

INTEGRA LIFESCIENCES I, LTD. v. MERCK KGAA:
RE-EXAMINING THE BROAD SCOPE OF THE
§ 271(E)(1) SAFE HARBOR

By Daniel Wobbekind

I. INTRODUCTION

In the 1984 case *Roche Products, Inc. v. Bolar Pharmaceutical Co.*,¹ the Federal Circuit found patent infringement where a generic drug manufacturer experimented on a patented drug solely for the purpose of obtaining U.S. Food and Drug Administration (FDA) approval for commercial sale of a generic drug equivalent once the patent expired.² This holding provided patent holders with a *de facto* patent extension while generic manufacturers sought regulatory approval for their generic drug equivalents. In response, Congress passed the Drug Price Competition and Patent Term Restoration Act (the 1984 Act). The 1984 Act added 35 U.S.C. § 271(e)(1), which extinguished the *de facto* patent extension by exempting from infringement uses of patented inventions that are “reasonably related to the development and submission of information” to the FDA.³

Although Congress intended § 271(e)(1) to provide a straightforward answer to *Roche*, the imprecise drafting of § 271(e)(1) has engendered a number of Supreme Court and Federal Circuit cases interpreting the plain language of the statute. The result of these cases is a statutory interpretation that stretches the limits of § 271(e)(1) protection as far as the statute’s plain language will tolerate, and perhaps beyond the original scope intended by Congress.

The most recent series of Supreme Court and Federal Circuit cases addressing the scope of § 271(e)(1) protection, *Integra Lifesciences I, Ltd. v.*

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1. 733 F.2d 858 (Fed. Cir. 1984).

2. *Id.* at 860-61, 865.

3. 35 U.S.C. § 271(e)(1) (2000) (“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.”); see H.R. Rep. No. 98-857, pt. I, at 45-46 (1984), as reprinted in 1984 U.S.C.C.A.N. 2647, 2678-79.

Merck KGaA (Integra I),⁴ *Merck KGaA v. Integra Lifesciences I, Ltd. (Merck)*,⁵ and *Integra Lifesciences I, Ltd. v. Merck KGaA (Integra II)*,⁶ addressed whether § 271(e)(1) protects pre-clinical experimentation on potential drug candidates. Scripps Research Institute (Scripps) and Merck KGaA (Merck) discovered potential anti-cancer properties in peptides patented by Integra Lifesciences I, Ltd. (Integra)⁷ and performed pre-clinical experiments on the peptides to evaluate their suitability as potential cancer drug candidates.⁸ Integra sued Merck and Scripps for patent infringement for the unauthorized pre-clinical experimentation with the patented peptides and Merck answered that the Scripps-Merck studies fell under the § 271(e)(1) safe harbor.⁹

In *Integra I*, the Federal Circuit attempted to narrow the scope of § 271(e)(1) protection by holding that it did not apply to pre-clinical experiments that failed to supply information for FDA submissions.¹⁰ In *Merck*, the Supreme Court reversed and reaffirmed the broad scope of § 271(e)(1) by holding that the statute protects pre-clinical experimentation “as long as there is a reasonable basis for believing that the experiments will produce” information relevant to an FDA filing.¹¹ On remand, the Federal Circuit held that § 271(e)(1) protected the Scripps-Merck pre-clinical experiments because those experiments yielded information concerning efficacy, pharmacology, pharmacokinetics, and mechanism of action and, as a result, were “reasonably related to the development and submission of information” to the FDA.¹²

This Note addresses three important problems that lurk in the shadows of *Integra I*, *Merck*, and *Integra II*. First, the broad scope of § 271(e)(1) protection creates: 1) clarity problems for researchers looking to the statute for guidance; and 2) administrability problems for courts attempting to apply the safe harbor. Second, some research uses that would benefit from protection, such as understanding or improving upon patented subject matter, may fall outside the protection of both § 271(e)(1) and the research use exemption under the common law. Finally, the status of research tools under § 271(e)(1) remains uncertain, but the broad scope of § 271(e)(1) pro-

4. 331 F.3d 860 (Fed. Cir. 2003).

5. 545 U.S. 193 (2005).

6. 496 F.3d 1334 (Fed. Cir. 2007).

7. *Integra I*, 331 F.3d at 863.

8. *Merck*, 545 U.S. at 198.

9. *Id.* at 200.

10. *Integra I*, 331 F.3d at 865.

11. *Merck*, 545 U.S. at 208.

12. *Integra Lifesciences I, Ltd. v. Merck KGaA (Integra II)*, 496 F.3d 1334, 1348 (Fed. Cir. 2007).

tection might protect uses of patented research tools that should not be protected.

This Note suggests that an approach modeled after Judge Newman's dissent in *Integra I* and the statutory schemes in Germany and the United Kingdom would solve these three problems. Judge Newman advocates creating an expanded research use exemption where uses of a patented invention during *research* could receive protection, but not uses during *development* and commercialization. Judge Newman further refines this approach by splitting "research" into protectable *research on* the patented subject matter, and unprotectable *research with* the patented subject matter. This approach would solve the clarity and administrability problems inherent to the broad construction of § 271(e)(1) by narrowing the statute's focus to activities related to the regulatory approval process as Congress presumably intended. Newman's approach would also provide protection for those beneficial uses under-protected by the current scheme, while denying protection to research uses of patented research tools.

Part II of this Note introduces the common law research use exemption. Part III outlines the enactment and subsequent interpretation of § 271(e)(1). Part IV summarizes the facts, case history, and holdings of *Integra II*. Part V analyzes the potential problems lurking after *Integra II* and proposes Judge Newman's approach as an appropriate solution.

II. THE COMMON LAW RESEARCH USE EXEMPTION

In the United States, the common law research use exemption provides an affirmative defense to patent infringement if the allegedly infringing use of the patented invention is for research purposes. This exemption originated in 1813 in a pair of opinions by Justice Joseph Story.¹³ In *Whittemore v. Cutter*,¹⁴ Justice Story stated, "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."¹⁵ In *Sawin v. Guild*,¹⁶ Story elaborated that patent infringement involves "the making [of a patented machine] with an intent to use for profit, and not for the mere purpose of philosophical experiment, or to ascertain the verity and exactness of the specification."¹⁷

13. *Integra I*, 331 F.3d at 874-75.

14. 29 Fed. Cas. 1120 (C.C.D. Mass. 1813).

15. *Id.* at 1121.

16. 21 Fed. Cas. 554 (C.C.D. Mass. 1813).

17. *Id.* at 555 (emphasis added).

In line with *Sawin v. Guild*, the Federal Circuit has reinforced the non-commercial focus of the common law research use exemption.¹⁸ In its most recent decision involving the common law research use exemption, *Madey v. Duke University*,¹⁹ the Federal Circuit appeared to further erode the “very narrow and strictly limited experimental use defense.”²⁰ In *Madey*, Dr. Madey used his own patented laser technology in his lab at Duke University.²¹ After Madey resigned from Duke, Duke continued to use Madey’s patented laser technology without his approval and Madey sued.²² The district court found that the common law research use exemption protected Duke’s use of the lasers because Duke used the laser technology in teaching and research that lacked a definite commercial purpose.²³ The Federal Circuit reversed, holding that Duke’s uses of the patented technology, while educational in purpose, still furthered Duke’s legitimate business objectives as a major research university and were “not solely for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry.”²⁴ The Federal Circuit’s holding makes it clear that the common law research use exemption will not protect uses of patented inventions that further the alleged infringer’s legitimate business objectives, whether or not the uses are commercial in nature.

III. HISTORY OF 35 U.S.C. § 271(e)(1)

At the same time that the Federal Circuit was narrowing the common law research use exemption, the Federal Circuit’s *Roche Products, Inc. v. Bolar Pharmaceutical Co.* decision²⁵ prompted Congress to enact 35 U.S.C. § 271(e)(1) in order to allow generic drug companies to test patented drugs for regulatory purposes prior the expiration of the patent.²⁶

18. *See Embrex, Inc. v. Service Eng’g Corp.*, 216 F.3d 1343, 1346-47, 1349 (Fed. Cir. 2000) (holding that the defendant’s testing of the patented invention in order to design around was expressly for commercial purposes and, therefore, not covered by the experimental use exemption); *Roche Prods., Inc. v. Bolar Pharm. Co.*, 733 F.2d 858, 863 (Fed. Cir. 1984) (holding that the experimental use exemption will not apply when the intended experimental use “has definite, cognizable, and not insubstantial commercial purposes”).

19. 307 F.3d 1351 (Fed. Cir. 2002).

20. *Id.* at 1361-63.

21. *Id.* at 1352.

22. *Id.* at 1352-53.

23. *Id.* at 1355.

24. *Id.* at 1361-63.

