

## Comment

### Testing Drugs and Testing Limits: *Merck KGaA v. Integra Lifesciences I, Ltd.* and the Scope of the Hatch-Waxman Safe Harbor Provision

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#### I. INTRODUCTION

The limits of the law are often ill-defined or uncertain. Nevertheless, it is a familiar rule to impose liability for exceeding those limits, as Oliver Wendell Holmes remarked as a Supreme Court Justice.<sup>1</sup> Holmes made this point about criminal law and probably would have been surprised to learn that in the future it would be relevant to drug research and development activities. Yet in the wake of the Supreme Court's decision interpreting the scope of the Hatch-Waxman safe harbor provision in *Merck KGaA v. Integra Lifesciences I, Ltd.*,<sup>2</sup> Justice Holmes's observation has continuing vitality.

The Hatch-Waxman safe harbor provision creates a limited exemption from patent infringement liability for using patented inventions to develop and submit information under federal laws that regulate drugs.<sup>3</sup> *Integra* involved Merck KGaA (Merck), an international pharmaceutical company, sponsoring research using certain peptides in various experiments to identify new drug candidates.<sup>4</sup> *Integra Lifesciences I, Ltd.* (*Integra*) sued Merck in federal district court, alleging that the use of the peptides infringed *Integra's*

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1. See *United States v. Wurzbach*, 280 U.S. 396, 399 (1930).

2. *Merck KGaA v. Integra Lifesciences I, Ltd.* (*Integra II*), 125 S. Ct. 2372 (2005).

3. See 35 U.S.C. § 271(e)(1) (2000).

4. See *Integra II*, 125 S. Ct. at 2377-79.

patents.<sup>5</sup> A jury found patent infringement and awarded damages.<sup>6</sup> On appeal, the Federal Circuit determined that the safe harbor did not protect Merck from liability because it did not apply to the type of activities at issue.<sup>7</sup> The Supreme Court granted certiorari and vacated the Federal Circuit's judgment, holding that the Federal Circuit had adopted an improperly narrow interpretation of the safe harbor provision.<sup>8</sup>

The safe harbor has perplexed courts and commentators because its broad language does not mesh well with the more limited scope suggested by its legislative history and purpose. While many believe the safe harbor was only intended to permit generic drug testing,<sup>9</sup> courts have relied on the broad statutory language to give the safe harbor a broader scope.<sup>10</sup> The Supreme Court's *Integra* decision continues the judicial trend of broadening the safe harbor by rendering it applicable to a wide array of new drug development activities. The impact of *Integra* is evident in recent patent infringement cases dismissed in whole or in part based on the Court's interpretation of the safe harbor.<sup>11</sup> But while the safe harbor is broad post-*Integra*, it nevertheless has limits. These limits remain somewhat vague after the decision and will most certainly be the subject of future debate and litigation.

The case is an excellent anchor for examination and analysis of the safe harbor and the drug research process it governs. Part II of this Comment provides background information on the science of drug research and development, the regulatory approval process, the Hatch-Waxman Amendments that include the safe harbor provision, and the interpretation courts have given the safe harbor. Part III describes the *Integra* case in detail. Part IV then analyzes the rationale and holding of *Integra* to show how the case affects

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5. See *id.* at 2379.

6. See *id.* at 2380.

7. See *id.*

8. See *id.* at 2384.

9. See, e.g., Douglas C. Gardner, *Integra Lifesciences I, Ltd. v. Merck KGaA: Upholding Fundamental Principles of Patent Law*, 44 JURIMETRICS J. 523 (2004).

10. See, e.g., *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661 (1990) (determining safe harbor includes medical device testing).

11. See, e.g., *Benitec Austl. Ltd. v. Nucleonics, Inc.*, No. Civ.A. 04-0174 JFJ, 2005 WL 2415959 (D. Del. Sept. 29, 2005); *Classen Immunotherapies, Inc. v. Biogen IDEC*, 381 F. Supp. 2d 452 (D. Md. 2005).

interpretation of the safe harbor provision, including consideration of the limits implied by the Court's opinion as applied to modern drug research. Finally, Part V concludes by noting the challenge for Congress, the courts, and industries involved in drug research to ensure that implementation of this unique provision of law remains within reason given the different policy considerations it implicates.

## II. THE COMPLEX SUBJECT MATTER OF *INTEGRA*

The conflict in *Integra* emerged from the modern drug research and development process and the complex legal regime in which that process occurs. This section provides background information on drug discovery, the FDA approval process, the patent regime, and the Hatch-Waxman Act including the safe harbor provision, and judicial interpretation of the safe harbor.

### A. THE MODERN DRUG DISCOVERY PROCESS

Contemporary drug research is the culmination of scientific and technological progress in several fields.<sup>12</sup> The science of pharmacology came into being as advances in chemistry and biology enabled understanding of the mechanisms by which drugs exert their effects on living systems.<sup>13</sup> This understanding led to the generation of novel drugs based on knowledge of the biological targets on which drugs act.<sup>14</sup> The rise of molecular biology and the completion of the human genome have yielded knowledge about the biological basis for disease that should increase both the quantity and quality of drug targets and potentially lead to individualized drug therapies.<sup>15</sup>

Modern drug research benefits from biotechnology, a broad term for the practical use of biological materials such as genes, proteins, cells, tissues, and whole organisms.<sup>16</sup> The products of biotechnology include research tools such as genes or gene

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12. See Jürgen Drews, *Drug Discovery: A Historical Perspective*, 287 *SCIENCE* 1960 (2000).

13. See *id.* at 1961.

14. See *id.* at 1961-62.

15. See, e.g., *id.*; David Golan, *Building Better Medicines*, *NEWSWEEK*, Summer 2005, at 37.

16. See Susanna Wu-Pong, *An Overview of Biotechnology*, in *BIOPHARMACEUTICAL DRUG DESIGN AND DEVELOPMENT 1* (Susanna Wu-Pong & Yongyut Rojanasakul eds., 1999).

fragments, cell lines, clones and cloning tools, and laboratory equipment and methods, as well as therapeutic products including gene therapy, diagnostic tests, vaccines, and drugs such as insulin.<sup>17</sup> Some fruits of biotechnology potentially straddle these categories and could be used either therapeutically in humans or as tools for further research and development.<sup>18</sup> The biotech industry could be described as the discovery arm of the pharmaceutical industry, providing discoveries “upstream” that help drug companies develop “downstream” products such as drugs.<sup>19</sup>

There are two basic approaches to discovering drugs. One approach, which may be called screening, is more or less random and involves simply testing various molecules in hopes of finding one with a desired biological effect.<sup>20</sup> The new paradigm of drug discovery, high-throughput screening, consists of testing large numbers of compounds in specific biological assays to identify compounds with activity.<sup>21</sup> The other approach is to use rational methods to predict molecules with biological activity. It is sometimes possible to design drugs based on knowledge of the structure of a potential drug target.<sup>22</sup> Alternatively, if active compounds for a particular drug target are already known, these compounds can be used to design new drugs with similar activity or modify and improve active compounds identified by screening.<sup>23</sup> Hence, drugs can

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17. See Michael S. Mireles, *An Examination of Patents, Licensing, Research Tools, and the Tragedy of the Anticommons in Biotechnology Innovation*, 38 U. MICH. J.L. REFORM 141, 149-50 (2004).

18. See Jian Xiao, *Carving out a Biotechnology Research Tool Exception to the Safe Harbor Provision of 35 U.S.C. § 271(e)(1)*, 12 TEX. INTELL. PROP. L.J. 23, 48 (2003).

19. See Wu-Pong, *supra* note 16, at 13; Drews, *supra* note 12, at 1960, 1963; PHARMACEUTICAL RESEARCH & MFRS. OF AM., PHARMACEUTICAL INDUSTRY PROFILE 2005, at v-vi (2005), <http://www.phrma.org/files/2005IndustryReport.pdf>.

20. See TERRY KENAKIN, *MOLECULAR PHARMACOLOGY: A SHORT COURSE* 17-18 (1997).

21. See RUTH R. LEVINE, *PHARMACOLOGY: DRUG ACTIONS AND REACTIONS* 431 (6th ed. 2000); Drews, *supra* note 12, at 1962.

22. See Amy C. Anderson, *The Process of Structure-Based Drug Design*, 10 CHEMISTRY & BIOLOGY 787 (2003); William L. Jorgensen, *The Many Roles of Computation in Drug Discovery*, 303 SCIENCE 1813 (2004).

23. See Elliot M. Ross & Terry P. Kenakin, *Pharmacodynamics: Mechanisms of Drug Action and the Relationship Between Drug Concentration and Effect*, in GOODMAN & GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS 31, 32 (Joel G. Hardman & Lee E. Limbird eds., 10th ed. 2001).

be used to develop other drugs.<sup>24</sup>

Both approaches to drug discovery require a multi-step process. The first step in drug discovery is drug target selection, which consists of target identification, target assessment, and target validation.<sup>25</sup> This step ensures that drug development efforts are directed at targets that meet criteria to maximize the probability of finding effective drugs.<sup>26</sup> After a drug target is validated, the process moves to the lead discovery and lead optimization phases.<sup>27</sup> Lead discovery consists of finding molecules active at the target.<sup>28</sup> Once compounds are identified, lead optimization involves subjecting the compounds to synthetic modification to optimize activity, selectivity, and bioavailability for the molecular target.<sup>29</sup> Lead optimization ensures that the best compound is chosen for drug trials.<sup>30</sup> The bottom line is that developing new drugs involves significant experimentation and trial-and-error even before extensive testing is begun in animals and humans.

#### B. DRUG TESTING AND THE FDA APPROVAL PROCESS

The FDA regulates drugs, medical devices, and biologics. The FDA's authority to regulate medical products is based on various laws passed over the years, often in response to well-publicized disasters involving medical products, perceived inadequacies with the existing regulatory regime, or technological innovation.<sup>31</sup> The resulting regulatory structure is complex and specifically tailored to the unique attributes of drugs, devices, and biologics.<sup>32</sup>

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24. See *id.* at 31 (explaining that an understanding of drug action "provides the basis for . . . the design of new and superior therapeutic agents").

25. See Ursula Egner et al., *The Target Discovery Process*, 6 CHEMBIOCHEM 468, 468 (2005).

26. See *id.* at 478.

27. See *id.* at 471.

28. See KENAKIN, *supra* note 20, at 17.

29. See Terry Kenakin, *Predicting Therapeutic Value in the Lead Optimization Phase of Drug Discovery*, 2 NATURE REVIEWS DRUG DISCOVERY 429, 429 (2003).

30. See *id.*

31. See generally Susan Bartlett Foote & Robert J. Berlin, *Can Regulation Be as Innovative as Science and Technology? The FDA's Regulation of Combination Products*, 6 MINN. J. L. SCI. & TECH. 619 (2005); Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753 (1996).

