

HOW SAFE IS THE HARBOR? CONSIDERING THE ECONOMIC IMPLICATIONS OF PATENT INFRINGEMENT IN SECTION 271(e)(1) ANALYSIS

I. INTRODUCTION

The Drug Price Competition and Patent Term Restoration Act of 1984 (“Hatch-Waxman”)¹ created a safe harbor² provision that protects a generic drug company from infringement liability when manufacturing and testing a brand-name (patented) drug before the patent expires.³ The Supreme Court reasoned that the safe harbor sought to eliminate a pioneer drug company’s *de facto* extension of patent rights beyond the expiration of the patent term.⁴

Before Hatch-Waxman, it was considered patent infringement for a generic competitor to begin the lengthy regulatory approval process prior to the expiration of a pioneer drug company’s brand-name patent, which effectively extended the life of the patent.⁵ The safe harbor created a defense to patent infringement that allowed generic manufacturers to test a

1. Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified at 21 U.S.C. § 355 (2000) & 35 U.S.C. § 271(e)(1) (2000)) (commonly referred to as the Hatch-Waxman Act because of its two primary sponsors, Senator Orrin Hatch (R-UT) and Congressman Henry Waxman (D-CA)). Drug Price Competition and Patent Term Restoration Act of 1984: Remarks on Signing S. 1538 Into Law, 20 WEEKLY COMP. PRES. DOC. 1359 (Sept. 24, 1984) [hereinafter Presidential Remarks].

2. 35 U.S.C. § 271(e)(1) (2000). This section is called the “safe harbor” provision because it allows a generic manufacturer to develop its version of a patented drug within a “safe harbor” or without fear of liability for patent infringement. Stephanie E. Piatt, Note, *Regaining the Balance of Hatch-Waxman in the FDA Generic Approval Process: An Equitable Remedy to the Thirty-Month Stay*, 59 N.Y.U. ANN. SURV. AM. L. 163, 172 (2003); see also *Integra Lifesciences I, Ltd. v. Merck KGaA*, 331 F.3d 860, 866 n.3 (Fed. Cir. 2003), cert. granted, 73 U.S.L.W. 3059 (U.S. Jan. 7, 2005) (No. 03-1237) (stating that although the express language of the safe harbor says “that ‘it shall not be an act of infringement’ to carry out research activities . . . the statute has been coined an ‘exemption’ in the case law, drawing from terminology used in the legislative history” (citing H.R. REP. NO. 98-857, pt. 2, at 5 (1984), reprinted in 1984 U.S.C.C.A.N. 2686, 2689)).

3. 35 U.S.C. § 271(e)(1) (stating “[i]t shall not be an act of infringement to make . . . a patented invention . . . for uses reasonably related to the development and submission of information under a Federal law”).

4. *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 670 (1990). Because a generic competitor could not “infringe” a patent to begin testing a generic version of a drug before the patent of the brand-name drug expired, the brand-name drug was afforded extended patent protection beyond the life of the patent to include the length of time necessary for the generic competitor to secure FDA approval for its own version of the drug (a situation referred to as a *de facto* extension of the pioneer drug company’s patent rights). *Id.* (discussing the *de facto* extension of a patentee’s monopoly rights); see also Jones, *infra* note 41, at 478 (describing the *de facto* extension of a patentee’s patent term as a “back-end distortion.”).

5. See *infra* notes 22–46 and accompanying text.

generic version of a patented drug for regulatory purposes before the patent expires;⁶ consequently, generic manufacturers can market their drug as soon as the brand-name patent expires. Initially, the safe harbor shielded infringers only if their activities were for the purpose of developing information that would be submitted to the Food and Drug Administration (“FDA”) for drug approval.⁷ However, courts have expanded the scope of the safe harbor to include medical devices⁸ and recombinant proteins even though the proteins cannot be approved under the new generic FDA approval process.⁹ Recently, one district court articulated the scope of the safe harbor infringement protection to “apply to all activities reasonably related to an actual or possible FDA application,”¹⁰ seemingly covering all activities along the chain of experimentation that may lead to new drugs subject to FDA approval. Confusion among courts regarding the scope of safe harbor protection left the biotechnology industry wondering whether its research tool patents would be protected against infringement.¹¹

Addressing this concern, the U.S. Court of Appeals for the Federal Circuit in *Integra Lifesciences I, Ltd. v. Merck KGaA*,¹² held that the safe harbor only applies to pre-patent-expiration activities “reasonably related”

6. See *infra* note 35 and accompanying text.

7. See *infra* notes 80–82 and accompanying text.

8. *Eli Lilly*, 496 U.S. 661 (holding that the testing and marketing of a cardiac defibrillator falls under the safe harbor exception).

9. See *infra* note 204 and accompanying text.

10. *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*, No. 95 Civ. 8833 (RPP), 2001 WL 1512597, at *6 (S.D.N.Y. Nov. 28, 2001); see also *id.* at *3 (adopting reasoning from *Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269, 1280 (N.D. Cal. 1991), that Congress did not intend for a party to lose the safe harbor exemption “simply because it turns out, after the fact, that some of that party’s otherwise infringing ‘uses’ either failed to generate information in which the FDA was interested” or were not necessary to secure FDA approval).

11. Richard J. Warburg & Stephen B. Maebius, *Warning: Research Dollars at Risk! IP Law Must Support Old Patents and New Research. Any Imbalance Threatens to Shut Down the New-Drug Pipeline*, LEGAL TIMES, Mar. 24, 2003, at 28, (stating biotechnology companies believed that patents would shield their research tool technology). However, recently courts have held that research on new drugs using patented tools does not infringe those patents under the safe harbor. *Id.* This conclusion could open up the gates for free use of biotechnology companies’ patented chemicals; as a result the biotechnology firms may lose the financial ability to continue innovation because they depend on revenue from larger pharmaceutical companies. *Id.*; see also 331 F.3d at 867 (realizing the potential effect on the biotechnology industry, the court reasoned that expansion of the safe harbor outside the scope of FDA approval would “effectively vitiate the exclusive rights of patentees owning biotechnology tool patents”); Dan L. Burk & Mark A. Lemley, *Policy Levers in Patent Law*, 89 VA. L. REV. 1575, 1676 (2003) (describing the biotechnology industry as “in part about pharmaceuticals—and therefore prospect theory—and in part about DNA research—and therefore anticommens theory”).

12. 331 F.3d 860 (Fed. Cir. 2003), cert. granted, 73 U.S.L.W. 3059 (U.S. Jan. 7, 2005) (No. 03-1237).

to acquiring FDA approval of a drug already on the market¹³ and does not “globally embrace all experimental activity that at some point, however attenuated, may lead to an FDA approval process.”¹⁴

While the Federal Circuit correctly decided the case, it failed to articulate a rule that reduces the vagueness surrounding the assessment of what activities are “reasonably related” to the FDA approval process.¹⁵ Currently, biotechnology assets are threatened because the safe harbor, which was originally enacted to permit drug manufacturers to use patented drugs to gain FDA approval of generic drugs, is being applied to biotechnology research tools.¹⁶ This Note proposes a new standard for evaluating infringement liability under the safe harbor that focuses on Congress’s original intent and ensures uniform application in the biotechnology and pharmaceutical industries. This Note will: (1) explain why the Hatch-Waxman safe harbor was needed;¹⁷ (2) examine the relationship between the FDA approval process and how it implicates the safe harbor;¹⁸ (3) analyze the case law leading up to the *Integra* decision;¹⁹ (4) assess the impact of the *Integra* decision as it applies to the safe harbor and the biotechnology industry;²⁰ and (5) propose a new test, based on the economic impact of the infringing activity, for evaluating whether activities that are otherwise infringing are protected by the safe harbor.²¹

II. THE HATCH-WAXMAN SAFE HARBOR: 35 U.S.C. § 271(e)(1)

Prior to 1984, there was no established FDA approval procedure for generic manufacturers seeking to produce brand-name drugs that were approved after 1962.²² Consequently, there were roughly 150 drugs

13. *Id.* at 867.

14. *Id.*

15. *See infra* notes 176–78 and accompanying text.

16. Jian Xiao, *Carving Out a Biotechnology Research Tool Exception to the Safe Harbor Provision of 35 U.S.C. § 271(e)(1)*, 12 TEX. INTELL. PROP. L.J. 23, 25–26 (2003) (discussing the biotechnology industry and the threat posed by the courts’ recent application of the safe harbor to research tools).

17. *See infra* Part II.

18. *See infra* Part III.

19. *See infra* Part V.

20. *See infra* Part VII.

21. *See infra* Part VIII.

22. H.R. REP. NO. 98-857, pt. 1, at 14 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647. In 1962, amendments to the Federal Food, Drug and Cosmetic Act (“FFDCA”) required all new generic and pioneer drugs be “approved as safe and effective prior to marketing.” *Id.* at 16. Thus, Abbreviated New Drug Applications (“ANDAs”) were available to generic manufacturers seeking approval of brand-name drugs approved before 1962 but not after. Hatch-Waxman created ANDA availability for generic manufacturers to pursue approval of a brand-name compound that was approved after 1962.

approved after 1962 that were “off patent” for which there was no generic equivalent.²³ As the pharmaceutical industry began to increase the prices of brand-name drugs, consumers became frustrated over the unavailability of less expensive substitutes.²⁴ Thus, in 1984, Congress passed the Hatch-Waxman Act²⁵ in an attempt to balance the needs of three groups: pioneer drug manufacturers, generic drug manufacturers, and consumers.²⁶

Prior to Hatch-Waxman, a brand-name (research-based) drug manufacturer’s monopoly rights were effectively extended for the time required for a generic manufacturer to gain regulatory approval because the generic manufacturer was prohibited from using the brand-name drug to apply for FDA approval during the term of the patent.²⁷ Also prior to Hatch-Waxman, the Federal Circuit in *Roche Products, Inc. v. Bolar Pharmaceutical Co.*²⁸ held that section 271(a)²⁹ prohibits “any and all uses of a patented invention,”³⁰ and the experimental use exception³¹ did not apply to infringement of a drug patent for the purpose of obtaining data required by the FDA.³² Thus, *Roche* required that a competing generic

23. *Id.* at 17. The Committee on Energy and Commerce noted that all of these drugs could be approved in generic form if there was an established procedure. *Id.* Also, the Committee estimated that the availability of generic versions of drugs approved by the FDA after 1962 “would save American consumers \$920 million over the next 12 years.” *Id.*

24. See *infra* note 43 and accompanying text.

25. 21 U.S.C. § 355 (2000).

26. Ralph G. Schroeder & Paul Papas, *Protecting the Balance of Hatch-Waxman: Understanding the Industry’s New Dynamics for the 21st Century*, 56 FOOD & DRUG L.J. 19 (2001). See generally Gerald J. Mossinghoff, *Overview of the Hatch-Waxman Act and Its Impact on the Drug Development Process*, 54 FOOD & DRUG L.J. 187 (1999) (giving a general overview of the Hatch-Waxman Act and its legislative history).

When President Ronald Reagan signed the bill into law on September 24, 1984, he articulated the balance achieved by the bill stating, “[s]o when you add it all up, this bill will provide regulatory relief, increased competition, economy in government, and best of all, the American people will save money, and yet receive the best medicine that pharmaceutical science can provide.” Presidential Remarks, *supra* note 1, at 1360.