25. 733 F.2d 858 (Fed. Cir. 1984).

26. *See* H.R. Rep. No. 98-857, pt. I, at 45-46 (1984), *as reprinted in* 1984 U.S.C.C.A.N. 2647, 2678-79.

Following this enactment, the Supreme Court and the Federal Circuit construed the imprecise language of § 271(e)(1) broadly, to protect additional uses of patented inventions that are arguably beyond the scope of the Congressional intent.

A. The Need for an FDA Regulatory Submission Exemption in *Roche*

In *Roche*, the Federal Circuit found patent infringement where a generic drug manufacturer experimented on a patented drug prior to the expiration of the patent, solely for the purpose of obtaining FDA approval for the commercial sale of a generic drug equivalent once the patent expired.²⁷ Roche Products, Inc. (Roche) held a patent for a sleeping pill containing flurazepam hydrochloride.²⁸ Bolar Pharmaceutical Co. (Bolar), a generic drug manufacturer, wanted to market a generic equivalent of the patented drug shortly after Roche's patent expired.²⁹ Because the FDA approval process can take at least two years, Bolar began experimenting on flurazepam hydrochloride to obtain data required for FDA approval prior to the expiration of Roche's patent.³⁰ Roche brought an infringement action against Bolar seeking to enjoin Bolar from using the patented drug for any purpose during the life of the patent.³¹

The Federal Circuit held that Bolar's use of flurazepam hydrochloride infringed Roche's patent under 35 U.S.C. § 271(a), which states, "whoever without authority makes, uses, or sells any patented invention, within the United States . . . during the patent term therefor, infringes the patent."³² The court noted that this decision would result in a *de facto* monopoly for a drug patent owner for at least two years after the patent's expiration because it would take generic drug manufacturers that long to complete the FDA approval process.³³ However, the court further noted that this *de facto* monopoly was offset by the fact that the effective life of a pioneer drug patent is as low as seven years, after accounting for the seven to ten years required for the development and approval of a pioneer drug.³⁴ The Federal Circuit concluded its opinion by urging Congress to

27. *Roche Prods., Inc. v. Bolar Pharms. Co.*, 733 F.2d 858, 860-61, 865 (Fed. Cir. 1984).

28. *Id.* at 860.

29. *Id.*

30. *Id.*

31. *Id.*

32. *Id.* at 861, 865.

33. *Id.* at 864.

34. *Id.*

enact legislation addressing the societal and economic problems at issue in this case.³⁵

B. Congress Responds with the 1984 Act

Congress reacted promptly to *Roche* and resultant lobbying efforts by generic drug companies. Mere months after *Roche* was decided, Congress enacted the Drug Price Competition and Patent Term Restoration Act, also referred to as the Hatch-Waxman Act.³⁶ The 1984 Act addressed the two distortions created by the requirement that certain products undergo pre-market regulatory approval that the Federal Circuit noted in *Roche*.³⁷ First, Congress attempted to alleviate the loss of seven to ten years of marketability under patents on pioneer drugs due to the development and approval process through the provisions in § 201 of the 1984 Act.³⁸ Section 201, codified at 35 U.S.C. § 156, provides a patent term extension of up to five years for patents on products requiring a regulatory review period prior to commercial marketing or use.³⁹ Covered products include: 1) human drug products (defined as the active ingredient of a new drug, antibiotic drug, or human biological product); and 2) any medical devices, food additives, or color additives subject to regulation under the Federal Food, Drug, and Cosmetic Act (FDCA).⁴⁰

Second, Congress addressed the patent owner's *de facto* patent monopoly of two years or more after the patent's expiration through § 202 of the 1984 Act.⁴¹ Section 202 added 35 U.S.C. § 271(e)(1), which 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 . . . 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.⁴²

35. *Id.* at 863-65.

36. Janice M. Mueller, *No "Dilettante Affair": Rethinking the Experimental Use Exception to Patent Infringement for Biomedical Research Tools*, 76 WASH. L. REV. 1, 25 (2001).

37. *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 669 (1990).

38. H.R. Rep. No. 98-857, pt. I, at 17-18, 37 (1984), *as reprinted in* 1984 U.S.C.C.A.N. 2647, 2650-51, 2670; *Eli Lilly*, 496 U.S. at 669-70.

39. 35 U.S.C. § 156(a) (2000); H.R. Rep. No. 98-857, pt. I, at 15, 37 (1984), *as reprinted in* 1984 U.S.C.C.A.N. 2647, 2648, 2670; *Eli Lilly*, 496 U.S. at 671.

40. 35 U.S.C. § 156(f) (2000); *Eli Lilly*, 496 U.S. at 670-71.

41. H.R. Rep. No. 98-857, pt. I, at 45-46 (1984), *as reprinted in* 1984 U.S.C.C.A.N. 2647, 2678-79; *Eli Lilly*, 496 U.S. at 671.

42. 35 U.S.C. § 271(e)(1) (2000).

The § 271(e)(1) safe harbor legislation effectively overturned *Roche* by allowing competitors to engage in otherwise infringing activities prior to the expiration of a patent, so long as such activities are “reasonably related” to the development and submission of information for FDA approval.⁴³

Thus, the 1984 Act achieved two important goals. The Act removed barriers to bringing generic drugs to market, thereby accelerating competition and providing the public with lower consumer costs for drugs and insurance, while simultaneously preserving incentives for pioneer drug companies to develop new drugs.⁴⁴

C. Courts Construe the Language of § 271(e)(1)

Although the Congressional intent in promulgating the 1984 Act seemed fairly straightforward, the imprecise drafting of the § 271(e)(1) safe harbor provision⁴⁵ spawned a number of Supreme Court and Federal Circuit cases wrangling over the terms “patented invention,” “reasonably related,” and “a Federal law.”

1. *The Supreme Court Interprets the Phrases “Patented Invention” and “a Federal law”*

In *Eli Lilly & Co. v. Medtronic, Inc.*,⁴⁶ the Supreme Court extended the § 271(e)(1) safe harbor provision to exempt an alleged infringer’s use of a patented Class III medical device⁴⁷ for the purpose of obtaining regulatory approval under the FDCA.⁴⁸ Eli Lilly & Co. (Eli Lilly) owned patents on an implantable cardiac defibrillator.⁴⁹ Medtronic, Inc. (Medtronic) performed testing on its own implantable cardiac defibrillator, which was covered by two of Eli Lilly’s patents, in order to develop and submit information required under the FDCA for pre-market approval of the medical device.⁵⁰ Eli Lilly filed suit to enjoin Medtronic from testing the medi-

43. H.R. Rep. No. 98-857, pt. I, at 45-46 (1984), as reprinted in 1984 U.S.C.C.A.N. 2647, 2678-79; *Eli Lilly*, 496 U.S. at 671.

44. Marlan D. Walker, *The Patent Research Tool Problem After Merck v. Integra*, 14 TEX. INTELL. PROP. L.J. 1, 20 (2005).

45. See *Eli Lilly*, 496 U.S. at 679 (“No interpretation we have been able to imagine can transform § 271(e)(1) into an elegant piece of statutory draftsmanship.”).

46. 496 U.S. 661 (1990).

47. Class III medical devices require pre-market approval to assure the device is safe and effective. 21 C.F.R. § 860.3 (2007).

48. *Eli Lilly*, 496 U.S. at 663-64, 679.

49. *Id.* at 664.

50. *Id.*

cal device and Medtronic defended on the ground that the § 271(e)(1) safe harbor protected its activities.⁵¹

In order to evaluate Medtronic's defense, the Court first found that the phrase "patented invention" in § 271(e)(1) includes all inventions, not just drug-related inventions.⁵² The Court then interpreted the phrase "a Federal law" in § 271(e)(1) to refer to the entirety of any Act (including the FDCA), not just the individual provisions of federal laws that regulate drugs.⁵³ Thus, the Court broadly held that § 271(e)(1) exempts uses of *any* patented inventions, such as cardiac defibrillators, reasonably related to the development and submission of information for regulatory approval under *any* federal act (such as the FDCA).⁵⁴

The Court also provided a narrower justification for its holding by finding that §§ 201 and 202 of the 1984 Act were meant to be complimentary, acting together to eliminate the pre-market regulatory approval distortions caused at both ends of the patent period.⁵⁵ Thus, the Court found that all products eligible for patent term extension under § 201 (new drugs, antibiotic drugs, human biological products, *medical devices*, food additives, and color additives) were also subject to the § 271(e)(1) safe harbor provided by § 202.⁵⁶ This finding further justified the Court's holding that the Class III medical device at issue in this case was subject to the § 271(e)(1) safe harbor.