32. See Foote & Berlin, *supra* note 31, at 619.

The Federal Food, Drug, and Cosmetic Act (FDCA)<sup>33</sup> requires the FDA to approve a new drug before it is released into interstate commerce.<sup>34</sup> First, a drug manufacturer must apply for authorization to conduct clinical trials by submitting an Investigational New Drug Application (IND) that includes the results of preclinical tests that justify clinical testing in humans.<sup>35</sup> Preclinical testing data must include extensive pharmacology and toxicology information based on *in vitro* and animal studies.<sup>36</sup> After clinical testing has begun, a drug manufacturer must submit a New Drug Application (NDA) to get approval to market the new drug.<sup>37</sup> The NDA must include the results of clinical studies that show the drug is both safe and effective for use,<sup>38</sup> as well as preclinical and clinical studies that demonstrate the drug's efficacy, toxicity, and pharmacological properties.<sup>39</sup>

Hence, obtaining FDA approval to market a new drug requires two phases of testing, a preclinical phase and a clinical phase. Pursuant to FDA regulations, clinical testing generally is further divided into three phases.<sup>40</sup> Phase I studies involve about twenty to eighty human subjects and aim to gain information on a drug's pharmacological effects, metabolism, side effects, and pharmacokinetics.<sup>41</sup> Phase II studies involve several hundred research participants who may benefit from the drug and evaluate the drug's effectiveness and short-term toxicity and side effects.<sup>42</sup> Phase III trials involve several hundred to several thousand individuals and include additional controlled and non-controlled studies to evaluate the safety and

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33. 21 U.S.C. §§ 301-397 (2000).

34. *See id.* § 355(a).

35. *See id.* § 355(i)(1)(A); 21 C.F.R. § 312.20(a) (2005).

36. *See* 21 C.F.R. § 312.23(a)(8) (2005). The pharmacological data should include information on the drug's effects, mechanism of action, and absorption, distribution, metabolism, and excretion, if known. *Id.* § 312.23(a)(8)(i). The toxicological data may include information on acute, subacute, and chronic toxicity, the drug's effect on reproduction or the developing fetus, *in vitro* toxicity tests, and any special toxicity resulting from mode of administration or conditions of use. *See id.* § 312.23(a)(8)(ii)(a).

37. *See* 21 U.S.C. § 355(b)(1); 21 C.F.R. § 314.50 (2005).

38. *See* 21 U.S.C. § 355(b)(1)(a).

39. *See* 21 C.F.R. §§ 314.50(d)(2), (5) (requiring preclinical and clinical studies).

40. *See* 21 C.F.R. § 312.21 (2005).

41. *See id.* § 312.21(a)(1).

42. *See id.* § 312.21(b).

effectiveness of the drug. These studies also determine the benefit-risk relationship and appropriate information for labeling.<sup>43</sup>

The drug research and development process is long and expensive. The total time involved in discovering a new drug and getting it approved runs between three and twenty years, with an average of about 8.5 years.<sup>44</sup> The total cost of getting a new drug to market has been estimated to be as high as \$897 million in year 2000 U.S. dollars.<sup>45</sup>

### C. THE HATCH-WAXMAN AMENDMENTS TO THE PATENT STATUTE AND FDCA

The Constitution empowers Congress “[t]o 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.”<sup>46</sup> Congress has implemented this power by creating the patent system.<sup>47</sup> A patent enables an inventor to prevent others from making, using, selling, or importing the invention in the United States.<sup>48</sup> This exclusive right lasts for twenty years from the date of filing of the patent application.<sup>49</sup> The patent system’s purpose is to encourage investment in innovation by allowing patent holders to capture some of the economic benefit from their inventions.<sup>50</sup> Patent protection is thought to encourage the development of new drugs. A study of new drug approvals in different countries has shown that countries with significant patent protection had a larger number of new drugs approved and more pharmaceutical research and development activity than countries with less patent protection.<sup>51</sup>

While the patent system is thought to encourage

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43. See *id.* § 312.21(c).

44. See Michael Dickson & Jean Paul Gagnon, *Key Factors in the Rising Cost of New Drug Discovery and Development*, 3 *NATURE REVIEWS DRUG DISCOVERY* 417, 418 fig.1 (2004). The Pharmaceutical Research and Manufacturers of America (PhRMA) maintains that the total time averages 14.2 years in recent decades. See *id.*

45. See *id.* at 423-26.

46. U.S. CONST. art. I, § 8, cl. 8.

47. See 35 U.S.C. §§ 1-376 (2000).

48. See *id.* § 154(a)(1).

49. See *id.* § 154(a)(2).

50. See DONALD S. CHISUM ET AL., *PRINCIPLES OF PATENT LAW* 1 (3d ed. 2004).

51. See Dickson & Gagnon, *supra* note 44, at 421.

innovation, it does not generally permit the unauthorized use of a patented invention in research to modify, improve upon, design around, or provide a substitute for the invention, although scholars have argued for such an experimental use exemption for some time.<sup>52</sup> While there is a judicially-created experimental use exemption, courts have been unwilling to expand it beyond a very narrow scope. The common law experimental use exemption only applies to uses “for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry” and does not cover acts in furtherance of legitimate business, even if the infringer is a non-profit institution such as a university.<sup>53</sup>

The time involved in getting a new drug developed and approved poses a special problem for patent protection of new drugs. Usually a new drug is not approved by the FDA until long after the patent has issued.<sup>54</sup> The drug manufacturer cannot begin to market the drug without FDA approval, so the long FDA approval process effectively shortens the length of market exclusivity for new drugs.<sup>55</sup>

The intersection of the FDCA with the patent system also created problems for drug manufacturers wanting to market a generic version of a drug once the patent expired. First, before 1984, drug manufacturers had to go through the same lengthy FDA approval process to market a generic version of an already approved drug.<sup>56</sup> This seemed like wasteful duplication. Second, a drug manufacturer could not begin testing a patented drug until the patent expired.<sup>57</sup> While drug companies may

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52. See, e.g., Rebecca S. Eisenberg, *Patents and the Progress of Science: Exclusive Rights and Experimental Use*, 56 U. CHI. L. REV. 1017 (1989); see also Maureen A. O'Rourke, *Toward a Doctrine of Fair Use in Patent Law*, 100 COLUM. L. REV. 1177 (2000) (arguing for a patent doctrine analogous to fair use in copyright law which would include, but not be limited to, experimental use of an invention).

53. See *Madey v. Duke Univ.*, 307 F.3d 1351, 1362-63 (Fed. Cir. 2002) (quoting *Embrex, Inc. v. Serv. Eng'g Corp.*, 216 F.3d 1343, 1349 (Fed. Cir. 2000)).

54. See H.R. REP. NO. 98-857, pt. 1, at 17 (1984), reprinted in 1984 U.S.C.C.A.N. 2647, 2650.

55. See H.R. REP. NO. 98-857, pt. 2, at 30 (1984), reprinted in 1984 U.S.C.C.A.N. 2686, 2714.

56. See *id.* at 30, reprinted in 1984 U.S.C.C.A.N. at 2688; H.R. REP. NO. 98-857, pt. 1, at 14 (1984), reprinted in 1984 U.S.C.C.A.N. (98 Stat. 1585) 2647, 2649.

57. See H.R. REP. NO. 98-857, pt. 2, at 5 (1984), reprinted in 1984



have believed such testing was protected by the common law experimental use exemption, this notion was squarely rejected in *Roche Products, Inc. v. Bolar Pharmaceutical Co.*<sup>58</sup> The result was in effect an extension of the patent term because it would be years after the patent expired before a generic version would be approved for marketing. Thus, the market exclusivity for a patented drug was distorted both at the front end of the patent term because of required FDA approval, and at the back end because of the prohibition on testing during the patent period.<sup>59</sup>

Congress acted to remedy these problems by passing the Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as the Hatch-Waxman Act.<sup>60</sup> The law changed the Patent Act and FDCA in three important respects. First, it enabled a drug manufacturer to file an Abbreviated New Drug Application (ANDA).<sup>61</sup> The ANDA enables a drug manufacturer to piggyback on the safety and effectiveness data submitted for a previously approved drug, simplifying the approval process of generic drugs.<sup>62</sup> Second, the law permitted patent term extension for products subject to a regulatory approval process before marketing, including human drugs, animal drugs, medical devices, and food and color additives.<sup>63</sup> This provision enables the manufacturer to recoup part of the patent term that is lost during product testing and regulatory

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U.S.C.C.A.N. 2686, 2689.

58. 733 F.2d 858, 864-65 (Fed. Cir. 1984) (holding that the common law experimental use exemption to patent infringement did not cover testing of a patented drug for purposes of seeking FDA approval), *superseded by statute*, Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended at 21 U.S.C. § 355 (2000), 35 U.S.C. §§ 156, 271, 282 (2000)).

59. See *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 669-71 (1990).

60. Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended at 21 U.S.C. § 355 (2000), 35 U.S.C. §§ 156, 271, 282 (2000)). For a history leading up to the law's passage, see Gerald J. Mossinghoff, *Overview of the Hatch-Waxman Act and Its Impact on the Drug Development Process*, 54 FOOD & DRUG L.J. 187 (1999).

61. See 21 U.S.C. § 355(j).

62. Generally, the ANDA must show that the indications for the new drug have been approved for the previously approved drug, that the active ingredient or ingredients are the same as for the approved drug, that the route of administration, dosage form, and strength are the same as the active drug, that the new drug is bioequivalent to the approved drug, and that the proposed labeling for the new drug is the same as the labeling approved for the approved drug. 21 U.S.C. § 355(j)(2)(A)(i)-(v).

63. See 35 U.S.C. § 156(a), (f).

review.<sup>64</sup> Finally, the law included a provision, commonly referred to as the safe harbor provision, which permits some otherwise-infringing uses of patented inventions in producing information required for FDA approval of a product, and which in current form reads as follows:

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 or veterinary biological products.<sup>65</sup>

The legislative history of the Hatch-Waxman Act contains several references to the safe harbor provision, and the committee reports suggest that the primary purpose is to facilitate approval of generic drugs.<sup>66</sup> The safe harbor does so by permitting a drug company to experiment with a patented drug for the purpose of seeking FDA approval.<sup>67</sup> Moreover, even when no application for approval is submitted, the experimenter is protected so long as the experiments are done

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64. The patent can be extended for half of the time spent in clinical testing and all of the time spent while the FDA reviews the product application. *See id.* § 156(c)(2), (g)(1)(B).

65. *Id.* § 271(e)(1).

66. *See* H.R. REP. NO. 98-857, pt. 1, at 15 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647, 2648 (stating that safe harbor provision provides that it is not an act of patent infringement for a generic drug maker to use a patented drug in preparation for seeking FDA approval); H.R. REP. NO. 98-857, pt. 2, at 5 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2686, 2689 (indicating that a generic manufacturer may obtain a supply of a patented drug and conduct tests for purposes of FDA approval); *id.* at 8, *reprinted in* 1984 U.S.C.C.A.N. at 2692 (stating that bill permitted only limited testing “so that generic manufacturers can establish the bioequivalency of a generic substitute”); *id.* at 29, *reprinted in* 1984 U.S.C.C.A.N. at 2713 (anticipating benefits to consumers from earlier availability of generic substitutes); *id.* at 30, *reprinted in* 1984 U.S.C.C.A.N. at 2714 (stating that generic manufacturer may not market a patented drug during the life of the patent, but only test the drug for purposes of submitting data to the FDA).