27. Ann K. Wooster, Annotation, *Construction and Application of Hatch-Waxman Act*, 180 A.L.R. FED. 487, 508 (2002). Specifically, Hatch-Waxman sought to ensure that the patentee’s rights did not *de facto* “extend past the expiration of the patent term because a generic competitor also could not enter the market without regulatory approval.” *Integra*, 331 F.3d at 865 (citing *Eli Lilly*, 496 U.S. at 669–70). See generally Elizabeth Stotland Weiswasser & Scott D. Danzis, *The Hatch-Waxman Act: History, Structure, and Legacy*, 71 ANTITRUST L.J. 585 (2003) (discussing the historical background of the Hatch-Waxman Act, generic drug competition, and the Hatch-Waxman safe harbor).

28. 733 F.2d 858 (Fed. Cir. 1984).

29. Section 271(a) states: “Except as otherwise provided in this title, whoever without authority makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent therefor, infringes the patent.” 35 U.S.C. § 271(a) (2000).

30. 733 F.2d at 861.

31. See *infra* note 154.

32. 733 F.2d at 863 (stating that Bolar’s use of flurazepam HCl to “derive FDA required test data

drug manufacturer wait until the expiration of the brand-name drug patent before beginning the clinical and laboratory trials that are required by the FDA and are necessary to market a generic version of the drug.³³

In response, Congress legislatively overruled the Federal Circuit's narrow interpretation of the common law experimental use doctrine in *Roche* by creating the Hatch-Waxman safe harbor.³⁴ The safe harbor allows competitors to manufacture and test the generic version of a drug³⁵ in advance of patent expiration as long as the infringing activities are "reasonably related" to securing regulatory approval.³⁶ The safe harbor provides that "it shall not be an act of infringement to make, use, offer to sell, or sell . . . a patented invention . . . which is primarily manufactured . . . solely for uses reasonably related [to the FDA approval process]."³⁷

is thus an infringement of [the patent]").

33. Nicholas Groombridge & Sheryl Calabro, *Integra Lifesciences v. Merck—Good for Research or Just Good for Research Tool Patent Owners?*, 22 BIOTECHNOLOGY L. REP. 462, 463 (2003). Bolar Pharmaceuticals wanted to produce a generic version of Roche's Dalmane (flurazepam HCl). 733 F.2d at 860. Because a generic drug's commercial success is based on how quickly it is brought to market after the brand-name patent expires and because of the lengthy FDA approval process, Bolar began to gather data for FDA submission while Roche's patent was still in force. *Id.* Bolar did not market or sell its drug prior to Roche's patent expiration. *Id.*

34. See *infra* note 79 and accompanying text.

35. See Pharmaceutical Research and Manufacturers of America, *Plain Talk About Prescription Drug Patents*, at <http://www.phrma.org/publications/policy/02.01.2002.426.cfm> (last visited Oct. 16, 2004) [hereinafter PHRMA] (stating Hatch-Waxman allows a generic drug manufacturer to "piggyback on the innovator's years of testing" and also allows the generic company to manufacture and test the generic drug before the patent expires); Holly Soehnge, *The Drug Price Competition and Patent Term Restoration Act of 1984: Fine-Tuning the Balance Between the Interests of Pioneer and Generic Drug Manufacturers*, 58 FOOD & DRUG L.J. 51, 52–53 (2003) (stating that generic manufacturers get simplified FDA approval requirements for generic versions of pioneer drugs); see also Laura J. Robinson, *Analysis of Recent Proposals to Reconfigure Hatch-Waxman*, 11 J. INTELL. PROP. L. 47, 51 (2003) (stating that Hatch-Waxman provided three major benefits to generic manufacturers: (1) the ANDA; (2) the right to make and test generic versions of a pioneer drug brand-name patent expires; and (3) the incentive of receiving 180 days of market exclusivity for being the first generic manufacturer on the market).

36. 35 U.S.C. § 271(e)(1) (2000); see also Weiswasser & Danzis, *supra* note 27, at 604–06 (discussing the section 271(e)(1) safe harbor).

37. 35 U.S.C. § 271(e)(1). The section 271(e)(1) safe harbor states:

It 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 (other than a new animal drug or veterinary biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Act of March 4, 1913) which is primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other processes involving site specific genetic manipulation techniques) 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.

Id.

Before various amendments, the original (1984) text of the safe harbor stated:

It shall not be an act of infringement to make, use, or sell a patented invention (other than a new animal drug or veterinary biological product (as those terms are used in the Federal

Hatch-Waxman also benefits pioneer drug companies. Due to the lengthy FDA approval process,³⁸ pioneer drug companies (research-based) found their effective patent life decreasing by the increasing amount of time it took for their product to secure FDA approval.³⁹ Hatch-Waxman amends the Patent Law Act (codified at 35 U.S.C.) and grants pioneer drug manufacturers an extension on their patent term due to the prolonged regulatory approval process.⁴⁰

Ultimately, Hatch-Waxman seeks to restore patent terms to pioneer drug manufacturers that have been eroded by the lengthy FDA approval process⁴¹ and to stimulate the generic drug industry,⁴² which would create access to less expensive medications for consumers.⁴³ While pioneer drug

Food, Drug, and Cosmetic Act and the Act of March 4, 1913)) 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.

35 U.S.C. § 271(e)(1) (1984).

38. In 2001, the FDA's median approval time for standard new molecular entities ("NMEs," or new drugs not given priority status) was 14 months. *FDA Talk Paper: Activities of FDA's Medical Product Centers in 2001* (Jan. 25, 2002), at <http://www.fda.gov/bbs/topics/answers/2002/ans01132.html>. See also *infra* notes 48–61 and accompanying text.

39. See *infra* note 41 and accompanying text.

40. 35 U.S.C. § 156 (2000). Section 156 states:

(a) The term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended in accordance with this section from the original expiration date of the patent, which shall include any patent term adjustment granted under section 154(b), if— . . . (4) the product has been subject to a regulatory review period before its commercial marketing or use

Id.

41. Phillip B.C. Jones, *Navigating the Hatch-Waxman Act's Safe Harbor*, 57 *FOOD & DRUG L.J.* 475, 478 (2002) (stating that the lengthy FDA approval process created a "front-end distortion," a decrease in the effective patent term of a pioneer drug"); see also Schroeder & Papas, *supra* note 26, at 25 (citing a study from the "Tufts Center for the Study of Drug Development [which] found that the mean effective patent life of new drugs . . . was 11.2 years. This compares to the 20 year full-term granted by a patent and an 18 year average effective patent life for inventions other than drugs.").

42. See Kristin E. Behrendt, *The Hatch-Waxman Act: Balancing Competing Interests or Survival of the Fittest?*, 57 *FOOD & DRUG L.J.* 247, 249 (2002) (stating that "[p]rior to 1984, generic drug manufacturing was not a robust industry."). In 1984 there were roughly 150 brand name drugs, whose patent protection had expired, with no generic equivalents. *Id.* Prior to 1984, there was little economic incentive for a generic drug manufacturer to enter the market due to the lengthy FDA approval process. *Id.* Now, the generic drug industry fills more than 40% of all drug prescriptions. Schroeder & Papas, *supra* note 26, at 19.

43. Behrendt, *supra* note 42, at 250 (stating that Hatch-Waxman, in part, intended to cater to consumer interests by making low cost generic drugs available). See Schroeder & Papas, *supra* note 26, at 19 (addressing the compromise between the consumer's need for low-priced drugs and the need of the pharmaceutical industry to protect innovation); see also Charles P. Alexander, *Prescription for Cheap Drugs: Congress Aims to Encourage Alternatives to Brand-Name Medicines*, *TIME*, Sept. 17, 1984, at 64 (discussing the frustration of consumers over the high price of prescription drugs and the financial benefit of generic drugs); Michael Waldholz, *Pillbox War: Drug Battle Heats up Between Brand-Name and Generic Makers—Big Firms Appeal to Doctors, Pharmacists and Courts to Stall Low-Cost Rivals*, *WALL ST. J.*, Aug. 13, 1984, at 8 (discussing the tension between brand-name drug

companies benefit from an extended patent term, generic manufacturers and consumers⁴⁴ benefit from Abbreviated New Drug Applications (“ANDAs”),⁴⁵ which truncate the generic drug approval process, and from the safe harbor exemption of section 271(e)(1), which allows generic drugs to complete the FDA approval process before the brand-name patent expires.⁴⁶ The cumulative effect for consumers is more generic drug alternatives in the marketplace; ideally more choices mean lower prices for consumers.⁴⁷

III. OVERVIEW OF THE FDA APPROVAL PROCESS FOR PRESCRIPTION DRUGS

In order to grasp the implications of the safe harbor on the pharmaceutical industry, it is important to understand the regulatory process for drug approval post-Hatch-Waxman. The FDA⁴⁸ approval

manufacturers and generic manufacturers and the desire for increased generic competition); Michael Waldholz, *Price of Prescription Drugs Soar After Years of Moderate Increases*, WALL ST. J., May 25, 1984, at 31 (stating customers are dissatisfied due to the increased cost of prescription drugs).

44. The benefits designed for the generic manufacturer are shared indirectly with the consumer. As ANDAs and the safe harbor allow generic manufacturers to enter the market immediately after a pioneer drug patent expires, consumers will have greater access and choice among medications (they can choose between a high-price or low-price product). As more drugs are on the market, the generic drugs will provide a less expensive alternative for consumers. David A. Balto & James F. Mongoven, *Antitrust Enforcement in Pharmaceutical Industry Mergers*, 54 FOOD & DRUG L.J. 255, 259 (1999) (stating that FTC investigations have found “a significant price difference between generic and brand name versions” of a drug). See Brian Urevig, Note, *Hatch-Waxman—Thoughtful Planning or Just Piling On: A Consideration of the Federal Trade Commission’s Proposed Changes*, 4 MINN. INTELL. PROP. REV. 367, 390 (2003) (stating that “[g]enerics are certainly cheaper than brand-name drugs”); see also *supra* note 43 (discussing the consumer benefit of Hatch-Waxman).

45. See *infra* note 59 and accompanying text. Hatch-Waxman requires all holders of approved New Drug Applications (“NDAs”) to notify the FDA if an approved product is covered by patents claiming the product. Jeffrey I.D. Lewis, *Declaratory Judgments of Patent Infringement: What They Forgot About Drug Applications*, 7 FED. CIR. B.J. 35, 41 (1997). The FDA then publishes a compilation of patents covering approved products in “The Approved Prescription Drug Product List,” also known as the Orange Book. *Id.* Any manufacturer wanting to utilize an ANDA must include a certification with the ANDA that the patent information in the Orange Book does not bar FDA approval of a generic version of the patented drug. *Id.* See 21 U.S.C. § 355(b)-(c) (discussing the Orange Book and the ANDA certification process). See generally Shashank Upadyhe, *Understanding Patent Infringement Under 35 U.S.C. § 271(e): The Collisions Between Patent, Medical Device and Drug Laws*, 17 SANTA CLARA COMPUTER & HIGH TECH. L.J. 1, 48–49 (2000) (discussing ANDAs, certification, and the Orange Book); Jacob S. Wharton, “Orange Book” Listing of Patents Under the Hatch-Waxman Act, 47 ST. LOUIS U. L.J. 1027 (2003) (discussing the Orange Book and its relationship to the FDA approval process under Hatch-Waxman).

46. Jones, *supra* note 41, at 478–79 (describing the provision as allowing generic competition to enter the market the day after the pioneer’s patent term expires); see also 35 U.S.C. § 271(e)(1) (2000).