2. *The Federal Circuit Applies Eli Lilly*

Relying on the Supreme Court's *Eli Lilly* decision, in *AbTox, Inc. v. Exitron Corp.*⁵⁷ the Federal Circuit held that the § 271(e)(1) safe harbor also applies to Class II medical devices, which are not subject to pre-market regulatory approval.⁵⁸ AbTox, Inc. (AbTox) owned a patent for a plasma sterilizer, a Class II medical device.⁵⁹ Prior to the expiration of AbTox's patent, MDT Corp. (MDT) developed a plasma sterilizer that

51. *Id.*

52. *Id.* at 665.

53. *Id.* at 665-66.

54. *Id.* at 666-69.

55. *Id.* at 670, 675.

56. *Id.* at 673.

57. 122 F.3d 1019 (Fed. Cir. 1997).

58. *Id.* at 1029. Class II medical devices may be marketed without pre-market approval, but manufacturers must comply with certain federal performance regulations. *See* 21 C.F.R. § 860.3 (2007). Class II devices enjoy an abbreviated approval process that is far less rigorous than the pre-market approval necessary for Class III devices. *AbTox*, 122 F.3d at 1028.

59. *Id.* at 1027.

was covered by the AbTox patent and conducted limited tests on the device to collect data necessary for FDA approval of its Class II medical device.⁶⁰ AbTox alleged that MDT's activity constituted patent infringement, and MDT moved for partial summary judgment on the basis that its activities fell under the § 271(e)(1) safe harbor.⁶¹ AbTox argued that § 271(e)(1) did not apply to Class II medical devices.⁶²

In determining whether § 271(e)(1) applied to Class II medical devices, the Federal Circuit considered two parts of *Eli Lilly*. First, the court cited the Supreme Court's narrow reasoning that all products eligible for patent term extension under § 201 of the 1984 Act are also subject to the § 271(e)(1) safe harbor provided by § 202.⁶³ Under this reasoning, the Federal Circuit stated that § 271(e)(1) would only apply to Class III medical devices because Class II medical devices are ineligible for patent term extension under § 201.⁶⁴ Second, however, the court held that the Supreme Court's broad holding "that section 271(e)(1) applies to any use reasonably related to regulation under the FDCA" would certainly include Class II devices.⁶⁵

Thus, *AbTox* makes it clear that the Federal Circuit will apply the Supreme Court's broad interpretation of § 271(e)(1) despite the "potential conflict with [the Supreme Court's] own reasoning" that §§ 201 and 202 of the 1984 Act were meant to complement and offset each other.⁶⁶

3. *The Federal Circuit Affirms a District Court Test for "Reasonably Related"*

In *Intermedics, Inc. v. Ventritex, Inc.*,⁶⁷ the U.S. District Court for the Northern District of California suggested a test for "reasonably related." The court noted that Congress included the phrase "reasonably related" to provide potential infringers with "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," and to avoid punishing potential infringers because their "otherwise infringing 'uses' either failed to generate information in which the FDA was interested or

60. *Id.* at 1027.

61. *Id.*

62. *Id.*

63. *Id.* at 1029.

64. *Id.*

65. *Id.* at 1028.

66. *Id.* at 1029.

67. 775 F. Supp. 1269 (N.D. Cal. 1991), *aff'd*, 991 F.2d 808 (Fed. Cir. 1993).

generated more information than turned out to be necessary to secure FDA approval.”⁶⁸ The court set forth a test for “reasonably related”:

[W]ould it have been reasonable, objectively, for a party in defendant’s situation to 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?⁶⁹

The Federal Circuit affirmed.⁷⁰

D. The Research Tools Question: Cause for Concern?

The expansive protection under § 271(e)(1) resulting from the foregoing Supreme Court and Federal Circuit construction has created concerns about the status of patent protection for a valuable set of laboratory resources known as research tools. The issue is that research tools are often difficult to define and categorize because the same resource can have multiple applications in several different contexts. For instance, the same molecule could have utility as a component of a screening assay and as a therapeutic drug. A further complication is that research tools are extremely valuable to researchers, who use research tools to make new discoveries and work more efficiently, and to research-tool makers, who derive economic value from these tools. Because research tools are so difficult to characterize, research tool patentees fear that the broad construction of § 271(e)(1) set forth in Supreme Court and Federal Circuit precedent could exempt infringing uses of their patented research tools, thereby diminishing the economic value of those tools and the incentives to create new tools.⁷¹ These issues came to light when a U.S. District Court in the Southern District of New York, applying the broad construction of § 271(e)(1), held that § 271(e)(1) exempted some infringing uses of patented research tools.⁷²

68. *Id.* at 1280.

69. *Id.*

70. *Intermedics, Inc. v. Ventritex, Inc.*, 991 F.2d 808 (Fed. Cir. 1993).

71. Brief for Invitrogen Corp. et al. as Amici Curiae in Support of Respondents at 6-7, *Merck KGaA v. Integra Lifesciences I, Ltd. (Merck)*, 545 U.S. 193 (2005) (No. 03-1237) [hereinafter *Invitrogen Brief*].

72. *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*, No. 95 Civ. 8833(RPP), 2001 WL 1512597, at *1, *4 (S.D.N.Y. Nov. 28, 2001).

1. NIH's Definition of Research Tools

The National Institutes of Health (NIH) defines the term “research tools” 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.’”⁷³ The NIH elaborates that “research tools” “include cell lines, monoclonal antibodies, reagents, animal models, growth factors, combinatorial chemistry libraries, drugs and drug targets, clones and cloning tools (such as PCR), methods, laboratory equipment and machines, databases and computer software.”⁷⁴ However, establishing whether a biotechnological discovery is a research tool is not always straightforward because many biotechnological discoveries, including pharmaceutical drugs, DNA sequences, and cell lines, may serve dual purposes as therapeutic or diagnostic end products for sale to customers, or as basic tools to assist in research.⁷⁵

2. Research Tools Require Protection

The research tool industry has played a major role in the rapid evolution of the pharmaceutical industry. Over the past thirty years, innovations in the research tool industry have made it possible to identify drug targets, such as previously undiscovered genes involved in major diseases, identify drug candidates matching those targets, and develop accurate procedures for testing those candidates.⁷⁶

In addition, advancements in the research tools field have led to more efficient research. For instance, high throughput technologies now allow thousands of proteins or genetic sequences to be assayed at once, reducing what previously took weeks or months of research into hours or minutes.⁷⁷ Also, advances in laboratory software have halved the time pharmaceutical companies need to screen potential drug candidates.⁷⁸ Such efficiencies lead to time-savings and lower costs for research tool users.⁷⁹

Developing biotechnology research tools is risky and costly.⁸⁰ Patent protection partially mediates the risks and costs by allowing biotech com-

73. Report of the National Institutes of Health (NIH) Working Group on Research Tools, Background (1998), <http://www.nih.gov/news/researchtools/index.htm> (last visited Apr. 5, 2008).

74. *Id.*

75. 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, 48 (2003).

76. Invitrogen Brief, *supra* note 71, at 10.

77. *Id.*

78. *Id.* at 10-11.

79. *Id.* at 11.

80. Xiao, *supra* note 75, at 59.

panies to profit from their research tools, primarily through licensing, and assuring that they can prevent potential users and competitors from making or using the patented invention during the lifetime of the patent.⁸¹

3. *A District Court Applies § 271(e)(1) to Research Tools*

In *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*,⁸² the U.S. District Court for the Southern District of New York held that the § 271(e)(1) safe harbor may apply to patented intermediates used in early-stage drug discovery.⁸³ Bristol-Myers Squibb Co. (Bristol) used intermediates patented by Rhône-Poulenc Rorer, S.A. (RPR) in research and development activities relating to the preparation of taxol analogs, the development of a structure-activity relationship (SAR) database, and the identification of potential drug candidates.⁸⁴ RPR sued Bristol for patent infringement and Bristol maintained that its activities were exempt under § 271(e)(1).⁸⁵ RPR alleged that Bristol's uses were "outside of the scope of the 271(e)(1) exemption because 1) the intermediates were not a patented invention within the meaning of 271(e)(1), and [2]) Bristol's uses were not 'reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use or sale of drugs.'"⁸⁶

The district court applied the broad interpretation of "patented invention" in *Eli Lilly* and *AbTox*, which includes "all patented inventions and discoveries, not merely those that are covered by Section 156," and held that RPR's patented intermediates were "patented inventions" for the purposes of § 271(e)(1).⁸⁷ The court then applied the "reasonably related" test from *Intermedics*.⁸⁸ The court found that while many of Bristol's uses of the patented intermediates did not directly result in information that could be submitted to the FDA or the filing of an FDA application, the uses "relat[ed] to a preliminary activity that may facilitate or be useful in generating information that could be submitted to the FDA," and were "made in order to determine whether or not an application for approval would be sought."⁸⁹ Thus, the court held that Bristol's uses were "reasonably related

81. *See id.*

82. No. 95 Cov. 8833(RPP), 2001 WL 1512597 (S.D.N.Y. Nov. 28, 2001).

83. *Id.* at *4.