67. *See* H.R. REP. NO. 98-857, pt. 1, at 45 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647, 2678 (“The purpose . . . is to establish that experimentation with a patented drug product, when the purpose is to prepare for commercial activity which will begin after a valid patent expires, is not a patent infringement.”); H.R. REP. NO. 98-857, pt. 2, at 27 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2686, 2711 (stating that provision will reverse the holding of *Roche Products, Inc. v. Bolar Pharmaceuticals Co.*); *id.* at 30, *reprinted in* 1984 U.S.C.C.A.N. at 2714 (stating that safe harbor provision is necessitated by the significant regulatory period for drugs to prevent artificial extension of patents); *id.* (suggesting provision would be analogous to fair use doctrine in copyright law).

to determine whether an application will be submitted.<sup>68</sup> Congress seemed to recognize that most patents falling under the safe harbor provision covered drugs or other FDA-regulated products.<sup>69</sup> It is evident that Congress did not intend to significantly reduce the commercial value of any patent affected by the safe harbor provision.<sup>70</sup>

#### D. JUDICIAL INTERPRETATION OF THE SAFE HARBOR PROVISION

The safe harbor provision has been widely interpreted by federal courts. Numerous commentators have discussed judicial interpretation of the safe harbor provision in detail.<sup>71</sup> The two main interpretive problems are the types of patents covered and the scope of activities permitted by the safe harbor provision.

*Eli Lilly & Co. v. Medtronic, Inc.*,<sup>72</sup> is a seminal U.S. Supreme Court case concerning the types of patented inventions within the safe harbor's meaning. In this case, Medtronic, Inc. was testing and marketing a heart defibrillator of its competitor, Eli Lilly & Co. Medtronic argued that this testing and marketing fell under the safe harbor provision as the activity was "reasonably related to the development and submission of information" under the FDCA.<sup>73</sup> In reaching its decision, the Court interpreted the phrase "patented invention" to include "all inventions, not drug-related inventions alone."<sup>74</sup> Moreover, the Court construed the phrase "under a Federal law which regulates the manufacture, use, or sale of drugs" to refer to an entire statute, not just an isolated statutory provision.<sup>75</sup> Declining to limit the safe harbor's scope based on the legislative history, the Court reasoned that "[i]t is not the law

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

69. See H.R. REP. NO. 98-857, pt. 2, at 61 n.20 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2686, 2721 n.20 ("It is important to note that most patent holders affected . . . will also receive a benefit from the bill in the form of patent term extension.")

70. See *id.* at 8, *reprinted in* 1984 U.S.C.C.A.N. at 2692 ("The patent holder retains the right to exclude others from the major commercial marketplace during the life of the patent. Thus, the nature of the interference with the rights of the patent holder is not substantial.")

71. See, e.g., Phillip B.C. Jones, *Navigating the Hatch-Waxman Act's Safe Harbor*, 57 FOOD & DRUG L.J. 475 (2002); Xiao, *supra* note 18.

72. 496 U.S. 661 (1990).

73. See *id.* at 664.

74. *Id.* at 665.

75. See *id.* at 665-69.

that a statute can have no effects which are not explicitly mentioned in its legislative history.”<sup>76</sup> Instead, the Court reasoned from the structure of the Hatch-Waxman Act that the safe harbor provision was part of a package that included the patent extension provision. Accordingly, since the extension provision explicitly included medical devices, food additives, and color additives, as well as drugs, all of these products were also included in the safe harbor provision.<sup>77</sup> The Court stated that the Act’s apparent purpose was to eliminate distortions to patent terms for FDA-regulated products caused by the prohibitions on marketing the products during the regulatory review period and testing the products during the patent term.<sup>78</sup> On this basis, the Court reasoned that excluding medical devices from the safe harbor would thwart this purpose because the devices were eligible for patent term extensions.<sup>79</sup> The Court noted, however, that some products may be eligible for patent term extension but not fall within the safe harbor, and vice versa.<sup>80</sup>

In the wake of *Eli Lilly*, courts have generally broadly interpreted the scope of patented inventions falling under the safe harbor. For example, in *Abtox, Inc. v. Exitron Corp.*,<sup>81</sup> the Federal Circuit held that medical devices not eligible for patent term extension nevertheless fell under the safe harbor provision.<sup>82</sup> The court contended that under *Eli Lilly*, symmetry in scope between the patent extension and safe harbor provisions was preferred but not required, and that the inventions at issue fell under the plain language of the safe harbor provision.<sup>83</sup>

By contrast, in *Infigen, Inc. v. Advanced Cell Technology, Inc.*,<sup>84</sup> the patents at issue covered a process for activating bovine egg cells and a culture media for growing the cells, both of which could be used to create transgenic cattle.<sup>85</sup> Such cattle

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76. *Id.* at 669 n.2 (quoting *Pittston Coal Group v. Sebben*, 488 U.S. 105, 115 (1988)) (internal quotation marks omitted).

77. *See id.* at 669-74.

78. *See Eli Lilly*, 496 U.S. at 669-71.

79. *Id.* at 672.

80. *Id.* at 671-72.

81. 122 F.3d 1019 (Fed. Cir. 1997).

82. *Id.* at 1029.

83. *See id.*

84. 65 F. Supp. 2d 967 (W.D. Wis. 1999).

85. *Id.* at 969-70.

potentially could produce milk containing the transgene product, which would be subject to FDA approval.<sup>86</sup> The *Infigen* court held that use of these patents did not fall within the safe harbor because neither patent was subject to the patent term extension provision.<sup>87</sup> This holding is in direct conflict with *Abtox* because the *Infigen* court held that symmetry in scope between patent term extension and the safe harbor provisions is required.

An important case construing the uses of patented inventions permitted by the safe harbor is *Intermedics, Inc. v. Ventritex, Inc.*<sup>88</sup> The patent at issue covered a medical device that Ventritex was using to generate data for an FDA application, and Intermedics argued that the safe harbor did not apply because Ventritex intended to commercialize the device.<sup>89</sup> The Northern District of California held that the scope of permissible activity concerns the actual use of the patented invention, not the purpose of the alleged infringer.<sup>90</sup> The court then articulated a test for determining permissible use that has since been widely used by courts:

[W]ould it have been reasonable, objectively, for a party in defendant's situation to believe that there was a decent prospect that the "use" in question would contribute (relatively directly) to the generation of kinds of information that was likely to be relevant in the processes by which the FDA would decide whether to approve the product?<sup>91</sup>

Following the *Intermedics* decision, courts have held that the safe harbor provision permits a variety of uses of patented inventions. For example, display of a patented medical device at conferences was within the safe harbor because the display was necessary to recruit investigators to conduct clinical trials.<sup>92</sup> Use of a patented protein by a competitor as a reference standard to evaluate an alternative manufacturing method was also within the safe harbor because the FDA presumably would have to approve the alternative manufacturing method.<sup>93</sup> In addition, conducting an *in vivo*

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86. *See id.* at 974.

87. *See id.* at 980.

88. 775 F. Supp. 1269 (N.D. Cal. 1991), *aff'd*, 991 F.2d 808 (Fed. Cir. 1993).

89. *See id.* at 1273.

90. *See id.* at 1275.

91. *Id.* at 1280.

92. *See* Teletronics Pacing Sys., Inc. v. Ventritex, Inc., 982 F.2d 1520, 1522-23 (Fed. Cir. 1992).

93. *See* Amgen, Inc. v. Hoechst Marion Roussel, Inc., 3 F. Supp. 2d 104,

purity test of that protein fell within the safe harbor because the test was necessary to confirm the purity of the product for use in clinical trials that would be submitted to the FDA.<sup>94</sup> Simply producing a commercial-size quantity of a patented product has also been held to be within the safe harbor because of the need to demonstrate suitable manufacturing capability for FDA approval.<sup>95</sup> By contrast, stockpiling a large batch of a drug in evident preparation to sell immediately following FDA approval was outside the scope of the safe harbor.<sup>96</sup>

Another notable case is *Bristol-Myers Squibb Co. v. Rhône-Poulenc Rorer, Inc.*,<sup>97</sup> which is significant because it involved new drug development activities and portended some of the issues in *Integra*. Rhône-Poulenc Rorer held patents on compounds that were intermediates in the synthesis of the drug paclitaxel.<sup>98</sup> Bristol-Myers Squibb used these intermediates in basic research to develop a structure-activity relationship database which in turn was used to screen more than 1000 compounds for biological activity, and also in studies to create analogs of paclitaxel by chemical modification.<sup>99</sup> Citing the *Intermedics* test, the District Court of Massachusetts found these research activities to fall within the safe harbor.<sup>100</sup> The court rejected the patent holder's argument that the safe harbor should not apply until a particular drug candidate is selected for further study or filed with the FDA, responding that this would prevent competitors from being able to experiment with a patented drug to create new and improved drugs.<sup>101</sup> The court reasoned that if the safe harbor only applied after a particular drug candidate was selected or filed with the FDA, the safe harbor would never be reached because the underlying research and development required to reach that stage could not be conducted.<sup>102</sup> The court held that the

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109 (D. Mass. 1998).

94. *See id.* at 109-10.

95. *See* NeoRx Corp. v. Immunomedics, Inc., 877 F. Supp. 202, 206 (D.N.J. 1994).

96. *See* Biogen, Inc. v. Schering AG, 954 F. Supp. 391, 396-97 (D. Mass. 1996).

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

98. *Id.* at \*1.

99. *See id.* at \*4-5.

100. *See id.* at \*6.

101. *See id.*

102. *See id.*

safe harbor applies to preliminary research that may not directly yield information that would be submitted to the FDA, as long as the research facilitates or would be useful in generating information that could be submitted.<sup>103</sup>

It is evident from these cases that the courts have given the safe harbor a wide berth. The safe harbor has been held to protect the use of a variety of patented products, and the range of activities permitted is similarly broad. While there is precedent for the proposition that the scope of the safe harbor is not unlimited, it is not readily apparent where the outer limits lie.

### III. TESTING THE LIMITS OF THE SAFE HARBOR: *INTEGRA*

The Supreme Court recently visited the issue of the limits of the safe harbor in *Merck KGaA v. Integra Lifesciences I, Ltd.*<sup>104</sup> The case involved the international drug manufacturer Merck KGaA (Merck), which was sponsoring various experiments aimed at developing new drugs using certain peptides. Integra Lifesciences I, Ltd. (Integra), a competitor of Merck, claimed these peptides were covered by its patents.<sup>105</sup> The facts of the case and the opinions of the Federal Circuit and the Supreme Court highlight the issues and concerns associated with different interpretations of the safe harbor.

#### A. FACTS AND BACKGROUND

Integra holds five patents related to a short tri-peptide sequence known as the RGD peptide.<sup>106</sup> The RGD peptide promotes cell adhesion to substrates *in vivo* and *in vitro* by interacting with a particular class of receptors on cell surface proteins called integrins.<sup>107</sup> Dr. David Cheresh, a scientist at the Scripps Institute (Scripps), discovered that blocking these receptors inhibits angiogenesis, a process involved in various pathologies.<sup>108</sup>

Merck agreed to collaborate with Scripps to test angiogenesis inhibitors as drug candidates and ultimately

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103. Bristol-Meyers, 2001 WL 1512597 at \*7.

104. 125 S. Ct. 2372 (2005).

105. See *Integra II*, 125 S. Ct. at 2377-79.

106. See *Integra Lifesciences I, Ltd., v. Merck KGaA (Integra I)*, 331 F.3d 860, 862 (Fed. Cir. 2003), *vacated*, 125 S. Ct. 2372 (2005).

