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COMMENT

Navigating the Research Exemption's Safe Harbor: Supreme Court to Clarify Scope—Implications for Stem Cell Research in California

Gina C. Freschi†

I. INTRODUCTION

In January 2005, the Supreme Court agreed to review the Federal Circuit's holding in *Integra LifeSciences I, Ltd. v. Merck KGaA*.¹ The decision, largely seen as a victory for research tool patentees in the biotechnology sector, would if affirmed, promote cross-licensing between universities and industry, as well as discourage misappropriation of unlicensed patented tools.² Pharmaceutical manufacturers argue that the decision is a limitation on drug development activities that could potentially benefit human health, and that restricting the use of tool patents in biomedical research could mean years of delay in the availability of new, life-saving drugs.³

The underpinnings of the *Integra* ruling involve federally enacted, 35 U.S.C. § 271(e)(1).⁴ To encourage development and expedite the introduction of pharmaceuticals into the marketplace,

† J.D., Santa Clara University School of Law, 2005; B.S./M.S., University of California at San Diego, Biochemistry and Cell Biology, 1999. The author would like to thank Professor Paul A. Stone, Esther Ko and Jennifer Chen for their critical assistance and commentary.

1. 331 F.3d 860 (Fed. Cir. 2003), *cert. granted*, 125 S. Ct. 823 (2005) (U.S. Jan. 7, 2005) (No. 03-1237).

2. Mark D. Uehling, *Bio-IP 'Harbor' No Longer Safe for Research?*, BIO-IT WORLD, Aug. 2003, at 1, 23–26.

3. See Petitioner's Appellate Petition for Writ of Certiorari at 1, *Merck KGaA v. Integra LifeSciences I, Ltd.*, 125 S. Ct. 823 (2005) (No. 03-1237).

4. 35 U.S.C. § 271(e)(1) (2000). The statute has come to be known as the "FDA research exemption" or "safe harbor," terms used interchangeably in this Comment. See *infra* text accompanying note 40.

Congress amended the patent laws in 1984 to insulate drug research from charges of infringement so long as such research is “solely for uses reasonably related to the development and submission of information” to the Food and Drug Administration (“FDA”).⁵ The statute renders activities that would otherwise constitute patent infringement noninfringing if they are undertaken for the purpose of developing and submitting to the FDA information necessary to obtain marketing approval for a new chemical entity, a medical device, or a food additive.⁶ Hence, the statute benefits competitors of a patentee by freeing them of liability for development work reasonably related to securing regulatory approval.

In interpreting the meaning of the phrase, “solely for uses reasonably related to,” the *Integra* court clarified that the FDA research exemption applies only to those activities that directly support information submitted for regulatory approval, such as bioequivalency data for generic drug analogs.⁷ Specifically, the court stated that the safe harbor did not “reach any exploratory research that may rationally form only a predicate for future FDA clinical tests.”⁸ The court held that Merck’s unlicensed use of *Integra*’s patented research tool could not fall within the safe harbor provisions of § 271(e)(1) because Merck was not involved in clinical testing to supply information to the FDA, but rather, had performed exploratory, pre-clinical biomedical research aimed at identifying a new drug candidate.⁹ Hence, according to the Federal Circuit, pre-clinical testing (that which occurs before human testing) falls outside the safe harbor.

Accordingly, the *Integra* decision affirms that “upstream” research activities do not enjoy the benefits of the safe harbor, i.e., there is no defense to infringement for the use of patented materials during the development of new drugs, or for general biomedical experimentation, or for so-called “drug hunting.”¹⁰ At the outset, this seems reasonable when read in the context of the policy objective of

5. 35 U.S.C. § 271(e)(1) (2000).

6. *Eli Lilly & Co. v. Medtronic, Inc.* 496 U.S. 661, 664, 672 (1990).

7. Paul Fehlner & Christina Yun-Ting Tsou, *Not Such a Safe Harbor After All*, INTELL. PROP. LITIG. REP. Aug. 2003, at 2–3, available at http://www.darbylaw.com/Files/tbl_s31Publications/FileUpload137/1802/INT%20Vol10%20Iss6.pdf.

8. *Integra LifeSciences I, Ltd. v. Merck KGaA.*, 331 F.3d 860, 867 (Fed. Cir. 2003), cert. granted, 125 S. Ct. 823 (2005) (U.S. Jan. 7, 2005) (No. 03-1237).

9. See *id.* at 865–68.

10. Fehlner & Tsou, *supra* note 7, at 2.

§ 271(e)(1), which was to facilitate the immediate entry of safe, effective generic drugs into the marketplace upon expiration of a pioneer drug patent.¹¹ Less than a year earlier, however, in *Madey v. Duke University*,¹² the Federal Circuit confirmed that the U.S. has a very narrow common law experimental use exemption, which excludes from immunity any use of unlicensed patented tools that is “in furtherance of the alleged infringer’s legitimate business.”¹³ Read together, the *Integra* and *Madey* decisions could limit what many academics have long seen as their right to use intellectual property under statutory and common law research exemptions. In *Madey*, when the court characterized the running of a university as a business aimed at attracting students, Duke University’s use of a patented laser was seen as an effort directed toward garnering tuition-paying students, and not as promoting learning for learning’s sake.¹⁴ Various commentators have expressed disagreement with these rulings as encroaching on the progress of biomedical research at universities.¹⁵

As the use of research tools in pre-clinical studies and basic science is widespread among research universities and not-for profit organizations, spectators are left wondering whether the Supreme Court will affirm the Federal Circuit’s ruling. Will biotechnology and/or other research productivity companies be able to successfully assert infringement of tool-type patents against university and not-for profit researchers?¹⁶ Where such research has potentially significant implications for public health, many have voiced an urgent need for a system that protects a patentee’s rights while simultaneously promoting basic research.¹⁷ At the same time, would an expansion of

11. *Integra*, 331 F.3d at 866–67; see also Brief of Amicus Curiae Generic Pharmaceutical Industry Association at 12, *Roche Prods., Inc. v. Bolar Pharm. Co.*, 733 F.2d 858 (Fed. Cir. 1984) (No. 84-560), cert. denied, 469 U.S. 856 (1984).

12. 307 F.3d 1351 (Fed. Cir. 2002), cert. denied, 539 U.S. 958 (2003).

13. *Id.* at 1362.

14. See *id.* at 1362–63.

15. See, e.g., Tom Saunders, *Renting Space on the Shoulders of Giants: Madey and the Future of the Experimental Use Doctrine*, 113 YALE L.J. 261, 262 (2003).

16. Public universities, as arms of the states, may be granted sovereign immunity from patent infringement liability under the Eleventh Amendment. In determining liability, courts have looked to whether state actors fail to provide a remedy, “or only inadequate remedies, to injured patent owners.” Fla. Prepaid Postsecondary Educ. Expense Bd. v. Coll. Savs. Bank, 527 U.S. 627, 643 (1999) (finding unconstitutional a federal statute abrogating state immunity from patent infringement).

17. Janice M. Mueller, *The Evanescent Experimental Use Exemption from United States Patent Infringement Liability: Implications for University and Nonprofit Research and Development*, 56 BAYLOR L. REV. 917, 921 (2004) (“A limited but meaningful experimental

the Federal Circuit's interpretation of the "safe harbor" exaggerate § 271(e)(1) out of context and remove the benefits of the Patent Act for biotechnological inventions?

The Supreme Court will consider whether the Federal Circuit erred in holding that the research exemption does not encompass drug development activities beyond those necessary to acquire information for FDA approval of a patented pioneer drug already on the market.¹⁸ In particular, the Court will address whether the safe harbor protects research studies back down the chain in the drug development process, studies the pharmaceutical industry contends are distantly, but still "reasonably related" to securing FDA approval.

This Comment explores the effect the decision will have on research that is too remote from the FDA approval process to fall within the statutory safe harbor, as well as research that is commercial in nature, such that it does not qualify for the common law research exemption articulated in *Madey*. Research associated with the California Institute for Regenerative Medicine ("CIRM") is likely to number among these kinds of research endeavors. Proposition 71, the California Stem Cell Research and Cures Initiative,¹⁹ was approved by voters on November 2, 2004.²⁰ This legislation provides roughly \$3 billion in state bond money over ten years for human embryonic stem cell research and facilities, specifically focused on embryonic stem cell and progenitor cell research,²¹ which would be unlikely to

use exemption would further the patent system's constitutionally mandated goal of 'promoting the progress of . . . the useful arts.'" (quoting U.S. CONST. art. I, § 8, cl. 8.)).

18. *Integra LifeSciences I, Ltd. v. Merck KGaA*, 331 F.3d 860, 867 (Fed. Cir. 2003), cert. granted, 125 S. Ct. 823 (2005) (U.S. Jan. 7, 2005) (No. 03-1237); see also Brief for Petitioner at i, *Merck KGaA v. Integra LifeSciences I, Ltd.*, 125 S. Ct. 823 (Feb. 15, 2005) (No. 03-1237) (framing the question presented as whether the FDA safe harbor protects the animal and test-tube studies that typically accompany an application to the FDA to allow a new drug to proceed to clinical trials with humans).

19. The California Institute for Regenerative Medicine (CIRM), official website, at <http://www.cirm.ca.gov> (last visited Apr. 3, 2005); see also California Research and Cures Coalition, official website, at <http://www.curesforcalifornia.com> (last visited Apr. 3, 2005).

20. See CALIFORNIA SECRETARY OF STATE, OFFICIAL VOTER INFORMATION GUIDE 147-49 § 5 (Nov. 2, 2004), available at <http://www.voterguide.ss.ca.gov/english.pdf>.

The [Independent Citizen's Oversight Committee] ICOC shall establish standards that require that all grants and loan awards be subject to intellectual property agreements that balance the opportunity of the State of California to benefit from the patents, royalties, and licenses that result from basic research, therapy development, and clinical trials with the need to assure that essential medical research is not unreasonably hindered by the intellectual property agreements.

Id. (referring to section 125290.3(h) to be added California's Health and Safety Code).

21. *Id.* at 147 § 3.

receive timely or sufficient federal funding due to current federal limitations on such research.

The Supreme Court's ruling will likely govern the use of research tools in state-funded stem cell research activities at universities and not-for profit organizations, as well as the use of such tools (including stem cell lines) generated by this research. As a result, the apparent commercial intent of stem cell research funded under Proposition 71 will be a critical factor in applying the Supreme Court's ruling. In addition, because stem cell research is in its early stages (arguably years away from the point of regulatory submissions) the Court's interpretation of "reasonably related to the development and submission of information under a Federal law,"²² will most certainly impact whether the unlicensed use of patented research tools by groups associated with CIRM falls within the statutory safe harbor. At the same time, because the state seeks to benefit from patents ultimately granted under CIRM, giving such intellectual property the broadest possible scope of protection is arguably in the state's best interest.

This Comment explores the three most likely outcomes of the pending Supreme Court decision and considers the implications in the area of licensing research tools, and in particular, the regulation of research using human embryonic stem cells in California with respect to Proposition 71. Would affirmation of the *Integra* ruling, when read in light of *Madey*, cause stem cell research to fall outside both the statutory and common law research exemptions due to its early stage of development and commercial purpose? Will this encumber academic research scientists by requiring them to license patented research tools that have until now appeared available to them under the statutory and common law research exemptions? Or, would affirmation of the Federal Circuit's ruling be in the state's best interest due to its intention of profiting from patents and royalties generated under CIRM?

In considering the various potential courses of action that the Supreme Court may take, Part IV weighs competing policies including: (1) the cost of drug research, (2) the incentive to develop new chemical entities and research tools, (3) the need for access to research tools, (4) the inability of academic institutions and nonprofit organizations to afford costly licenses, and (5) the legislative history. Part II presents (1) a background of policy concerns in patent doctrine

22. 35 U.S.C. § 271(e)(1) (2000).

and the emergence of the experimental use exemption, (2) the development of the statutory FDA research exemption, (3) the facts of the cases at issue, (4) a study of activities that have thus far been held exempt from patent infringement, (5) a discussion of the definition of “research tools,” and (6) a description of stem cells as research tools. Finally, Part IV argues that affirmation of the ruling is the best way to preserve the incentives of the Patent Act, and that the legislature is the best equipped branch of the government to specify the parameters of the research exemption.

II. BACKGROUND

A. Competing Policy Concerns in Patent Doctrine and the Experimental Use Exception

Article I of the United States Constitution states:

The Congress shall have the Power . . . To promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries.²³

Patent protection laws were later enacted to embody these Constitutional provisions. For example, the 1984 Patent Act characterizes patent infringement in its preliminary paragraphs, providing, in part:

[w]hoever 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.²⁴

Yet, two divergent policy concerns—a patentee’s interest in protecting his invention (and the commercial value thereof), and the public’s interest in benefiting from the technology²⁵—continue to compete for lawmakers’ recognition.