84. *Id.*

85. *Id.* at *1.

86. *Id.* at *2.

87. *Id.* at *3.

88. *Id.*

89. *Id.* at *7.

to the development and submission of information under a Federal law,” and were thereby exempt from infringement under § 271(e)(1).⁹⁰

For research tool patent holders, this decision was cause for concern. Invoking the broad construction of § 271(e)(1) under Supreme Court and Federal Circuit precedent, the district court extended protection to otherwise infringing uses of patented research tools only tenuously related to obtaining FDA approval. Here, Bristol’s allegedly infringing research activities 1) involved *research with* the patented inventions, using the inventions for their intended purpose to identify drug candidates, not *research on* the subject matter of patented inventions themselves⁹¹ and 2) were conducted before the identification of a compound for which FDA approval would be sought, and far up-stream of the FDA approval process. The Federal Circuit did not take long to attempt to quell the concerns of research tool patent holders.

IV. THE FEDERAL CIRCUIT ATTEMPTS TO NARROW § 271(e)(1) AND THE SUPREME COURT REVERSES

In *Integra I*, the Federal Circuit attempted to narrow the expanding scope of § 271(e)(1) by holding that the safe harbor did not apply to pre-clinical experiments which only identified drug candidates for future testing under FDA processes and failed to supply information for FDA submissions.⁹² The Supreme Court reversed in *Merck*, holding that pre-clinical experimentation was “protected under § 271(e)(1) as long as there is a reasonable basis for believing that the experiments will produce ‘the types of information that are relevant to an IND or NDA.’”⁹³ On remand in *Integra II*, the Federal Circuit held that the challenged Scripps experiments were exempt from infringement under § 271(e)(1) because such ex-

90. *Id.* at *8.

91. In contrast, the allegedly infringing research activities in *Roche*, *Eli Lilly*, and *AbTox* all involved *research on* the subject matter of the patented invention. *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 664 (1990) (stating that Medtronic’s allegedly infringing activities were research on the subject matter of Eli Lilly’s patented cardiac defibrillator to obtain information for regulatory approval); *AbTox, Inc. v. Exitron Corp.*, 122 F.3d 1019, 1027 (Fed. Cir. 1997) (noting that MDT’s allegedly infringing activities were research on the subject matter of AbTox’s patented plasma sterilizer to obtain information for regulatory approval); *Roche Prods., Inc. v. Bolar Pharm. Co.*, 733 F.2d 858, 860 (Fed. Cir. 1984) (establishing that Bolar’s allegedly infringing activities were research on the subject matter of Roche’s patented sleeping pill to obtain information for regulatory approval).

92. *Integra Lifesciences I, Ltd. v. Merck KGaA (Integra I)*, 331 F.3d 860, 865-68 (Fed. Cir. 2003).

93. *Merck KGaA v. Integra Lifesciences I, Ltd. (Merck)*, 545 U.S. 193, 208 (2005).

perimentation, “if successful, would be appropriate to include in a submission to the FDA.”⁹⁴ This Part explains this course of litigation.

A. Background

Integra Lifesciences I, Ltd. (Integra) owns five patents⁹⁵ issued between 1988 and 1997 relating to RGD peptides, short tri-peptide segments of fibronectin having the sequence arginine (R)—glycine (G)—aspartic acid (D).⁹⁶ RGD peptides promote cell adhesion by attaching to cell surface receptors known as $\alpha_v\beta_3$ integrins.⁹⁷ Integra’s patented inventions relate to ways of using the RGD peptides to promote, block, and disrupt cell attachment.⁹⁸

In 1988, Merck KGaA (Merck) began funding research conducted at the Scripps Research Institute (Scripps).⁹⁹ In the early 1990’s, Dr. David Cheresh, a scientist at Scripps, discovered that blocking $\alpha_v\beta_3$ integrins could halt tumor growth by inhibiting angiogenesis (the process of new blood vessel formation) in tumor cells.¹⁰⁰ Recognizing the importance of Dr. Cheresh’s findings, Merck extended its collaboration with Scripps during the mid-1990s for Dr. Cheresh to identify potential drug candidates for blocking $\alpha_v\beta_3$ integrins.¹⁰¹ Merck also agreed to fund the “necessary experiments to satisfy the biological bases and regulatory (FDA) requirements for the implementation of clinical trials” for any potential drug candidates.¹⁰² From 1995 to 1998, Scripps performed experiments on several RGD peptides provided by Merck to evaluate their suitability as potential drug candidates.¹⁰³ The Scripps-Merck experiments included pre-clinical testing in animals to evaluate efficacy, specificity, toxicity, mechanism of action and pharmacokinetics.¹⁰⁴ In 1997, Scripps chose to pursue RGD peptide EMD 121974 in clinical development and initiated the regulatory

94. *Integra Lifesciences I, Ltd. v. Merck KGaA (Integra II)*, 496 F.3d 1334, 1348 (Fed. Cir. 2007).

95. U.S. Patent Nos. 4,988,621 (’621 patent), 4,792,525 (’525 patent) 5,695,997 (’997 patent), 4,879,237 (’237 patent), and 4,789,734 (’734 patent).

96. *Integra I*, 331 F.3d at 862, 873.

97. *Id.* at 862.

98. *Integra II*, 496 F.3d at 1336.

99. *Merck*, 545 U.S. at 197.

100. *Integra I*, 331 F.3d at 863.

101. *Merck*, 545 U.S. at 198.

102. *Integra I*, 331 F.3d at 863.

103. *Merck*, 545 U.S. at 198.

104. *Id.* at 198-99.

approval process in the United States and Europe.¹⁰⁵ In 1998, an Investigational New Drug application (IND) was filed for EMD 121974.¹⁰⁶

On July 18, 1996, Integra filed a patent infringement suit against Merck and Scripps in the U.S. District Court for the Southern District of California.¹⁰⁷ Integra alleged that Merck willfully infringed Integra's patents and induced others to infringe by supplying the RGD peptides to Scripps, and that Scripps infringed by experimenting with the RGD peptides.¹⁰⁸ Merck answered that the Scripps-Merck studies on RGD peptides were protected from patent infringement by either the § 271(e)(1) safe harbor or the common law research use exemption.¹⁰⁹

At trial, the jury found that the 1995-98 Scripps-Merck activities infringed Integra's five patents.¹¹⁰ The district court sustained the verdict, finding that the connection between the 1995-98 Scripps-Merck experiments and the FDA review process was "insufficiently direct to qualify" for the § 271(e)(1) exemption.¹¹¹ In regards to the common law research use exemption, the district court found that all but one of Scripps's pre-1995 activities relating to RGD peptides constituted basic scientific research and were protected by the common law research use exemption, but that none of the 1995-98 activities were protected by the common law research use exemption.¹¹²

B. The Federal Circuit Affirms in *Integra I*

Merck appealed to the Federal Circuit on the grounds that the 1995-98 activities were covered under the § 271(e)(1) safe harbor.¹¹³ The court assessed whether the 1995-1998 pre-clinical experiments conducted under the Scripps-Merck agreement were "solely for uses reasonably related to the development and submission of information" to the FDA so as to qualify for the safe harbor.¹¹⁴ Based on the legislative history of the 1984 Act, the court reasoned that § 271(e)(1) was narrowly tailored to have a *de*

105. *Integra I*, 331 F.3d at 863.

106. *Merck*, 545 U.S. at 199.

107. *Id.* at 200.

108. *Id.*

109. *Integra Lifesciences I, Ltd. v. Merck KGaA (Integra II)*, 496 F.3d 1334, 1336-37 (Fed. Cir. 2007).

110. *Integra I*, 331 F.3d at 863. The district court granted Merck's motion for summary judgment of invalidity of claim 2 of the '621 patent. *Id.* at 862.

111. *Integra II*, 496 F.3d at 1338.

112. *Id.* at 1337.