107. See *id.*

108. See *id.* at 863.

submit an IND to the FDA.<sup>109</sup> Pursuant to the agreement, Dr. Cheresh conducted research using various RGD peptides supplied by Merck.<sup>110</sup> The research consisted of *in vitro* and *in vivo* experiments on the RGD peptides to determine their efficacy, specificity, toxicity, mechanism of action, and pharmacokinetics to find suitable candidates to develop as drugs to inhibit angiogenesis.<sup>111</sup> Scripps also conducted research to find other compounds that would have a similar effect as the RGD peptides. For these experiments, the RGD peptides were used as positive controls against which to measure the efficacy of the compounds studied.<sup>112</sup> Merck eventually took steps to guide one of the RGD peptides through the FDA approval process.<sup>113</sup>

While these studies were ongoing, Integra filed a patent infringement suit in federal district court against Merck, Scripps, and Dr. Cheresh for use of the RGD peptides.<sup>114</sup> The district court's jury instruction essentially recited the *Intermedics* test to determine whether the safe harbor shielded Merck from patent infringement liability.<sup>115</sup> The jury instruction provided that information did not have to be actually submitted to the FDA for the safe harbor to apply.<sup>116</sup> The jury determined that the safe harbor was not applicable, found patent infringement by the defendants, and awarded \$15 million in damages.<sup>117</sup> In response to post-trial motions, the district court dismissed the claims against Scripps and Dr. Cheresh. The district court, however, affirmed the damage award against Merck because the trial evidence was sufficient to show that the connection between the research activities and FDA review was too attenuated for the safe harbor provision to apply.<sup>118</sup>

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109. See *Integra II*, 125 S. Ct. at 2378.

110. See *id.*

111. See *id.* at 2378-79.

112. See *id.* at 2379.

113. See *id.*

114. See *id.*

115. See *Integra II*, 125 S. Ct. at 2379.

116. See *id.*

117. See *id.* at 2380.

118. See *id.*



## B. THE FEDERAL CIRCUIT DECISION

## 1. The Majority Opinion

Merck filed a timely appeal with the Federal Circuit Court of Appeals asserting, among other things, error in the district court's interpretation of the safe harbor provision.<sup>119</sup> The court's analysis began with a discussion of the safe harbor provision's legislative history.<sup>120</sup> The court concluded that based on the legislative history the provision was intended to permit testing of generic drugs and interference with the rights of the patent holder was intended to be minimal.<sup>121</sup> Furthermore, the court determined the word "solely" in the statutory text limits the extent of activities protected by the safe harbor.<sup>122</sup> "[R]easonably related to the development and submission of information" also limits the scope of the provision to activities that produce information for the FDA, although the court conceded that this includes some activities that are not experiments.<sup>123</sup>

The court found that the research Merck had sponsored "was not clinical testing to supply information to the FDA, but only general biomedical research to identify new pharmaceutical compounds."<sup>124</sup> Concluding that the FDA was not interested in "the hunt for drugs that may or may not later undergo clinical testing" for approval and that the agency "does not require information about drugs other than the compound" included in an IND, the court determined that the work Merck had sponsored "was not 'solely for uses reasonably related' to clinical testing for FDA."<sup>125</sup>

The court stated that in this context the safe harbor "simply does not globally embrace all experimental activity that at some point, however attenuated, may lead to an FDA approval process."<sup>126</sup> Hence, the court determined that the provision does not cover all stages of the development of new

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119. See *Integra I*, 331 F.3d 860, 864 (Fed. Cir. 2003), *vacated*, 125 S. Ct. 2372 (2005).

120. See *id.* at 864-65.

121. See *id.* at 865.

122. See *id.* at 866.

123. See *id.*

124. *Id.*

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

126. *Id.* at 867.

drugs.<sup>127</sup> The court further concluded that extending the safe harbor to all stages of new drug development would result in more than minimal encroachment on the rights of patent holders and potentially vitiate the value of patented research tools, which derive their primary commercial value from use in research.<sup>128</sup> The court feared that an overly expansive safe harbor “would swallow the whole benefit of the Patent Act for some categories of biotechnological inventions.”<sup>129</sup> For these reasons, the court affirmed the district court’s interpretation of the safe harbor provision.<sup>130</sup>

## 2. The Dissent

Judge Newman dissented from the court’s opinion.<sup>131</sup> She discussed the research conducted by Merck and Scripps and the common law experimental use exemption.<sup>132</sup> She argued that because the research was aimed at understanding, improving upon, or modifying the patented subject matter, the experimental use exception applied.<sup>133</sup> She agreed with the majority that the safe harbor provision did not include all stages of new drug development, but she contended that the experimental use exception covered the research not included in the safe harbor and that the safe harbor “took up where the research exemption left off.”<sup>134</sup> Regarding the court’s fear that exemption from patent infringement liability would diminish the value of patented research tools, she maintained that use of a research tool is different from study of the tool itself, and thus that the RGD peptides were not used as research tools by Merck and Scripps.<sup>135</sup>

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127. *See id.*

128. *See id.*

129. *See id.*

130. *See id.* at 868. The court went on to determine that the district court correctly concluded that the RGD peptides used by Merck and Scripps fell within the claims of Integra’s patents. *See id.* at 868-69. The court also analyzed the jury’s damage award and held that it was not supported by the evidence. *See id.* at 869-72. These holdings are not pertinent to the subject of this comment and thus are not discussed further.

131. *See Integra I*, 331 F.3d at 872-78 (Newman, J., dissenting).

132. *See id.* at 873-76. She referred to the exemption as the “common law research exemption.” *Id.* at 874.

133. *See id.* at 876.

134. *See id.* at 878.

135. *See id.*

## C. THE SUPREME COURT DECISION

The Supreme Court granted certiorari to review the Federal Circuit's construction of the safe harbor provision.<sup>136</sup> Writing for a unanimous Court, Justice Scalia quoted the statutory language and stated the safe harbor "provides a wide berth for the use of patented drugs in activities related to the federal regulatory process."<sup>137</sup> Based on the text, the Court held that the safe harbor applies to activities reasonably related to the development and submission of any information under the FDCA; thus, preclinical studies of patented compounds were included within the safe harbor.<sup>138</sup> The Court noted that the statutory language does not limit the phases of research or types of submissions included within the safe harbor.<sup>139</sup>

Addressing Integra's argument that only preclinical studies pertaining to safety of drugs in humans were of interest to the FDA, the Court pointed to the FDA's requirement that INDs contain information about a drug's pharmacological, pharmacokinetic, toxicological, and biological qualities in animals.<sup>140</sup> The Court maintained that such information generally must be obtained through preclinical *in vitro* and *in vivo* studies.<sup>141</sup> Furthermore, the FDA requires an IND to include information that enables the agency to make a risk-benefit assessment on whether to allow clinical trials, and "[s]uch information necessarily includes preclinical studies of a drug's efficacy in achieving particular results."<sup>142</sup>

Turning to the Federal Circuit's rationale, the Court rejected the notion that the safe harbor applies only to experiments actually included in an FDA submission.<sup>143</sup> The Court noted that scientific testing is a trial-and-error process. Drug companies generally do not know in advance which experiments will be successful. Hence, they do not know in advance which experiments will be appropriate to include in an

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136. See *Integra II*, 125 S. Ct. 2372, 2380 (2005).

137. *Id.* at 2380. The language of the safe harbor provision, codified at 35 U.S.C. § 271(e)(1) (2000), is quoted at note 65 and accompanying text.

138. See *Integra II*, 125 S. Ct. at 2380.

139. See *id.*

140. See *id.* at 2381 (citing 21 C.F.R. § 312.23(a)(5) (2005)).

141. See *id.*

142. *Id.*

143. See *id.* at 2382-83.

FDA submission.<sup>144</sup> Referring to the “reasonably related” language in the statute, the Court posited that the relationship of an experiment “to the ‘development and submission of information’ to the FDA does not become more attenuated (or less reasonable) simply because the data from that experiment are left out of the submission that is ultimately passed along to the FDA.”<sup>145</sup> Rather, the safe harbor leaves room for “experimentation and failure” in drug development and approval.<sup>146</sup> Moreover, the Court stated, drug companies also face uncertainty about what research to include in an IND or NDA to get FDA approval.<sup>147</sup>

The Court further reasoned that limiting the safe harbor to testing on a compound actually included in an FDA submission would effectively limit the safe harbor to generic drug approval, because the only way researchers will know for certain that experiments on an identical compound will be appropriate to include in an FDA submission is if the compound is already approved.<sup>148</sup> Referring again to the statutory text, the Court rejected the claim that the safe harbor is limited to generic drug approval.<sup>149</sup> Rather, the safe harbor protects “*all* uses of patented compounds ‘reasonably related’ to the process of developing information for submission under *any* federal law regulating the manufacture, use, or distribution of drugs.”<sup>150</sup> Addressing the Federal Circuit’s concern about depriving patented research tools of much of their value, the Court expressly declined to decide whether use of such tools fell under the safe harbor, claiming that it was evident from the record that the RGD peptides were not used as research tools.<sup>151</sup>

The Court agreed with the Federal Circuit’s assertion that the safe harbor does not cover all activity that may lead to an FDA approval process.<sup>152</sup> In particular, “[b]asic scientific

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144. See *Integra II*, 125 S.Ct. at 2382-83.

145. *Id.* at 2383.

146. *Id.*

147. See *id.* (citing 21 C.F.R. § 312.22(b) (2005) (noting that the amount of information that must be submitted in an IND for a particular drug depends on several factors)).

148. See *id.*

149. See *id.* (citing 35 U.S.C. § 271(e)(1) (2000)).

150. *Integra II*, 125 S.Ct. at 2383 (citing *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 674 (1990)).

151. See *id.* at 2382 n.7.

152. See *id.* at 2382.

research on a particular compound, performed without the intent to develop a particular drug or a reasonable belief that the compound will cause the sort of physiological effect the researcher intends to induce” does not satisfy the “reasonably related” standard set by the statutory language.<sup>153</sup> However, the Court posited that the safe harbor applies when a compound is chosen based on particular expectations about its mechanism of action and effect and used in research aimed at producing the type of information appropriate to submit to the FDA:

[W]here a drugmaker has a reasonable basis for believing that a patented compound may work, through a particular biological process, to produce a particular physiological effect, and uses the compound in research that, if successful, would be appropriate to include in a submission to the FDA, that use is “reasonably related” to the “development and submission of information under . . . Federal law.”<sup>154</sup>

The Court indicated that the jury instruction given by the district court was “consistent with, if less detailed than, the construction . . . that we adopt today.”<sup>155</sup> Because the Court found that the Federal Circuit used a flawed interpretation of the safe harbor provision when it rejected Merck’s challenge to the sufficiency of the evidence supporting the jury verdict, the Court vacated the Federal Circuit’s judgment and remanded the case for further proceedings.<sup>156</sup> The Federal Circuit has since reinstated the appeal with the original panel of judges and ordered the parties to submit new briefs that take account of the Supreme Court opinion.<sup>157</sup> As of the printing of this article no decision has been reported.

#### IV. ANALYZING *INTEGRA*: THE SAFE HARBOR AND ITS LIMITS

##### A. INTERPRETATION OF THE SAFE HARBOR AFTER *INTEGRA*

The Federal Circuit and Supreme Court opinions in *Integra* reflect differing views of the Hatch-Waxman safe harbor provision. A similar dichotomy pervades the academic literature, with some commentators arguing that the safe

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153. *Id.*

154. *Id.* at 2383 (quoting 35 U.S.C. § 271(e)(1) (2000)).

155. *Id.* at 2384.

156. *See Integra II*, 125 S. Ct. at 2384.