The rights inherent in a patent term of twenty years are set forth in federally enacted 35 U.S.C. § 154(a)(1):

Every patent shall contain a short title of the invention and a grant to the patentee, his heirs or assigns, of the right to exclude others from making, using, offering for sale, or selling the invention

23. U.S. CONST. art. I, § 8, cl. 8.

24. 35 U.S.C. § 271(a) (2000).

25. DONALD S. CHISUM ET AL., PRINCIPLES OF PATENT LAW 1205 (Robert C. Clark et al. eds., 2d ed. 2001).

throughout the United States or importing the invention into the United States, and, if the invention is a process, of the right to exclude others from using, offering for sale or selling throughout the United States, or importing into the United States, products made by that process, referring to the specification for the particulars thereof.²⁶

It follows that a patentee has a statutory right to exclude others from acts that infringe his patent. Yet this right may be limited by a defense of “experimental use,” a doctrine whose origins are often linked to an opinion written by Circuit Justice Joseph Story in a case before the Massachusetts Circuit Court in 1813.

In *Whittemore v. Cutter*,²⁷ Justice Story reasoned in dicta regarding the alleged infringement of a patent covering a machine that produced playing cards: “[I]t could never have been the intention of the legislature to punish a man, who constructed such a [patented] machine merely for philosophical experiments, or for the purpose of ascertaining the sufficiency of the machine to produce its described effects.”²⁸ Subsequently, in *Sawin v. Guild*,²⁹ Justice Story fashioned an experimental use defense to exempt alleged patent infringers who did not intend to profit by way of the infringing activity. Use of a patented invention “for the mere purpose of philosophical experiment, or to ascertain the verity and exactness of the specification” describing the invention would not constitute patent infringement.³⁰ Hence, the test seemed to turn on the commercial intent of the patent user. Almost fifty years later, Judge Shipman wrote, “It has been held, and no doubt is now well settled, that an experiment with a patented article for the sole purpose of gratifying a philosophical taste, or curiosity, or for mere amusement, is not an infringement of the rights of the patentee,”³¹ thereby further developing the common law experimental use doctrine, so that it protected use of patented

26. 35 U.S.C. § 154(a)(1) (2002).

27. 29 F. Cas. 1120 (C.C.D. Mass. 1813) (No. 17,600).

28. John F. Duffy, *Harmony and Diversity in Global Patent Law*, 17 BERKELEY TECH. L.J. 685, 717–18 (2002) (quoting *Whittemore v. Cutter*, 29 F. Cas. 1120, 1121 (C.C.D. Mass. 1813) (No. 17,600)). *But see* Rebecca S. Eisenberg, *Patent Swords and Shields*, 299 SCIENCE 1018, 1018 (2003) (contending that “Justice Story’s early-19th-century picture of a gentleman scientist driven by idle curiosity predates the rise of the modern research university”).

29. 21 F. Cas. 554 (C.C.D. Mass. 1813) (No. 12,391).

30. *Id.* at 555.

31. *Poppenhusen v. Falke*, 19 F. Cas. 1048, 1049 (C.C. S.D.N.Y. 1861) (No. 11,279).

inventions for amusement or verification of the workings of the invention, but excluded activities motivated by financial gain.³²

Thus, the common law experimental use doctrine in patent law makes an exception for infringers who use patented inventions for the sole purpose of experimentation, or purely philosophical inquiry. The “experimentation” described refers to a study of the patented inventions—clearly not the use of a patented invention to investigate an altogether different experiment, such as using patented microarray technology to study cancer cells. Therefore, the issue that remains is to define “philosophical inquiry” in today’s society.³³ In our technology-driven economy, close ties between academic and commercial research are commonplace, making it difficult to draw a clear line between academic inquiry for the purposes of basic research, and research conducted with some expectation of future monetary gain. The same discrepancy may be found in the interpretation of the terms “science” and “technology.” Some have opined that when the common law research exemption emerged almost 200 years ago, “science” must have been considered separate from “technology,” as basic scientists had little to do with industry, and basic and applied research were thought to be distinct fields.³⁴

While courts continue to acknowledge the existence of the common law experimental use doctrine, they frequently find a commercial motive behind the accused infringing activity. In the pharmaceutical industry, there is ongoing tension between the simultaneous need to establish incentives for pioneer-drug companies (typically large pharmaceutical companies) to invest in the research and development of new drugs, and the need to enable generic competitors to bring competitively priced analogs to the market. Discoveries made in biomedical research often have spectacular applications in the multi-billion dollar healthcare market. The combination of high-stakes economic value and contemporaneous

32. *Id.* See also Eisenberg, *supra* note 28, at 1018 (noting that only one case since 1861 generated a published opinion holding that use of a patented invention in a university laboratory qualifies for the defense; see *Ruth v. Stearns-Roger Mfg. Co.*, 13 F. Supp. 697, 713 (D. Colo. 1935)).

33. *Integra LifeSciences I, Ltd. v. Merck KGaA*, 331 F.3d 860, 874–75 n.8 (Fed. Cir. 2003), *cert. granted*, 125 S. Ct. 823 (2005) (Newman, J., dissenting) (“By ‘philosophical’ experiments Justice Story was referring to ‘natural philosophy,’ the term then used for what we today call ‘science.’”).

34. Graeme B. Dinwoodie & Rochelle Cooper Dreyfuss, *International Intellectual Property Law and the Public Domain of Science*, 7 J. INT’L ECON. L. 431, 433 (2004).

improvements in the quality of healthcare has required balancing these two priorities.³⁵

This conflict came to a head in *Roche Products, Inc. v. Bolar Pharmaceutical, Co.* when the Federal Circuit found that defendant generic drug manufacturer, Bolar, had infringed Roche's drug patent when it used samples for bioequivalency testing of their generic product submitted for FDA regulatory approval.³⁶ The seeming unfairness of the ruling sparked a heated Congressional debate: If the *Roche* ruling would not allow generic competitors to begin bioequivalency testing until after a patent expires—and bioequivalency testing can take years to complete—would the effect be an artificial extension of the length of the pioneer drug patent's term? The patentee's original drug would remain the only drug on the market while competitors completed testing. Indeed, if performing the necessary tests to produce generic copies of patented drugs constituted patent infringement, the *Roche* result appeared unfair. It has since been re-emphasized that innovation in certain scientific areas would be impossible, or, at least impractical, without some kind of experimental use exemption.³⁷

B. The Statutory FDA Research Exemption—35 U.S.C. § 271(e)

After the *Roche* ruling, Congress enacted 35 U.S.C. § 271(e)(1), also known as the Hatch-Waxman Act (1984).³⁸ Its response to *Roche* was to “ensure that a patentee's rights did not *de facto* extend past the expiration of the patent term because a generic competitor . . . could not enter the market without regulatory approval.”³⁹

35. Peter J. Prommer, *The Pioneer and Generic Drug Manufacturer Agreements: Is the Sherman Act Big Enough to Swallow These Pills?*, 2002 U. ILL. J.L. TECH. & POL'Y 215, 216 (2002).

36. *Roche Prods., Inc. v. Bolar Pharm. Co.*, 733 F.2d 858, 863 (Fed. Cir. 1984); see also CHISUM, *supra* note 25, at 1204.

37. See Rebecca S. Eisenberg, *Patents and the Progress of Science: Exclusive Rights and Experimental Use*, 56 U. CHI. L. REV. 1017 (1989) (offering suggestions on the proper scope of an experimental use defense in light of the intent of the patent laws and the needs of the research community).

38. Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585, 1603 (1984) (codified at 35 U.S.C. § 271(e)(1) (2000)) (effectively overruling *Roche*); 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, 22–27 (2001) (describing the judicial and legislative developments leading to the enactment of the Hatch-Waxman Act).

39. *Integra LifeSciences I, Ltd. v. Merck KGaA*, 331 F.3d 860, 865 (Fed. Cir. 2003), cert. granted, 125 S. Ct. 823 (2005) (U.S. Jan. 7, 2005) (No. 03-1237).

There are three provisions of the 1984 Act, one of which is a research exemption that defines a “safe harbor” against patent infringement:

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 . . .⁴⁰

As stated above, this arm of the statute permits competitors to conduct experiments in advance of patent expiration as long as the research activities are reasonably related to securing FDA regulatory approval. The purpose of enacting this provision was to encourage generic competitors to enter the drug market immediately upon expiration of the original drug’s patent.⁴¹ Now, competitors are allowed to conduct experiments in advance of patent expiration so that extensive approval processes and time consuming experiments do not “artificially” extend the pioneer drug’s patent term, thereby preventing generic manufacturers from entering the market as soon as possible. Hence,

[e]xperimental use as a defense to infringement is likely to be particularly important where it is difficult or impossible to evaluate a product or design around a patent without reproducing the product itself . . . The experimental use doctrines accommodate the general rules of patent law to the needs of iterative industries in which copying or open use of prototypes is a practical necessity.⁴²

Many, including Henry Waxman and Senator Orin Hatch, believed that this provision would simultaneously promote the development of lower cost, generic drugs while encouraging

40. 35 U.S.C. § 271(e)(1) (2000); *see also* Mueller, *supra* note 38, at 25 n.126 (citing Bayer AG v. Elan Pharm. Research Corp., 212 F.3d 1241, 1244 (Fed. Cir. 2000) (explaining that submission of information to the FDA by generic drug manufacturers usually occurs in the form of an Abbreviated New Drug Application (“ANDA”), which requires that the generic drug be the bioequivalent of a “listed drug”).

41. Brief of Amicus Curiae Generic Pharmaceutical Industry Association at 3–4, Roche Prods., Inc. v. Bolar Pharm., Co., 733 F.2d 858 (Fed. Cir. 1984) (No. 84-560) (stating that the granting of Roche’s injunction “would effectively extend all drug patent monopolies by at least two (2) years, thereby undermining the public policy favoring the availability of lower costing generic drugs and causing economic injury to the public as well as to the companies engaged in the manufacture and sale of generic drugs”).

42. Brief of Amicus Curiae Bar Association of the District of Columbia—Patent, Trademark & Copyright Section In Support of Neither Party at 5–6, Merck KGaA v. Integra LifeSciences I, Ltd., 125 S. Ct. 823 (No. 03-1237) (quoting Dan L. Burk & Mark A. Lemley, *Policy Levers in Patent Law*, 89 VA. L. REV. 1575, 1648 (2003)).

innovation in the pharmaceutical industry.⁴³ And, many contend that both sides have thrived as a result.⁴⁴ Since § 271(e)(1) was enacted in 1984, the generic share of the pharmaceutical market has risen from less than twenty percent to nearly fifty percent.⁴⁵ On June 17, 2003, Bruce N. Kuhlik, Senior Vice President and General Counsel of the Pharmaceutical Research and Manufacturers of America (“PhRMA”), testified before the Senate Judiciary Committee that, “[t]he Hatch-Waxman Act of 1984 is achieving its purpose of speeding market entry of generic drugs.”⁴⁶

Kuhlik and others also argue that patent laws provide a key incentive for continued innovation in medicines.⁴⁷ Better treatments and new cures will emerge if patent incentives are maintained. Indeed, the expense of developing an innovative therapeutic has increased sharply to an estimated \$800 million over the course of the entire research and development process.⁴⁸ This is a conservative estimate, according to another study, which pinpoints the cost at \$1.7 billion when additional costs are considered.⁴⁹ Furthermore, there is significant risk in investing in the development of a single pharmaceutical. It takes ten to fifteen years on average for an experimental drug to travel from the lab to U.S. patients.⁵⁰ Only five

43. See Press Release, Pharmaceutical Research and Manufacturers of America, Patent Incentives for Discovery of New Medicines Must Be Maintained, PhRMA Tells Lawmakers (June 17, 2003), at <http://www.phrma.org/mediaroom/press/releases/17.06.2003.747.cfm>.

44. Frederick Tong, *Widening the Bottleneck of Pharmaceutical Patent Exclusivity*, 24 WHITTIER L. REV. 775, 775 (2003) (“Both the generic and pioneer drug manufacturers have thrived since the enactment of the *Hatch-Waxman Act*. The generic drug industry now routinely handles over forty percent of prescription medications, while the pioneer drug manufacturers have consistently posted strong profits.”).

45. Testimony of Gregory J. Glover, Pharmaceutical Research and Manufacturers of America, before the Federal Trade Commission and the Department of Justice Antitrust Division (Mar. 19, 2002), at <http://www.phrma.org/publications/quickfacts/24.06.2002.432.cfm>.