113. The issue of whether the 1995-98 Scripps-Merck experiments were protected by the common law research use exemption was not presented on appeal. *Id.*

114. *Integra I*, 331 F.3d at 866.

minimis impact on the patentee's right to exclude even though it exempts from infringement a generic drug company's "pre-expiration activities 'reasonably related' to acquiring FDA approval of a [generic version of a] drug already on the market."¹¹⁵ In light of the legislative history, the court held that § 271(e)(1) would not "encompass drug development activities far beyond those necessary to acquire information for FDA approval of a [generic version of a] patented pioneer drug already on the market."¹¹⁶ The court concluded that:

§ 271(e)(1) simply does not globally embrace all experimental activity that at some point, however attenuated, may lead to an FDA approval process. . . . Extending § 271(e)(1) to embrace all aspects of 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.¹¹⁷

Accordingly, a split panel of the Federal Circuit affirmed the district court's ruling that the § 271(e)(1) safe harbor did not apply to the 1995-98 Scripps-Merck experiments because those pre-clinical experiments "did not supply information for submission to the [FDA], but instead identified the best drug candidate to subject to future clinical testing under the FDA processes."¹¹⁸ This holding appeared to limit the expanding scope of infringing patent uses protected by § 271(e)(1).

1. *The Federal Circuit Addresses the Research Tools Issue*

The Federal Circuit cautioned that interpreting § 271(e)(1) to "include the Scripps Merck activities would effectively vitiate the exclusive rights of patentees owning biotechnology tool patents."¹¹⁹ The court noted that patent owners often use research tools in early-stage research to identify drug candidates and in later-stage safety and efficacy experiments on those drugs.¹²⁰ The court assumed that the use of research tools in the later-stage safety and efficacy-related experiments would fall within the § 271(e)(1) safe harbor, leaving the only remaining commercial value of these research tools in their early-stage research uses.¹²¹ The court concluded that holding § 271(e)(1) to apply to such early-stage research, like the Scripps-

115. *Id.* at 867.

116. *Id.*

117. *Id.*

118. *Id.* at 865, 868.

119. *Id.* at 867.

120. *Id.*

121. *Id.*

Merck activities, would eliminate this remaining commercial value and “swallow the whole benefit of the Patent Act for some categories of biotechnological inventions.”¹²² Such an effect would run counter to Congress’s intent in drafting § 271(e)(1) to maintain a *de minimis* impact on the patentee’s rights.¹²³

2. Judge Newman Dissents

In dissent, Judge Newman argued that the challenged Scripps-Merck activities were “discovery-based research” that should be protected either by § 271(e)(1) or the common law research use exemption.¹²⁴ Judge Newman agreed with the panel majority that § 271(e)(1) should not “reach back down the chain of experimentation to embrace development and identification of new drugs,” but she argued that where the reach of § 271(e)(1) ends, the common law research use exemption should begin, and that either exemption could protect the Scripps-Merck experiments.¹²⁵

Judge Newman did not agree that the Scripps-Merck activities should automatically fall outside of the common law research use exemption simply because the ultimate goal of the Scripps-Merck research was commercializing a cure for cancer.¹²⁶ Instead, she advocated a shift away from the non-commercial focus of the common law research use exemption and towards “recogniz[ing] the exemption for research conducted in order to understand or improve upon or modify the patented subject matter.”¹²⁷ She remarked that this “is how the patent system has always worked: the patent is infringed by and bars activity associated with *development* and commercialization of infringing subject matter, but the *research* itself is not prohibited, nor is comparison of the patented subject matter with improved technology or with designs whose purpose is to avoid the patent.”¹²⁸

Judge Newman also argued that the research tools problem raised by the panel majority is a misperception.¹²⁹ She stated that “[t]here is a fundamental distinction between research into the science and technology disclosed in patents, and the use in research of patented products or meth-

122. *Id.*

123. *Id.*

124. *Integra Lifesciences I, Ltd. v. Merck KGaA (Integra I)*, 331 F.3d 860, 873 (Fed. Cir. 2003) (Newman, J., concurring in part, dissenting in part).

125. *Id.* at 877.

126. *Id.* at 876.

127. *Id.*

128. *Id.* (emphasis added).

129. *Id.* at 877.

ods, the so-called ‘research tools.’”¹³⁰ She noted that investigation into, or *research on*, patented inventions has always been permitted, whereas investigation using, or *research with*, patented inventions has never been permitted.¹³¹ She maintained that the Scripps-Merck syntheses and evaluations of new RGD peptides was *research on* the RGD peptides, not *research with* the Integra products as research tools.¹³²

C. The Supreme Court Reverses in *Merck*

Merck petitioned the case to the Supreme Court, who then granted certiorari on the question of “whether uses of patented inventions in preclinical research, the results of which are not ultimately included in a submission to the Food and Drug Administration (FDA), are exempted from infringement by 35 U.S.C. § 271(e)(1).”¹³³

The Federal Circuit, in *Integra I*, relied on the legislative history to narrow the scope of § 271(e)(1) to exclude Scripps’s early-stage drug discovery experimentation.¹³⁴ However, the Supreme Court responded that the “statutory text makes clear that [§ 271(e)(1)] provides a wide berth for the use of patented drugs in activities related to the federal regulatory process.”¹³⁵ The Court stated that the § 271(e)(1) exemption “extends to all uses of patented inventions that are reasonably related to the development and submission of *any* information under the FDCA” regardless of the “phase of research in which [such information] is developed or the particular submission in which [such information] could be included.”¹³⁶ The Court then stated that the “reasonably related” requirement, properly construed:

leaves adequate space for experimentation and failure on the road to regulatory approval: At least where a drugmaker has a reasonable basis for believing that a patented compound may work, through a particular biological process, to produce a particular physiological effect, and uses the compound in research that, if successful, would be appropriate to include in a submission to the FDA.¹³⁷

130. *Id.* at 877-78.

131. *Id.* at 878 n.10.

132. *Id.* at 878.

133. *Merck KGaA v. Integra Lifesciences I, Ltd. (Merck)*, 545 U.S. 193, 195 (2005).

134. *Integra I*, 331 F.3d at 866-67.

135. *Merck*, 545 U.S. at 202.

136. *Id.* (emphasis in original).

137. *Id.* at 207.

The Court held that “the use of patented compounds in preclinical studies is protected under § 271(e)(1) as long as there is a reasonable basis for believing that the experiments will produce ‘the types of information that are relevant to an IND or NDA.’”¹³⁸ The Court vacated the judgment and remanded the case to the Federal Circuit.¹³⁹

The Supreme Court explicitly left the research tools question undecided. Although the Federal Circuit was concerned that “expansion of § 271(e)(1) to include the Scripps-Merck activities would effectively vitiate the exclusive rights of patentees owning biotechnology tool patents,”¹⁴⁰ the Supreme Court declined to address the issue. In a footnote, the Court reasoned that Integra never argued that Scripps used the RGD peptides as research tools and that the record indicated that the RGD peptides were not used as research tools.¹⁴¹ The Court concluded: “We therefore need not—and do not—express a view about whether, or to what extent, § 271(e)(1) exempts from infringement the use of ‘research tools’ in the development of information for the regulatory process.”¹⁴²

D. Federal Circuit’s Decision on Remand (*Integra II*) and Judge Rader’s Dissent

On remand, the Federal Circuit reversed its previous holding of infringement from *Integra I*.¹⁴³ The court found that all the Scripps-Merck experiments implicated in the case, which were conducted after the discovery that RGD peptides could inhibit angiogenesis, yielded information concerning efficacy, pharmacology, pharmacokinetics, and mechanism of action that would be appropriate to include in an IND application to the FDA.¹⁴⁴ Following *Merck*, the Federal Circuit held that the challenged Scripps experiments were “reasonably related to research that, if successful, would be appropriate to include in a submission to the FDA” and thereby exempt from infringement under § 271(e)(1).¹⁴⁵

Judge Rader dissented on the grounds that the panel majority’s decision on remand expanded the § 271(e)(1) exemption beyond the scope dictated by the Supreme Court and effectively eliminated patent protection

138. *Id.* at 208.

139. *Id.*

140. *Integra I*, 331 F.3d at 867.

141. *Merck*, 545 U.S. at 205 n.7.

142. *Id.*

143. *Integra Lifesciences I, Ltd. v. Merck KGaA (Integra II)*, 496 F.3d 1334, 1348 (Fed. Cir. 2007).

144. *Id.* at 1345, 1347.

