of safety and efficacy data for the drug, a generic applicant must provide in the ANDA information showing that the active ingredient in the generic is identical to that in the NDA drug and that the generic drug is “bioequivalent” to the NDA drug. By showing active ingredient

106. 21 U.S.C. § 355(j).

identity and bioequivalence in the generic, the generic drug is presumed to be as safe and effective as the NDA drug. Reliance on the safety and efficacy information contained in the NDA drug application allows the generic developer to avoid the costs associated with generating preclinical and clinical test data.

a. Establishing Bioequivalence

ANDA filer must demonstrate that the active ingredient is identical to the previously approved drug

Instead of the preclinical and clinical testing data previously submitted by the NDA applicant to demonstrate the safety and efficacy of a drug, the generic applicant must include in the ANDA evidence that the generic drug contains the same active ingredient and is bioequivalent to the previously approved NDA drug. The active ingredient of a drug “is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the body[.]”¹⁰⁷ The requirement for active ingredient identity is generally applied to the chemical composition of the generic drug. The active ingredient of the generic can be permitted to differ in physical characteristics from the NDA drug active ingredient yet still be considered identical (for example, differences in crystalline structure between the active ingredient of the generic drug and the NDA drug).

For the purposes of an ANDA application, “bioequivalence” is established by showing that the generic drug does not significantly differ in the rate and extent to which the active ingredient becomes available in the body or at the site of action as compared to the NDA drug. Thus, a generic applicant can meet this requirement by submitting data relating to the absorption of the drug into the bloodstream.

b. Other ANDA Requirements

ANDA filing must mirror the previously approved drug application with respect to labeling; usage, dosage, and administration; and manufacturing information

The ANDA application mirrors the previously approved drug application by requiring that the generic drug match the approved drug in labeling; usage, dosage, and route of administration; and manufacturing information.

An ANDA application must include copies of the labeling of the previously approved drug and proposed labeling of the generic drug, and with

107. 21 C.F.R. § 210.3(b)(7) (2006).

an annotated comparison identifying differences between the two labels. Compliance with this requirement by the ANDA applicant can be achieved by identical labeling by using for the generic a verbatim copy of the NDA drug labeling with necessary differences in manufacture information, expiration date, formulation (e.g., permitted differences in active ingredient as noted previously, and differences in inactive ingredients), bioavailability, patent markings, and any deviations from the NDA drug labeling necessitated by changes in FDA labeling requirements. As an additional incentive to copy the previously approved label, ANDA applicants cannot be sued for a failure to warn under state tort law, as long as their labeling complies with the FDA mandated labeling for the NDA drug.¹⁰⁸

An ANDA application must also include information demonstrating that the usage, dosage, and route of administration of the generic drug are the same as the NDA drug. “Dosage form” is defined neither in statute nor regulations and is typically evaluated based on a comparison of the physical appearance and method of administration of the drugs. An ANDA filer can petition the FDA for permission to deviate from the active ingredient of the NDA drug (from a plurality of active ingredients in the NDA drug), usage, dosage, route of administration, and/or strength.¹⁰⁹ The ANDA filer may not avoid infringement, however, by filing a stipulation or “guarantee” in district court litigation that it will manufacture a drug that deviates from the patented portions of an NDA in ways that are not addressed in the ANDA specification.¹¹⁰

2. “Safe Harbor”

ANDA applicants are immune from infringement for drug uses “related” to FDA approval process

The Hatch-Waxman Act provides infringement immunity to the ANDA applicant for activities related to its development of the generic drug. This exemption from infringement actions is codified at 35 U.S.C. § 271(e)(1) and the scope of the exemption is clarified by the Supreme Court in *Merck KGaA v. Integra Lifesciences I, Ltd.*¹¹¹

108. *Pliva, Inc. v. Mensing*, 131 S. Ct. 2567, 2580–81 (2011). Federal preemption also bars generics from strict liability under state design-defect laws, where the alleged defect is the FDA-approved ANDA product or label and avoidance of the defect would essentially require exiting the market. See *In re Fosamax (Alendronate Sodium) Prods. Liab. Litig.* (No. II), 751 F.3d 150, 162–65 (3d Cir. 2014).

109. 21 U.S.C. § 355(j)(2)(C).

110. *Sunovion Pharm., Inc. v. Teva Pharm. USA, Inc.*, 731 F.3d 1271, 1279–80 (Fed. Cir. 2013).