47. See *supra* notes 43–45.

48. In 1938, Congress enacted the Federal Food, Drug, and Cosmetic Act to regulate the safety of pharmaceuticals, which led to the establishment of the FDA. Vivian I. Orlando, *The FDA’s*

process for new drugs begins when the sponsor of a new drug submits an Investigational New Drug Application (“IND”) to the FDA.⁴⁹ If the FDA determines it is safe to move forward, the drug sponsor will begin Phase One clinical trials.⁵⁰ At the end of Phase Three studies, a drug sponsor can file a New Drug Application (“NDA”) and ask the FDA to consider the drug for marketing in the United States.⁵¹ An FDA review team⁵² then reviews the NDA to evaluate the sponsor’s research on safety and effectiveness.⁵³ Next, the FDA will review the information on the drug’s label, including the usage instructions, and it will inspect the drug manufacturing facilities.⁵⁴ Finally, the FDA reviewers will either approve the drug, find it “approvable,” or find it “not approvable.”⁵⁵

Accelerated Approval Process: Does the Pharmaceutical Industry Have Adequate Incentives for Self-Regulation?, 25 AM. J.L. & MED. 543, 543 (1999). See Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 (2000) (the basic food and drug law of the United States); see also 21 U.S.C. § 393(b) (2000) (codifying the FDA and articulating its function, mission, and responsibilities).

49. Michelle Meadows, *The FDA’s Drug Review Process: Ensuring Drugs are Safe and Effective*, FDA CONSUMER, July–Aug. 2002, at http://www.fda.gov/fdac/features/2002/402_drug.html [hereinafter *FDA Drug Review*]. The IND must contain information on animal and toxicology studies, manufacturing information, clinical protocols and investigator information. Ctr. for Drug Eval. & Research, U.S. Food and Drug Admin., *Investigational New Drug (IND) Application Process*, at http://www.fda.gov/cder/regulatory/applications/ind_page_1.htm (last visited Oct. 16, 2004) (discussing the applicable provisions in the Code of Federal Regulations, 21 C.F.R. §§ 312, 314 (2003)) [hereinafter CDER].

50. *FDA Drug Review*, *supra* note 49, states that a drug must successively pass through four phases of clinical trials before the drug can be considered for marketing in the United States: (1) Phase One studies are conducted on healthy volunteers with the goal of determining the drug’s most frequent side effects and how the drug is metabolized; (2) Phase Two studies emphasize effectiveness with the goal of determining whether the drug works in people with certain diseases and conditions; (3) Phase Three studies “gather more information about safety and effectiveness” focusing on different dosages, while monitoring drug interaction when used in combination with other drugs; (4) Phase Four studies occur after a drug is approved and explore long-term effects, new uses, and participant responses to different doses. *Id.* Cf. Orlando, *supra* note 48, at 547 (describing the Accelerated Approval Exemption as allowing pharmaceutical companies to provide terminally ill patients with potentially life-saving medication, usually after Phase One, before the drug has completed all of the mandatory phases of FDA clinical trials).

51. *FDA Drug Review*, *supra* note 49. This is the formal step for asking the FDA to approve a drug. *Id.* When a NDA is submitted, the FDA’s Center for Drug Evaluation and Research (CDER) reviews the NDA no later than ten months after receiving it. *Id.*

52. *Id.* (the review team consists of medical doctors, chemists, statisticians, microbiologists, pharmacologists, and other experts). Each reviewer prepares a report that is considered by team leaders, division directors, or office directors, depending on the type of application. *Id.* Also, the FDA can call on advisory committees made up of outside experts to assist with drug application decisions. *Id.*

53. *Id.*

54. *Id.* See Marian Segal, *FDA Consumer Report on New Drug Development in the United States, An Inside Look at FDA On-Site*, (Jan. 1995), at <http://www.fda.gov/cder/about/whatwedo/testtube-7.pdf> (stating that an inspection can last from two days to several weeks depending on its purpose and scope). Generally, there are three types of inspections: preapproval, postapproval, and good manufacturing practice (“GMP”) inspections. *Id.* After a drug is approved, the FDA conducts a

Brand-name drugs are frequently under patent protection while they are being reviewed for FDA approval.⁵⁶ When preparing to market a brand-name drug, generic or non-pioneering manufacturers can submit an application to the FDA to sell generic versions⁵⁷ of the drug.⁵⁸ Instead of filing an NDA, generic manufacturers may file an ANDA,⁵⁹ which utilizes the preclinical (animal) and clinical (human) data from the pioneer manufacturer's studies, to establish safety and efficacy.⁶⁰ Thus, instead of submitting information duplicating the lengthy clinical trials already conducted by the pioneer company, generic applicants must simply demonstrate that the generic drug is the bioequivalent to the previously approved drug.⁶¹ In other words, the generic drug performs the same function as the pioneer drug.

postapproval inspection to validate that the firm can consistently manufacture a drug product "within tight parameters from batch to batch, day to day, year to year." *Id.* The investigators also verify that the firm has not altered its "manufacturing, labeling, or quality control testing" for a specified drug. *Id.* GMP inspections are "routine" inspections that, unlike the pre- and postapproval inspections, are not product-specific and involve a comprehensive review of the firm's manufacturing operations. *Id.*

55. *FDA Drug Review*, *supra* note 49. If the FDA determines that the benefits of a drug outweigh the risks, the drug will be approved and can be marketed in the United States. *Id.* "Approvable" means that a drug can probably be approved if some issues are resolved first. *Id.* "Not Approvable" is utilized when there are deficiencies significant enough that it is not clear whether approval can be obtained in the future. *Id.*

56. Ctr. for Drug Eval. & Research, U.S. Food and Drug Admin., *Drug Approval Application Process*, at <http://www.fda.gov/cder/regulatory/applications/default.htm> (last visited Oct. 16, 2004).

57. A generic drug is one that is a bioequivalent to the patented or pioneering drug product in "dosage, form, safety, strength, route of administration, quality, performance characteristics and intended use." Ctr. for Drug Eval. & Research, U.S. Food And Drug Admin., *Office of Generic Drugs*, at <http://www.fda.gov/cder/ogd> (last visited Oct. 16, 2004) [hereinafter OGD]; *see also* Justina A. Molzon, *The Generic Drug Approval Process*, 5 J. PHARMACY & L. 275 (1995) (comparing the generic drug approval process with the brand name approval process).

58. CDER, *supra* note 49.

59. ANDAs "are termed 'abbreviated' because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness." Ctr. for Drug Eval. & Research, U.S. Food And Drug Admin., *Abbreviated New Drug Application Process (ANDA) for General Drugs*, at <http://www.fda.gov/cder/regulatory/applications/ANDA.htm> (last visited Oct. 16, 2004).

By allowing ANDAs to be used for drugs patented after 1962, Hatch-Waxman stimulated generic drug development. Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified at 21 U.S.C. § 355 (2000) & 35 U.S.C. § 271(e)(1) (2000)).

60. OGD, *supra* note 57.

61. *Id.* This helps to minimize or eliminate the *de facto* extension of patent rights that pharmaceutical patent holders previously enjoyed and enhances public access to generic drugs. *See supra* note 4 and accompanying text.

IV. *INTEGRA* BACKGROUND

When a drug manufacturer seeks protection under the safe harbor after being accused of patent infringement, the manufacturer will likely assert that its activities were related to the FDA approval process and are, therefore, protected under the safe harbor. This is the defense Merck asserted in *Integra*.⁶² The plaintiff, *Integra*, owned five patents⁶³ related to a short tri-peptide segment of fibronectin⁶⁴ (“RGD peptide”) that was shown to attach to receptors⁶⁵ on the cell surface and stimulate angiogenesis.⁶⁶ The defendant, Merck, hired Scripps and Dr. David Cheresh to research and “identify potential drug candidates that might inhibit angiogenesis.”⁶⁷ Dr. Cheresh⁶⁸ was the scientist who discovered that blocking the same cell receptors that the RGD peptide stimulates inhibits angiogenesis.⁶⁹ That discovery led to the discovery of EMD

62. *Integra Lifesciences I, Ltd. v. Merck KGaA*, 331 F.3d 860, 863 (Fed. Cir. 2003), *cert. granted*, 73 U.S.L.W. 3059 (U.S. Jan. 7, 2005) (No. 03-1237) (“Merck answered that its work with Scripps falls under the safe harbor afforded by 35 U.S.C. § 271(e)(1).”).

63. U.S. Patent No. 4,789,734 (issued Dec. 6, 1988); U.S. Patent No. 4,792,525 (issued Dec. 20, 1988); U.S. Patent No. 4,879,237 (issued Nov. 7, 1989); U.S. Patent No. 5,965,997 (issued Oct. 12, 1999); U.S. Patent No. 4,988,621 (issued Jan. 29, 1991) (held to be invalid in *Integra*, 331 F.3d at 862).

64. 331 F.3d at 862. It is called the “RGD peptide” because it has the amino acid sequence Arg-Gly-Asp. *Id.* All proteins can be thought of as a polymer of amino acids. GEOFFREY L. ZUBAY, *BIOCHEMISTRY* 60 (Ron Worthington ed., Wm. C. Brown Publishers 4th ed. 1998). There are 20 common amino acids, of which Arg is the abbreviation for Arginine, Gly is the abbreviation for Glycine, and Asp is the abbreviation for Aspartic Acid. *Id.* at 60–62. Structurally, amino acids have common features that allow them to be linked together (like the *Integra* “RGD peptide”). *Id.* at 60.

65. $\alpha_v\beta_3$ receptors are located on the surface of cells. 331 F.3d at 863. A receptor is “[a] structural protein molecule on the cell surface or within the cytoplasm that binds to a specific factor, such as a drug, hormone, antigen, or neurotransmitter.” *STEDMAN’S MEDICAL DICTIONARY* 1529 (27th ed. 2000).

66. Angiogenesis refers to the development of new blood vessels. *STEDMAN’S MEDICAL DICTIONARY*, *supra* note 65, at 81. Angiogenesis is controlled by “chemicals produced in the body” that “stimulate cells to repair damaged blood vessels or form new ones.” NATIONAL CANCER INSTITUTE, *Cancer Facts: Angiogenesis Inhibitors in the Treatment of Cancer*, at http://cis.nci.nih.gov/fact/7_42.htm (last visited Jan. 25, 2004). Angiogenesis is an important factor in the proliferation of cancer as new blood vessels supply cancer cells with oxygen and nutrients, allowing the cells to grow, or metastasize. *Id.*

67. Merck entered into an agreement with Scripps to “fund ‘the necessary experiments to satisfy the biological basis and regulatory (FDA) requirements for the implementation of clinical trials.’” 331 F.3d at 863. Scripps refers to The Scripps Research Institute, “one of the country’s largest, private, non-profit research organizations . . .” See The Scripps Research Institute, *About TSRI*, at <http://www.scripps.edu/intro/intro.html> (last visited Jan. 5, 2005); see also 331 F.3d at 860 (naming The Scripps Research Institute as a defendant).