157. *See Integra Lifesciences I, Ltd. v. Merck KGaA*, 421 F.3d 1289, 1289 (Fed. Cir. 2005).

harbor should be restricted to generic drug testing or clinical testing, and others contending that the safe harbor should protect a broader range of activities and cover a wider variety of patents.<sup>158</sup> These distinct views arise from different interpretations of statutory text, structure, and legislative history. The dichotomy also arises in part from distinct policy considerations evident in the *Integra* opinions: the Federal Circuit approached its task with a view toward the dangers of an overly broad safe harbor while the Supreme Court approached the same task emphasizing the pitfalls of a narrow safe harbor. The cogency of the arguments in both opinions testifies to the merits of both positions: the safe harbor should be interpreted neither too broadly nor too narrowly. While *Integra* binds future courts to a broad view of the safe harbor, these courts should recognize that the opinion describes limits on the scope of activities permitted, and that the opinion is not inconsistent with, and implicitly supports, limits on the types of patented inventions that may be used within the safe harbor.

The Court invoked the statutory text for the proposition that the safe harbor “provides a wide berth for the use of patented drugs in activities related to the federal regulatory process.”<sup>159</sup> The plain language of the provision indeed sweeps very broadly. The provision uses the term “patented invention” rather than “patented drug” or “patented drug already approved for use.”<sup>160</sup> The current statutory language specifically excludes new animal drugs or veterinary biological products prepared by site specific genetic manipulation techniques, suggesting that other products are not excluded from the safe harbor’s scope.<sup>161</sup> Nor does the statutory language that follows impose such limits, at least not directly. While the safe harbor restricts the use of patented inventions to the production of information “under a Federal law which

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158. Compare, e.g., Gardner, *supra* note 9 (arguing that the Federal Circuit was correct to narrow the scope of the safe harbor), with Alison Ladd, *Integra v. Merck: Effects on the Cost and Innovation of New Drug Products*, 13 J.L. & POLY 311 (2005) (arguing in the wake of the Federal Circuit decision that a broad safe harbor is necessary to control drug costs and encourage new drug development and innovation).

159. *Integra II*, 125 S. Ct. at 2380.

160. 35 U.S.C. § 271(e)(1) (2000).

161. See *id.* When Congress provides exceptions in a statute, the natural inference is that Congress considered the issue of exceptions and limited the statute to the exceptions set forth. See *United States v. Johnson*, 529 U.S. 53, 58 (2000).

regulates . . . drugs or veterinary biological products,”<sup>162</sup> this seems like an unlikely way to limit the term “patented invention.” It would have been more natural to do so by qualifying or elaborating on the patented inventions covered.<sup>163</sup>

The uses of patented inventions permitted by the safe harbor are governed by the phrase “solely for uses reasonably related to the development and submission of information” under a federal law regulating drugs or veterinary biological products.<sup>164</sup> The word “solely” could be construed to restrict the scope of permissible activities as the Federal Circuit suggested, but this reading would be in tension with the further modifier “reasonably related,” which suggests some leeway in what is permitted. The fact that the statute includes the word “uses” instead of “purposes” suggests that the inquiry is an objective one focused on the actual uses to which the invention is put, not on the subjective purposes of the user.<sup>165</sup> The phrase “reasonably related to the development and submission of information” seems to encompass activities that produce the type of information included in FDA submissions such as INDs and NDAs, even if the activities do not in fact produce information that is actually included. Moreover, the term “reasonably related” indicates that some activities that do not directly produce such information are included. Although the modifier “reasonably” also limits the range of these activities, courts after *Integra* are bound by the Court’s refusal “to read the ‘reasonable relation’ requirement so narrowly as to render . . . protection of activities leading to FDA approval for all drugs illusory.”<sup>166</sup>

In holding that the safe harbor extends to new drug development activities, the *Integra* Court implicitly rejected a limit to the safe harbor’s scope arguably implied by the structure of the statutory scheme created by the Hatch-Waxman amendments. The *Eli Lilly* Court reasoned that the Hatch-Waxman provisions aim to eliminate the distortions in marketing exclusivity conferred by patent terms for products subject to FDA approval, and hence patent term extension and the safe harbor provisions should both generally apply to the

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162. See 35 U.S.C. § 271(e)(1).

163. See *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 667-68 (1990).

164. 35 U.S.C. § 271(e)(1).

165. For an excellent elaboration of this point, see *Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269 (N.D. Cal. 1991), *aff’d*, 991 F.2d 808 (Fed. Cir. 1993).

166. *Integra II*, 125 S. Ct. 2372, 2383 (2005).

same products.<sup>167</sup> On this view, the safe harbor exists to permit testing and regulatory approval of an otherwise infringing product, such as a generic drug or similar medical device, so that commercial marketing can begin as soon as the patent on the pioneer product expires. This logic does not extend to new drug development because a new drug by definition differs from existing drugs. Because a new drug differs from existing drugs, a new drug does not prevent distortion in marketing exclusivity at the back end of the patent term for these existing drugs. On the basis of the structural argument in *Eli Lilly*, a court before *Integra* could have concluded that the safe harbor does not extend to new drug development activities. Indeed, the Federal Circuit's constrained view of permissible activities in *Integra* was partially based on the proposition that the safe harbor allows for pre-expiration testing of a patented drug already on the market to facilitate generic approval.<sup>168</sup>

This structural argument, however, was only part of the rationale in *Eli Lilly*. The Court also rested its holding on the plain language of the safe harbor provision.<sup>169</sup> Before *Integra*, courts have differed over whether the safe harbor's scope is to be determined by its plain language or by its purpose as indicated by the statutory structure. Some courts have focused on the plain language to extend the safe harbor beyond the scope suggested by the structural argument in *Eli Lilly*.<sup>170</sup> At least one court, however, has relied on the structural argument to hold that the safe harbor only applies to products eligible for patent term extension.<sup>171</sup>

The *Integra* Court resolved this question by resting its holding on the statutory language, which on its face does not limit the safe harbor to generic product testing.<sup>172</sup> The reasoning of *Integra* may make future courts less likely to read limitations into the safe harbor based on statutory structure or

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167. See *Eli Lilly*, 496 U.S. at 669-74 (1990).

168. See *Integra I*, 331 F.3d 860, 866-67 (Fed. Cir. 2003), *vacated*, 125 S. Ct. 2372 (2005).

169. See *Eli Lilly*, 496 U.S. at 665-69.

170. See, e.g., *Abtox, Inc. v. Exitron Corp.*, 122 F.3d 1019, 1029 (Fed. Cir. 1997) (holding that the safe harbor applies to testing of medical devices not eligible for patent term extension).

171. See *Infigen, Inc. v. Advanced Cell Tech., Inc.*, 65 F. Supp. 2d 967, 980 (W.D. Wis. 1999).

172. See *Integra II*, 125 S. Ct. 2372, 2383 (2005).



purpose, although *Integra* does not render these considerations illegitimate. The *Integra* opinion resists taking the safe harbor to the limit that a literal reading of the statutory language would permit. Thus, *Integra* should be read as endorsing a broader statutory purpose than generic drug testing or the prevention of patent term distortion; it should not be read as an outright abandonment of purpose-based interpretation in favor of a literal statutory reading.

Legislative history also did not sway the *Integra* Court to adopt a more constrained view of the safe harbor's scope. The Court did not cite or mention the legislative history of the Hatch-Waxman Amendments. In contrast, the *Eli Lilly* Court mentioned, without much elaboration, that the legislative history "sheds no clear light" on interpretation of the safe harbor.<sup>173</sup> The reason the legislative history was not examined more thoroughly may be that both the *Eli Lilly* and *Integra* opinions were authored by Justice Scalia, who has argued that judges should not rely on legislative history in statutory interpretation.<sup>174</sup> Several commentators have pointed to the legislative history in arguing that Congress intended the safe harbor to only protect testing and approval of generic versions of patented drugs already on the market.<sup>175</sup> In *Integra*, the Federal Circuit referred to legislative history concluding that the safe harbor should be construed narrowly.<sup>176</sup> However, because the Supreme Court in *Integra* determined that the safe harbor encompasses new drug development activities, future courts are constrained from using legislative history to limit the safe harbor to generic product testing, although they may be able to limit the safe harbor's scope in other respects based on legislative history.

The realities of drug testing and approval are prominent in the Court's interpretation of the safe harbor, and rightly so. Based on the trial-and-error nature of the drug discovery and development process, the Court appropriately reasoned that the safe harbor must be wide enough to accommodate

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173. See *Eli Lilly*, 496 U.S. at 669.

174. See, e.g., *Conroy v. Aniskoff*, 507 U.S. 511, 518-28 (1993) (Scalia, J., concurring in the judgment).

175. See, e.g., Courtenay C. Brinckerhoff, *Can the Safe Harbor of 35 U.S.C. § 271(e)(1) Shelter Pioneer Drug Manufacturers?*, 53 FOOD & DRUG L.J. 643 (1998); Gardner, *supra* note 9.

176. See *Integra I*, 331 F.3d 860, 865 (Fed. Cir. 2003), *vacated*, 125 S. Ct. 2372 (2005).

experimentation and failure.<sup>177</sup> The safe harbor must also be wide enough to cover the entire range of activities that produce the extensive safety and effectiveness information the FDA requires, which means more than just clinical trials.<sup>178</sup> The pragmatic message for future courts is that interpretation of the safe harbor should not be divorced from the realities of the subject matter the law governs.

The *Integra* Court formulated a view of the safe harbor best described as a special experimental use exemption for using patented drugs and potential drugs in research to be submitted for federal approval (as opposed to a more general experimental use exemption, which would not be limited to approval activities for FDA-regulated products). The Court repeatedly referred to the safe harbor as protecting the use of patented compounds in research to produce information for an FDA application.<sup>179</sup> The safe harbor applies when the researcher has a reasonable basis for believing that a compound has a particular mechanism of action and effect and uses that compound in research that, if successful, would be appropriate for FDA submission.<sup>180</sup> Hence, *Integra* is most consistent with the view that the safe harbor, at its core, protects the use of patented compounds in research to develop a particular drug, be it a generic version of an already approved drug or an entirely new drug. Because the safe harbor extends

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177. See *Integra II*, 125 S. Ct. at 2382-84. While the Court did not cite legislative history, the committee reports for the Hatch-Waxman amendments support the Court's view that the safe harbor is not limited to activities that produce information actually submitted to the FDA. See H.R. REP. NO. 98-857, pt. 1, at 45 (1984), reprinted in 1984 U.S.C.C.A.N. 2647, 2678 ("The information which can be developed under this provision is the type which is required to obtain approval of the drug. A party which develops such information, but decides not to submit an application for approval, is protected as long as the development was done to determine whether or not an application for approval would be sought.").

178. See *Integra II*, 125 S. Ct. at 2381.

179. *Id.* at 2380 (stating the safe harbor "provides a wide berth for the use of patented drugs in activities related to the federal regulatory process"); *id.* (the safe harbor "necessarily includes preclinical studies of patented compounds that are appropriate for submission to the FDA"); *id.* at 2382 (noting the safe harbor "is sufficiently broad to protect the use of patented compounds" in experiments not ultimately submitted to the FDA); *id.* at 2383 (stating the safe harbor covers "all uses of patented compounds 'reasonably related' to the process of developing information for submission under any federal law regulating the manufacture, use, or distribution of drugs").

180. See *id.* at 2383.

to other FDA-regulated products such as medical devices,<sup>181</sup> *Integra's* holding can be generalized as protecting the use of patented products or potential products subject to FDA review in research to develop and approve competing products, whether the same as or substantially similar to the original product or substantially different from the original product.