111. 545 U.S. 193 (2005).

a. 35 U.S.C. § 271(e)(1)

35 U.S.C. § 271(e)(1) exempts from patent infringement all uses of a patented invention “reasonably related” to the pursuit of FDA drug approval. Commonly referred to as the “safe harbor” provision, the section specifically provides:

[i]t shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.¹¹²

As noted earlier in this chapter, one of the two principal policy concerns addressed by the Hatch-Waxman Act was the distortion of protection at the end of the patent term protecting a patented drug. As shown in the decision of the Federal Circuit in *Roche v. Bolar*, prior to the enactment of the Hatch-Waxman Act and the safe harbor provision provided in § 271(e)(1), generic applicants could avoid infringement only by beginning development activities for the generic drug after expiration of the patent protecting the patented drug. Despite the stated goal of providing protection for the development of generic drugs during the patent term of corresponding patented drugs, the statutory language and lack of legislative history fail to define and provide guidance for several key terms, including “solely for uses reasonably related.” For over two decades after passage of the Hatch-Waxman Act, it was unclear which types of activities by the generic applicant and at which stages of research and development were immune from infringement claims by the patented drug developer. Upon considering the issue, the Supreme Court provided a broad scope for “reasonably related” activities.

b. *Scope of Exemption*

Broad judicial interpretation: Merck v. Integra

Judicial interpretation of the safe harbor provision has set broad definition for “reasonably related” in § 271(e)(1). The Supreme Court set the current standard for determining “reasonably related” in *Merck KGaA v. Integra Lifesciences I, Ltd.*,¹¹³ where the Court considered whether “uses of patented inventions in preclinical research, the results of which are

112. 35 U.S.C. § 271(e)(1).

113. 545 U.S. 193 (2005).

not ultimately included in a submission to the FDA are exempted from infringement by 35 U.S.C. § 271(e)(1).¹¹⁴

The case arose from Merck's activities in developing cancer treatments utilizing RGD peptides to identify potential drug candidates for further development and possible submission for regulatory approval. Integra owned patents relating to the RGD peptides and consequently sued Merck for infringement on the basis that since Merck's activities focused on research, rather than clinical testing, the safe harbor provision did not protect Merck.

At trial, Merck was found liable for infringement and the Federal Circuit affirmed the trial decision on appeal. The Federal Circuit found that Merck's drug development activities were not meant to produce clinical testing information to provide to the FDA, but amounted only to general research in an effort to identify new pharmaceutical compounds. The Federal Circuit indicated that the safe harbor provision of § 271 does not exempt all activities that may eventually lead to an FDA submission.

The Supreme Court reversed, holding that "the statutory text makes clear that it [the safe harbor provision] provides a wide berth for the use of patented drugs in activities related to the federal regulatory process."¹¹⁵ The Court found that the research outside of the direct scope of development of a generic drug for an ANDA approval falls within the § 271 safe harbor provision. The Court acknowledged that the safe harbor provision provides for "experimentation and failure on the road to regulatory approval" and that the infringement exemption applies to all phases of research, including preclinical studies using patented compounds. The Court noted that a generic developer is exempt from infringement even if an ANDA application is never filed, as long as the developer has a reasonable basis for believing that a patented compound will be effective for use and could be used in an ANDA.

In addition to the broad interpretation of "reasonably related" activities, the generic developer is not barred from using any patented invention in developing the generic drug. Thus, the generic developer, in addition to using the patented drug, can also use patented research tools in uses reasonably related to the production of data for the ANDA without infringing the patents that claim those tools.

In recent years, various Federal Circuit panels have appeared to split over whether safe harbor should extend to post-FDA-approval activity. In 2008, a Federal Circuit panel confined the scope of "safe harbor" under

114. *Id.* at 195.

115. *Id.* at 202.

35 U.S.C. § 271(e)(1) to premarket approval activities.¹¹⁶ In 2015, another Federal Circuit panel refused to extend safe harbor to certain methods used for the routine post-approval tests necessary to maintain FDA approval.¹¹⁷ That decision brought the Federal Circuit's precedent back in line with a 2011 panel decision holding that "[t]he statute does not apply to information that may be routinely reported to the FDA, long after marketing approval has been obtained."¹¹⁸

3. 180-Day Exclusivity

First ANDA filer receives 180-day exclusivity over subsequent generics

The Hatch-Waxman Act establishes a 180-day exclusivity period for the first to file an ANDA that includes a paragraph IV certification. This portion of the act was intended to promote development of generic drugs, especially those generics copying patented NDA drugs considered to have weak or vulnerable patent protection. Since the filing of an ANDA with paragraph IV certification is a technical act of patent infringement, the market exclusivity period is designed, in part, to reward the ANDA filer's risk of provoking an infringement suit by filing a paragraph IV certification.

The language of the Hatch-Waxman Act outlining the exclusivity period was vague, and FDA implementation of the exclusivity period served as the impetus for litigation relating to who is entitled to the exclusivity period, when the exclusivity period commences, and how the exclusivity period can be forfeited. The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 revised the portion of the statute relating to the 180-day exclusivity period.¹¹⁹ The MMA provisions relating to market exclusivity apply to ANDA applications filed with a first paragraph IV certification after December 8, 2003. The following section addresses the current statutory framework of the exclusivity period.

116. *Proveris Scientific Corp. v. Innovasystems, Inc.*, 536 F.3d 1256, 1265 (Fed. Cir. 2008).