46. Press Release, Pharmaceutical Research and Manufacturers of America, Patent Incentives for Discovery of New Medicines Must Be Maintained, PhRMA Tells Lawmakers, *supra* note 43.

47. See *id.*

48. Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151–85 (2003); see also TUFTS CENTER FOR THE STUDY OF DRUG DEVELOPMENT, *OUTLOOK 2002*, at <http://csdd.tufts.edu/infoservices/outlookpdfs/outlook2002.pdf> (last visited Feb. 16, 2005).

49. James Gilbert et al., *Rebuilding Big Pharma's Business Model*, IN VIVO, Nov. 2003, at 4, available at http://www.bain.com/bainweb/PDFs/cms/Marketing/rebuilding_big_pharma.pdf.

50. Pharmaceutical Research and Manufacturers of America, *New Medicines in Development: The Drug Development and Approval Process*, at <http://www.phrma.org/newmedicines/resources//2000-09-18.74.cfm> (last visited Apr. 2, 2005).

in 5,000 compounds that enter preclinical testing make it to human testing, and only one of these five tested in people is approved by the FDA.⁵¹ Accordingly, many believe that the system needs financial incentives and the protections afforded by the patent system; otherwise, competitors could simply rob the fruits of millions of dollars worth of investment.

While most would acknowledge the benefits of the Act, the problem in applying the statute lies in defining the language “solely for uses reasonably related to the development and submission of information under a Federal law.” Although the intent of the Act was directed toward the preparatory experimental work of generic manufacturers, the wording of the provision is general enough to be applied more broadly.⁵² For example, was the language “patented invention,” as used in the statute, intended to embrace patented research tools or only pioneer drugs? Further, and most relevant to the case at issue, at what point are experimental activities too attenuated to no longer be considered “reasonably related” to securing FDA approval? The Federal Circuit stated that the district court was correct in confining the § 271(e)(1) exemption, based on a test from *Intermedics, Inc. v. Ventritex, Inc.*, to activities that “would contribute (relatively directly) to information the FDA considers in approving a drug.”⁵³ The interpretation of this phrase lies at the core of current controversy; hence, the Supreme Court is likely to clarify its meaning.

C. *Facts of the Cases at Issue*

1. Merck v. Merck KGaA

Between 1994 and 1998, Merck KGaA (“Merck”), The Scripps Research Institute (“TSRI”) and Dr. David Cheresh allegedly infringed patents to fibronectin peptides held by plaintiffs, Integra LifeSciences I, Ltd. (“Integra”), The Burnham Institute, and Telios Pharmaceuticals, Inc.⁵⁴ Integra is a manufacturer of medical devices,

51. Jeffrey P. Cohn, *The Beginnings: Laboratory and Animal Studies*, FDA CONSUMER SPECIAL REP., Jan. 1995, available at <http://www.fda.gov/fdac/special/newdrug/begin.html>.

52. 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, 367 (2004).

53. *Integra LifeSciences I, Ltd. v. Merck KGaA*, 331 F.3d 860, 867 (Fed. Cir. 2003), cert. granted, 125 S. Ct. 823 (2005) (U.S. Jan. 7, 2005) (No. 03-1237) (quoting *Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269, 1280 (N.D. Cal. 1991)).

54. *Integra*, 331 F.3d at 862 n.1 (stating that as of December 1996, Integra acquired all of Telios’ property rights in the asserted patents).

including tissue regeneration products, with headquarters in Plainsboro, New Jersey and a research facility in La Jolla, California.⁵⁵ In 1998, Integra licensed a technology for making synthetic peptides from The Burnham Institute, also in La Jolla, California.⁵⁶ The license included the synthetic tripeptide arginine-glycine-aspartic acid (“RGD”), which is useful for promoting adhesion in cell culture and *in vivo* through attachment to receptors on the surface of cells.⁵⁷ Before 1997, Dr. Cheresch, working independently as a scientist at TSRI (a not-for profit institution), saw that blocking various cell receptors would inhibit angiogenesis, or blood vessel development.⁵⁸ Inhibiting angiogenesis has shown to be an effective means of preventing tumor growth by limiting the vascularization around tumors, thereby “starving” dividing cancer cells.⁵⁹ Anti-angiogenic therapies may also be promising in the treatment of diabetic retinopathy, rheumatoid arthritis and psoriasis, among other diseases.⁶⁰ Merck, having taken note of the importance of this discovery, hired TSRI and sponsored Dr. Cheresch to identify potential drug candidates for clinical development in the form of RGD peptides that would inhibit tumor vascularization.⁶¹ Telios, which had been unsuccessful in commercializing a product making use of the patented tripeptide,⁶² learned of TRSI’s application of its patent and believed the angiogenesis research was part a commercial endeavor.⁶³ It then offered Merck a license, which Merck declined, claiming its research was exempt from patent infringement under § 271(e)(1).⁶⁴

55. See Integra Lifesciences Corp., official website, at http://www.integra-ls.com/corporate_info/profile.asp (last visited Apr. 2, 2005).

56. See The Burnham Institute, official website, at <http://www.burnham.org> (last visited Apr. 3, 2005).

57. Erkki Ruoslahti & Michael D. Pierschbacher, *New Perspectives in Cell Adhesion: RGD and Integrins*, 238 SCIENCE 491 (1987).

58. Staffan Strömblad & David A. Cheresch, *Cell Adhesion and Angiogenesis*, 6 TRENDS IN CELL BIOLOGY 462, 462–68 (1996).

59. Vicki Brower, *Less Is More*, 4 EMBO REP. 831, 832 (2003).

60. Peter Carmeliet & Rakesh K. Jain, *Angiogenesis in Cancer and Other Diseases*, 407 NATURE 249, 251 (2000).

61. *Integra LifeSciences I Ltd. v. Merck KGaA*, 331 F.3d 860, 863 (Fed. Cir. 2003), cert. granted, 125 S. Ct. 823 (2005) (U.S. Jan. 7, 2005) (No. 03-1237).

62. Brief of Amicus Curiae Bar Association of the District of Columbia—Patent, Trademark & Copyright Section in Support of Neither Party at 2, *Merck KGaA v. Integra LifeSciences I, Ltd.*, 125 S. Ct. 823 (No. 03-1237).

63. *Integra*, 331 F.3d at 863.

64. *Id.*; see also Respondents’ Brief on the Merits at 15, *Merck KGaA v. Integra LifeSciences I, Ltd.*, 125 S. Ct. 823 (No. 03-1237).

Telios and the Burnham Institute brought suit in a district court in southern California in 1996, and Integra joined the action as a plaintiff when it acquired Telios's patent rights.⁶⁵ Following the jury's determination of infringement, the plaintiffs were awarded a reasonable royalty of \$15 million.⁶⁶ Merck appealed to the Federal Circuit, which affirmed the lower court's ruling, finding that defendants' research activities fell outside the scope of the safe harbor as they were not "solely for uses reasonably related" to provision of information to the FDA under § 271(e)(1).⁶⁷ As stated earlier, subsection (e)(1) of 35 U.S.C. § 271 permits generic competitors to conduct experiments in advance of patent expiration as long as those activities are "reasonably related" to securing regulatory approval.⁶⁸ Applying this rule to the facts of the case, the Federal Circuit found that Merck's work was not clinical testing conducted to supply information to the FDA, but *pre-clinical* biomedical research aimed at identifying the best drug candidate to subject to future FDA clinical testing.⁶⁹ The court reasoned that such "drug hunting" would require extensive clinical testing to gain FDA approval, while creating a generic copy would not.⁷⁰ Thus, Merck's use of Integra's patented tripeptide was not "reasonably related" to clinical testing for the sole purpose of supplying information to the FDA, but rather exploratory biomedical research aimed at identifying a new drug candidate.⁷¹

2. Madey v. Duke University

In an altogether different matter, more than a year before the *Integra* ruling, Plaintiff John M.J. Madey ("Madey") initiated a patent infringement suit against Duke University.⁷² Madey, an electromagnetic radiation research scholar, invented and patented the free electron laser while a tenured professor at Stanford.⁷³ Duke recruited Madey to create a free electron laser laboratory for its

65. *Integra*, 331 F.3d at 862 n.1.

66. *Id.* at 869. The damages award was subsequently vacated by the Federal Circuit due to the uncertainty of whether any useful drug would be developed at the time the RDG peptide was being used. The court suggested that this should have been factored into the damages calculation. *See id.* at 869-72.

67. *Id.* at 866, 868.

68. *See supra* text accompanying note 6.

69. *Integra*, 331 F.3d at 866.

70. *Id.*

71. *Id.*

72. *Madey v. Duke Univ.*, 307 F.3d 1351,1352 (Fed. Cir. 2002), *cert. denied*, 539 U.S. 958 (2003).

73. *Id.*

physics department.⁷⁴ Subsequently, Duke succeeded in removing Madey from the position of lab director after a disagreement surfaced between the two parties.⁷⁵ Despite this move, Duke continued to use the laboratory equipment Madey had designed.⁷⁶ After bringing suit, Madey lost at the district court level, which placed Duke's actions within the scope of the common law experimental use exception, and partially dismissed his claim for failure to "sufficiently establish that [Duke's] use of the patent had 'definite, cognizable, and not insubstantial commercial purposes.'"⁷⁷ The Federal Circuit reversed-in-part, holding that the lower court erred in partially granting Duke's motion to dismiss based on the common law experimental use defense.⁷⁸ The court held that this defense is available only if the use of the patented invention is "solely for amusement, to satisfy the idle curiosity, or for strictly philosophical inquiry."⁷⁹ In addition, the court emphasized that the defense does not apply if the use is "in furtherance of the alleged infringer's legitimate business."⁸⁰ The court reasoned that the University is in the business of education and attracting students, and that the lab's equipment advanced this purpose.⁸¹ The Federal Circuit disapproved of the district court reasoning, which it said attached too much weight to the not-for profit status of Duke, and effectively concealed the fact that Duke's activities were in accordance with a reasonable interpretation of its legitimate business objectives.⁸²

D. Activities That Have Thus Far Been Held Exempt from Patent Infringement

In 1995, after acquiring the now-invalid patent rights to "Taq" as well as the PCR DNA amplification reaction that uses the "Taq" enzyme, Hoffman-La Roche (Roche) attempted to bring suit against more than forty U.S. universities and research institutes (including Harvard, Stanford, Massachusetts Institute of Technology, the Salk Institute, The Scripps Research Institute, and the National Cancer

74. *Id.*

75. *Id.* at 1352-53.

76. *Id.* at 1352.

77. *Madey v. Duke Univ.*, 266 F. Supp. 2d 420, 425 (M.D. N.C. 2001) (quoting *Roche Products v. Bolar Pharm. Co.*, 733 F.2d 858, 863 (Fed. Cir. 1984)).

78. *Madey*, 307 F.3d at 1352.

79. *Id.* at 1362.

80. *Id.*

81. *Id.*

82. *Id.*

Institute) as well as more than 200 private scientists for allegedly infringing these patents.⁸³ Although Roche was not successful in this suit due to the subsequent invalidation of the patent, the mere accusation brought an angry response.⁸⁴ Following the filing of the complaint in federal court in 1995, Nobel laureate Dr. Arthur Kornberg of Stanford University described Roche's attempt to restrict the use of the PCR technology at research universities as "violat[ing] practices and principles basic to the advancement of knowledge for the public welfare."⁸⁵

Roche's allegations may have been the result of a movement in U.S. district courts toward expanding the scope of the research exemption after the 1984 enactment of 35 U.S.C. § 271(e)(1). According to Charles Raubicheck et al., in *Integra v. Merck: A Mixed Bag for Research Tool Patents*, U.S. District Courts had adopted the trend of interpreting the research exemption broadly.⁸⁶ All activities directed toward drug discovery seemed as though they would be exempt, thereby reducing the value of research tool patents.⁸⁷

For example, a district court in Massachusetts extended the research exemption to pre-clinical drug discovery activities in *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*⁸⁸ Hoechst manufactured and used large quantities of Amgen's genetically-engineered, patented erythropoietin ("EPO") while it attempted to develop a competing product.⁸⁹ The court held that Hoechst's export of Amgen's EPO to Japan, purity testing, demonstration of consistency by manufacturing three consecutive batches of EPO, functional characterization, viral clearance tests in Europe, and plans for radio-labeling studies on the patented invention, were all activities exempt from patent infringement under § 271(e)(1).⁹⁰

83. Mueller, *supra* note 38, at 3 n.7 (citing Marcia Barinaga, *Scientists Named in PCR Suit*, 268 SCIENCE 1273-74 (1995)).