145. *Id.* at 1348.

for research tools.¹⁴⁶ Judge Rader maintained that the Supreme Court construed the § 271(e)(1) exemption to cover “the *use of patented drugs* in activities related to the federal regulatory process,” but the Court did not address research tools, such as patented methods or processes, that “measure, analyze, and assess the characteristics of those compounds during experimentation and development.”¹⁴⁷ Judge Rader noted that two of the patents-in-suit, the ’237 and ’734 patents, were not for patented drugs, but rather for research tools with no application outside of the laboratory.¹⁴⁸ The ’237 patent covers “[a] method for detaching animal cells from a substrate,” and the ’734 patent covers “[a] method of isolating cell surface receptors utilizing a short peptide sequence bound to an affinity column.”¹⁴⁹ Both patents claim only methods, or research tools, for use in laboratory settings.¹⁵⁰

Judge Rader provided a hypothetical example to illustrate the danger of including research tools within the § 271(e)(1) exemption. Suppose an inventor obtains a patent for a research tool that does not itself fight cancer but can test pharmaceutical compounds for cancer-fighting characteristics.¹⁵¹ The tool is therefore useful to the pharmaceutical industry and beneficial the public.¹⁵² Although the patent system “would wish to protect this invention and give incentives for more investment in developing this kind of valuable research tool,” including research tools within the § 271(e)(1) exemption “could obliterate all value for the hypothetical invention discussed above and with it the incentives for development of these inventions outside of the pharmaceutical industry itself.”¹⁵³

V. ANALYSIS

In light of the Supreme Court and Federal Circuit precedents, the status of common law and § 271(e)(1) protection from infringement liability for uses of a patented invention in drug research remains unclear. The common law research use exemption is extremely narrow and rarely applied, while the statutory language of the § 271(e)(1) safe harbor has been interpreted and applied broadly. This dichotomy generates clarity and administrability issues for researchers and courts, and potentially overpro-

146. *Id.* (Rader, J., dissenting in part and concurring in part).

147. *Id.* at 1349 (emphasis in original).

148. *Id.* at 1350.

149. *Id.* at 1350-51.

150. *Id.* at 1350.

151. *Id.* at 1352.

152. *Id.*

153. *Id.*

fects uses of patented research tools while under-protecting other beneficial research uses.

This Part highlights holes in standing precedent regarding the common law research use exception and the § 271(e)(1) safe harbor, and suggests an alternative course of action. Section V.A addresses problems inherent in Supreme Court and Federal Circuit precedent. Section V.B first suggests that Judge Newman's proposal to create a broad research use exemption and apply § 271(e)(1) narrowly as a regulatory approval exemption would alleviate these problems. Then, Section V.B illustrates that both Germany and the United Kingdom have statutory schemes that reflect Newman's approach.

A. Problems With the Current Supreme Court and Federal Circuit Precedents Regarding § 271(e)(1) and the Common Law Research Use Exemption

The current precedent raises three key concerns. First, the broad scope of § 271(e)(1) is unclear and provides minimal guidance to researchers and administrability problems for courts attempting to apply the statute. Second, taken together, § 271(e)(1) and the common law research use exemption may fail to provide a safe harbor for some beneficial research uses, such as experimentation to better understand, improve upon, and explore new uses for patented subject matter. Third, the status of research tools under § 271(e)(1) remains undecided, but the broad scope of § 271(e)(1) may improperly exempt from infringement other uses of patented research tools, thereby reducing economic incentives to further develop beneficial research tools.

1. The Application of § 271(e)(1) is Unclear for Researchers and Difficult for Courts to Administer

Despite the Supreme Court's broad construction of § 271(e)(1), the statute's focus on "the development and submission of information" for regulatory approval makes it unclear exactly which uses of a patented invention, especially uses in early stage research activities, fall under the safe harbor. The Federal Circuit held that the § 271(e)(1) exemption "does not globally embrace all experimental activity that at some point, however attenuated, may lead to an FDA approval process."¹⁵⁴ The Supreme Court agreed, but shifted the focus of the analysis to the researcher's intent, stating that "[b]asic scientific research on a particular compound, performed without the *intent* to develop a particular drug or a reasonable belief that

154. *Integra Lifesciences I, Ltd. v. Merck KGaA (Integra I)*, 331 F.3d 860, 867 (Fed. Cir. 2003).

the compound will cause the sort of physiological effect the researcher intends to induce, is surely not ‘reasonably related to the development and submission of information’ to the FDA.”¹⁵⁵ The Supreme Court further held that § 271(e)(1) applies as long as the researcher has a “reasonable basis for believing” that the experiments will produce information relevant to a regulatory submission.¹⁵⁶

These holdings fail to clearly define the scope of § 271(e)(1). As a result, researchers and drug companies will find it difficult to know exactly when uses of a patented invention amount to infringement, especially in the early stages of research where the development of information may not be directed towards any sort of regulatory approval process. Such uncertainty makes it difficult for researchers to properly plan a course of experimentation and efficiently allocate resources when choosing between purchasing a pricey patent license for potentially protected activities and facing litigation if their activities are not protected. Moreover, an intent-based test that focuses on a researcher’s “reasonable basis for believing” that his experiments will produce information relevant to a regulatory submission will prove difficult for courts to administer, due to the complicated nature of an inquiry into the objective and subjective reasonability of the researcher’s belief and intent during the research in question.

2. *Taken Together, § 271(e)(1) and the Common Law Research Use Exemption May Fail to Protect Some Experimental Uses that Merit Protection*

The Supreme Court’s approach may also fail to protect some socially beneficial research uses. Examples include early-stage experimentation conducted to understand, improve upon, or explore new uses for the patented subject matter. Such early stage experiments are socially beneficial, but often do not generate data useful for submission to the FDA and are not conducted with the “reasonable basis for believing” that the experiments would produce information relevant to a regulatory submission, thereby pushing these types of uses beyond the protection of § 271(e)(1).

The pre-1995 Scripps-Merck experiments illustrate the types of beneficial basic research potentially unprotected under the current safe harbor. Through this experimentation, Dr. Cheresch established that RGD peptides could halt tumor growth by binding to $\alpha_v\beta_3$ integrins and inhibiting angiogenesis. This capability was unknown to Integra, the RGD peptide patent holder. Without experimentation like Dr. Cheresch’s, novel, socially bene-

155. Merck KGaA v. Integra Lifesciences I, Ltd. (*Merck*), 545 U.S. 193, 205-06 (2005) (emphasis added).

156. *Id.* at 208.

ficial uses of patented inventions, like the power to halt tumors, could go undiscovered.

Fortunately for Scripps and Merck, the district court held that the common law research exception protected all but one of the pre-1995 Scripps-Merck activities relating to RGD peptides.¹⁵⁷ Although the Federal Circuit did not consider this issue on appeal, the court could easily have applied its holding in *Madey*, finding that these early Scripps-Merck activities were both conduct “in keeping with the alleged infringer’s legitimate business” as a research institute and funded by Merck with a commercial purpose in mind.¹⁵⁸ Such a finding would push Dr. Cheresh’s activities outside the protection of the narrow common law research use exemption. Moreover, Dr. Cheresh may have lacked the “reasonable basis for believing” that the pre-1995 experimentation would produce information relevant to a regulatory submission, leaving it outside the protection of § 271(e)(1). This result would leave this type of beneficial experimentation (experimentation done to understand, improve upon, or explore new uses for the patented subject matter) liable for infringement.

In sum, focusing on a researcher’s “reasonable basis for believing” that experiments will produce information relevant to a regulatory submission indicates that more experimental and uncertain research is less likely to be protected under § 271(e)(1). Coupled with the very limited application of the common law research use exemption, this may mean that some socially beneficial experimental uses fall outside the safe harbor protection afforded by § 271(e)(1) and the common law research use exemption.

3. *The Status of Research Tools is Left Unclear*

As Judge Rader vigorously argues in his *Integra II* dissent, the Federal Circuit’s decision leaves open the question of whether certain unauthorized uses of patented research tools could be exempt from patent infringement and receive protection from § 271(e)(1). Extending the § 271(e)(1) safe harbor to unauthorized uses of patented research tools could severely impact the economic incentives to further develop beneficial research tools.

a) The Current Statutory Interpretation of § 271(e)(1) Improperly Protects Research Uses of Patented Research Tools

Under the Supreme Court’s interpretation of the plain language of § 271(e)(1), one can derive the following rule: § 271(e)(1) exempts from infringement *all* uses of a *patented* invention (defined to include *all* inven-

157. *Integra II*, 496 F.3d at 1337.

158. *See Madey v. Duke Univ.*, 307 F.3d 1351, 1362 (Fed. Cir. 2002).

tions, not just drug-related inventions) reasonably related to the process of developing *any* information for submission under *any* federal law regulating the manufacture, use, or distribution of drugs; regardless of the phase of research in which the information is developed, the particular submission in which the information could be included, or whether such information is ever actually submitted.¹⁵⁹ Thus, the Supreme Court has construed § 271(e)(1) as broadly as the plain language of the statute allows.