117. *Momenta Pharm., Inc. v. Teva Pharm. USA Inc.*, 809 F.3d 610 (Fed. Cir. 2015) (holding that the exemption from infringement for use of the patented process to provide information as part of the federal process of regulating drugs did not apply to information reported concerning the testing of the anticoagulant, since the reporting was routine after marketing approval was obtained and was unrelated to facilitating such approval); reversing *Momenta Pharm., Inc. v. Amphastar Pharm., Inc.*, 686 F.3d 1348, 1358–61 (Fed. Cir. 2012).

118. *Classen Immunotherapies, Inc. v. Biogen IDEC*, 659 F.3d 1057, 1070 (Fed. Cir. 2011).

119. MMA § 1102.

a. *First to File*

“First to file” is the first to make paragraph IV certification, that is, first to challenge the validity of the listed patent(s)

The MMA makes clear that the first generic company to submit a substantially complete ANDA with a paragraph IV certification is considered the “first applicant” for purposes of enjoying the 180-day market exclusivity. Under this provision, it is possible for more than one company to obtain the benefit of the market exclusivity in the event multiple companies file on the same day a substantially complete ANDA with a paragraph IV certification for a drug for which a substantially complete ANDA with a paragraph IV certification has not previously been filed. For the purposes of this requirement, a “substantially complete” ANDA contains all required information for a substantive review.¹²⁰

b. *Subsequent Filers*

First ANDA filer’s exclusion applies against a subsequent applicant filing an ANDA on the same drug, dosage strength, and paragraph IV certification

The 180-day exclusivity period delays market entry over subsequent ANDA applicants with a paragraph IV certification for the same drug. There are three exceptions to the exclusivity period for the first applicant: (1) the later ANDA application does not include a paragraph IV certification, (2) the later ANDA application is for a different dosage, and (3) the patented NDA drug manufacturer produces an authorized generic.

The first paragraph IV filer has market exclusivity only over subsequent ANDA applicants who include a paragraph IV certification for any patents listed in the first-filed ANDA. A subsequent ANDA filer avoids the exclusivity period of the first filer by not including a paragraph IV certification.

For purposes of drug applications, the FDA considers a variation in dosage strength in drugs having the same active ingredient(s) as a new drug. Thus, the first paragraph IV certifier enjoys exclusivity over later applicants only for the same drug at the same dosage strength. The first applicant cannot use its market exclusivity period against a subsequent applicant for a generic for the same NDA drug who gains approval for a petition to vary dosage strength from the NDA drug.

Finally, the first paragraph IV certifier cannot enjoy market exclusivity over the patented NDA manufacturer’s authorized generic. A patented

120. 21 U.S.C. § 355(j)(2)(A).

NDA drug manufacturer is permitted to market an unbranded version of its drug based on the information of the original NDA.

c. “Commercial Marketing”

First filer’s 180-day exclusivity period commences when first filer begins “commercial marketing”

The 180-day exclusivity period is calculated from the first date of “commercial marketing” of the generic drug by the first filer.¹²¹ This is a modification from the Hatch-Waxman Act under which commenced the exclusivity period from the date of a favorable district court decision for the generic applicant. Thus, the generic producer has some control over the start date of the exclusivity period and the opportunity to undertake product launch activities after the approval of the ANDA and termination of infringement litigation.

d. Losing Exclusivity

Failure to timely commence marketing results in forfeiture of first filer’s exclusivity

The first paragraph IV ANDA filer can forfeit its exclusivity rights for failing to bring the generic drug to market within certain time limits. The first paragraph IV ANDA filer will forfeit its exclusivity rights for failure to market the generic drug by within any one of: 75 days after FDA approval of the ANDA or 30 months after filing the ANDA; 75 days after a nonappealable favorable district court or favorable Federal Circuit decision; 75 days after a favorable settlement; or 75 days after the patent protecting the drug expires or is withdrawn. These timing requirements were established in the MMA. The Hatch-Waxman Act did not include the requirement to bring the generic to market or risk forfeiture of the exclusivity period. Additionally, a first filer can lose the exclusivity rights by amending or withdrawing the paragraph IV certification from its ANDA.

e. Change and Clarifications to 180-Day Exclusivity

As noted previously, the MMA instituted a forfeiture policy, regarding the 180-day exclusivity period, for first filers failing to timely market the approved generic. The new legislation also applies forfeiture to the following acts: (1) withdrawal of an ANDA, (2) the failure to obtain tentative approval within 30 months of filing, (3) the ANDA filer’s entry into an anticompetitive agreement, and (4) expiration of all patents subject to the paragraph IV certification.

121. *Id.* § 505(j)(5)(B)(iv).

The MMA also codifies certain FDA policies regarding the 180-day exclusivity, specifically:

- Exclusivity is determined on a drug-by-drug basis, rather than for each separate patent challenged under a paragraph IV certification.
- Exclusivity is shared by all ANDAs with paragraph IV certifications filed on the same day that the first ANDA with a paragraph IV certification is filed.

A forfeited 180-day exclusivity period does not pass to a subsequent ANDA filer; that is, there is no “rolling exclusivity.”