84. Eliot Marshall, *Battling Over Basics*, 277 SCIENCE 25 (1997).

85. Mueller, *supra* note 38, at 3 (quoting *Hoffman-La Roche Challenges Freedom of Researchers; List of "Infringers" Includes Hundreds of Researchers and Dozens of Government-Supported Laboratories*, BUS. WIRE, May 24, 1995).

86. Charles Raubicheck et al., *Integra v. Merck: A Mixed Bag for Research Tool Patents*, 21 NATURE BIOTECHNOLOGY 1099, 1100 (2003).

87. *Id.*

88. 3 F. Supp. 2d 104 (D. Mass. 1998).

89. *Id.* at 106.

90. *Id.* at 109-11.

A New York district court found along the same lines in *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*⁹¹ There, Bristol-Myers used various chemical intermediates claimed in a Rhone-Poulenc patent directed to processes for preparing the anti-cancer drug, Taxol.⁹² Bristol-Myers employed the intermediate in experiments for the development of a closely related competitor.⁹³ The court held that these uses were exempt from infringement under § 271(e)(1) because they represented preliminary studies that could ultimately facilitate or be useful in generating information for submission to the FDA.⁹⁴ Specifically, the court adopted the argument that use of the patented intermediates was reasonably related to an FDA application “even where each such use does not directly result in an FDA application being filed, so long as the use was made in order to determine whether or not an application for approval would be sought.”⁹⁵ Further, the court agreed that even though each use of the patented intermediates may not directly yield information that could be submitted to the FDA, such use would be noninfringing if related to a preliminary activity that *could facilitate or be useful in generating* information that could be submitted to the FDA.⁹⁶ Hence, in applying a broad construction of the language “reasonably related to,” the court found all Bristol’s activities exempt from infringement, a ruling that runs directly counter to *Integra*.

Similarly, a district court in Delaware took an expansive view of the research exemption in *Nexell Therapeutics, Inc. v. AmCell Corp.*,⁹⁷ wherein AmCell used Nexell’s patented CD34 antibodies for the development of a magnetic cell separating device (CliniMACS) it planned to submit for FDA approval.⁹⁸ While the court stated that activities only exceed the safe harbor “when they have no objectively reasonable application towards obtaining FDA approval,”⁹⁹ it held many of AmCell’s activities exempt from infringement even though

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

92. *Id.* at *1.

93. *Id.*

94. *Id.* at *7.

95. *Id.*

96. *Id.*

97. 199 F. Supp. 2d 197 (D. Del. 2002).

98. *Id.* at 198.

99. *Id.* at 205.

they appeared to be in furtherance of marketing the product.¹⁰⁰ The *Nexell* court stated that the allegedly infringing activities were conducted pursuant to soliciting clinicians to enter into FDA-approved clinical trials.¹⁰¹ Therefore, the research activities were reasonably related to obtaining FDA approval, and covered by § 271(e)(1).¹⁰² The court observed in dicta that excluding preliminary activities from the safe harbor would “chill parties from engaging in the very pre-approval testing that Congress sought to encourage.”¹⁰³

These cases and others are referenced in a comprehensive list of activities that have been found exempt from patent liability by various courts since the enactment of 35 U.S.C. § 271(e)(1).¹⁰⁴ More recently, since the *Integra* ruling, a district court in Florida extended the protections of § 271(e)(1) to defendant Arriva Pharmaceuticals for its use of a patented process covering the treatment of eye and ear infections through the application of a therapeutic protein, Alpha 1-Antitrypsin (“AAT”).¹⁰⁵ Arriva’s main corporate mission at the time of its creation was to develop a genetically engineered version of Prolastin for use in pulmonary and topical applications.¹⁰⁶ The company began to focus on the development and commercialization of recombinant protease inhibitors for treatment of a wide range of human diseases, including eye and ear infections.¹⁰⁷ Plaintiff Alphamed Pharmaceuticals alleged that Arriva infringed its patent by collaborating with the University of Florida with respect to preclinical research studies associated with AAT.¹⁰⁸

Distinguishing the facts from those in *Integra*, the court found that there were no allegations that the purportedly infringing activities consisted of research into new compositions that would lead to new

100. See *id.* at 204. These activities included, *inter alia*, advertising CliniMACS in medical journals, providing the CliniMACS device to FDA-approved clinical investigators for free, and giving the CD34 reagent kits to the investigators on a cost-recovery basis.

101. *Id.*

102. *Id.*

103. *Nexell Therapeutics, Inc.*, 199 F. Supp. 2d at 204.

104. John R. Wetherell et al., *Integra’s Win May Give Cause for Re-Evaluation of Future Exploratory Research Activities*, Pillsbury Winthrop LLP, Aug. 6, 2003, at http://www.pillsburywinthrop.com/files/tbl_s31Publication/PDFUpload208/8875/BiotechLifeSciencesNews1.pdf.

105. *Alphamed Pharms. Corp. v. Arriva Pharms., Inc.*, No. 03-20078-CIV, 2005 WL 357326 (S.D. Fla. Jan. 5, 2005).

106. *Id.* at *1.

107. *Id.*

108. *Id.* at *5.

drugs or FDA approval for different drugs.¹⁰⁹ Rather, the complaint merely contained allegations “that Arriva has been conducting clinical trials relating to AAT for use in ear infections, precisely the kind of research that the safe harbor provision protects.”¹¹⁰ Thus, the court held that Alphamed failed to allege any activities on the part of defendant that would constitute infringement of plaintiff’s patents.

The *Madey* and *Integra* cases represent recent and compelling examples of patent infringement suits in which a patentee was successful in asserting his rights against a university and a pharmaceutical company with ties to a not-for profit institution, before the Federal Circuit.¹¹¹ The *Integra* ruling is the first Federal Circuit decision to indicate a possible break from a trend of broadly reading § 271(e)(1) at the district court level.¹¹² Accordingly, many research productivity companies owning research tool patents are looking to the Supreme Court to affirm the Federal Circuit’s ruling. To be sure, some commentators contend that “the Federal Circuit is correct in acknowledging the immense value of research tools and the worthiness of a system that helps produce them.”¹¹³ The last time the Supreme Court addressed § 271(e)(1) was in *Eli Lilly & Co. v. Medtronic, Inc.*¹¹⁴ There, in an opinion written by Justice Scalia, the Court focused on different language in the statute, namely, “a Federal law which regulates the manufacture, use, or sale of drugs.”¹¹⁵

109. *Id.* at *8.

110. *Id.*

111. The federal district courts have original jurisdiction of any civil action arising under any Act of Congress relating to patents. In 1982, Congress created the Court of Appeals for the Federal Circuit to have exclusive appellate jurisdiction over most cases involving patent issues. The Supreme Court rarely grants certiorari in patent cases, making the Federal Circuit the court of last resort in most instances. Therefore, U.S. patent law is predominantly shaped by the decisions of the Federal Circuit. See Tao Huang, Note, *The Experimental Purpose Doctrine and Biomedical Research*, 11 MICH. TELECOMM. & TECH. L. REV. 97, 98 n.3 (2004) (citing 4 DONALD S. CHISUM, CHISUM ON PATENTS § 11.06 (2004)).

112. Raubicheck et al., *supra* note 86, at 1101; see also Huang, *supra* note 111, at 102, 105 (noting that “[w]hile the district courts were utilizing § 271(e)(1) to circumvent *Roche*, the Federal Circuit sat quietly,” and that in *Integra*, “the Federal Circuit cut back the district courts’ broad interpretations of § 271(e)(1)”).

113. Peter Lee, *Patents, Paradigm Shifts, and Progress in Biomedical Science*, 114 YALE L.J. 659, 691–93 (2004). Lee proposes a new model for patents on research tools in which a robust experimental use exception would exist for a finite period of time immediately following the granting of a patent in which noncommercial experimental use of the patented research tool would be permitted. Upon expiration of this safe harbor, any nonlicensed use of the patented material, even for experimentation with no commercial application, would constitute infringement.

114. 496 U.S. 661 (1990); see *infra* text accompanying note 6.

115. See *Eli Lilly*, 496 U.S. at 665–69.

Recognizing a good deal of legislative imprecision and ambiguity in § 271(e)(1), the Court affirmed the Federal Circuit's ruling in favor of respondent Medtronic, holding that its use of Eli Lilly's patented implantable defibrillator was not infringement because it was related to obtaining FDA approval for a generic substitute intended to be sold commercially only after the patent expired.¹¹⁶ Thus, the *Medtronic* Court held that the scope of § 271(e)(1) encompasses not only the testing and manufacture of generic drugs, but medical devices as well.

E. Defining "Research Tools"

A research tool is a product or method whose purpose is *use* in the conduct of research.¹¹⁷ Biological tool patents protect technology used to conduct preliminary experiments as first steps in the pre-clinical stages of drug discovery, most often for the validation of drug targets, as well as for the diagnosis of disease. Examples include reagents for molecular biology, such as enzymes, synthetic peptides¹¹⁸ and short oligonucleotides, non-therapeutic antibodies used for screening assays, and full length genes or proteins which may be actual drug targets.¹¹⁹ A host of tools are available for uncovering gene function and activity, such as RNAi, a technique employed for the functional analysis of genes, and specifically, the antagonism of individual gene activity,¹²⁰ as well as microarrays of DNA or proteins used for measuring changes in RNA or protein production.¹²¹ The National Institutes of Health ("NIH") Working Group on Research Tools defines "research tool" in its broadest sense as "embrac[ing] the full range of resources that scientists use in the laboratory," including "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

116. See *id.* at 666–74.

117. *Integra LifeSciences I, Ltd. v. Merck KGaA*, 331 F.3d 860, 878 (Fed. Cir. 2003), cert. granted, 125 S. Ct. 823 (2005) (U.S. Jan. 7, 2005) (No. 03-1237) (Newman, J., dissenting) (emphasis added).

118. Justice Newman, however, disagreed that the RGD-containing peptide is a "research tool." See *id.*

119. See Sandy M. Thomas et. al., *Shares in the Human Genome—The Future of Patenting DNA*, 20 NATURE BIOTECHNOLOGY 1185, 1186 (2002) (asserting that "[a]ny DNA sequence that has a use in research can be classed as a research tool").

120. Michael T. McManus & Phillip A. Sharp, *Gene Silencing in Mammals by Small Interfering RNAs*, 3 NATURE REVIEWS GENETICS 737 (2002).

121. See Robert F. Service, *Microchip Arrays Put DNA on the Spot*, 282 SCIENCE 396, 396–99 (1998).

equipment and machines, databases and computer software.”¹²² In her article, *No “Dilettante Affair”: Rethinking the Experimental Use Exception to Patent Infringement for Biomedical Research Tools*, Professor Janice M. Mueller composed a list of some of the most noteworthy biotechnological research tools, all of which are currently subject to proprietary restraints.¹²³ They include,

patented technology used to create “conditional mutants,” [which are] mice in whom a targeted gene is deleted when the *cre* gene encounters two *loxP* DNA segments bracketing the targeted gene[.]¹²⁴

...

[t]he Cohen-Boyer patents covering the basic method and plasmids for gene cloning, assigned to the University of California and Stanford University[.]¹²⁵

....

[t]he tumor-prone “oncomouse,” [which] is useful as a model in cancer research[.]¹²⁶

...

expressed sequence tags (ESTs) . . . believed to be useful as probes in searching for corresponding full-length genes[, and]¹²⁷

[h]uman embryonic stem cells, from which any type of human tissue can [potentially] be grown.¹²⁸

122. NATIONAL INSTITUTES OF HEALTH, REPORT OF THE NATIONAL INSTITUTES OF HEALTH (NIH) WORKING GROUP ON RESEARCH TOOLS (June 4, 1998), at <http://www.nih.gov/news/researchtools/index.htm>; see also Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources: Final Notice, 64 Fed. Reg. 72,090, 72,092 n.1 (Dec. 23, 1999) (concluding that “[research tools] embrace the full range of tools that scientists use in the laboratory, including cell lines, monoclonal antibodies, reagents, animal models, growth factors, combinatorial chemistry and DNA libraries, clones and cloning tools (such as PCR), methods, laboratory equipment and machines”).

123. Mueller, *supra* note 38, at 12.

124. *Id.*

125. *Id.* at 12–13.

126. *Id.* at 13; see also Andrea D. Brashear, *Evolving Biotechnology Patent Laws in the United States and Europe: Are They Inhibiting Disease Research?*, 12 IND. INT’L & COMP. L. REV. 183, 206 (2001).

127. Mueller, *supra* note 38, at 13–14.

128. *Id.* at 14.

Hence, research tools enable new biological understanding, facilitate new drug discoveries and development, and make it possible for researchers to work more quickly, more efficiently, and less expensively.¹²⁹ Their value will be discussed more fully in Part IV.A. For the purposes herein, this Comment adopts Professor Mueller's definitions of "research tools," which reflect the NIH's definitions in their broadest sense.