Note that while in this view the safe harbor is not limited to generic drug testing or the prevention of patent term distortion, *Integra* stops short of taking the safe harbor to the limit permitted by its literal language. The provision permits the use of "a patented invention," which does not necessarily limit the safe harbor to the use of products subject to FDA approval. However, by expressly declining to comment on whether the safe harbor covers use of patented research tools,<sup>182</sup> the Court avoided the question of whether the safe harbor applies to use of any patented invention. In fact, compelling legal reasons weigh against reading the safe harbor to cover any patented invention. Fear that an overly broad safe harbor would cover, and potentially vitiate the value of, biotechnology tool patents was part of the Federal Circuit's rationale in adopting a narrow view of the safe harbor's scope.<sup>183</sup> However, the Supreme Court, based on the realities of drug development and the requirements for FDA approval, offered a powerful critique of the Federal Circuit's view. The better solution to prevent inappropriate applications of the safe harbor is to simply read limitations on the types of patented inventions that may be used, although the Supreme Court failed to provide much guidance on this matter.

While the Court did not cite legislative history, it is important to note that the legislative history is not necessarily inconsistent with the result in *Integra*. The committee reports' several references to generics do not necessarily mean that Congress intended to limit the safe harbor to generic drug testing.<sup>184</sup> There is no express statement limiting the safe harbor to generic testing in either the statutory text or the committee reports. Moreover, much of the rationale in the committee reports suggests that the safe harbor should also

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181. See *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 669-74 (1990) (holding that the safe harbor includes medical device testing).

182. See *Integra II*, 125 S. Ct. at 2382 n.7.

183. See *Integra I*, 331 F.3d 860, 867 (Fed. Cir. 2003), *vacated*, 125 S. Ct. 2372 (2005).

184. See *supra* Part II.C for a survey of the legislative history of the Hatch-Waxman Amendments.

apply to new drug development activities. If a limited amount of testing using a patented compound does not significantly affect the commercial value of the patent, it is hard to understand why it should matter whether the testing is done to develop a generic drug or a new drug.

One might respond that the safe harbor exists to prevent patent term distortion, and that new drugs, unlike generic drugs, do not prevent patent term distortion for existing drugs, as discussed previously. However, the inclusion of new drug development prevents the marketing exclusivity for existing drugs from being bloated in other ways. The inability of drug manufacturers to use patented compounds in research is problematic not only for timely development of generic drugs, but also for research and development of new drugs to compete with approved drugs. A fundamental reality of drug research is that existing drugs are important tools for discovering new drugs.<sup>185</sup> Hence, the inability to use patented compounds in research impedes the discovery of new drugs as well as the emergence of generics. This rationale applies to manufacturers trying to make a new drug with similar properties to an approved drug or to manufacturers wanting to use a competitor's lead compounds in product development, even if those compounds have never been subject to the FDA approval process. The ability to use a competitor's patented compounds in research enables the development of compounds with similar properties that otherwise might not be developed until some time after the relevant patent expired. The inability to conduct such testing would give the patent holder not only market exclusivity for a particular drug but also the ability to potentially hinder the emergence of alternative new drugs.

The bottom line is that Congress had good reason to write the safe harbor provision in broad terms that would include new drug development activities. So while the rationale of *Integra* may seem insistently focused on the statutory text, the Court was correct to read the text as including new drug development activities. This reading is consistent with the Court's acknowledgement of the realities of drug research and development in the *Integra* opinion. And while the legislative history and statutory structure may suggest more limited purposes for the safe harbor, neither necessarily indicates that new drug development is excluded. Consequently, *Integra*

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185. See *supra* Part II.A.

should not be read as rendering statutory structure, legislative history, or purpose irrelevant to interpretation of the safe harbor, nor should it be read as extending the safe harbor to the far limits of the provision's literal language. Rather, the opinion should be read as providing for broad but not unlimited experimental use of certain types of patented inventions for use in developing competing products for FDA approval. As future courts determine the exact contours of the safe harbor post-*Integra*, they should account both for the necessities and realities of the modern drug development and approval process and for the purposes and policies the safe harbor serves.

## B. SCOPE AND LIMITS OF THE SAFE HARBOR AFTER *INTEGRA*

### 1. Activities Included in the Safe Harbor

In addressing the scope of activities included in the safe harbor, the Court made certain propositions quite clear. First, the safe harbor applies to both preclinical and clinical studies.<sup>186</sup> Since the FDA requires information from animal and *in vitro* studies for certain submissions, uses of patented inventions in such studies fall within the safe harbor. Second, the fact that a particular activity is not included in an FDA submission does not remove that activity from the exemption.<sup>187</sup> The safe harbor is broad enough to accommodate this uncertainty involved in the drug research process. While these acknowledgements should provide comfort for those engaged in drug research and development, the exact scope of activities protected by the safe harbor is not entirely clear. Even as the decision stills any doubts that the safe harbor provides a "wide berth" for research activities, the Court made equally clear that the safe harbor does not encompass all research aimed at developing new drugs.

The Court articulated a two-pronged test to determine whether a particular experiment is included in the safe harbor. The first prong requires a researcher to have "a reasonable basis for believing that a patented compound may work, through a particular biological process, to produce a particular physiological effect."<sup>188</sup> The second prong requires that the compound be used "in research that, if successful, would be

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186. See *Integra II*, 125 S. Ct. 2372, 2380 (2005).

187. See *id.* at 2383.

188. *Id.*

appropriate to include in a submission to the FDA.”<sup>189</sup> Evidently, both prongs must be satisfied for the safe harbor to apply, but since the *Integra* Court’s premise is that the safe harbor includes new drug development activities, courts may be lenient in applying the prongs so that essential steps in new drug development are covered.

Several aspects of the standard are salient. First is the emphasis on particular expectations. The mere use of a compound in an experiment does not trigger the safe harbor. The research must be done with an expectation that the compound works through a particular mechanism to produce a particular effect. Hence, the safe harbor is keyed to hypothesis-driven research and does not protect activities undertaken with a purely shotgun approach. That is, it does not protect experiments done without any basis for expecting a particular outcome.

Second, the standard requires that the activity be part of research that has the potential to produce information appropriate to include in an FDA submission such as an IND or an NDA. Not all research qualifies. The Court left no doubt on this matter: “[b]asic scientific research on a particular compound, performed without the intent to develop a particular drug or a reasonable belief that the compound will cause the sort of physiological effect the researcher intends to induce” does not satisfy the “reasonably related” standard set by the statutory language.<sup>190</sup>

It is not clear, however, exactly what triggers the safe harbor’s protection. It could be intent to develop a particular type of drug, intent to take a particular compound of interest through further research and development that will lead to the FDA approval process, or testing and experimentation that will produce information of the type that are appropriate to include in an FDA submission, such as experiments to determine a compound’s mechanism of action, toxicity, or pharmacokinetics. Note that the second prong of the Court’s test requires the use of the compound in “research”—not in “experiments”—to be submitted to the FDA if successful. The term “research” suggests a whole line of experiments, some of which may be preliminary to the type capable of producing information the FDA would actually consider. Given the necessity of such

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189. *Id.*

190. *Id.* at 2382.

preliminary experiments in drug development, they are likely to be included in the safe harbor.<sup>191</sup>

Third, the test refers to using “patented compounds” in research. This indicates that basic research before the identification of active compounds does not fall in the safe harbor. It also indicates that the safe harbor, at least at its core, covers research using patented drugs and potential drugs; it does not provide a license to infringe any type of patent in the advanced stages of drug research. Although the safe harbor provision uses the term “patented invention,” it may be inappropriate for courts to countenance the unauthorized use of patented inventions other than potential drugs and other FDA-regulated products, even though such use may fall within the literal language of the safe harbor provision.

The process of developing a new drug and getting FDA approval involves several stages. The Court’s test suggests that activities in some of these stages are certainly within the safe harbor, activities at other stages certainly fall outside, and certain activities may fall in a gray area.

The FDA requires extensive information about a compound’s pharmacological characteristics, such as mechanism of action, metabolism, excretion, pharmacokinetics, and toxicity, based on *in vitro*, animal, and human studies. Once a company has settled on a particular compound and is in the process of completing these studies, the safe harbor clearly applies. These studies lie at the core of the second prong of the Court’s standard, protecting research that, if successful, would produce information appropriate to include in an FDA submission. The first prong is also satisfied. A compound at this stage has been selected to go through the FDA approval process because of previously acquired knowledge of its mechanism and effects. Thus, manufacturers can be confident of the safe harbor’s protection at the point a selected drug candidate undergoes preclinical and clinical testing.

On the other hand, the stages of basic research leading up to and through drug target selection and validation seem to fall outside the safe harbor. The Court’s formulation requires research to have progressed to the point of testing compounds

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191. *See id.* at 2383 (refusing “to read the ‘reasonable relation’ requirement so narrowly as to render . . . protection of activities leading to FDA approval for all drugs illusory”); *see also* Bristol-Myers Squibb Co. v. Rhône-Poulenc Rorer, Inc., No. 95 Civ. 8833(RPP), 2001 WL 1512597, at \*7 (S.D.N.Y. Nov. 28, 2001).

for the safe harbor to apply, so all research before the identification of lead compounds is excluded.

The phases of lead compound identification and optimization precede the preclinical and clinical testing phases; therefore, this type of research may be a gray area for safe harbor applicability. At these stages of research, a company first identifies active compounds and subjects these compounds to various modifications to optimize their drug-like properties. Although compounds are involved at these stages, the Court made clear that not all research, even using compounds, falls within the safe harbor.<sup>192</sup>

The lead optimization stage involves trying various chemical modifications to an active molecule to improve its drug-like properties before clinical trials. At this point, it is known that the molecule has a particular pharmacological mechanism and effect, so the first prong of the Court's test is probably satisfied. However, data from lead optimization studies may be inappropriate for FDA submission because, at this stage, the researchers have not settled upon the exact compound that will go through the approval process. Thus lead optimization studies may not satisfy the second prong if it is construed very strictly. Courts are unlikely to do so, however. At this phase the researchers have found a promising lead compound for further development and potentially for clinical trials. Lead optimization is generally necessary before the potential drug can go through the approval process, and finding studies at this phase to be outside the safe harbor simply because the particular experiments will not be included in a submission seems to be exactly the sort of reasoning the *Integra* Court rejected. Thus, courts are likely to find research in this phase to fall within the safe harbor.

The lead identification phase precedes lead optimization and is the phase at which a drug target has been selected and active molecules are first identified. Experiments that simply identify lead compounds are not appropriate for FDA submission because the exact compound that will go through the FDA approval process has not yet been chosen. Therefore, like lead optimization studies, these experiments may not satisfy the second prong of the Court's test. However, as with lead optimization activities, the experiments are essential prerequisites for getting to the approval process. Moreover, at

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192. See *Integra II*, 125 S. Ct. at 2383.



this point the company has selected a drug target (a significant investment of time and money in itself) and thus has a concept for a drug to be developed. *Integra* could be read to indicate that “intent to develop a particular drug” may be sufficient to trigger the safe harbor.<sup>193</sup> However, based on the Court’s test and the opinion’s distinction between basic research and research “reasonably related to the development and submission of information” to the FDA,<sup>194</sup> it seems likely that “intent to develop a particular drug” refers to intent to take a particular compound through development and FDA approval, not simply intent to develop a particular type of drug.