68. Dr. Cheresh was a scientist at Scripps. 331 F.3d at 863.

69. *Id.* Antiangiogenic therapies show promise as a means to slow tumor growth by starving rapidly dividing cells (such as cancer), and to “treat diabetic retinopathy, rheumatoid arthritis, psoriasis, and inflammatory bowel disease.” *Id.* The American Cancer Society describes

121974, which was selected for clinical development.⁷⁰ Upon learning of the Scripps-Merck research, Integra offered Merck licenses to the RGD-related patents because it believed that the anti-angiogenesis research was a commercial project that infringed its RGD peptide patents.⁷¹ Merck declined the Scripps license, claiming that its work was related to the FDA approval process and consequently fell within the Hatch-Waxman safe harbor.⁷²

In response, Integra filed suit against Merck alleging patent infringement of its RGD-related patents.⁷³ At trial, the district court found Merck liable for patent infringement on four of the five patents belonging to Integra and held that Merck's activity was not protected by the Hatch-Waxman safe harbor.⁷⁴ Merck filed motions for judgment as a matter of law before and after jury deliberations asserting, *inter alia*, that its actions were protected by the safe harbor.⁷⁵ The district court denied Merck's motions,⁷⁶ and Merck appealed. On appeal, the U.S. Court of Appeals for the Federal Circuit affirmed the narrow scope of the safe harbor, holding that the safe harbor "does not reach any exploratory research that may rationally form a predicate for future FDA clinical tests"⁷⁷ and that Merck's biomedical experimentation, which may be subject to FDA approval at some time, was not protected by the safe harbor.⁷⁸

V. CASE LAW DEVELOPMENT OF THE SAFE HARBOR'S SCOPE

When enacting the Hatch-Waxman safe harbor, Congress's main purpose was to overrule *Roche v. Bolar*⁷⁹ and stimulate the generic drug

antiangiogenesis therapy as "promising," and suggests that studies have shown that the antiangiogenic drugs may be able to fight cancer while causing fewer side effects than treatments currently in use. AMERICAN CANCER SOCIETY, *Antiangiogenesis Therapy*, at http://www.cancer.org/docroot/ETO/content/ETO_1_4x_Introduction_Antiangiogenesis_Therapy.asp?sitearea=ETO (last visited Jan. 25, 2004).

70. 331 F.3d at 863. Scripps' research led to the discovery of EMD 85189, which led to the development of EMD 121974. *Id.* Tests to assess the toxicology, circulation, diffusion, histopathology, half-life, and proper mode of administration led the Scripps research team to choose EMD 121974 for development. *Id.*

71. *Id.*

72. *Id.* Merck declined the licenses after lengthy negotiations with Integra. *Id.*

73. *Id.* at 862.

74. *Integra Lifesciences I, Ltd v. Merck KGaA*, No. 96-CV-1307, 1999 WL 398180 (S.D. Cal. Feb. 9, 1999). The court also found that Merck owed Integra \$15 million. *Id.*

75. 331 F.3d at 864.

76. *Id.*

77. *Id.* at 867.

78. *Id.* at 868.

79. 733 F.2d 858 (Fed. Cir. 1984). See Brian D. Coggio & F. Dominic Cerrito, *The Safe Harbor*

industry by allowing generic manufacturers to perform the FDA required bioequivalency testing⁸⁰ before a brand-name patent expired.⁸¹ It seems that the congressional intent was to exclude the testing of a drug, solely for the purpose of submitting data to the FDA, from patent infringement liability.⁸² However, the language of the statute has left many courts struggling to determine the scope⁸³ of the safe harbor, which has led to a very broad application of this infringement defense.⁸⁴ By applying the safe harbor broadly to biotechnology, the integrity of the biotechnology industry's intellectual property is threatened.⁸⁵

In *Eli Lilly & Co. v. Medtronic, Inc.*⁸⁶ the Supreme Court provided the foundation for a broad interpretation of the safe harbor's scope. The issue

Provision of the Hatch-Waxman Act: Present Scope, New Possibilities, and International Considerations, 57 FOOD & DRUG L.J. 161, 162 (2002) (stating Congress's main purpose was to overrule *Roche v. Bolar*); Jones, *supra* note 41, at 478–79 (stating that the safe harbor was a legislative overrule to the *Roche* decision); *see also* Weiswasser & Danzis, *supra* note 27, at 604–05 (discussing Hatch-Waxman's reversal of the Federal Circuit's *Roche* decision).

80. The House Committee initiating the safe harbor defined the pre-market approval activities allowed by the safe harbor as “a limited amount of testing so that generic manufacturers can establish the bioequivalency of a generic substitute.” H.R. REP. NO. 98-857, pt. 2, at 8 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2686, 2692. Bioequivalency is defined in H.R. REP. NO. 98-857, pt. 1, at 31 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647, 2664 as:

A drug shall be considered bioequivalent to a listed drug if the rate and extent of absorption of the generic drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses.

Id.

81. Coggio & Cerrito, *supra* note 79, at 162 (stating Congress wanted to immunize the bioequivalency testing needed by generic manufacturers to secure FDA approval). *See* Soehnge, *supra* note 35, at 53, 56–58 (discussing Congress's intent to balance the competing interests of generic and pioneer drug manufacturers); *see also* Robinson, *supra* note 35, at 50–56 (discussing the objectives of Congress when it created the safe harbor).

82. H.R. REP. NO. 98-857, pt. 2, at 30 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2686, 2714 (stating “all that the generic can do is to test the drug for purposes of submitting data to the FDA for approval”).

83. Coggio & Cerrito, *supra* note 79, at 162 (stating that recent cases are still trying to decipher the scope of the safe harbor provision); Weiswasser & Danzis, *supra* note 27, at 606 (stating an area of controversy is the scope of activities covered by the safe harbor). *See infra* note 84 and accompanying text.

84. Coggio & Cerrito, *supra* note 79, at 162 (stating that section 271(e)(1) protection has been construed very broadly); *see also* William Feiler & Paula Wittmayer, *Expanding Exemptions for Generics*, MANAGING INTELL. PROP., June 1, 2003, at 46 (stating that the scope of the provision has been expanded); Paul Fehlner, *Not Such a Safe Harbor After All*, 10 INTELL. PROP. LITIG. REP. 18 (2003) (describing the broad expansion of the safe harbor); Eric K. Steffe & Timothy J. Shea, Jr., *Drug Discovery Tools and the Clinical Research Exemption from Patent Infringement*, 22 BIOTECHNOLOGY L. REP. 369, 370–71 (2003) (describing the uncertainty in applying the safe harbor and the broadening of its scope).

85. *See supra* note 11 and accompanying text.

86. 496 U.S. 661 (1990).

before the Court was whether the safe harbor was limited only to drugs.⁸⁷ The Court determined that the safe harbor afforded protection to the pre-market development of medical devices as well as drugs.⁸⁸ The Court conceded that the legislative history did not clearly support its interpretation.⁸⁹ However, based on the construction of the statute,⁹⁰ the majority reasoned that Congress did not intend the safe harbor to be limited only to drugs.⁹¹ Furthermore, the Court asserted that Congress created section 156⁹² to allow a patent extension for inventions subject to a lengthy regulatory approval process. Because the safe harbor is the counterbalance to that provision,⁹³ it seems “implausible” that Congress would have intended the safe harbor to apply only to drugs when medical devices are also subject to the same lengthy regulatory approval.⁹⁴ Accordingly, the Court held that the clinical trial exception of the Hatch-Waxman safe harbor also applies to medical devices that are subject to FDA approval.⁹⁵

87. *Id.* at 663–64. Specifically, the controversy concerned whether the statutory phrase, “a Federal law which regulates the manufacture, use, or sale of drugs,” refers “only to those individual provisions of federal law that regulate drugs” or “to the entirety of any Act . . . at least some of whose provisions regulate drugs.” *Id.* at 665–66.

88. *Id.* at 669.

89. *Id.* (stating that while both parties to the litigation attempt to enlist the legislative history to buttress their interpretation of the statute, the history “sheds no clear light” to support either interpretation).

90. *Id.* at 666–67 (discussing Congress’s word choice in constructing various phrases of the statute).

91. *Id.*

92. See *supra* note 40 and accompanying text.

93. See *supra* notes 27, 35 and accompanying text.

94. 496 U.S. at 672–73. Referring to the balancing of interests attempted by the Hatch-Waxman provisions, the Court stated:

It seems most implausible to us that Congress, being demonstrably aware of the *dual* distorting effects of regulatory approval requirements in this entire area—*dual* distorting effects that were roughly offsetting, the disadvantage at the beginning of the term producing a more or less corresponding advantage at the end of the term—should choose to address both those distortions only for drug products; and for other products named in § 201 [which created § 156] should enact provisions which not only leave in place an anticompetitive restriction at the end of the monopoly term but simultaneously expand the monopoly term itself, thereby not only failing to eliminate but positively aggravating distortion of the 17-year patent protection. It would take strong evidence to persuade us that this is what Congress wrought, and there is no such evidence here.

Id.

95. *Id.* at 679. The Court held that section 271(e)(1) is to be read in conjunction with 35 U.S.C. § 156. *Id.* at 669–74. Also, the Court stated that the safe harbor only applies to those patents subject to a regulatory review process identified in subsections 156(a)(4) and (5). *Id.* at 674 n.6. This includes: new drugs, veterinary biological products, and methods of manufacturing a product using recombinant DNA technology. 35 U.S.C. § 156(a)(4)–(5) (2000).

The dissent in *Eli Lilly*⁹⁶ underscores the conflict inherent in determining the scope of the safe harbor. The minority finds persuasive the statutory interpretation that affords infringement protection only to drugs.⁹⁷ The dissent takes issue with the majority's interpretation of the statute in reaching its decision,⁹⁸ criticizing the implication of congressional intent asserted by the majority.⁹⁹

Struggling to determine what was protected under the safe harbor, the district court for the Northern District of California, in *Intermedics Inc. v. Ventritex, Inc.*,¹⁰⁰ created a two-prong test.¹⁰¹ The district court's test, cited with approval by the U.S. Court of Appeals for the Federal Circuit,¹⁰² determined that an infringing medical device maker was protected under the safe harbor if the infringer used clinical trial data to solicit investment capital.¹⁰³ Rejecting a narrow interpretation of the safe harbor, the district court reasoned that Congress intended the statute to be read broadly¹⁰⁴ to

96. The decision was a 6–2 split with Justice O'Connor taking no part in consideration of the case. *Id.* at 662. Justice Kennedy wrote the dissent, joined by Justice White. *Id.* at 679.

97. *Id.* at 680 (stating that section 271(e)(1) does not privilege the pre-market testing of medical devices). Justice Kennedy stated, “[w]hen § 271(e)(1) speaks of a law which regulates drugs, I think that it does not refer to particular enactments or implicate the regulation of anything other than drugs.” *Id.* Justice Kennedy also stated that the safe harbor “refers only to the actual regulation of drugs, and does not exempt the testing of a medical device from patent infringement.” *Id.* at 682.

98. *Id.* at 680–81. Justice Kennedy criticized the implied meaning given to the safe harbor by the majority stating that “[n]umerous statutory provisions and court decisions, from a variety of jurisdictions, use words almost identical to those of § 271(e)(1), and they never mean what the Court says they mean here.” *Id.* at 680. Justice Kennedy explained:

For instance, in delineating the scope of pre-emption by the Employee Retirement Income Security Act of 1974 (ERISA), Congress stated that “nothing in this title shall be construed to exempt or relieve any person from any law of any State which regulates insurance, banking, or securities.” 88 Stat. 897, 29 U.S.C. § 1144(b)(2)(A) (emphasis added). Interpreting this language as the Court interprets § 271(e)(1) would imply that Congress intended to give the States a free hand to enact any law that conflicts with ERISA so long as some portion of the state enactment regulates insurance, banking, or securities. No one would contend for this result.

Id. at 681.

99. *Id.* at 680 (stating that the Court cannot tell Congress how to express its intent). Justice Kennedy stated that intent should be discerned by assuming that “Congress employs words and phrases in accordance with their ordinary usage.” *Id.*

100. 775 F. Supp. 1269 (N.D. Cal. 1991).

101. *Id.* at 1280.

102. *Telectronics Pacing Systems, Inc. v. Ventritex, Inc.*, 982 F.2d 1520, 1525 n.5 (Fed. Cir. 1992).

103. 775 F. Supp. at 1281.