F. *Stem Cell Research and Research Tool Patents*

Stem cells are unspecialized precursor cells with the ability to self-renew and differentiate into specialized cells in response to appropriate signals.¹³⁰ Serving as a sort of repair system for the body, stem cells can theoretically divide without limit to replenish other cells.¹³¹ They integrate perfectly into whatever site they may come to occupy, adopting the character and behavior that normal cells would show at that site.¹³²

Perhaps the most important potential application of human stem cells is the generation of cells and tissues that could be used for cell-based therapies.¹³³ Donated organs and tissues are often used to replace ailing or destroyed tissue; however, the need for transplantable tissues and organs far outweighs the available

129. Brief of Amici Curiae Invitrogen Corp. et al. at 10, Merck KGaA v. Integra LifeSciences I, Ltd., 125 S. Ct. 823 (No. 03-1237) (noting that as a result of the invention of DNA microarrays "what used to take a post-doc[toral student] in the laboratory approximately six months with proper front-end research can now be done in 20 minutes") (quoting FED. TRADE COMM'N., TO PROMOTE INNOVATION: THE PROPER BALANCE OF COMPETITION AND PATENT LAW AND POLICY 19-20 (2003)).

130. Sheng Ding & Peter G. Schultz, *A Role for Chemistry in Stem Cell Biology*, 22 NATURE BIOTECHNOLOGY 833 (2004) (citing NATIONAL INSTITUTES OF HEALTH, STEM CELLS: SCIENTIFIC PROGRESS AND FUTURE RESEARCH DIRECTIONS (2001), at <http://stemcells.nih.gov/info/scireport>).

131. See NATIONAL INSTITUTES OF HEALTH, STEM CELLS: SCIENTIFIC PROGRESS AND FUTURE RESEARCH DIRECTIONS 1 (2001), at <http://stemcells.nih.gov/info/scireport> (last visited May 4, 2005).

132. MOLECULAR BIOLOGY OF THE CELL § 5.22 (Bruce Alberts et al. eds., 2d ed. 2001)

In the normal adult body, different classes of stem cells are responsible for the renewal of different types of tissue. Some tissues, however, seem incapable of repair by the genesis of new cells because no competent stem cells are present. Recent discoveries have opened up new possibilities for manipulating stem-cell behavior artificially so as to repair tissues that previously seemed unrepairable.

Id.

133. NATIONAL INSTITUTES OF HEALTH, STEM CELL BASICS: VI. WHAT ARE THE POTENTIAL USES OF HUMAN CELLS AND THE OBSTACLES THAT MUST BE OVERCOME BEFORE THESE POTENTIAL USES WILL BE REALIZED?, at <http://stemcells.nih.gov/info/basics/basics6.asp> (last visited Apr. 5, 2005) [hereinafter NATIONAL INSTITUTES OF HEALTH VI].

supply.¹³⁴ Stem cells, if directed to differentiate into specific cell types, offer the possibility of a renewable source of replacement cells and tissues to treat diseases including, but not limited to, Parkinson's and Alzheimer's diseases, spinal cord injury, stroke, burns, heart disease, diabetes, osteoarthritis, and rheumatoid arthritis.¹³⁵

In 2001, research conducted in animal model systems suggested that stem cells derived from bone marrow might be used to treat heart disease.¹³⁶ These reports, along with successive studies that used other tissue types as a source for human embryonic stem cells, have created a great deal of excitement over the enormous potential of stem cell therapy to treat human disease. There is also a powerful commercial incentive to conduct this research, and in particular for heart disease therapy, since it is the leading cause of death in the U.S., with over \$300 billion dollars spent annually on treatment.¹³⁷

Stem cells are also themselves research tools used to investigate basic biological processes, as well as therapeutic methods for treating human disease; i.e., they can be used to test new drugs.¹³⁸ For example, new medications can be tested for safety on differentiated cells generated from human pluripotent¹³⁹ cell lines.¹⁴⁰ Other kinds of cell lines are already used in this way, such as cancer cell lines employed to screen potential anti-tumor drugs.¹⁴¹ The University of Wisconsin and the Wisconsin Alumni Research Foundation hold U.S. patents that include stem cell lines and genetic markers used to identify stem cells.¹⁴² However, only a limited number of embryonic stem cell lines are publicly available, with the actual number of

134. *Id.*

135. *Id.*

136. Donald Orlic et al., *Bone Marrow Cells Regenerate Infarcted Myocardium*, 410 NATURE 701 (2001); see also, Kenneth R. Chien, *Lost in Translation*, 428 NATURE 607 (2004); Helen Pearson, *The Heart of the Matter*, 10 NATURE MEDICINE 445 (2004).

137. NATIONAL CENTER FOR CHRONIC DISEASE PREVENTION AND HEALTH PROMOTION, CHRONIC DISEASE OVERVIEW, at <http://www.cdc.gov/nccdphp/overview.htm> (last visited Apr. 5, 2005).

138. NATIONAL INSTITUTES OF HEALTH VI, *supra* note 133.

139. NATIONAL INSTITUTES OF HEALTH, STEM CELL INFORMATION: GLOSSARY, at <http://stemcells.nih.gov/info/glossary2.asp>. (last visited Apr. 4, 2005) (defining pluripotent as the ability of a single stem cell to develop into many different cell types of the body).

140. NATIONAL INSTITUTES OF HEALTH VI, *supra* note 133; see NATIONAL INSTITUTES OF HEALTH, STEM CELL INFORMATION: GLOSSARY, *supra* note 139.

141. NATIONAL INSTITUTES OF HEALTH VI, *supra* note 133; see NATIONAL INSTITUTES OF HEALTH, STEM CELL INFORMATION: GLOSSARY, *supra* note 139.

142. Gretchen Vogel, *Stem Cell Claims Face Legal Hurdles*, 305 SCIENCE 1887 (2004).

existing lines the subject of much current debate.¹⁴³ In particular, the federal NIH research funds now exclude the generation of new human embryonic stem cell lines.¹⁴⁴ At the same time, the suitability of legacy cell lines is questionable, such that the generation of new lines is an attractive target for firms seeking to create and profit from stem cells as valuable research tools.

Like other medical research, the development of stem cell therapeutics will doubtlessly require the use of patented research tools. In particular, molecules that prevent allogenic¹⁴⁵ rejection or that direct embryonic stem cells to develop into a desired cell type will be necessary. For example, researchers induced embryonic stem cells to differentiate into dopamine expressing midbrain neurons by providing an exogenous source of the *Nurr1* gene.¹⁴⁶ These cells have the potential to treat Parkinson's disease, and are the focus of research at the Gaithersburg, Maryland firm NeuralStem.¹⁴⁷ Researchers have also developed screens to select among millions of compounds that control the development of stem cell lines into a particular desired cell type.¹⁴⁸ Compounds identified in such screens are obvious candidates for research tools used to manipulate embryonic stem cells.

III. IDENTIFICATION OF THE ISSUES

The Supreme Court is scheduled to decide within the next few months whether the statutory research exemption will act as a defense to patent infringement for pre-clinical research studies conducted early in the drug development process. The main issue to be addressed by the Court is whether such studies are "reasonably related to the development and submission of information" to the FDA. A direct implication of such a decision is whether commercial drug manufacturers will be able to invoke the safe harbor provisions

143. See Gretchen Vogel, *Bush Squeezes Between the Lines on Stem Cells*, 293 SCIENCE 1242, 1242–45 (2001) (noting that the Bush Administration currently allows the National Institutes of Health to fund work using human embryonic stem cells—but only work using cell lines derived before the announcement of this decision on Aug. 9, 2001).

144. *Id.* at 1244.

145. Being genetically different although belonging to, or obtained from the same species. See, e.g., NATIONAL INSTITUTES OF HEALTH, STEM CELLS: SCIENTIFIC PROGRESS AND FUTURE RESEARCH DIRECTIONS app. F, at <http://stemcells.nih.gov/info/scirereport/appendixF.asp> (last visited Apr. 4, 2005).

146. Jong-Hoon Kim et. al., *Dopamine Neurons Derived From Embryonic Stem Cells Function in an Animal Model of Parkinson's Disease*, 418 NATURE 50, 50–56 (2002).

147. See *id.*

148. Ding & Schultz, *supra* note 130, at 835.

of § 271(e)(1) for “upstream” research similar to that conducted by Merck in *Integra*. Such preliminary research encompasses various kinds of biomedical work, including research conducted via collaborative efforts with universities and not-for profit organizations. University research has traditionally been protected from patent infringement under the common law research exemption. The *Madey* ruling, however, states that such research should refrain from furthering the institution’s legitimate business objectives, if it is to invoke the protection of the common law research exemption.¹⁴⁹ As a result, the combination of these two decisions may exclude early stage research that furthers an institution’s legitimate business from any sort of research exemption altogether.

One example that is particularly relevant in California is human embryonic stem cell research though the California Institute for Regenerative Medicine (“CIRM”). Stem cell research is an area with exciting potential in biomedical experimentation, much of which takes place in university research labs and not-for profit organizations.¹⁵⁰ Proposition 71 contains an implicit expectation of commercial gain from taxpayers’ investment in stem cell research, including the advancement of California’s biotechnology industry.¹⁵¹ Stem cell research is also in its early stages; in fact, no such research appears to be at the stage of FDA submissions.¹⁵² Thus, a potential

149. See *Madey v. Duke Univ.*, 307 F.3d 1351 (Fed. Cir. 2002), *cert. denied*, 539 U.S. 958 (2003).

150. According to the analysis of Proposition 71 by the Legislative Analyst, printed in the ballot pamphlet for the General Election of Nov. 2, 2005, universities have long since been dubbed “playgrounds” for innovation. Proposition 71 acknowledges that the University of California is currently engaged in stem cell research. See CALIFORNIA SECRETARY OF STATE, OFFICIAL VOTER INFORMATION GUIDE 68 (Nov. 2, 2005), *available at* <http://www.voterguide.ss.ca.gov/english.pdf>.

In addition, the measure intends to apply up to ten percent of the funds available for grants and loans to develop scientific and medical research facilities for not-for profit entities within the first five years of the implementation of the measure. *Id.* at 70. The Independent Citizens Oversight Committee (“ICOC”) is the governing board for the California Institute for Regenerative Medicine, and represents California’s leading public universities, including the University of California, non-profit academic and research institutions, patient advocacy groups as well as the biotechnology industry. See California Institute for Regenerative Medicine, official website, *at* <http://www.cirm.ca.gov/about> (last visited Apr. 5, 2005).

151. See CALIFORNIA SECRETARY OF STATE, OFFICIAL VOTER INFORMATION GUIDE 73 (Nov. 2, 2005), *available at* <http://www.voterguide.ss.ca.gov/english.pdf>.

152. For example, a recent search of the FDA clinical trials database identifies numerous clinical trials using stem cells; most trials use autologous transplantation of stem cells from a patient’s own bone marrow, usually as an adjunct treatment for cancer. A single trial was found for stem cells as a treatment for heart disease using autologous stem cell transplantation. No trials were found using embryonic stem cells. See ClinicalTrials.gov, official website, *at* <http://www.clinicaltrials.gov> (last visited Apr. 8, 2005).

problem for universities and not-for profit researchers involved with CIRM is whether there is a research exemption available to them, or if they will be held to costly licenses. The question that remains is whether the remnants of the common law or statutory experimental use exemptions will apply to any Proposition 71-funded research. On the other hand, the state of California seeks to profit from patents that result from research performed through CIRM; therefore, the state, as well as other investors, will ultimately be interested in the broadest possible intellectual property rights.

The three most likely outcomes of the pending Supreme Court review are: (1) leave the scope of the research exemption the same as that interpreted by the Federal Circuit, (2) constrict the scope of the research exemption, or (3) expand the scope to be broader than the interpretation given by the Federal Circuit.

In developing the effects of these potential decisions, this Comment considers the following questions: Would affirming or narrowing the scope of the research exemption encumber academic research scientists involved in basic research studies that are far removed from the point of FDA regulatory submissions by requiring them to license patented research tools that have until now been accessible to them? Could this in turn have a chilling effect on drug discovery and the development of potentially life-saving therapeutics? Or, if the research exemption is broadened, would this undermine the value of research tool patents, thereby diminishing incentives for smaller companies to innovate such tools? Could this arguably be the most damaging effect for California, seeing as the state seeks to benefit from any patents that result from research funded by the new taxpayer bonds?