High-throughput screening of patented compounds or libraries of compounds are likely to fail the first prong of the Court’s test. With high-throughput screening, the experimenter does not know in advance if any particular compound will work; this is exactly what the screen determines. Hence, use of patented compounds that are selected for the screen for no particular reason is probably not within the safe harbor.<sup>195</sup> However, if a set of compounds is chosen in advance for screening based on knowledge of their likely biological effect or mechanism (based on structure-activity relationships, perhaps), the first prong may be satisfied. Note that the first prong refers to having “a reasonable basis” for believing that a compound will work, not to certainty or high likelihood. For this reason, if a company has a scientific rationale for selecting a particular compound for further testing, the first prong is likely satisfied. The Court’s test favors rational methods for identifying lead compounds.

The screening of patented compounds should be distinguished from the use of a known drug or lead compound to either determine the characteristics of active compounds to assist with screening (as in *Bristol-Myers Squibb Co.*<sup>196</sup>) or as a

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193. *See id.* at 2382.

194. *See id.*

195. At oral argument, in response to Justice Scalia’s question about whether the screening of different compounds to find active ones was basic research, counsel urged that the safe harbor must apply at the screening stage because otherwise researchers would have to infringe patents on compounds before getting to the research stage at which the safe harbor applied. *See* Transcript of Oral Argument at \*26-28, *Integra II*, 125 S. Ct. 2372 (2005) (No. 03-1237), 2005 WL 1106575. This is a compelling argument given the necessary steps in drug research, but there was no indication at argument that the Justices agreed.

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

positive control against which to measure the activity of other compounds (as in *Integra*<sup>197</sup>). Such uses of patented drugs or lead compounds are likely to be within the safe harbor. Because these compounds are chosen for their known properties, the first prong of the Court's test is satisfied, and the second prong is probably satisfied because such uses of a competitor's patented compounds are the first step in developing a competing drug candidate to take through FDA approval.

Note finally that the Court's test is drug-specific in that it is stated in terms of "compounds." To determine whether uses of medical devices fall within the safe harbor, medical device testing will likely continue to be governed by the standard set forth in *Intermedics, Inc. v. Ventritex, Inc.*<sup>198</sup> The *Intermedics* test is better suited to the medical device context (in which the test itself arose), and in *Integra* the Court ostensibly endorsed the *Intermedics* standard.<sup>199</sup> Hence *Integra* seems unlikely to disturb the cases decided under the *Intermedics* standard, particularly the cases involving medical device testing. The *Integra* test is formulated for drug research and will likely replace the *Intermedics* test in cases involving drug patents.

In summary, some drug research and development activities are clearly within the safe harbor; others certainly fall outside it. At the edges of the safe harbor lie the activities clustered around the phase when active compounds are first identified. These activities fall into a gray area—the activities may or may not be protected. Whether they are protected depends on how strictly courts choose to apply the Supreme Court's *Integra* test. Note that the *Integra* Court remanded the case to the Federal Circuit, which in turn reinstated the appeal and ordered new briefs to be filed to account for the Supreme Court's opinion.<sup>200</sup> The Federal Circuit's eventual decision will be an important precedent and a bellwether on application of *Integra*'s two-pronged test.

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197. See *Integra II*, 125 S. Ct. at 2379.

198. 775 F. Supp. 1269 (N.D. Cal. 1991), *aff'd*, 991 F.2d 808 (Fed. Cir. 1993).

199. *Integra II*, 125 S. Ct. at 2384.

200. See *Integra Lifesciences I, Ltd. v. Merck KGaA*, 421 F.3d 1289, 1289 (Fed. Cir. 2005).

## 2. Types of Patented Inventions That May Be Used Within the Safe Harbor

One issue the *Integra* Court did not resolve satisfactorily is whether certain inventions are outside the scope of the safe harbor. The safe harbor provision protects the use of “patented inventions.”<sup>201</sup> The Supreme Court has held that this includes “all inventions, not drug-related inventions alone.”<sup>202</sup> Thus, neither the statutory text nor the Court’s precedent limits the safe harbor to drugs or other FDA-regulated products. A literal reading of the text suggests that anything goes.

Nevertheless, drug researchers should not assume that anything goes, for while the plain language of the safe harbor may permit the use of any patented invention, all other indicia of statutory meaning point toward a more limited exemption. The statutory structure suggests that the safe harbor’s purpose is to prevent the distortion in commercial marketing exclusivity associated with the patents of FDA-regulated products.<sup>203</sup> Similarly, the legislative history indicates that the safe harbor protects only limited use of the patented inventions it covers.<sup>204</sup> Nothing in the legislative history suggests an intent to create a blanket license to ignore patent rights in product research and development. The committee reports state plainly that the safe harbor was not intended to significantly diminish the rights of patent holders.<sup>205</sup>

Another important consideration is the takings clause of the United States Constitution, which provides that private property may not “be taken for public use, without just compensation.”<sup>206</sup> Application of current takings jurisprudence to patent rights involves many legal subtleties beyond the scope of this article.<sup>207</sup> The basic concept is that patent rights are

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201. See 35 U.S.C. § 271(e)(1) (2000).

202. See *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 665 (1990).

203. See *id.* at 669-74.

204. See *supra* Part II.C.

205. See H.R. REP. NO. 98-857, pt. 2, at 30 (1984), *reprinted in* 1984 U.S.C.C.A.N. at 2714 (analogizing the safe harbor provision to the fair use doctrine in copyright law); *id.* at 8, *reprinted in* 1984 U.S.C.C.A.N. at 2692 (stating that the safe harbor would not interfere with the patent holder’s rights in the major commercial marketplace).

206. U.S. CONST. amend. V.

207. For an excellent discussion of this topic, see *Zoltek Corp. v. United States*, 58 Fed. Cl. 688 (2003); see also J. Nicholas Bunch, *Takings, Judicial Takings, and Patent Law*, 83 TEX. L. REV. 1747 (2005) and Shubha Ghosh, *Toward a Theory of Regulatory Takings for Intellectual Property: The Path Left Open After College Savings v. Florida Prepaid*, 37 SAN DIEGO L. REV. 637

property rights which the federal government may not appropriate without compensation.<sup>208</sup> The Supreme Court has held that regulation affecting the value of trade secrets, which are intangible property rights analogous to patent rights, may constitute a taking under the regulatory takings doctrine.<sup>209</sup> Regulatory takings occur *per se* when government action either subjects a property owner to a permanent physical invasion of his or her property or deprives property of all economic value. Otherwise, regulatory takings may occur according to several factors prominently including interference with distinct investment-based expectations.<sup>210</sup> Hence, applications of the safe harbor that vitiate or significantly diminish the value of the patented inventions used may constitute regulatory takings. Congress considered exactly this question and concluded that the safe harbor did not amount to a regulatory taking, in part because the patent owner retained the right to exclude others from the commercial marketplace.<sup>211</sup> In this view, application of the safe harbor is inappropriate where use of a patented invention significantly reduces the commercial value of the invention.

Modern drug research has been catalyzed by technological progress. The rise of biotechnology in particular has facilitated new drug discovery by providing products that can be used either as tools in research or for therapeutic or diagnostic purposes. Because the plain language of the safe harbor ostensibly permits the use of patented research tools, manufacturers of such tools, including many biotech firms, understandably fear that drug companies are free to infringe research tool patents with impunity in drug research. This fear prompted several research tool manufacturers to file an amicus brief in *Integra* asking the Supreme Court to state unequivocally that research tool patents in fact are not

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(2000).

208. See *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 730 (2002) (holding that a patent confers a limited monopoly that is a property right); *James v. Campbell*, 104 U.S. 356, 357-58 (1881) (holding that patents may not be appropriated by the federal government without just compensation).

209. See *Ruckelshaus v. Monsanto Co.*, 467 U.S. 986, 1001-05 (1984).

210. See *Lingle v. Chevron U.S.A. Inc.*, 125 S. Ct. 2074, 2081-82 (2005).

211. See H.R. REP. NO. 98-857, pt. 2, at 61 n.19 (1984), reprinted in 1984 U.S.C.C.A.N. 2648, 2721.

included in the safe harbor.<sup>212</sup> The brief argued that permitting pharmaceutical firms to infringe research tool patents would significantly diminish the commercial value of such patents because the tools derive significant value from use in drug research.<sup>213</sup> The Court expressly declined to consider whether the safe harbor applied to research tools, stating that the record indicated that the RGD peptides at issue in the case were not used as research tools.<sup>214</sup>

In doing so, the Court suggested a distinction between a research tool and the subject of the research.<sup>215</sup> This distinction is problematic. Known drugs and compounds with biological activity are frequently used in research to discover or measure the activity of other compounds. The RGD peptides in *Integra* and the paclitaxel intermediates in *Bristol-Myers Squibb* were used for these purposes.<sup>216</sup> In either case the compounds or biotech products are the subject of research, but since these themselves are vital inputs of the research from which discoveries emerge, they are functionally as much research tools as are microscopes, centrifuges, incubators, and the like.<sup>217</sup> But although known drugs and compounds with biological activity are used as research tools in a sense, such use is at the core of the safe harbor, at least to the extent it protects new drug development activities as *Integra* affirmed.

By the same token, the fact that a patented invention is not a research tool does not necessarily render the safe harbor exemption appropriate. Consider this hypothetical: a telecommunications company develops new technology expressly for drug companies to send voluminous research data and information to the FDA. The technology is expensive, so to save money many drug companies have their engineers duplicate the technology instead of buying it from the telecommunications company. Because use of this patented invention involves submitting information to the FDA, it would be allowed by the literal language of the safe harbor provision.

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212. See Brief for Invitrogen Corp. et al. as *Amici Curiae* in Support of Respondents, *Integra II*, 125 S. Ct. 2372 (2005) (No. 03-1237), 2005 WL 682093.

213. See *id.*

214. See *Integra II*, 125 S. Ct. 2372, 2382 n.7 (2005).

215. See *id.*

216. See *id.* at 2379; *Bristol-Myers Squibb Co. v. Rhône-Poulenc Rorer, Inc.*, No. 95 Civ. 8833(RPP), 2001 WL 1512597, at \*1 (S.D.N.Y. Nov. 28, 2001).

217. See *In re Fisher*, 421 F.3d 1365, 1380 (Fed. Cir. 2005) (Rader, J., dissenting).

However, this would be one of the most strained applications of the safe harbor imaginable, even though the technology is not being used as a research tool.

Thus, while certain applications of the safe harbor may be inappropriate, the distinction to make is not a facile one between research tool patents and non-research tool patents. Upon close examination, that distinction proves to be neither clear nor useful. Rather, courts should consider a particular application in light of the safe harbor's core meaning suggested by statutory structure, purpose, and legislative history. That core meaning is an exemption for using patented drugs and other FDA-regulated products in research to develop competing products, as *Integra* suggested with its many references to using "compounds" in experiments. Moreover, the safe harbor was not intended to impinge more than minimally on the commercial value of affected patents. Applications of the safe harbor to inventions other than the type the FDA regulates, or applications that significantly reduce the commercial value of the patent affected, are more or less anomalous. While the *Integra* Court declined to determine whether research tools are included in the safe harbor, it recognized that a separate issue was presented that future courts may need to consider. Those future courts should take this as an invitation to screen out applications of the safe harbor that are anomalous for the reasons just given.