104. 775 F. Supp. at 1279 (stating that “business purposes” are the type of infringing activities that the statute “clearly covers” and “Congress could not have intended the exemption to apply only to those whose purposes were purely scientific, or to those who were motivated simply by a driving curiosity”). In support of commercial coverage under the safe harbor, the court reasoned:

We believe that in enacting this exemption Congress clearly decided that it wanted potential competitors to be able to ready themselves, fully, during the life of the patent, to enter the

allow competition, and the courts should use their discretion in determining whether potentially infringing activities are protected by the safe harbor.¹⁰⁵ Thus, infringing commercial activities qualified for safe harbor protection even though the accused activities were not related to the FDA approval process.¹⁰⁶

Intermedics analysis requires that: (1) only infringing uses be analyzed under the safe harbor, and (2) exemption is available only for those infringing activities “reasonably related” to the development and submission of information to the FDA.¹⁰⁷ After *Intermedics*, an infringing activity is exempt if it would have been reasonable for a party to believe there was a prospect that the use in question would generate data that may be relevant in the FDA approval process.¹⁰⁸

Perhaps believing that the safe harbor scope was ballooning through misinterpretation by the courts,¹⁰⁹ the district court for the Western District of Wisconsin sought to temper the amount of protection allowed by the safe harbor in *Infigen, Inc. v. Advanced Cell Technology, Inc.*¹¹⁰ Here, defendant Advanced Cell Technology infringed a patent owned by Infigen that covered a process for activating bovine oocytes¹¹¹ (unfertilized eggs)

commercial marketplace in a large scale way as soon as the relevant patents expired . . . [to give] the public prompt access to new medical products at the lowest commercially feasible prices.

Id. at 1277.

105. *Id.* at 1280 (“Congress [phrased the statute] to communicate its intention that the courts give parties some latitude in making judgments about the nature and extent of the otherwise infringing activities they would engage in as they sought to develop information to satisfy the FDA.”).

106. Although using clinical trial data to solicit investment capital is not directly related to establishing bioequivalency through the FDA process, the court exercised its power to construe the safe harbor broadly and viewed the capital solicitation activities as being “reasonably related” to the FDA approval process. *Id.* (stating that the phrase “‘reasonably related’ reflects Congress’s acknowledgement that it will not always be clear to parties setting out to seek FDA approval for their new product exactly which kinds of information . . . it will take to win the agency’s approval.”).

107. *Id.*; see also Feiler & Wittmayer, *supra* note 84, at 48–49 (describing the two-prong analysis of the *Intermedics* court).

108. 775 F. Supp. at 1280. Acts are covered under the safe harbor if the party could reasonably “believe that there was a decent prospect that the ‘use’ in question would contribute (relatively directly) to the generation of kinds of information that was likely to be relevant in the processes by which the FDA would decide whether to approve the product.” *Id.*

109. The District Court of Massachusetts also read the safe harbor language broadly and held that a competitor who infringed a patent and conducted testing primarily for commercial purposes was protected under the safe harbor because some of the resulting data was “reasonably related” to the FDA approval process. *Abtox, Inc. v. Exitron Corp.*, 888 F. Supp. 6, 8 (D. Mass. 1995). The court held that an infringer’s ulterior motives were irrelevant to its ability to invoke protection of the safe harbor. Feiler & Wittmayer, *supra* note 83, at 48, 50.

110. 65 F. Supp.2d 967 (W.D. Wis. 1999).

111. The technology at issue involves the cloning of transgenic cattle. *Id.* at 970. “A transgenic cow is one that has had DNA introduced artificially into one or more of its cells. The value of such a cow is that it is capable of producing a transgene product, that is, one not naturally present in cattle,

used in cloning transgenic cattle for commercial purposes.¹¹² The court considered whether the infringing company's use of the patented process for preclinical activities, such as drug development, was protected under the safe harbor.¹¹³ The court looked to the Supreme Court's decision in *Eli Lilly* and determined that the safe harbor is to be read in conjunction with section 156.¹¹⁴ The court held that the safe harbor is only applicable to infringing activities on patents that are identified as being subject to regulatory approval in 35 U.S.C. § 156(a)(4) and (5) and, because the patent at issue is not identified in section 156, the safe harbor does not apply.¹¹⁵ The *Infigen* court refused to apply the infringement exemption to a research process¹¹⁶ and did not read the safe harbor as loosely as the *Intermedics* court. However, the narrow interpretation of the safe harbor by the *Infigen* court has largely been ignored.¹¹⁷

The protection for infringement liability under the safe harbor continued to expand in *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*¹¹⁸ The issue presented to the *Amgen* court originated in *Intermedics*; at issue was whether safe harbor protection is intended for infringement of a drug patent for purposes that may be related to FDA approval but where the patent is infringed for other ulterior purposes.¹¹⁹ Amgen owned several patents covering a genetically engineered (recombinant) form of erythropoietin ("EPO"), a hormone that stimulates the production of red blood cells.¹²⁰ Amgen's EPO patents were allegedly infringed by Hoechst in a variety of ways for regulatory and commercial reasons.¹²¹ Reaffirming the *Intermedics* logic, the court held that the infringers were protected

such as a pharmaceutical drug." *Id.*

112. *Id.* at 973–74.

113. *Id.* at 980.

114. *Id.* at 979–80. See *supra* notes 94–95 and accompanying text.

115. 65 F. Supp.2d at 980 (stating that "*Eli Lilly* makes clear, the patent extension is the quid pro quo for the protection from infringement actions and vice versa.").

116. *Id.* ("My own research shows no cases granting the § 271(e)(1) exemption from the otherwise infringing use of any product other than those drugs, medical devices, food and color additives defined specified in § 156.").

117. See Feiler & Wittmayer, *supra* note 84, at 48 (stating that the *Infigen* decision is contrary to the Court of Appeals in *Abtox* and had the parties not settled, the decision likely would have been reversed on appeal).

118. 3 F. Supp.2d 104 (D. Mass. 1998).

119. *Id.* at 107–08.

120. *Id.* at 106. Erythropoietin "is used in the treatment of anemia, particularly in patients suffering chronic renal failure." *Id.*

121. *Id.* at 108–11 (identifying six potentially infringing activities: export to Japan, rabbit pyrogen studies, consistency batches, characterization of the generic (competing) product, viral clearing tests designed to meet European regulatory standards, and radiolabeling).

under the safe harbor.¹²² Here, the court allowed ulterior uses that may be related to FDA approval, but are utilized for purposes other than obtaining FDA approval, to be protected.¹²³

The judicial expansion of the possible acts or “uses” that are protected under the safe harbor led the court in *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*,¹²⁴ to consider whether the safe harbor applied to all activities “reasonably related” to an *actual* or *possible* FDA application from the very first synthesis of an intermediate compound (i.e., research tool).¹²⁵

Essentially, the court had to determine how far down the research chain in the drug discovery process the safe harbor exemption would reach.¹²⁶ Here, Bristol used some of Rhone’s patented intermediates (i.e., research tools)¹²⁷ to further its own research into taxol analogs (generic versions of a brand-name drug).¹²⁸ Rhone claimed that “Bristol’s use of the patented intermediates is outside the scope of Section 271(e)(1) because 1) the intermediates are not a ‘patented invention’ within the meaning of that

122. *Id.* at 113 (stating that the defendants’ activities fell within the safe harbor exemption).

123. *Id.* at 107–08 (stating uses that may be related to FDA approval yet conducted for other purposes are not precluded from the safe harbor exemption because the Federal Circuit precedents indicate that such ulterior motives are allowed). The court, following *Intermedics*, held “In order to come within protection of section 271(e)(1), the Defendants thus must make, use, or sell the patented invention in ways that *objectively bear reasonable prospects* of yielding information that *might be relevant* in the FDA approval process.” *Id.* at 108. (emphasis added).

The court’s broad language expanded the types of activities that are “reasonably related” to FDA approval and thus subject to exemption under the safe harbor.

124. 2001 U.S. Dist. LEXIS 19361 (S.D.N.Y. Nov. 27, 2001).

125. *Id.* at **4–5 (framing the issue in terms of using drug “intermediates”). Intermediate compounds can be considered research tools because they can be used to synthesize other drugs, drug precursors, or drug analogs. *Id.* at *3. The National Institute of Health (“NIH”) uses “the term ‘research tool’ in its broadest sense to embrace the full range of resources that scientists use in the laboratory, while recognizing that from other perspectives the same resources may be viewed as ‘end products.’” *Report of the National Institute of Health (NIH) Working Group on Research Tools*, presented to the Advisory Committee to the Director on June 4, 1998, at 3, at <http://www.nih.gov/news/researchtools/index.htm> (last visited Sept. 16, 2004); see also Janice M. Mueller, *No “Dilettante Affair”: Rethinking the Experimental Use Exception to Patent Infringement for Biomedical Research Tools*, 76 WASH. L. REV. 1, 10–17 (2001) (describing research tools); Natalie M. Derzko, *In Search of a Compromised Solution to the Problem Arising from Patenting Biomedical Research Tools*, 20 SANTA CLARA COMPUTER & HIGH TECH. L.J. 347, 348–53 (2004) (describing research tools and their potential uses).

126. Steffe & Shea, *supra* note 84, at 371 (framing the issue of the *Bristol* court).

127. 2001 U.S. Dist. Lexis 19361, at *3 (the research tool patent discloses and claims semi-synthetic processes for preparing taxol (“paclitaxel”) and four intermediates obtained and used during research).

128. *Id.* at *4. “Bristol embarked on a taxane research and development program in an attempt to discover a new, more active drug that could replace taxol as the preeminent anti-cancer drug” when the taxol patent expired. *Id.* at *14.

term in Section 271(e)(1) and 2) Bristol's uses were not 'reasonably related' to the [FDA approval process]."¹²⁹

The court held that the language of Hatch-Waxman does not indicate that Congress intended to restrict the safe harbor only to products covered under 35 U.S.C. § 156.¹³⁰ After determining that a research tool is a patented invention within the meaning of the safe harbor,¹³¹ the court held that Bristol's experiments using Rhone's research tools were "reasonably related" to the submission of information to the FDA, and thus exempt from patent infringement liability.¹³² After *Bristol*, research tools and other drug analogs appeared to be within the scope of the Hatch-Waxman safe harbor, in effect, pushing the safe harbor protection afforded patent infringers further down the research chain and eviscerating the value of many research tool patents.¹³³

Essentially, the court decisions before *Integra* encouraged companies to discount or ignore the value of research tool patents as long as the infringing company was working to develop a new drug.¹³⁴ Following *Bristol*, the level of protection afforded biotechnology intellectual property was uncertain; the expanded liability shield protecting infringers and the uncertainty surrounding the scope of the safe harbor seemed poised to have detrimental effects on the biotechnology industry.¹³⁵ Biotechnology

129. *Id.* at *5.

130. *Id.* at *6. In support of its interpretation, the court noted, "[d]espite the broad scope of the language used in Section 271(e)(1) having been expressly brought to the attention of members of Congress, no attempt was made to refine or narrow the language used in the text of Section 271(e)(1)." *Id.* at *10 n.6.

131. *Id.* at *9 (holding that the patented intermediates come within the meaning of section 271(e)(1)).

132. *Id.* at **19–20. The court reasoned:

A rational jury could only conclude based on these undisputed facts that it was reasonable, objectively, for a party in Bristol's position to believe that there was a "decent prospect" that its use of the RPR [Rhone] intermediates in Bristol's experiments "would contribute (relatively directly) to the generation of kinds of information that was likely to be relevant in the process by which the FDA would decide whether to approve the product." *Intermedics*, 775 F. Supp. at 1280. Accordingly, Bristol's experiments with the RPR patented intermediates are entitled to the exemption Congress provided in 35 U.S.C. § 271(e)(1)

Id.