IV. ANALYSIS

A. Freedom to Operate and the Value of Research Tools in Drug Discovery

The impact of the Supreme Court's decision will be widespread. Biotechnology tool patents are often the main products of biotechnology companies, thereby representing a considerable source of their revenue. At the same time, progress in the pharmaceutical industry and among basic researchers, depends heavily on the use of patented research tools due to the critical roles they play in biomedical labwork. The use of patented research tools is also significant in terms of time, spanning up to 6.5 years in the preclinical

stage of drug development (*see* Fig. 1, below). It is important to note that use of these tools shortens this period. Additional costs and limited access to research tools would perhaps result in a longer time to identify and validate a drug target.

Clinical Trials

	Discovery / Preclinical Testing	File IND at FDA				File NDA at FDA				Phase IV	
Years	6.5								1.5	15 Total	
Test Population	Laboratory and animal studies	20 to 100 healthy volunteers	100 to 500 patient volunteers	1,000 to 5,000 patient volunteers							
Purpose	Assess safety, biological activity and formulations	Determine safety and dosage	Evaluate effectiveness, look for side effects	Confirm effectiveness, monitor adverse reactions from long-term use					Review process / approval		Additional post-marketing testing required by FDA
Success Rate	5,000 compounds evaluated	5 compounds enter trials							1 approved		

FIGURE 1: A timeline of drug development. Reproduced and modified from Pharmaceutical Research and Manufacturers Association, *One New Drug = \$500 Million and 12-15 Years of R&D*, at <http://www.phrma.org/publications/quickfacts/01.03.2001.34.cfm> (last visited Apr. 2, 2005).

At the academic level, scientific work requires broad access to research tools, many of which are patented. Access to a range of tools, and the freedom to use them to test the functioning of patented technologies, hypotheses, or to improve upon patented technologies is at the heart of discovery and innovation in our society. Such innovation is essential to our technology-driven economy and advances in healthcare. Many scholars have argued that the increase in patents on research tools in the biotechnological sector has resulted in stacking royalty obligations that could have a chilling effect on innovation and the development of new drugs at the academic level.¹⁵³ Critics of the Federal Circuit's rulings in *Madey* and *Integra* contend that the holdings could also unduly restrict university and other not-for profit research. In his article, *Renting Space on the Shoulders of Giants: Madey and the Future of the Experimental Use Doctrine*, Tom Saunders asserts that the Federal Circuit's ruling in *Madey* "undermines the balance between innovation and access that lies at the heart of the Patent Act."¹⁵⁴

In theory, this could be true. This Comment, however, argues that in actuality it is unlikely. Considering a world devoid of this freedom to operate, if a university scientist found that he needed five patented tools to conduct a year's worth of research that had no obvious prospect of commercial gain, he may need to theoretically contract individually with each of the five patentees and pay upfront for five separate licenses. Naturally, this would create a significant bureaucratic burden on scientists—not to mention a significant expense—especially if he is operating on federally funded grants, 20–30% of which may be taken by the university itself for overhead costs.¹⁵⁵ One can imagine the stifling effect such a scenario would have on the totality of university researchers.

From a practical standpoint, however, a patentee has little motivation to bring an infringement suit against a university or a not-

153. See, e.g., Mueller, *supra* note 38, at 7 (describing assertions by scientists that "the stacking of intellectual property obligations as successive tools are used in the course of an extended research project has the potential to impede or even preclude the development of new and better diagnostic and therapeutic products"); see also Rebecca S. Eisenberg, *Technology Transfer and the Genome Project: Problems with Patenting Research Tools*, 5 RISK 163, 168 (1994) (stating that patents on research tools "can create obstacles to subsequent [research and development] and add to a thicket of rights that firms must negotiate their way past before they can get their products on the market").

154. Saunders, *supra* note 15, at 262.

155. David P. Hamilton, *Indirect Costs: Round II*, 254 SCIENCE 788, 788–89 (1991) (noting that Congress "capped the portion of administrative expenses that can be assigned to indirect costs at 26%").

for profit institution. Damages are likely to be small, if any. And, the incentive to obtain an injunction would be mitigated by potential revenues on any invention commercialized under the patent, as well as the high cost of initiating and maintaining an infringement suit.

Further, many large universities are sophisticated players in biomedical research.¹⁵⁶ Commentators assert that not only are large universities actively involved in patent applications and licensing, they are also diligent about protecting their patent rights.¹⁵⁷ Moreover, there is little evidence to support the contention that universities are threatened by the biotechnology industry through patent infringement suits.¹⁵⁸ Hence, some argue that it is research productivity companies who are on the defense,¹⁵⁹ and caution against disabling biotechnology firms from using legal strategies to capture a fair share of the value that their discoveries contribute to subsequent downstream innovation.¹⁶⁰ Indeed, this would dissuade companies from sharing their innovations with the public, and arguably eliminate a market for business models based on licensing schemes.

Still, some scholars have described examples of how reduced access to patented research tools has played out in the academic sector. University technology licensing directors have noted the challenge of “[r]estricted availability or delays in exchange of ‘research tools’ (such as vectors or transgenic mice) in biological research,”¹⁶¹ and researchers who use microarrays to screen patients for genetic variations have voiced their concern that a license might

156. Huang, *supra* note 111, at 109 (contending that *Madey* and *Integra* were decided correctly and that the concerns expressed by critics of the decisions are unfounded).

157. *Id.*

158. *Id.* at 112 (demonstrating that “[t]he only case in which a university was sued for patent infringement was *Madey* in which the plaintiff was not an industrial entity, but rather a disgruntled former faculty member”).

159. *Id.*

160. Rebecca S. Eisenberg, *Reaching Through the Genome*, in PERSPECTIVES ON PROPERTIES OF THE HUMAN GENOME PROJECT: ADVANCES IN GENETICS 113 (F. Scott Kieff ed., 2003).

161. Mueller, *supra* note 38, at 8 (quoting Lita Nelsen, *The Rise of Intellectual Property Protection in the American University*, 279 SCIENCE 1460, 1461 (1998)); see also NATIONAL INSTITUTES OF HEALTH, REPORT OF THE NATIONAL INSTITUTES OF HEALTH (NIH) WORKING GROUP ON RESEARCH TOOLS (June 4, 1998), at

<http://www.nih.gov/news/researchtools/index.htm> (acknowledging that “[m]any scientists and institutions involved in biomedical research are frustrated by growing difficulties and delays in negotiating the terms of access to research tools”); Eliot Marshall, *A Deluge of Patents Creates Legal Hassles for Research*, 288 SCIENCE 255, 257 (2000).

be required for each of the thousands of DNA sequences hybridized to a microchip.¹⁶²

Further, in the area of patient care, some physicians have reported a bottleneck that prevents them from obtaining and sharing with patients information that could improve their health. Dr. Edwin M. Stone and colleague Val C. Sheffield, both Howard Hughes Medical Institute Investigators at the University of Iowa College of Medicine in Iowa City, had been running genetic tests on their eye patients for over a decade as part of a research program.¹⁶³ Because some of the genes tested have subsequently been patented, they found themselves in the position of notifying the patentees of the genes used in their work.¹⁶⁴ Dr. Stone now offers genetic tests for eye diseases as a clinical service of the university rather than as a research project, with the important caveat that no one—neither the university nor those who own the genes through patents—can make any profit from the tests.¹⁶⁵ This is his solution to the possibility of being held liable for infringement, and as of August 2003, among the seventy-two patentees he notified (traced to twenty-six different patented genes), twelve have responded and none has objected to his plan.¹⁶⁶

*Greenberg v. Miami Children's Hospital Research Institute, Inc.*¹⁶⁷ is the first reported lawsuit alleging that a gene patent hindered research.¹⁶⁸ When the parents of various children with Canavan disease¹⁶⁹ solicited the help of a researcher to develop a prenatal genetic test using genetic material from the families, the researcher proceeded to patent the test.¹⁷⁰ Thereafter, the patentee allegedly began charging the families for testing as well as actively enforcing

162. Mueller, *supra* note 38, at 8 n.34 (citing Robert F. Service, *Will Patent Fights Hold DNA Chips Hostage?*, 282 SCIENCE 396, 397 (1998)).

163. Ron Winslow, *Researchers Have Plan for Genetic Eye Tests Ignored by Industry*, WALL ST. J., Aug. 29, 2003, at B1.

164. *Id.*

165. *Id.*

166. *Id.*

167. 264 F. Supp. 2d 1064 (S.D. Fla. 2003).

168. *Gene Patenting Run Amok? Lawsuit Alleges Patent Hinders Research*, BIORESEARCH ONLINE, Nov. 21, 2000, at

<http://www.bioresearchonline.com/content/news/article.asp?DocID={D729C405-BF95-11D4-8C7F-009027DE0829}&Bucket=&Featured=&VNETCOOKIE=NO>.

The case involved Canavan disease. Children with Canavan disease suffer myelin sheath destruction with the first symptoms appearing between three and six months of age.

169. *Greenberg*, 264 F. Supp. 2d at 1066.

170. *Id.* at 1066–67.

his rights by limiting other research efforts.¹⁷¹ The families brought suit, claiming that the patentee used resources dedicated to the public to obtain a patent, charge royalties, and limit testing availability.¹⁷² The district court granted the research institute's motion to dismiss-in-part because extending a duty of informed consent to cover economic interests as well as conversion rights would "chill medical research" and "give rise to a type of dead-hand control that research subjects could hold because they would be able to dictate how medical research progresses."¹⁷³ This case illustrates a dramatic example of how asserting rights to patented tools can potentially block research with important consequences for human health.

Yet, patent holders do not seek to block research. They seek market realized solutions, such as business models based on licensing proposals. In reality, there has never been a broad experimental use exception in the U.S. Based on the legislative history, the federal research exemption appears to have been specifically enacted to enable generic competitors to bring competitively priced drug analogs, devices and other food additives to the market. Most patent attorneys understand this; hence, it is fairly clear that university and not-for profit research activities that make use of unlicensed patents infringe those patents. Due to the impracticability of bringing an infringement suit and the minimal potential damages involved, the cases noted are in many ways rare. Even still, the research landscape requires legislative clarification regarding the scope and depth of the statutory research exemption.

B. *Implications of the Pending Supreme Court Decision in Integra*

1. Affirmation of the Federal Circuit's Decision

If the Supreme Court affirms the Federal Circuit's decision, the ruling will strengthen the protection of patents.¹⁷⁴ It will be seen as a plus for research tool patentees, and likely induce more cross-licensing and less frequent misappropriation of unlicensed patented tools. Biotechnology companies could attempt to enforce their patent rights against academics and not-for profit scientists who have been

171. *Id.* at 1067.

172. *Id.* at 1068.

173. *Id.* at 1070-71.

174. Huang, *supra* note 111, at 98.

using patented research tools without licenses; however, as stated above, this would be unlikely.

Many academic researchers are likely to continue business as usual, maintaining that most or all research done in an academic setting is basic, and not applied research. Some will argue that applied medical research is related to the discovery of drug candidates, and therefore falls within the provisions of the statutory safe harbor. A broad look at the academic landscape, however, suggests that this defense will not be available for many of the academic users of patented research tools.¹⁷⁵ The majority of not-for-profit scientists are not conducting experiments to support FDA submissions, which must be done under conditions in strict compliance with good laboratory practice (“GLP”) guidelines. In addition, many are engaged in “cross-over” or translational research that falls outside the scope of the Federal Circuit’s reading of the common law research exemption. Moreover, Merck’s claim that its research supported the provision of data for regulatory approval was easily shot down; the Federal Circuit declared that at minimum, a clinical drug candidate must have been identified at the time of infringing activity for this exemption to apply.¹⁷⁶

2. *Integra* Read in Light of *Madey*

While academic research may be considered “purely philosophical” in certain cases, it is unlikely to ever be seen as having no bearing whatsoever on a given university’s legitimate business of attracting and retaining students. The *Madey* court set the bar quite high in this regard by arguing that most academic research is a financial plus for any university trying to attract students, as well as federal funding.¹⁷⁷ Under this view, such research will rarely be considered purely academic for learning’s sake. Perhaps this will cause scientists to attempt to “cloak” their work—commercial or not—under the guise of “pure” academic research. As it stands, both avenues of potential exemption from patent infringement appear to be closed off for university and not-for profit researchers.

175. Mueller, *supra* note 38, at 18.

176. Michael S. Greenfield & Kevin E. Noonan, *Biotechnology Tool Patent Owners Breathe Sigh of Relief*, The Association of Patent Law Firms, at <http://www.aplf.org/news/integra.shtml> (last visited Apr. 6, 2005).

177. *Madey v. Duke Univ.*, 307 F.3d 1351, 1362–63 (Fed. Cir. 2002), *cert. denied*, 539 U.S. 958 (2003).