Without any limits on the type of use or the category of invention, the Court's construction suggests that any use of a research tool, during any phase of research, to develop information that could potentially be submitted to the FDA, would be exempt from infringement under § 271(e)(1). Such an interpretation could eliminate incentives to develop research tools by diminishing the research tool manufacturers' ability to recover high development costs.¹⁶⁰

Some comfort stems from the Supreme Court's acknowledgement of the Federal Circuit's suggestion that "a limited construction of § 271(e)(1) is necessary to avoid depriving so-called 'research tools' of the complete value of their patents." The Court further declined to "express a view about whether, or to what extent, § 271(e)(1) exempts from infringement the use of 'research tools' in the development of information for the regulatory process" because the respondents failed to put forth such an argument.¹⁶¹ Nevertheless, given the Court's strict adherence to the plain statutory language, the use of research tools to develop information for the FDA could easily fall under the § 271(e)(1) exemption.

b) Congress Did Not Intend the Use of Patented Research Tools to be Protected under § 271(e)(1)

Although the current Supreme Court interpretation of § 271(e)(1) may encompass research tools, the text and legislative history of the 1984 Act indicate that Congress did not intend § 271(e)(1) to apply to research tools. As noted in *Eli Lilly*, the 1984 Act attempted to correct distortions to both ends of the patent term caused by the regulatory approval process.¹⁶² Congress enacted § 271(e)(1) to allow generic drug companies to test patented drugs for regulatory approval purposes prior to patent expiration and

159. See *Merck*, 545 U.S. at 202, 206-07; *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 665 (1990).

160. Jonathan McPherson, Note, *The Impact of the Hatch-Waxman Act's Safe Harbor Provision on Biomedical Research Tools after Merck v. Integra Lifesciences I, Ltd.*, 10 MICH. ST. U. J. MED. & L. 369, 376 (2006).

161. *Merck*, 545 U.S. at 205 n.7.

162. *Eli Lilly*, 496 U.S. at 669.

to prevent the *de facto* term extension at the end of the life of the patent. Further, § 156 provided a term extension to the pioneer patent holder to correct for the regulatory approval process at the beginning of the patent's lifetime.¹⁶³ While § 271(e)(1) does not explicitly define the meaning of "patented invention," § 156 covers human drug products, and any medical devices, food additives, or color additives subject to regulation under the FDCA.¹⁶⁴ Given the congressional intent behind the 1984 Act, one can logically conclude that the term "patented invention" in § 271(e)(1) refers only to those inventions explicitly listed in § 156.¹⁶⁵ Accordingly, research tools, which are not listed in § 156 and are not the subject of regulatory approval, should not fall under the § 271(e)(1) safe harbor.¹⁶⁶

Moreover, as noted in Judge Rader's *Integra II* dissent, Congress explicitly stated that under the 1984 Act, the "nature of the interference with the rights of the patent holder" would not be "substantial," but "*de minimus* [sic]."¹⁶⁷ Unlike patented drugs, which are ultimately sold to the general public, the predominant commercial market for research tools is researchers and drug developers. Thus, sweeping research tools under the § 271(e)(1) exemption would allow many research tool users to infringe those patents in uses that generate data for the FDA. As Judge Rader's majority opinion in *Integra I* concluded, this result would "vitate the exclusive rights of patentees owning biotechnology tool patents" and "swallow the whole benefit of the Patent Act for some categories of biotechnological inventions."¹⁶⁸ Such a conclusion stands contrary to the stated intention of Congress in the legislative history to the 1984 Act.

B. Judge Newman's Approach as a Potential Alternative

In her *Integra I* dissent, Judge Newman proposes expanding the common law research use exemption to provide broad protection for beneficial research uses of patented inventions. This protection would thus be achieved without requiring courts to stretch the limits of § 271(e)(1) protection as far as the statute's plain language will tolerate. As a result, courts could apply § 271(e)(1) narrowly as the regulatory approval exemp-

163. *Id.* at 670-71.

164. 35 U.S.C. § 156(f) (2000); *Eli Lilly*, 496 U.S. at 670-71.

165. The Supreme Court followed a similar analysis in *Eli Lilly* to find that medical devices are covered by § 271(e)(1). *See Eli Lilly*, 496 U.S. at 669-73.

166. Walker, *supra* note 44, at 38.

167. *Integra Lifesciences I, Ltd. v. Merck KGaA (Integra II)*, 496 F.3d 1334, 1350 (Fed. Cir. 2007) (Rader, J., dissenting in part and concurring in part) (citing 1984 U.S.C.C.A.N. at 2692, 2714).

168. *Integra Lifesciences I, Ltd. v. Merck KGaA (Integra I)*, 331 F.3d 860, 867 (Fed. Cir. 2003).

tion that Congress originally intended. Such an approach would achieve the same results as the *Integra II* decision without the creating the same problems addressed above.

Judge Newman advocates shifting away from the current non-commercial determinant for protection under the common law research use exemption, and moving towards “recogniz[ing] the exemption for research conducted in order to understand or improve upon or modify the patented subject matter.”¹⁶⁹ Judge Newman suggests drawing the line for the research use exemption between the *research* phase and the *development* phase of the drug development pipeline.¹⁷⁰ She remarks that this “is how the patent system has always worked: the patent is infringed by and bars activity associated with *development* and commercialization of infringing subject matter, but the *research* itself is not prohibited, nor is comparison of the patented subject matter with improved technology or with designs whose purpose is to avoid the patent.”¹⁷¹ Judge Newman also suggests this approach removes the “limbo” between protection under the common law exemption and protection under the § 271(e)(1) exemption. Instead, “the statutory immunity of § 271(e)(1) takes effect wherever the research exemption ends.”¹⁷²

In addition to the *research/development* distinction, Judge Newman further refines *research* to distinguish between *research on* and *research with* the patented subject matter. She finds “a fundamental distinction between research into the science and technology disclosed in patents, and the use in research of patented products or methods, the so-called ‘research tools.’”¹⁷³ She states that investigation into, or *research on*, patented things with a goal to understand, improve upon, or modify the patented subject matter has always been permitted and should not constitute infringement because this activity provides the public with improvements and competition in the marketplace.¹⁷⁴ On the other hand, she argues that investigation using, or *research with*, patented things for their intended purpose in research has never been permitted and should constitute infringement because such activities eliminate the value in these patented things.¹⁷⁵

169. *Id.* at 876 (Newman, J., concurring in part, dissenting in part).

170. *Id.*

171. *Id.* (emphasis added).

172. *Id.* at 876-77.

173. *Id.* at 877-78.

174. *Id.* at 878 n.10.

175. *Id.*

1. *Judge Newman's Approach Solves the Problems Created by Supreme Court and Federal Circuit Precedent*

First, Judge Newman's approach solves some of the administrability and clarity problems arising under the current statutory interpretation of § 271(e)(1). Currently, the focus of the § 271(e)(1) analysis is on determining what qualifies as "development and submission of information" for regulatory approval and whether the researcher has a "reasonable basis for believing" that the experiments will produce information relevant to a regulatory submission. These determinations provide unclear guidance to researchers as to whether experimentation amounts to infringement and force judges to make inherently difficult determinations regarding reasonableness of belief and researcher intent. Judge Newman's approach, on the other hand, shifts the focus to the more concrete question of whether the activities in question constitute *research*, whereby such activities are protected by the common law research use exemption, or *development*, whereby such activities are protected under § 271(e)(1).

Judge Newman's approach also protects the beneficial experimental uses of patented inventions that may be left unprotected under the current § 271(e)(1) and common law research use exemption precedent. As applied to the pre-1995 Scripps-Merck experiments, the current precedent would likely leave this basic and socially beneficial research unprotected due to the narrow non-commercial application of the common law research use exemption and § 271(e)(1)'s focus on the researcher's intent and the experiments' usefulness to FDA submissions. However, using Judge Newman's *research/development* distinction, the pre-1995 Scripps-Merck experimentation clearly constitutes research that would be protected under the research use exemption.