133. Feiler & Wittmayer, *supra* note 84, at 50; Steffe & Shea, *supra* note 84, at 371–75.

134. Stephen B. Maebius & Richard J. Warburg, *Federal Circuit Reins in Free Use of Patented Research Tools*, LEGAL TIMES IP MAGAZINE, July 21, 2003, at 9; see also Weiswasser & Danzis, *supra* note 27, at 606 (discussing the controversy surrounding the scope of what is "reasonably related" to FDA approval and broad construction by the courts).

135. See Steffe & Shea, *supra* note 84, at 372–73 (stating that "[n]umerous biotechnology companies have been formed on the basis of a drug discovery platform as the core technology"); Groombridge & Calabro, *supra* note 33, at 462 (stating "many commentators felt that the trend in the recent case law was undermining the value of biotechnology patents"). Cf. Linda R. Judge, *Biotechnology: Highlights of the Science and Law Shaping the Industry*, 20 SANTA CLARA COMPUTER

companies that have research tools as their primary assets rely on stringent patent protection for conducting business essential to the firm's survival.¹³⁶ As such, the *Bristol* decision left commentators from the patent bar to contemplate the decision's effect on the biotechnology market, saying it would "open[] up the floodgates for free use of patented chemicals and methods by any company developing drugs for sale in the American market."¹³⁷

VI. *INTEGRA* NARROWS THE SAFE HARBOR

Integra Lifesciences I, Ltd. v. Merck KGaA,¹³⁸ presented the U.S. Court of Appeals for the Federal Circuit with the challenges of interpreting the scope of the Hatch-Waxman Act and of determining whether the safe harbor "reaches back down the chain of experimentation to embrace development and identification of new drugs that will, in turn, be subject to FDA approval."¹³⁹ The court held that Congress only intended to benefit generic drug makers,¹⁴⁰ yet, because the court had considered the limitations of the statutory language before, it followed *Eli Lilly and Intermedics* in allowing clinical trials and demonstrations of medical devices to be protected under the safe harbor.¹⁴¹

& HIGH TECH. L.J. 79, 85 (2003) (stating "[t]he protection afforded by the patent statutes and federal case law interpreting those statutes, together with legislation which provides favorable incentives to patenting biotechnology-based inventions, have contributed to the leading position of the United States in the biotechnology industry worldwide."). For a discussion of biotechnology industry developments and the corresponding patent law changes, see *id.*

136. Steffe & Shea, *supra* note 84, at 374 (stating "emerging companies having research tools as their primary assets . . . view patents . . . as being critical for raising venture capital . . . [and] necessary to leverage alliances with other companies").

137. Groombridge & Calabro, *supra* note 33, at 467 (citing Warburg & Maebius, *supra* note 11, at 26); see also Steffe & Shea, *supra* note 84, at 375 (stating that adopting the rule set forth by the district court in *Bristol* would leave drug discovery tool patent owners "with little recourse when attempting to assert their patent rights against competitors"). Under the *Bristol* ruling, "the value of drug discovery tool patents [is being] diluted . . . by expanding the experimental use exemption from patent infringement." *Id.*

138. 331 F.3d 860 (Fed. Cir. 2003), *cert. granted*, 73 U.S.L.W. 3059 (U.S. Jan. 7, 2005) (No. 03-1237).

139. *Id.* at 865–66. The Federal Circuit also considered Merck's claim that the district court erred in construing some of *Integra*'s patent claims and that the damages awarded *Integra* by the district court were unreasonable. *Id.* at 868–69. Because these issues are outside the scope of the safe harbor analysis in this Note, they are omitted.

140. *Id.* at 865 (relying on House Committee testimony that describes the pre-market approval activity allowed under the safe harbor as a limited amount of testing so as to establish bioequivalence). All that a generic manufacturer can do is test the drug for purposes of submitting data to the FDA for approval. *Id.* at 866.

141. *Id.* at 865 (following *Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269 (N.D. Cal. 1991)).

However, the court broke from the trend of increasing infringement protection under the safe harbor and noticeably restricted those activities that may be thought of as being related to the FDA approval process.¹⁴² In support of its interpretation of the statute, the court focused on the term “solely” in the statutory language as limiting the activities that qualify for exemption.¹⁴³ The court explained that the statutory protection extends only to activities that are specified in section 271(e)(1)—namely the FDA approval process.¹⁴⁴ The court emphasized that the original intent of Congress in drafting the Hatch-Waxman safe harbor was only to allow activities that are “reasonably related” to the development and submission of FDA required safety and efficacy information.¹⁴⁵

The court did recognize that the term “reasonably” in the statute permits some otherwise unqualified activities to be exempt under the safe harbor.¹⁴⁶ However, these activities strain the central purpose of the safe harbor—the submission of information to the FDA.¹⁴⁷ Here, the work sponsored by Merck was not clinical testing for FDA safety and efficacy purposes, “but only general biomedical research to identify new pharmaceutical compounds.”¹⁴⁸ Thus, the court held that (the safe harbor does not protect Merck’s general biomedical research)¹⁴⁹ Merck’s activities were not “solely for uses reasonably related” to the FDA approval process because the FDA has no interest in the search for potential drugs that may undergo testing.¹⁵⁰

The majority seemingly rejected the *Intermedics* and *Amgen* courts’ endorsement of ulterior motives and commercial purposes as being protected by the safe harbor¹⁵¹ by not expanding the phrase “reasonably

142. *Id.* at 866.

143. *Id.* (“The term ‘solely’ places a constraint on the inquiry into the limits of the exemption.”). The court notes that “[t]he exemption cannot extend *at all* beyond uses . . . specified in § 271(e)(1).” *Id.* (emphasis added).

144. *Id.*

145. *Id.* (stating that to qualify for the exemption, an infringing activity must reasonably relate to the FDA’s safety and effectiveness requirement). The court states that the “expedited approval process requires the generic drug company to perform safety and effectiveness tests on its product before expiration of the patent on the pioneer drug . . .” *Id.* at 867.

146. *Id.* at 866 (“The term ‘reasonably’ permits some activities that are not themselves the experiments that produce FDA information to qualify” for the exemption).

147. *Id.* (“The meaning of the phrase ‘reasonably related to the development and submission of information’ as set forth in § 271(e)(1) is clearer in the context of the role of the 1984 Act in facilitating expedited approval of a generic version of a drug previously approved by the FDA.”).

148. *Id.*

149. *Id.* at 868.

150. *Id.* at 866 (“The FDA has no interest in the hunt for drugs that may or may not later undergo clinical testing for FDA approval.”).

151. *See supra* notes 100–08, 118–23 and accompanying text.

related” to embrace the commercial development of new drugs that will eventually need FDA approval.¹⁵² To do so, the court stated, would ignore the language of the statute and the intent of Congress given the context in which the safe harbor was enacted.¹⁵³

Judge Newman disagreed with the majority, concluding that Merck’s actions were immune from infringement liability under either the common law research exemption¹⁵⁴ or the Hatch-Waxman safe harbor.¹⁵⁵ Judge Newman disagreed with the majority’s characterization of Merck’s research activities as “discovery-based research.”¹⁵⁶ According to Judge Newman, labeling Merck’s activities as “discovery-based research” is a conclusion that is not required by law,¹⁵⁷ and in doing so, the majority effectively misinterpreted the purpose of the patent system¹⁵⁸ and

152. 331 F.3d at 867. The court states that the safe harbor “does not globally embrace all experimental activity that at some point, however attenuated, may lead to an FDA approval process.” *Id.*

153. *Id.* Addressing the potential impact on the biotechnology industry, the court stated:

Extending § 271(e)(1) to embrace new drug development activities would ignore its language and context with respect to the 1984 Act in an attempt to exonerate infringing uses only potentially related to information for FDA approval. . . . [E]xaggerating § 271(e)(1) out of context would swallow the whole benefit of the Patent Act for some categories of biotechnological inventions.

Id.

154. *Id.* at 874–75 (Newman, J., concurring and dissenting) (citing *Whittemore v. Cutter*, 29 Fed. Cas. 1120 (C.C.D. Mass. 1813); *Sawin v. Guild*, 21 Fed. Cas. 554 (C.C.D. Mass. 1813); *Chesterfield v. United States*, 159 F. Supp. 371 (1958)). Judge Newman cited *Whittemore* as the origin of Justice Story’s common law research exemption, which states that in creating patent rights, “it could never have been the intention of the legislature to punish a man, who constructed such a machine merely for philosophical experiments, or for the purpose of ascertaining the sufficiency of the machine to produce its described effects.” 331 F.3d at 874–75 (citing *Whittemore*, 29 Fed. Cas. at 1121).

155. 331 F.3d at 874. Judge Newman framed the question differently than the majority: “[t]he question is whether, and to what extent, the patentee’s permission is required in order to study that which is patented.” *Id.* at 872–73. *But see supra* note 139 and accompanying text (the majority’s framing of the issue); 331 F.3d at 863 n.2 (comparing Judge Newman’s advocacy of the common law experimental use exception with the issue before the jury).

156. *Id.* at 873 (stating that the panel majority held that Merck’s activities were discovery-based research and there is no right to conduct such research under the common law research exemption or section 271(e)(1)).

157. *Id.* Judge Newman stated that neither law nor policy requires the conclusion that Merck’s actions were not protected by the common law research exemption or the safe harbor. *Id.*

158. *Id.* In her dissent, Judge Newman described the purpose of the patent system:

The purpose of a patent system is not only to provide a financial incentive to create new knowledge and bring it to public benefit through new products; it also serves to add to the body of published scientific/technologic knowledge. The requirement of disclosure of the details of patented inventions facilitates further knowledge and understanding of what was done by the patentee, and may lead to further technologic advance. The *right to conduct research to achieve such knowledge need not, and should not, await expiration of the patent.*

Id. (emphasis added); *see also infra* note 195 (discussing the philosophical theories behind the U.S. patent system).

eliminated the common law research exemption.¹⁵⁹ As such, in Judge Newman's view, the refusal to recognize the common law research exemption cannot be squared within the framework of modern patent law.¹⁶⁰ The dissent suggested that "[t]he better rule is to recognize the exemption for research conducted to understand or improve upon or modify the patented subject matter, whatever the ultimate goal."¹⁶¹

The dissent also disagreed with the majority's refusal to grant Merck immunity under the safe harbor.¹⁶² Judge Newman relied on *Eli Lilly* as evidence that the statute should be read broadly¹⁶³ and concluded that if Merck's activities are not protected under the common law research exemption they are protected by the Hatch-Waxman safe harbor.¹⁶⁴ Judge Newman agreed that the safe harbor does not reach "back down the chain of experimentation to embrace development and identification of new drugs;"¹⁶⁵ however she opined that Merck's laboratory experiments and development of data that would be submitted to the FDA was immune from infringement liability¹⁶⁶ because holding otherwise would create a gray area between the common law exploratory research exemption and the Hatch-Waxman safe harbor.¹⁶⁷ In conclusion, Judge Newman stated

159. *Id.* (stating that the "court disapproves and essentially eliminates the common law research exemption," a change that is "ill-suited to today's research-founded, technology-based economy"). *Cf.* Mueller, *supra* note 125, at 1 (advocating a broadened view of research tool use that would permit scientists to use certain research tools without prior authorization and pay the research tool patent owner based upon the commercial success of the new product); Derzko, *supra* note 125, at 347 (discussing the need for research tool availability to further biomedical research).

160. 331 F.3d at 875 (stating that the prohibition of all research that might lead to competition or challenge a patented technology "cannot be squared with the framework of the patent law"). The dissent suggests that it is necessary for the advancement of technology that the subject matter of patents be studied in order to improve, find a new use for, modify or design around the patent. *Id.*

161. *Id.* at 876 (reasoning that "the patent is infringed by and bars activity associated with development and commercialization of infringing subject matter, but the research itself is not prohibited.").