Pushing university scientists further away from any form of research exemption under the common law doctrine, as interpreted in *Madey*, is a strong trend at academic institutions toward industrial collaborations.¹⁷⁸ There is a current move from basic research into translational research, in which universities take equity in companies as part of a diversified technology transfer licensing agreements.¹⁷⁹ Technology transfer is the formal transferring of new discoveries and innovation resulting from scientific research conducted at universities to the commercial sector.¹⁸⁰ This transfer often involves the patenting and licensing of new inventions. The gross licensing received plus royalties on product sales for universities is in the billions of dollars.¹⁸¹ Much of this cross-over is said to have been prompted by the Bayh-Dole Act of 1980, which allowed universities to retain title to inventions made with the use of federal funds, thereby enhancing the incentives for such collaborations.¹⁸² In turn, there has also been a dramatic increase in biotechnology patenting in the last thirteen years; a graphical representation of the total number of U.S. biotechnology patents granted per year shows a rise from less than 2,000 patents issuing in 1985 to more than 7,000 patents issuing in 1998 (see Fig. 2, below).¹⁸³ Currently, no federal law addresses whether this sort of cross-over research should fall inside or outside a safe harbor. One

178. Shreefal Mehta, *The Emerging Role of Academia in Commercializing Innovation*, 22 NATURE BIOTECHNOLOGY 21 (2004); see also Huang, *supra* note 111, at 116 (“[T]he distinction between academic and commercial entities, at least in [sic] respect to biomedical research, is fading.”).

179. Mehta, *supra* note 178, at 21.

180. Act of Dec. 12 1980 Pub. L. No. 96-517, § 6(a), 94 Stat. 3015, 3019-28 (Dec. 12, 1980) (codified as amended at 35 U.S.C. §§ 200-212 (2000)).

181. See Huang, *supra* note 111, at 108-09 (providing a detailed look at research universities actively engaged in licensing and collecting royalties from their patents).

182. See Eisenberg, *supra* note 28, at 1018 (“[U]niversities have become players in the patent system in a way that could hardly have been imagined before the Bayh-Dole Act. Universities owned 1.1% of U.S. corporate-owned patents issued between 1969 and 1989; by 1999 that number had risen to 4.8%.” (citing U.S. Patent and Trademark Office, *U.S. Colleges and Universities—Utility Patent Grants, Calendar Years 1969-2000*, available at http://www.uspto.gov/web/offices/ac/ido/oeip/taf/univ/univ_toc.htm (last visited May 4, 2005))); see also Eyal Press & Jennifer Washburn, *The Kept University*, ATL. MONTHLY, Mar. 2000, at 47 (“The clustering of computer-engineering and biotech firms around academic-research centers in Silicon Valley; Austin, Texas; Route 128 in Massachusetts; and the Research Triangle, in North Carolina, derives in large measure from the synergy between universities and industry that Bayh-Dole has fostered.”).

183. Biotechnology Industry Organization, *Biotechnology Industry Facts* (2003), available at <http://www.bio.org/speeches/pubs/er/statistics.asp> (last visited Apr. 3, 2005). See also Fig. 2, below, for a U.S. Patent and Trademark Office report capturing the volume of biotechnological patent examining activity by the U.S. Patent Examining Technology Center Groups 1630-60 (formerly Patent Examining Group 1800) between 1989 and 2002.

can only presume that it does not; however, newly enacted legislation should clarify if, and at what point researchers would be required to take licenses.

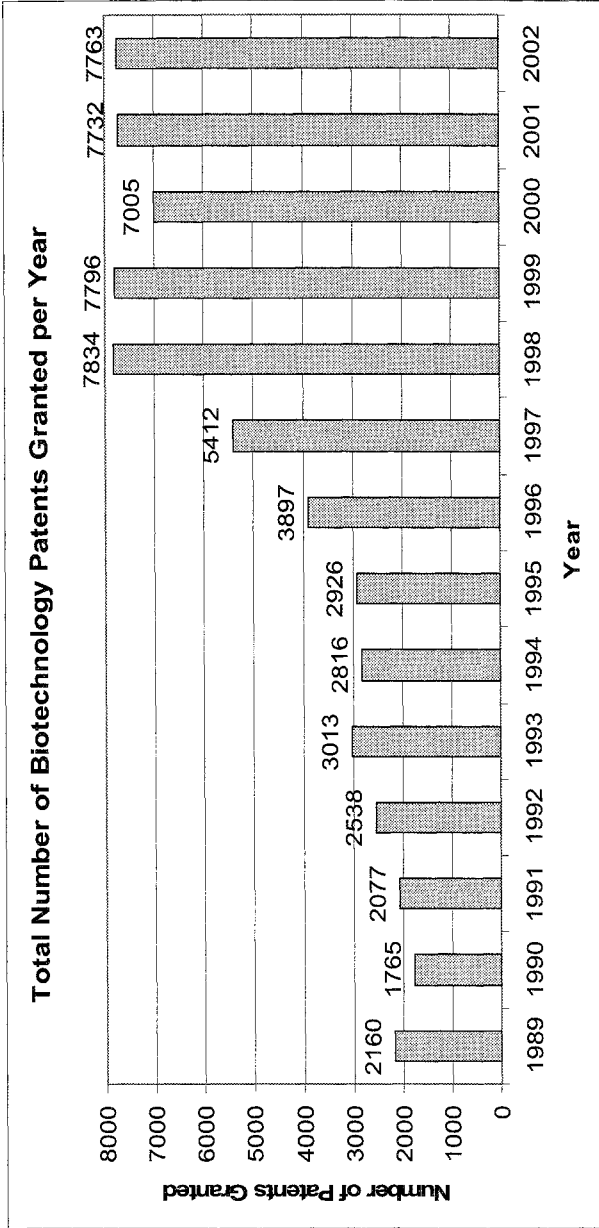


FIGURE 2: Modified from a U.S. Patent and Trademark Office report that captures the volume of biotechnological patent examining activity by the U.S. Patent Examining Technology Center Groups 1630-1660 (formerly Patent Examining Group 1800). Biotechnology Industry Organization, *Biotechnology Industry Facts* (2003), available at <http://www.bio.org/speeches/pubs/er/statistics.asp> (last visited Apr. 3, 2005).

a. *Proposition 71*

Consider, for example, how an affirmation of the Federal Circuit's holding would play out in California with respect to the new stem cell legislation. Much of the research funded by Proposition 71 will include collaborations between universities and industry.¹⁸⁴ In *Madey*, the Federal Circuit emphasized that the common law research exemption would not apply "so long as the [research] is in furtherance of the alleged infringer's legitimate business."¹⁸⁵ The commercial purpose of Proposition 71 in California is brought to light by the economic implications of the legislation: the state seeks to share in royalties from patents and licenses for products developed in the program.¹⁸⁶ Further, to the extent that the University of California receives a share of the grants awarded by the CIRM, it could attract additional federal or private research funding for this same purpose.¹⁸⁷ The University of California system could also eventually receive significant revenues from patents, royalties, and licenses.¹⁸⁸ Thus, it is reasonable to expect that the holding in *Madey* will extend to Proposition 71 collaborations that include university researchers that currently operate under a research exemption.

In addition, embryonic stem cell research is still at a formative stage, i.e., it is relatively far from the point of FDA approval. Accordingly, it falls outside the Federal Circuit's reading of the statutory safe harbor. On one hand, an affirmation of the Federal Circuit's decision could stifle university research by requiring

184. See CALIFORNIA SECRETARY OF STATE, OFFICIAL VOTER INFORMATION GUIDE 147 § 3 (Nov. 2, 2004), available at <http://www.voterguide.ss.ca.gov/english.pdf> ("It is the intent of the people of California in enacting this measure to: Authorize an average of \$295 million per year in bonds over a 10-year period to fund stem cell research and dedicated facilities for scientists at California's universities and other advanced medical research facilities throughout the state.").

185. *Madey v. Duke Univ.*, 307 F.3d 1351, 1362 (Fed. Cir. 2002), cert. denied, 539 U.S. 958 (2003).

186. See CALIFORNIA SECRETARY OF STATE, OFFICIAL VOTER INFORMATION GUIDE 147-49 § 5 (Nov. 2, 2004), available at <http://www.voterguide.ss.ca.gov/english.pdf>.

The ICOC shall establish standards that require that all grants and loan awards be subject to intellectual property agreements that balance the opportunity of the State of California to benefit from the patents, royalties, and licenses that result from basic research, therapy development, and clinical trials with the need to assure that essential medical research is not unreasonably hindered by the intellectual property agreements.

Id. (referring to section 125290.3(h), to be added to California's Health and Safety Code).

187. See CALIFORNIA SECRETARY OF STATE, OFFICIAL VOTER INFORMATION GUIDE 68 (Nov. 2, 2004), available at <http://www.voterguide.ss.ca.gov/english.pdf>.

188. See *id.*

universities and not-for profit entities to take costly licenses. At the same time, the value of research tool patents will be expanded by such a decision; and paradoxically, research tools include compounds, methods and primary stem cell lines used to develop such therapeutics. Thus, an affirmative ruling would cut both ways among stem cell researchers in California. The state, seeking to patent innovations that result from research funded by the grant monies would surely be interested in the broadest possible exclusionary rights. And, because it is generally unlikely that patentees will bring suit against universities, affirmation of the ruling is probably the best route for the Supreme Court. This would keep the value of tool patents high, and allow the legislature to refine the parameters of the research exemption, or craft a new exemption altogether.

3. Narrowing the Scope of the Research Exemption

In *Integra*, the Federal Circuit confirmed that with respect to biomedical research and drug manufacturing, the statutory research exemption applies only to activities that would contribute (relatively directly) to information the FDA considers in approving a drug.¹⁸⁹ It is unlikely that the Supreme Court would narrow the Federal Circuit's interpretation of the research exemption as this would further constrict the federal safe harbor. Genentech has argued that "limiting the scope of the FDA exemption to activities in connection with the abbreviated or generic drug approval process would have a disproportionately harsh impact on the biologics sector of the pharmaceutical industry."¹⁹⁰ This is because "the developer of a new biologic must employ a diverse and broad range of investigative technologies in conducting such research, some or all of which may be subject to patents."¹⁹¹ Further, the American Intellectual Property Law Association (AIPLA) has argued that limiting the safe harbor protection to clinical trials that are reasonably related only to the exact drug for which FDA approval is sought would leave the statute too narrow because "[l]imitation of the safe harbor to 'clinical'

189. *Integra LifeSciences I, Ltd. v. Merck KGaA*, 331 F.3d 860, 867 (Fed. Cir. 2003), cert. granted, 125 S. Ct. 823 (2005) (U.S. Jan. 7, 2005) (No. 03-1237).

190. Brief of Amici Curiae Genentech and Biogen Idec, Inc. in Support of Petitioner at 18, *Merck KGaA v. Integra LifeSciences I, Ltd.*, 125 S. Ct. 823 (No. 03-1237).

191. *Id.*

experiments would ignore the extensive preclinical data required by the FDA.”¹⁹²

In California, a narrowing of the research exemption by the Supreme Court would play out in much the same way as affirming; a further limitation of the exemption would surely reach into the domain of basic medical research carried out by universities and not-for profit organizations. With respect to research funded under Proposition 71, narrowing the safe harbor protection to clinical trials that are reasonably related to only the exact drug for which FDA approval is sought could be impracticable for stem cell research, due to the fact it is still in its early stages.¹⁹³ In addition, the clearly identifiable commercial goals of the legislation would brand state funded stem cell research as applied research, making the common law experimental use exemption unavailable. This situation would arguably be a strong deterrent for academic researchers interested in exploring new methods and uses for embryonic stem cells. This effect runs counter to the expectations set by proponents of Proposition 71, namely by creating a possible stifling effect on progress in human embryonic stem cell research. But, affirming or narrowing the Federal Circuit's interpretation of the scope of the safe harbor would strengthen the value of research tool patents—a result that would reinforce any intellectual property rights the state acquires, thereby improving their position as patent holders in the long run.

4. Expanding the Scope of the Research Exemption

If the Supreme Court expands the scope of the research exemption to be broader than the interpretation given by the Federal Circuit, a consequence would be a decrease in the perceived value of research tool patents. In its brief before the Court, Merck argues that the FDA exemption covering any uses “reasonably related to the development and submission of information” to the FDA should be interpreted broadly.¹⁹⁴ Merck states that any research that is “directed at developing information relevant to an IND [‘investigational new drug’] application” should fall under the § 271(e)(1) safe harbor.¹⁹⁵ The pharmaceutical company claims that the allegedly infringing

192. Brief of Amicus Curiae The American Intellectual Property Law Association in Support of Neither Party at 9, *Merck KGaA v. Integra LifeSciences I, Ltd.*, 125 S. Ct. 823 (No. 03-1237).