Finally, Judge Newman's distinction between *research on* the patented subject matter and *research with* the patented subject matter would ensure that *research on* a patented research tool with a goal to understand, improve upon, or modify the patented subject matter would be exempt from infringement, while *research with* a patented research tool for its intended purpose in research would constitute infringement. This approach would prevent § 271(e)(1) from protecting *research with* research tools and thereby preserve the value of those tools.¹⁷⁶

176. The dissenting opinion of Judge Rader also proposes adopting the distinction between research *into*, or research on a patented invention and research *using*, or research with a patented invention. *Integra Lifesciences I, Ltd. v. Merck KGaA (Integra II)*, 496 F.3d 1334, 1353 (Fed. Cir. 2007) (Rader, J. concurring in part and dissenting in part). Judge Rader notes that many international statutes and court decisions protect research

2. Validation for Judge Newman's Approach

Judge Newman's approach is not new. More than a decade before *Integra I*, Congress considered a similar research use exemption in the Patent Competitiveness and Technological Innovation Act of 1990 (the 1990 Act).¹⁷⁷ That proposed legislation embraced the *research/development* distinction and the *research on/research with* distinction later proposed by Judge Newman. Moreover, both Germany and the United Kingdom have broad statutory research use exemptions that hinge on the *research on/research with* distinction coupled with narrower regulatory approval exemptions.

a) Judge Newman's Approach as Foreshadowed in the Patent Competitiveness and Technological Innovation Act of 1990

In the 1990 Act, Congress considered a research use exemption similar to the approach Judge Newman advocated in *Integra I*. That bill would have amended § 271, adding:

(j) It shall not be an act of infringement to make or use a patented invention solely for research or experimentation purposes unless the patented invention has a primary purpose of research or experimentation. If the patented invention has a primary purpose of research or experimentation, it shall not be an act of infringement to manufacture or use such invention to study, evaluate, or characterize such invention or to create a product outside the scope of the patent covering such invention. This subsection does not apply to a patented invention to which [§ 271](e)(1) applies.¹⁷⁸

The committee report accompanying this legislation further elucidated how the act was meant to function:

The easiest method of limiting and describing the 'experimental use of research exception' is to differentiate between experimentation on a patented invention and experimentation using a patented invention in order to accomplish another purpose, the former type of experimentation constituting the scope of the exception. Under this approach the following acts would not constitute patent infringement:

tool inventions "when used for their intended purpose while allowing experimentation to improve the tool itself" or to learn its method of operation. *Id.*

177. H.R. Rep. No. 101-960, pt. I (1990).

178. *Id.* at 47.

- (1) testing an invention to determine its sufficiency or to compare it to prior art;
 - (2) tests to determine how the patented invention works;
 - (3) experimentation on a patented invention for the purpose of improving on it or developing a further patentable invention;
 - (4) experimentation for the purpose of ‘designing around’ a patented invention;
 - (5) testing to determine whether the invention meets the tester's purposes in anticipation of requesting a license; and
 - (6) academic instructional experimentation with the invention.
- Business testing is clearly not an experimental use, and would not be authorized by Title IV.¹⁷⁹

Thus, the proposed act embraced the *research/development* distinction later proposed by Judge Newman, by attempting to codify a statute that would create a broad exemption for uses of patented inventions in research or experimentation. Moreover, like Judge Newman, Congress also recognized the *research on/research with* distinction and attempted to limit its research use exemption to research on patented inventions and not for research using patented inventions.

The proposed act was never brought to a vote and did not move beyond the House of Representatives.¹⁸⁰

- b) Both Germany and the United Kingdom Employ Broad Research Use Exemptions Similar to Judge Newman’s Approach

Both Germany and the United Kingdom have adopted statutory research use provisions pursuant to Article 31 of the European Community Patent Convention of 1976.¹⁸¹ Both countries’ research use provisions focus on the distinction between *research on* and *research with*.

German Patent Law Section 11, the German experimental use provision, specifies that “[t]he effects of a patent shall not extend to (1) acts done privately and for non-commercial purposes; (2) acts done for experimental purposes relating to the subject matter of the patented inven-

179. *Id.* at 30.

180. Walker, *supra* note 44, at 30.

181. Sean O’Connor, *Enabling Research or Unfair Competition? De Jure and De Facto Research Use Exceptions in Major Technology Countries*, in *COMPARATIVE PATENT LAW: A HANDBOOK OF CONTEMPORARY RESEARCH* (Toshiko Takenaka & Rainer Moufang eds., Edward Elgar forthcoming 2008) (manuscript at 10, on file with author), available at <http://ssrn.com/abstract=1069222>.

tion; . . .”¹⁸² Under the plain language of this statute, German patent law allows *research on* a patented invention (“relating to the subject matter of the patented invention”) regardless of whether it is private or non-commercial, while *research with* a patented invention is allowed only where the research is private and non-commercial.¹⁸³ The German Supreme Court confirmed and expanded this interpretation in *Klinische Versuche I*,¹⁸⁴ holding that § 11 of the German Patent Act:

exempts all experimental acts as long as they serve to gain information and thus to carry out scientific research into the subject-matter of the invention, including its use. There are then included, for example, utilization acts for experimental purposes undertaken with the subject-matter of the invention in order to discover the effects of a substance or possible new uses hitherto unknown. Since the provision makes no limit, either qualitative or quantitative, on the experimental acts, it cannot matter whether the experiments are used only to check the statements made in the patent or else to obtain further research results, and whether they are employed for wider purposes, such as commercial interests.¹⁸⁵

Like German Patent Law Section 11, U.K. Patents Act Sections 60(5)(a) and (b) state that “[a]n act which . . . would constitute an infringement of a patent for an invention shall not do so if—(a) it is done privately and for purposes which are not commercial; (b) it is done for experimental purposes relating to the subject matter of the invention; . . .”¹⁸⁶ U.K. Patents Act Section 60(5)(a) permits either *research on* or *research with* the patented invention so long as the research is private and non-commercial, while § 60(5)(b) also permits *research on* the patented invention (“relating to the subject matter of the invention”) where such research is experimental.¹⁸⁷

Additionally, in response to a 2004 directive from the European Union, both Germany and the U.K. amended their research use provisions to

182. German Patent Law § 11, THE NEW GERMAN PATENT LAW (1981) IN ENGLISH AND GERMAN 24-27 (Dr. Hermann Kinkeldey & Dr. Wilfried Stockmair trans., 1981).

183. O’Connor, *supra* note 181, at 10-11.

184. *Klinische Versuche I*, [1997] R.P.C. 623 (German Supreme Court).

185. *Id.* at 639.

186. Patents Act, 1977, c.37, 60(5) (U.K.)

187. O’Connor, *supra* note 181, at 13.

include a regulatory approval exemption similar to § 271(e)(1).¹⁸⁸ The amended German Patent Law Section 11 No. 2b, states:

The rights conferred by a patent shall not extend to . . . studies and trials and the consequential practical requirements necessary for obtaining an authorization to market a drug in the European Union or for obtaining an authorization to market a drug in the Member States of the European Union or in other countries.¹⁸⁹

U.K. Patents Act Section 60(5)(i) reads:

An act which, apart from this subsection, would constitute an infringement of a patent for an invention shall not do so if . . . it consists of—(i) an act done in conducting a study, test or trial which is necessary for and is conducted with a view to the application of [the regulatory approval processes of various EU Directives], or (ii) any other act which is required for the purpose of the application of those paragraphs [of the Directives].¹⁹⁰

Thus, statutory systems in both Germany and the U.K. parallel Judge Newman's proposed approach. Both countries use broad research use exemptions based on the distinction between *research on* and *research with* patented subject matter. Additionally, both countries have enacted separate, narrow regulatory approval exemptions that function much as § 271(e)(1) would in the context of Newman's approach.

VI. CONCLUSION

Despite the Federal Circuit's recent *Integra II* decision, the status of protection from infringement liability for uses of a patented invention in drug research remains uncertain. Problems remain between the narrow and rarely-applied common law research use exemption and the broadly-interpreted and oft-applied § 271(e)(1) regulatory submission exemption. These include: 1) administrability and clarity problems for courts and researchers in the application § 271(e)(1); 2) potential under-protection of

188. *Id.* at 17-18. In 2004, the European Union passed Directive 2004/27/EC which amended Article 10(6) of Directive 2001/83/EC to read: "Conducting the necessary studies and trials with a view to [satisfying the abbreviated regulatory approval process for generic medicines] and the consequential practical requirements shall not be regarded as contrary to patent rights or to supplementary protection certificates for medicinal products." *Id.* at 17.

189. *Id.* at 17-18.

190. U.K. Patents Act 1977, § 60(5), available at <http://www.ipo.gov.uk/patentsact1977.pdf>; O'Connor, *supra* note 181, at 17.

beneficial early stage research; and 3) potential over-protection of research tool uses that should not be protected.

One potential solution to these problems is to create an expanded research use defense similar to the one proposed in Judge Newman's dissent in *Integra I* and employed in other countries' statutory schemes. This research use defense could either be created judicially by expanding the exceedingly narrow U.S. common law research use exemption or legislatively by enacting statutes modeled after those in Germany and the United Kingdom. Such a defense would allow *research* using patented inventions, but restrict *development* using patented inventions; and would allow *research on* patented inventions, but restrict *research with* patented inventions. This approach would provide clarity and administrative ease by narrowing § 271(e)(1)'s application to activities related to the regulatory approval process as Congress initially intended. This approach also provides protection for those beneficial uses that might be unprotected under the current scheme, while ensuring that research tool uses would not be protected.

The courts have tried to use a broad statutory interpretation of § 271(e)(1) to overcome the limitations posed by the narrow common law research use exemption, but this is an inefficient and inappropriate way to achieve the desired results. Instead, either the legislature should step in to craft an appropriately broad statutory research use exemption and a limited § 271(e)(1) regulatory approval exemption, or the courts should attempt to accomplish similar means by expanding the common law research use exemption.