162. *Id.* at 877.

163. *Id.*

164. Judge Newman stated: "[T]he territory that the Scripps/Merck research traversed, from laboratory experimentation to development of data for submission to the FDA, was either exempt exploratory research, or was immunized by § 271(e)(1)." *Id.*

165. *Id.*

166. *Id.* Judge Newman disagreed with the majority's categorization of the Integra patents as "research tools." *Id.* at 878. She reasoned that the RGD-peptides are not a "tool" used in research, "but simply new compositions having certain biological properties;" thus the majority's statement that "acceptance of a common law research exemption would eliminate patents on 'research tools'" is a misperception. *Id.* at 877. *Cf. supra* note 125 (discussing the NIH's use of the term "research tool"). Judge Newman's narrow application of what constitutes a "research tool" differs from the NIH's broad construction of "research tool."

167. 331 F.3d at 877. Judge Newman stated:

It would be strange to create an intervening kind of limbo, between exploratory research subject to exemption, and the FDA statutory immunity, where the patent is infringed and the

that the research performed by Merck was within the common law research exemption, and “the development shielded by § 271(e)(1) took up where the research exemption left off.”¹⁶⁸

VII. ANALYSIS: IMPACT OF THE *INTEGRA* DECISION

The U.S. Court of Appeals for the Federal Circuit correctly refused to protect Merck from patent infringement liability under the Hatch-Waxman safe harbor.¹⁶⁹ Clearly Merck’s use of Integra’s peptide sequence (the RGD peptide) was not for the purpose of obtaining FDA approval for a generic version of a pioneer drug.¹⁷⁰ The use of Integra’s patented research tool to develop a new drug was not the type of protection contemplated by Congress when it created the safe harbor.¹⁷¹ Rewarding Merck with protection from infringement liability would have run counter to a major policy justification of the safe harbor: the *quid pro quo* exchange of infringement protection for prompt access to less expensive generic pharmaceuticals for consumers.¹⁷² Here, Merck did not have the immediate prospect of offering a generic version of a drug through its infringing activities.¹⁷³ As such, Merck’s research was purely exploratory¹⁷⁴ and was correctly characterized as infringing Integra’s patent rights.

By focusing on statutory language,¹⁷⁵ the *Integra* court attempted to define the limits of safe harbor protection based on congressional intent. The legislative history of the safe harbor indicates a desire by Congress to

activity can be prohibited. That would defeat the purposes of both exemptions; the law does not favor such an illogical outcome.

Id.

168. *Id.* at 878.

169. By not allowing safe harbor protection for infringement related to the development and identification of new drugs that will *eventually* be subject to FDA testing, the court avoided making a slippery-slope determination of what activities are for the development of new drugs versus activities that are aimed at FDA approval.

170. *See supra* notes 67–72, 78 and accompanying text (characterizing the nature of Merck’s use of the RGD-related patents); *see also Integra*, 331 F.3d at 866 (stating “Merck used the Integra inventions, and thus infringed its patents”).

171. *See infra* note 176 and accompanying text.

172. *See supra* notes 22–27 and accompanying text; *see also infra* note 195 (describing the policy justifications behind U.S. patent system).

173. Merck was merely performing “general biomedical research.” *Integra*, 331 F.3d at 866; *see also supra* note 170 and accompanying text.

174. 331 F.3d at 866 (characterizing Merck’s infringement activity as “general biomedical research”); *see also id.* at 868 (describing Merck’s infringement as “general biomedical experimentation”).

175. *See supra* notes 140, 143, 146, 147 and accompanying text.

protect only the *limited* activities that will allow generic manufacturers to establish bioequivalency.¹⁷⁶ Following the language of Congress, the court limited the liability protection afforded by the safe harbor umbrella, and excluded experimental infringement that is not “reasonably related” to the submission of safety and efficacy information to the FDA.¹⁷⁷

However, the *Integra* majority failed to define exactly what activities are “reasonably related” to the FDA approval process.¹⁷⁸ The failure to articulate a bright-line rule is unusual for the Federal Circuit.¹⁷⁹ Contrary to its ruling in *Integra*, the Federal Circuit has a proclivity to create formalistic substantive rules¹⁸⁰ under its congressional mandate to promote

176. During deliberation, the Committee on the Judiciary considered six amendments to the Hatch-Waxman legislation. H.R. REP. NO. 98-857, pt. 2, at 7 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2686, 2691. In rejecting the Moorhead amendment, which would have delayed the FDA related testing of generic drug manufacturers, the Committee addressed Mr. Moorhead’s concerns that the bill was an unconstitutional taking of intellectual property without compensation:

The only activity which will be permitted by the bill is a limited amount of testing so that generic manufacturers can establish the bioequivalency of a generic substitute. The patent holder retains the right to exclude others from the major commercial marketplace during the life of the patent. Thus, the nature of the interference with the rights of a patent holder is not substantial.

Id. at 2692.

177. 331 F.3d at 866. The court stated that the safe harbor will not embrace general biomedical experimentation. *Id.* at 868.

178. The court discussed the meaning of the words “solely” and “reasonably” as they are used in the statute. *See supra* notes 143, 146, 147 and accompanying text. When articulating which activities are “reasonably related” to the FDA approval process, the court notes that the role of Hatch-Waxman in facilitating expedited approval of a generic version of a drug previously approved by the FDA gives the phrase’s meaning a context. 331 F.3d at 866. Thus, the activities protected by the safe harbor are those that involve pre-expiration activities “reasonably related” to acquiring FDA approval of a drug on the market. *Id.* at 867. Nonetheless, there is no guidance from the court as to which pre-expiration activities are reasonably related to the FDA approval process.

179. *See* Timothy R. Holbrook, *The Supreme Court’s Complicity in Federal Circuit Formalism*, 20 SANTA CLARA COMPUTER & HIGH TECH. L.J. 1, 1 (2003) (stating that the Federal Circuit has a tendency towards bright-line rules that transcends any particular issue in patent law); John R. Thomas, *Formalism at the Federal Circuit*, 52 AM. U. L. REV. 771, 792 (2003).

Patent jurisprudence increasingly reflects a trend towards adjudicative rule formalism. Some of the most prominent principles of the patent law, governing the subject matter that can be patented, rights acquisition, and the scope of protection, have become more rulebound. . . . The Federal Circuit seems ever more prone to the pronouncement of categorical rules meant to govern future patent disputes.

Id. at 792–93.

See generally Arti K. Rai, *Engaging Facts and Policy: A Multi-Institutional Approach to Patent System Reform*, 103 COLUM. L. REV. 1035, 1040 (2003) (discussing the implications of the Federal Circuit’s bright-line rulemaking policy).

180. Holbrook, *supra* note 179, at 9 (stating that the Federal Circuit has a penchant to articulate formalistic substantive rules). For example, in *Markman v. Westview Instruments, Inc.*, the Federal Circuit determined that claim construction was always a matter of law which eliminated the role of juries in patent cases. 52 F.3d 967, 976–79 (Fed. Cir. 1995) (holding that “in a case tried to a jury, the court has the power and obligation to construe as a matter of law the meaning of language used in the

uniformity and certainty in patent law.¹⁸¹ Despite its tendencies, the *Integra* court leaves pharmaceutical manufacturers and biotechnology patentees wondering about the scope of activities that will be protected under the safe harbor in the future.¹⁸² While correctly decided, if the *Integra* court's goal was to promote certainty in patent law, defining the pharmaceutical activities that are "reasonably related" to the FDA approval process would have advanced that goal.

Furthermore, it is peculiar that the Federal Circuit overlooked the Southern District of New York's *Bristol* decision.¹⁸³ Both cases have similar fact patterns, yet reached different outcomes.¹⁸⁴ Because the *Bristol* court held that the infringing activities were protected by the safe harbor, the Federal Circuit could have enhanced the certainty behind its ruling by addressing any perceived differences with the *Bristol* decision.¹⁸⁵ Although not binding on the Federal Circuit, the court's failure to mention *Bristol* was unusual because that case "open[ed] up the floodgate" for free use of methods and patented chemicals by any company developing a new drug.¹⁸⁶ Essentially, *Bristol* was one of the first cases that threatened the biotechnology industry's intellectual property assets.

Nonetheless, the Federal Circuit's *Integra* decision does put research-based pharmaceutical companies on notice. Despite previous decisions by other courts, the Federal Circuit will not tolerate the infringement of research tool patents for the commercial development of a new drug. As a

patent claim"). And recently the Federal Circuit concluded that "any amendment to a claim precludes all equivalents as to that added claim limitation." *Holbrook*, *supra* note 179, at 5 (discussing *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 234 F.3d 558 (Fed. Cir. 2000)). However, the Court's bright-line rules tend to sacrifice fairness in patent law. *Id.* at 1.

181. See *Holbrook*, *supra* note 179, at 1. In *Control Resources, Inc. v. Delta Electronics, Inc.*, Judge Young recognized the Federal Circuit as "a court with a mission." 133 F. Supp.2d 121, 123 (D. Mass. 2001). Congress charged the Federal Circuit with "providing more consistent guidance to innovative industry, the Patent Office, and others impacted by the patent system." Thomas, *supra* note 179, at 793. The Supreme Court stated, "[i]t was just for the sake of such desirable uniformity that Congress created the Court of Appeals for the Federal Circuit as an exclusive appellate court for patent cases." *Markman v. Westviews Instruments, Inc.*, 517 U.S. 370, 390 (citing H.R. REP. NO. 97-312, at 20-23 (1981)).

182. See *Groombridge & Calabro*, *supra* note 33, at 463 (stating that *Integra* may create uncertainty as to what is permitted under the safe harbor and may actually impede the progress of biomedical innovation).

183. See *supra* notes 124-32 and accompanying text.

184. See *supra* notes 62-78, 124-33 and accompanying text.

185. Like the *Bristol* court, the Federal Circuit recognizes the importance of biotechnology tool patents to the industry; stating, "[b]ecause the downstream clinical testing for FDA approval falls within the safe harbor, these patented tools would only supply some commercial benefit to the inventor when applied to general research." 331 F.3d at 867.

186. See *Warburg & Maebius*, *supra* note 11, at 28 (discussing the dangers of the *Bristol* decision).

result, innovating pharmaceutical companies must conduct thorough research when using research tools to develop drugs, in order to discover which research tools are in the public domain and which are under patent protection.¹⁸⁷ While the *Integra* court has narrowed the scope of the Hatch-Waxman safe harbor, its future implication on the biotechnology industry remains unclear.

VIII. PROPOSAL: A TEST FOR DETERMINING WHEN ACTIVITIES FALL WITHIN THE SAFE HARBOR

Initially, the purpose of the safe harbor was to overrule *Roche* and create a means for generic drug manufacturers to enter the market as soon as the brand-name patent expired.¹⁸⁸ The 1984 Committee on Energy and Commerce, which considered the bill, further explained that the purpose of the safe harbor is to exclude from patent infringement liability experimentation with a patented drug product, when the purpose is to prepare for commercial activity beginning when a valid patent expires.¹⁸⁹

The justification expressed by Congress in overruling *Roche* was that the pharmaceutical “experimental activity does not have any adverse economic impact on the patent owner’s exclusivity during the life of a patent, but prevention of such activity would extend the patent owner’s commercial exclusivity beyond the patent expiration date.”¹⁹⁰

The 98th Congress explained the safe harbor in terms of drugs and the pharmaceutical industry.¹⁹¹ While Congress admitted that other products are affected by pre-marketing and manufacturing regulations, the safe harbor is explained in the context of drug approval and the FDA.¹⁹² In this context, it is hard to imagine that Congress, with no knowledge of the present-day biotechnology industry, intended to allow research tool infringers to escape liability.