193. See *supra* text accompanying note 152.

194. Brief for Petitioner at 26, *Merck KGaA v. Integra LifeSciences I, Ltd.*, 125 S. Ct. 823 (No. 03-1237).

195. *Id.*

experiments in its case fall within the safe harbor statute because (i) it was reasonably believed that the compound was a viable drug candidate, and (ii) the experiments produced information that is considered in an IND application.¹⁹⁶

It is interesting to note that in 1984, the Pharmaceutical Manufacturers Association (PMA) took the opposite point of view as amicus curiae in *Roche Products, Inc. v. Bolar Pharmaceutical, Co.*¹⁹⁷ There, the group of 135 companies argued that because pharmaceutical innovation is a very costly and lengthy process, allowing generic drug manufacturers to make unlicensed use of pioneer drugs for testing in view of FDA approval would reduce incentives for the future innovation of new pharmaceutical products.¹⁹⁸ The PMA urged the Federal Circuit to hold that any use of a patented drug for testing or other purposes to satisfy regulatory requirements should be considered an illegal infringement.¹⁹⁹ Now, Merck, having found itself on the opposite side of bench, urges the Court to find otherwise. Clearly, a broader interpretation of the research exemption is most favorable to any party wishing to use patented research tools without a license.

The U.S. government, which filed a brief in support of Merck's petition for certiorari, as well as one on the merits of the case, is playing a significant role in arguing for a broadening of the research exemption. Specifically, the government claims that the statutory research exemption should protect "all activities that are undertaken in the course of attempting to develop a particular drug and are reasonably related to the development of the types of information that would be relevant to an investigational new drug application or new drug application."²⁰⁰ Further, it asserts that the exemption should apply to pre-clinical studies, and that it should begin to apply once research progresses "beyond basic research and is engaged in focused efforts to develop a particular drug."²⁰¹

In their amicus brief before the Court, Eli Lilly & Co., Wyeth, and Pfizer, Inc. argue that an affirmation of the Federal Circuit's ruling would be seen as a tightening of the bottleneck for commercial

196. *Id.* at 27.

197. See Brief of Amicus Curiae Pharmaceutical Manufacturers Association, Roche Prods., Inc. v. Bolar Pharm., Co., 733 F.2d 858 (Fed. Cir. 1984) (No. 84-560).

198. *Id.* at 2.

199. *Id.* at 3.

200. Brief of Amicus Curiae United States Supporting Petitioner at 8, Merck KGaA v. Integra LifeSciences I, Ltd., 125 S. Ct. 823 (No. 03-1237).

201. *Id.* at 16 (emphasis added).

research.²⁰² Analogizing innovative new drug development to a funneling process,

[t]he [Federal Circuit's] decision enables patent holders to prevent others from entering, or moving down the funnel. As a result, drug development will slow and its costs will mount in what is already a lengthy, high risk, high cost process; patients will be deprived of timely access to new, safer, more effective drugs; the entry of generic equivalents will be delayed; promising drugs to treat unmet medical needs will never be developed; and drug development activities along with valuable American jobs will be exported to countries having more favorable legal environments.²⁰³

Eli Lilly and associated amici curiae state that for pharmaceutical companies, almost every experiment is reasonably related to FDA approval.²⁰⁴ Due to the length of time, risks and high costs involved in drug research, every action in the process must be carefully planned and directed toward obtaining FDA approval.²⁰⁵ Further, they argue that whether an activity is reasonably related under § 271(e)(1) must be determined on a case by case basis, based on an examination of the facts surrounding each use of a patented invention.²⁰⁶

These arguments are in direct conflict with the interests of smaller companies with ownership in patent portfolios they seek to license to the public. Despite the widespread use of patented tools in many areas of the drug discovery process, and over long periods of time, a potential expansion of the research exemption would most certainly bring their value into question. In many cases, "but for" the use of patented tools, research may not have continued to the point of identification of a valuable drug candidate. And, even if their use did not lead to the creation of a blockbuster drug, such use may have allowed researchers to rule out poor candidates, thereby saving time and money early in the discovery process. A broad interpretation of the research exemption would therefore vitiate any value that is currently attributed to research tool patents.²⁰⁷

202. Brief of Amici Curiae Eli Lilly & Co., Wyeth, and Pfizer, Inc. in Support of Petitioner, *Merck KGaA v. Integra LifeSciences I, Ltd.*, 125 S. Ct. 823 (No. 03-1237).

203. *Id.* at 4.

204. *See id.* at 1.

205. *Id.* at 2.

206. *Id.* at 15.

207. *Integra LifeSciences I, Ltd. v. Merck KGaA*, 331 F.3d 860, 867 (Fed. Cir. 2003), *cert. granted*, 125 S. Ct. 823 (2005) (U.S. Jan. 7, 2005) (No. 03-1237) ("[E]xpansion of §

In their brief before the Court as amici curiae in support of respondent, Invitrogen Corporation, Affymetrix, Inc., Symyx Technologies, Inc. and other high-tech companies argue that,

[i]f patents on such tools can be readily infringed in the course of developing information for submission to the Food and Drug Administration (FDA), the economic value of the patents will be essentially lost and the incentives crucial to support creation of new and better tools in the future will be slowed, if not completely eliminated, along with the related discoveries, efficiencies, and cost-savings.²⁰⁸

Therefore, a broad reading of § 271(e)(1) to include research tools would also arguably hinder drug research and development. As a consequence of a decrease in the perceived value of tool patents, companies that need licenses on patented research tools may be emboldened to negotiate for lower prices.²⁰⁹ Furthermore, without the ability of patentees to assert the value of a blockbuster drug in subsequent litigation, they may be forced to accept lower prices in licensing negotiations.²¹⁰

Invitrogen and associated amici curiae also contend that the absence of litigation in which § 271(e)(1) has been successfully invoked to defend against infringement claims of research tool patents is consistent with the longstanding understanding among members of the patent and scientific communities, including pharmaceutical companies, that the statute does not authorize the infringing use of patented research tools.²¹¹

Pharmaceutical companies seem to want the ability to use patented research tools without licensing them for the development of their own new chemical entities, as well as the benefits of the patent system once a new pharmaceutical is ready to market. But just as pharmaceutical manufacturers are rewarded with patent exclusivity for the discovery of new chemical entities, so should every link in the innovation chain be rewarded with exclusivity, whether it involves

271(e)(1) to include the Scripps Merck activities would effectively vitiate the exclusive rights of patentees owning biotechnology tool patents.”)

208. Brief of Amici Curiae Invitrogen Corp. et al. at 3–4, *Merck KGaA v. Integra LifeSciences I, Ltd.*, 125 S. Ct. 823 (No. 03-1237).

209. Stephen B. Maebius & Richard J. Warburg, *Federal Circuit Reins in Free Use of Patented Research Tools*, 26 *LEGAL TIMES* 9 (2003) (noting the results of remanding and vacating the \$15 million damage award by the Federal Circuit in *Integra*).

210. *Id.*

211. Brief of Amici Curiae Invitrogen Corp. et al. at 7, *Merck KGaA v. Integra LifeSciences I, Ltd.*, 125 S. Ct. 823 (No. 03-1237).

the discovery of research tools, devices or new chemical entities—all of which play significant roles in the drug discovery process.

For stem cell research, an expansive reading of the research exemption could mean a paradoxical opportunity for stem cell researchers to enjoy the best of both worlds. Academics collaborating with the biotechnology industry might be free to carry out much of the more “basic” research in an academic setting, under the experimental use exemption. At the same time, biotechnology firms and the state of California could share the potential royalties from intellectual property developed under such collaborations. For patients, this situation provides a climate most suitable for more rapid discovery of stem cell therapeutics. But, for existing patent holders, as well as the state of California, an expanded exemption carries a reduction in the value of biotechnology intellectual property. Such a paradoxical situation is best addressed by the legislature.

C. Legislating a New Research Exemption

The potential problem of gaining access to patented research tools due to expense and availability, combined with the need to encourage and reward innovation, indicates the need on the part of Congress to specify the scope of the experimental use exemption as it stands after the *Integra* court ruling, and in light of *Madey v. Duke University*. The problem lies in creating a new version of the research exemption that rewards the patentee, while simultaneously maintaining access to patented tools, thereby reducing liability in the academic sector. Several plans have emerged that suggest specific instructions for legislating an updated version of the research exemption.²¹²

A newly tailored research exemption should minimize the burden on basic scientists. If scientists are required to jump through numerous hoops, such as complicated and expensive licensing contracts, simply to conduct basic research, they will be less inclined to do so. Another possible implication of burdensome licensing

212. Numerous legal scholars have proposed models for a revised experimental use defense. See Rochelle Dreyfuss, *Protecting the Public Domain of Science: Has the Time for an Experimental Use Defense Arrived?*, 46 ARIZ. L. REV. 457 (2004); Rebecca S. Eisenberg, *Patents and the Progress of Science: Exclusive Rights and Experimental Use*, 56 U. CHI. L. REV. 1017 (1989); Donna M. Gitter, *International Conflicts Over Patenting Human DNA Sequences in the United States and the European Union: An Argument for Compulsory Licensing and a Fair-Use Exemption*, 76 N.Y.U. L. REV. 1623, 1637 (2001); Mueller, *supra* note 38, at 17; Maureen A. O'Rourke, *Toward a Doctrine of Fair Use in Patent Law*, 100 COLUM. L. REV. 1177, 1205 (2000).

requirements might be an infringer's attempt to circumvent U.S. patents by moving research offshore.²¹³ Further, some university researchers argue that biological inventions can simultaneously have commercial applications as well as important roles in basic research. The current research exemption seems to require classifying them as one or the other.

Recently, Professor Mueller has suggested that Congress amend the U.S. Patent Act by enacting "a narrowly defined, carefully balanced experimental use provision that preserves incentives for innovation while permitting unlicensed use of patented inventions in certain instances of legitimate scientific research."²¹⁴ She recommends that lawmakers consider at least several important factors when implementing legislation, including: (1) the availability of consensual licenses; (2) whether the challenged use amounts to experimenting on a claimed invention or experimenting with it; (3) the degree to which the alleged experimental activity is necessarily incident to subsequent commercial exploitation; and (4) the balance of harms invoked in the granting or denial of an experimental use defense under the particular facts at hand.²¹⁵ Taken together, these factors will be key in assisting legislators in crafting a balanced solution that protects the value of the patent system, thereby rewarding innovation, while still granting exemptions in certain circumstances. Indeed, calling for legislative action to define the scope of the patent right is warranted. This is more appropriately a task for the legislative branch than the executive or judicial branches of the government.

V. CONCLUSION

The Federal Circuit's interpretation of the § 271(e)(1) safe harbor in *Integra*, which confirms that it is reserved solely for clinical regulatory data gathering, as well as its reading of the common law experimental use exemption in *Madey*, suggests that neither of these defenses are likely to be available to the great majority of university scientists who use (or would like to use) patented research tools. This is because many academic scientists have ties to commercial

213. See *Bayer AG v. Housey Pharms., Inc.*, 340 F.3d 1367 (Fed. Cir. 2003); see also Mueller *supra* note 17, at 920 (stating that without an experimental use exemption, "scientific research functions that require the use of patented inventions are more likely to be shifted offshore to legally hospitable forums").

214. Mueller, *supra* note 17, at 980.

215. *Id.* at 973.

endeavors. And, even if they do not, their work is unlikely to be defined as “purely philosophical” under the *Madey* Court’s reading of the exemption, since all research—in one way or another—contributes to the furtherance of a university’s legitimate business (of attracting and retaining students). While there may be little incentive to enforce patent rights against universities, the language of the statute, “solely for uses reasonably related to,” requires clarification.

If the Supreme Court’s decision narrows or affirms the Federal Circuit’s ruling, it will have a profound effect on Proposition 71 and stem cell research in California. Stem cell research is not at the stage of FDA regulatory submissions, and it is decidedly commercial in purpose. For academic scientists in this field, the unfettered use of patented research tools, long available under the common law and statutory research exemptions, may now be subject to the same restrictions applied to commercial researchers. At the same time, an expansive reading of the federal research exemption could exaggerate § 271(e)(1) beyond the purpose for which it was enacted, resulting in an unwanted reduction in the value of research tool patents, many of which are held by the University of California. Patent protection will be critical in encouraging investment in the next generation of research tools, which are likely to reduce the cost and time spent in the clinical trial phase. To promote the incentives of the Patent Act, the Supreme Court should affirm the Federal Circuit’s decision, and permit the legislature to enact new laws that specify what sort of unlicensed use of patented research tools among universities and not-for profit institutions is protected by the safe harbor, and when licenses should be taken.