187. See Marc S. Friedman & Joel N. Bock, *A New Toll Booth on the Research Highway for Pharmas: Reconsidering the Research Use Exemption to Patent Infringement*, NEW JERSEY LAWYER, Oct. 2003, at 17, 19 (stating that failing to define which activities are “reasonably related” to the FDA approval process could lead to other problems for owners of research tool patents in the biotechnology industry; despite the Federal Circuit’s decision, there are other roads a company can travel to “avoid and exploit such limitations on the use of patented research tools”); see also *supra* note 182.

188. See *supra* notes 79–82 and accompanying text.

189. H.R. REP. NO. 98-857, pt. 1, at 45 (1984), reprinted in 1984 U.S.C.C.A.N. 2647, 2678.

190. *Id.* at 2679.

191. *Id.* at 2678–79.

192. *Id.*

While the Federal Circuit in *Integra* seemed to recognize that research tools were not protected by the safe harbor,¹⁹³ it failed to articulate a test that would ensure equal application of the safe harbor in the pharmaceutical and biotechnology industry. The court seemed to say that research tool infringement is never protected by the safe harbor and everything else must be “reasonably related” to the FDA approval process.

Instead of the uncertainty inherent in determining whether activities are “reasonably related” to the FDA approval process, and whether a patented technology is a drug or research tool, a three-part test should be used when evaluating whether infringing activities are shielded from liability under the Hatch-Waxman safe harbor. First, infringing activity *must* be for the purpose of establishing bioequivalence *that will be used* for FDA approval. Second, the infringing activity must not have any adverse economic impact on the patent owner’s exclusive use.¹⁹⁴ Third, as a policy consideration, prevention of the infringing activity must not cause a *de facto* extension of the patent owner’s commercial exclusivity beyond the patent expiration date.¹⁹⁵

193. *Integra Lifesciences I, Ltd. v. Merck KGaA*, 331 F.3d 860, 867 (Fed. Cir. 2003), *cert. granted*, 73 U.S.L.W. 3059 (U.S. Jan. 7, 2005) (No. 03-1237) (stating that exaggerating the safe harbor out of context would “swallow the whole benefit of the Patent Act” for some biotechnological inventions).

194. This prong of the test mirrors the intent of Congress when they enacted section 271(e)(1). *See supra* text accompanying note 190.

195. *Id.* Policy considerations are derived by examining the purpose of the federal patent system. A patent gives the inventor the right to “exclude others from making, using, or selling the invention” in the United States. MARTIN J. ADELMAN, RANDALL R. RADER, JOHN R. THOMAS & HAROLD C. WEGNER, *CASES AND MATERIALS ON PATENT LAW* 6–7 (2d ed. 2003). As such, the U.S. patent system:

embodies a carefully crafted bargain for encouraging the creation and disclosure of new, useful, and nonobvious advances in technology and design in return for the exclusive right to practice the invention for a period of years. . . . In consideration of its disclosure and the consequent benefit to the community, the patent is granted.

Id.

There are four primary philosophical theories (policy considerations) that form the foundation of the patent system: (1) “natural rights;” (2) “reward for services rendered;” (3) “monopoly profits incentive;” and (4) “exchange for secrets.” JANICE M. MUELLER, *AN INTRODUCTION TO PATENT LAW* 23–26 (2003). The natural rights theory is “based on the work of John Locke . . . who believed that God gave the earth to people in common;” when people mix their labor with objects found in the common they make it their property. *Id.* at 24. The reward for services rendered theory simply suggests that society should reward inventors for the useful service (invention) that they perform for society. *Id.* at 25. The monopoly profits incentive theory rests on the assumption that “innovation is good for society, and that the correct incentive” to disclose this innovation is market exclusivity. *Id.* at 25. The exchange for secrets theory rests on the assumption that “most innovation would remain secret, but for the incentive to disclose;” thus, the patent system is often viewed as a *quid pro quo* exchange of secrets for the right to exploit the invention. *Id.* at 26. Note, these policy considerations are utilized to buttress the dissent of Judge Newman in *Integra*. *See supra* note 158.

Evaluating *Integra* using this test reveals the usefulness of its application. Even if Merck could have shown that its activities were reasonably related to the FDA approval process, its activities would still be unprotected by the safe harbor because the activities would have an adverse effect on the value of *Integra*'s research tool patent.¹⁹⁶ Generally, research tools are developed as a product to be used in research, and the very use of a research tool infringes the economic interest of the biotechnology developer. Conversely, drugs are developed as a product for sale and a drug manufacturer will not be adversely affected as long as the infringer does not offer the drug for sale while it is under patent protection.¹⁹⁷ Finally, preventing this type of infringement does not cause a *de facto* extension of the patent owner's commercial exclusivity beyond the patent term.¹⁹⁸ Essentially, this test eliminates the slippery-slope logic inherent in the "reasonably related" language and protects the biotechnology industry by ensuring that assets patented as research tools may not be infringed upon.

196. By using the research tool, Merck used a patented product in the same manner in which it derives its economic value.

197. The product differentiation between a research tool and a drug is instrumental to this analysis. For the purpose of this test, the key difference between the two is how they derive their value. Cf. *supra* note 125 (the NIH distinguishes research tools from "end products"); Derzko, *supra* note 125, at 350–51 (discussing research tools and "end products"). Commercially, research tools are created to be licensed or sold for the purpose of discovery research. See *supra* note 125. They derive royalties because they can be used in the research process. However, drugs are typically products that are bought and sold. They derive their commercial value from sales based upon a market price. Thus, infringement activities which have an adverse economic impact on research tools and drugs include any activity that mirrors how research tools and drugs derive their commercial value. In some instances, the characteristics of drugs and research tools may overlap in a particular product. However, because the focus of the test is on economic impact and not compound classification, the test should not be rejected.

The test is uniformly applied to both research tools and drugs once the distinction is made between the different ways infringement can have an adverse economic impact on the patentee. A generic drug offered for sale while the brand-name drug is under patent protection is straight patent infringement and not within the guise of the safe harbor. Thus, the determination of whether the infringement has an adverse economic impact on the patentee will only be relevant if it is the type of infringement sought to be protected by the safe harbor: establishing bioequivalency.

Also, differences in compound classification can ultimately affect the analysis of a court. See *supra* note 166 (discussing Judge Newman's disagreement over what constitutes a research tool). One of the key advantages of the adverse economic impact test is that it protects research tools and drug intermediates (compounds that could be end-product drugs or research tools) while shielding the courts from having to determine whether a compound is a drug, drug intermediate, or research tool.

198. By preventing the *de facto* extension of a patent right, the test remains true to the policy theories underlying the U.S. patent system. See *supra* note 195. The third prong of the test maintains the balance behind the unilateral exchange of market exclusivity for innovation while not allowing the patentee to usurp extra economic rewards. Essentially, this ensures that competitors are not penalized and patentees are not rewarded for delays caused by the FDA.

Applying this test to the *Bristol* case¹⁹⁹ illustrates the value of its utility. Bristol was shielded from liability when it infringed Rhone's drug intermediates, or research tools, to develop a new drug.²⁰⁰ Applying the "reasonably related" test, the court held that the infringement activity was for the development of a new drug that would eventually lead to FDA approval, and thus Bristol was not liable.²⁰¹ Under the first prong of the proposed test, it is not entirely clear that Bristol's infringing activity was for the purpose of establishing bioequivalence that *will be* used for FDA approval. Bristol's infringement was in a "search and development program"²⁰² to find a "preeminent anti-cancer drug,"²⁰³ which may not qualify under the bioequivalence prong.

Assuming, *arguendo*, that Bristol's activities satisfy the first part of the test, it must then be shown that its infringing activities did not have an adverse economic effect on Rhone's research tools. Here Rhone would need to show that its research tools derived their value from use in drug discovery, and they were not end-product drugs themselves. If this is true, then Bristol has infringed a patent to the economic detriment of Rhone and is liable for patent infringement because utilization of the research tool patent to discover new drugs is how the research tool derives its value (just as selling a drug is the means by which drugs derive their value). Finally, holding Bristol liable for its infringing activities would not have enhanced Rhone's commercial exclusivity of the patent beyond its term's expiration. There is no regulatory process for research tools;²⁰⁴ consequently, there is

199. See *supra* notes 124–33 and accompanying text.

200. See *supra* notes 124–33 and accompanying text.

201. See *supra* notes 130–32 and accompanying text.

202. 2001 U.S. Dist. LEXIS 19361, at *14.

203. *Id.*

204. Cf. Anna Wilde Mathews & David P. Hamilton, *FDA Takes Step Toward Allowing Generic Versions of Biotech Drugs*, WALL ST. J., Feb. 18, 2004, at A1 (stating that there is no FDA process for approving generic versions of biotechnology drugs). Furthermore, the Hatch-Waxman Act did not cover the "then-new field of biotechnology. Today, nearly all biotechnology medicines are regulated under a different law from the one covering traditional drugs." *Id.* at A6. The reason for treating the biotechnology industry different from the pharmaceutical industry is due to the nature of the product produced:

Traditional chemical drugs are easier to duplicate than biotech medicines, in part because the active ingredients are relatively small molecules that are straightforward to analyze. . . .

Biotech medicines, by contrast, are generally produced by splicing a genetic sequence that corresponds to a particular protein, such as human insulin, into living cells.

Id. at A1.

While generic makers of chemical drugs have been able to utilize Hatch-Waxman provisions to shortcut the FDA approval process, the FDA contends it lacks the authority to approve generic versions of most biotechnology products. *Id.* Thus, no matter how one views biotechnology research tools, either as an intermediate or end compound, they are not subject to the same regulatory processes as chemical drugs.

no delay involved in procuring the research tool as soon as the patent expires.

Applying a test that considers the economic distinction between drug and research tool patent infringement creates certainty regarding which activities are protected from infringement liability under the Hatch-Waxman safe harbor. Focusing on the type of product infringed upon and how that product derives its value (e.g., sale versus use) ensures a uniform application of the safe harbor in the biotechnology and pharmaceutical industries while remaining true to the policy considerations inherent in the U.S. patent system.²⁰⁵

IX. CONCLUSION

Integra gave the Federal Circuit the opportunity to determine how far down the chain of experimentation the Hatch-Waxman safe harbor reaches to shield patent infringers from liability. Case history reveals a trend on behalf of the courts to increase the scope of the safe harbor to afford greater protection for patent infringement.²⁰⁶ In deciding the issue at hand, the *Integra* court correctly determined that infringing use of a research tool is not protected under the safe harbor. However, contrary to its formalistic nature, the court failed to create a bright-line rule to determine which infringing activities are shielded from liability by the safe harbor.

To remedy this situation and enhance the certainty in safe harbor litigation, this Note proposes utilizing a three part test that accurately reflects the congressional intent and policy considerations behind the safe harbor. By focusing on the economic impact that the infringing action has on the patent holder's rights, the Hatch-Waxman safe harbor will achieve a uniform application in the pharmaceutical and biotechnology industries, which are two industries that receive different treatment from the FDA.²⁰⁷ Furthermore, the proposed test helps remedy the uncertainty inherent in the "reasonably related" analysis currently applied by the courts, and

205. See *supra* note 195 (discussing the policies behind the U.S. patent system).

206. See *supra* Part IV.

207. See *supra* note 204 and accompanying text.

protects firms in the biotechnology industry that rely on research tools as income-generating assets.²⁰⁸

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208. For a different approach to protecting biotechnology research tools, see Xiao, *supra* note 16 (proposing an exception to the section 271(e)(1) safe harbor for research tools).

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