Courts should not feel bound by the literal statutory language to permit applications of the safe harbor that are unjust, absurd, or otherwise far removed from the core statutory meaning. The statutory language need not be read to permit the use of any patented invention; considering the statutory structure, purpose, and legislative history, the term "patented invention" could be limited to the type of inventions subject to FDA approval. This would not necessarily contradict *Eli Lilly's* statement that the safe harbor applies to all patented inventions. Taken in the context of that case, the statement meant that the safe harbor applies to medical devices, not just drugs. Courts should avoid literal interpretations of statutes that lead to absurd results when alternative constructions are available consistent with legislative purpose or the meaning of the statute taken as a whole.<sup>218</sup> Because certain applications of the safe harbor may

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218. See *Griffin v. Oceanic Contractors, Inc.*, 458 U.S. 564, 575 (1982);

deprive patented inventions of a significant part of their commercial value, the safe harbor should not be construed to permit such applications as it would raise issues under the takings clause. Courts should construe statutes to avoid such constitutional doubt.<sup>219</sup> Alternatively, a court could avoid an anomalous application citing the lack of a plain statement in the statutory text that the safe harbor requires such an application.<sup>220</sup> Even assuming that the literal language includes such applications, the Supreme Court has previously recognized that something can be in the literal language of a statute and yet not within its meaning.<sup>221</sup>

The main problem with these arguments is the rationale of the several cases, up to and including *Integra*, that have refused to limit the scope of the safe harbor because of its broad statutory language. For example, the safe harbor has been held to protect experimentation with medical devices not eligible for patent term extension.<sup>222</sup> *Integra* applied the safe harbor to new drug development activities, although the safe harbor was arguably only intended for generic drug development. However, these applications were not particularly anomalous. In both cases the inventions used were of the same general type to which the safe harbor undoubtedly applies—FDA-regulated products—and the inventions were used experimentally in research to develop competing products. Even if such applications were not intended by Congress, they may be regarded as reasonable incidents of the statutory scheme. Courts may distinguish these applications from others

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Heydenfeldt v. Daney Gold & Silver Mining Co., 93 U.S. 634, 638 (1876).

219. See *I.N.S. v. St. Cyr*, 533 U.S. 289 (2001) (applying canon to avoid constitutional doubt to find that statutes had not repealed habeas jurisdiction for resident aliens despite contrary suggestion from literal reading of statutory text). In *Eli Lilly*, the Court rejected a constitutional doubt argument in applying the safe harbor to medical devices. See *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 678 n.7 (1990). The Court did so, however, because while the safe harbor may significantly affect the commercial value of some medical devices, it probably similarly affects the value of some drugs, so the alternative interpretations in the case did not differ with respect to constitutional doubt. See *id.* Certain applications of the safe harbor may be distinguished if the user of the invention would otherwise be an ordinary buyer of the invention, in which case the safe harbor has a direct, as opposed to incidental, effect on the commercial value of the invention.

220. See *St. Cyr*, 533 U.S. at 298-99 (applying plain statement rule in finding that statutes had not repealed habeas jurisdiction for resident aliens).

221. See *United Steelworkers of Am. v. Weber*, 443 U.S. 193, 201 (1979) (citing *Holy Trinity Church v. United States*, 143 U.S. 457, 459 (1892)).

222. See *Abtox, Inc. v. Exitron Corp.*, 122 F.3d 1019, 1029 (Fed. Cir. 1997).

that seem unjust or absurd, such as the telecommunications technology hypothetical discussed above.

The potential for application of the safe harbor to patented biotechnology research tools has led to calls to amend the safe harbor provision to remove such products from its scope.<sup>223</sup> However, some biotech products, such as the RGD peptides in *Integra*, have drug-like activity and could be used as drugs or as tools to develop other drugs. When such products are tested with intent to seek FDA approval, application of the safe harbor is not particularly unreasonable. Indeed, the proliferation of biotechnology patents in recent years has the potential to stymie downstream research and seems to make application of the safe harbor all the more appropriate.<sup>224</sup> However, if a particular biotechnology product is commercially available and can simply be bought for use in research, application of the safe harbor is questionable, especially if the product is not being used in the research for its drug-like properties.

The most dubious applications of the safe harbor's literal language are unauthorized uses of patented inventions that the researcher can simply buy. This is true for two reasons. First, such inventions can be used in product research and development even before the relevant patents expire, thereby removing the justification behind the safe harbor. Second, application of the safe harbor to such uses would directly reduce the commercial value of such inventions, especially for inventions used mainly or entirely in drug research. That would possibly amount to an uncompensated regulatory taking and would certainly be contrary to the legislative intent in enacting the safe harbor. For these reasons, courts are unlikely to countenance the use of patented inventions for which the drug company would otherwise be an ordinary buyer. This may have been the reason underlying one court's holding that the safe harbor did not permit use of a patented culture medium in research, although the culture medium at issue was not sold by

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223. See Xiao, *supra* note 18.

224. See Kyle Jensen & Fiona Murray, *Intellectual Property Landscape of the Human Genome*, 310 *SCIENCE* 239 (2005) (noting that almost one-fifth of human genes are claimed in patents); Mireles, *supra* note 17, at 172 (asserting that patents on biotech products could hinder downstream research); Wendy Thai, *Toward Facilitating Access to Patented Research Tools*, 6 *MINN. J.L. SCI. & TECH.* 373 (2004) (evaluating proposals to address this problem).



the patent holder.<sup>225</sup>

Because the *Integra* opinion refused to comment on whether certain patents could not be infringed within the safe harbor, courts may or may not address this issue. One case decided in the wake of *Integra* involved patented methods for evaluating the safety of vaccine administration schedules.<sup>226</sup> The District Court of Maryland cited to *Integra* and held that use of these methods in vaccine research to provide post-marketing information to the FDA was protected by the safe harbor.<sup>227</sup> The court had *Integra*'s holding correct in that the safe harbor extended to post-marketing research required by the FDA, but the court should have analyzed whether it was appropriate to include such patents in the safe harbor's scope. This was not a case of a company duplicating an invention it could otherwise simply buy. Still, if one company holds a patent on a research method, use of that method by another company seems to infringe directly on the patent's main value, that being the ability to exclude others from using the research method.

Future cases will undoubtedly test courts' willingness to forestall questionable applications of the safe harbor, and if courts are unwilling to do so, it may be appropriate for Congress to act. In the mean time, the Court's reliance on the statutory text in *Integra* does not mean that the safe harbor extends to the limits of its literal statutory language. To the contrary, *Integra* expressly declined to comment on whether certain inventions were outside the safe harbor's scope, and courts have many reasons to fill in this blank by answering that the safe harbor does not provide carte blanche to ignore patent rights in drug research. While courts have consistently broadened the safe harbor, they have not exceeded the bounds of reason, and neither should private parties. Rather, those taking advantage of the safe harbor should heed Justice Holmes's warning that the law sometimes imposes vague but real limits.

#### C. THE EXPERIMENTAL USE EXEMPTION AFTER *INTEGRA*

One other facet of *Integra* should be considered briefly.

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225. See *Infigen, Inc. v. Advanced Cell Tech., Inc.*, 65 F. Supp. 2d 967, 974 (W.D. Wis. 1999).

226. See *Classen Immunotherapies, Inc. v. Biogen IDEC*, 381 F. Supp. 2d 452, 453-54 (D. Md. 2005).

227. See *id.* at 455-56.

The dissenting judge in the Federal Circuit's *Integra* decision argued that the portion of Merck's sponsored research that was not covered by the safe harbor was protected by the common law experimental use exemption.<sup>228</sup> The Supreme Court did not address this issue,<sup>229</sup> hence the opinion does not change the legal landscape for the common law experimental use exemption, which has been construed very narrowly by the courts.<sup>230</sup>

But while courts are unwilling to expand the experimental use exemption, the safe harbor post-*Integra* should inform the debate about whether Congress should do so. Scholars have argued in favor of a broader experimental use exemption that would permit the use of patented inventions in research to modify or improve upon the inventions.<sup>231</sup> The safe harbor as interpreted by *Integra* is, at least at its core, a special experimental use exemption for using FDA-regulated products in development of competing products. The consequences of this special experimental use exemption for drug research and development should be useful in policy analysis for creation of a general experimental use exemption.

Because of the time and expense required to develop a new drug, the need for strong patent rights as an incentive to invent reaches its zenith in the pharmaceutical industry.<sup>232</sup> If the pharmaceutical industry can nevertheless thrive with a robust experimental use exemption in drug development, the argument for a general experimental use exemption is compelling. The value of a patent for a new drug is significantly reduced by competition from other new drugs and generic drugs, competition enhanced by the Hatch-Waxman regime.<sup>233</sup> However, the number of new drugs in Phase III clinical trials has remained relatively constant over recent

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228. See *Integra I*, 331 F.3d 860, 872-78 (Fed. Cir. 2003) (Newman, J., dissenting), *vacated*, 125 S. Ct. 2372 (2005).

229. At oral argument when the Justices questioned the parties about the relevance of the experimental use exemption to the case, the parties responded that the exemption was not part of their respective arguments and should not be considered by the Court. See Transcript of Oral Argument at \*6, \*28, \*51, *Integra II*, 125 S. Ct. 2372 (2005) (No. 03-1237), 2005 WL 1106575.

230. See, e.g., *Madey v. Duke Univ.*, 307 F.3d 1351, 1362-63 (Fed. Cir. 2002).

231. See *supra* note 52 and accompanying text.

232. See Dan L. Burk & Mark A. Lemley, *Policy Levers in Patent Law*, 89 VA. L. REV. 1575, 1615-17 (2003).

233. See Dickson & Gagnon, *supra* note 44, at 421-22.

years, while the number of new drugs in earlier phases of testing has actually been increasing over the same period.<sup>234</sup> This robust new drug development activity suggests that the safe harbor has not diminished the industry's drive to discover new drugs. On the other hand, it is possible that the ability to experiment with a competitor's compounds contributes to the phenomenon of so-called "me-too" drugs that closely imitate existing pioneer drugs, although these incrementally innovative drugs may still have some positive value.<sup>235</sup> The full effects of the safe harbor on drug research and development deserve further study and analysis to determine more definitively if experimental use is a net positive or a net negative. Such studies should help inform policymakers on the desirability of a general experimental use exemption.

### CONCLUSION

The proper scope of the Hatch-Waxman safe harbor provision has been unclear because the broad terms in the statutory language may not fit with the arguably narrower purpose evident from legislative history and statutory structure. The Supreme Court in *Integra* set the course for future courts by construing the safe harbor to provide for broad experimental use of drugs and potential drugs in product development. While the safe harbor is wide, it is still limited by its purpose and by the rights of patent holders. While the Court only partially described the limits in *Integra*, those taking advantage of the safe harbor should remember that the law sometimes imposes limits that are vague but nevertheless real, and crossed at peril.

The safe harbor provision is a seemingly simple provision of law that poses interpretive challenges because of the complexity of the subject matter governed. The freedom to use patented inventions in otherwise infringing uses has important ramifications for the various industries involved in drug research, ensuring that the safe harbor will continue to generate controversy and litigation. Careful attention should

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234. See Fredric J. Cohen, *Macro Trends in Pharmaceutical Innovation*, 4 NATURE REVIEWS DRUG DISCOVERY 153, 157 (2005).

235. See *id.* at 153 (arguing that these imitating drugs often have attributes that distinguish them from the prototype drug such as improved efficacy, selectivity, or reduced toxicity, and that the drugs play a role in maintaining industry profits and research and development funds because of their inherently lower cost of development and risk).

be paid to how industry and the drug approval process generally fare under *Integra's* broad experimental use regime. From a policy perspective it is desirable to promote the discovery and approval of new drugs, but it is highly undesirable to do so by significantly undermining existing patent rights. The safe harbor implicates different policy objectives that require delicate balancing and judgment by Congress, the courts, and the drug industry, all of whom share responsibility for implementing the law within reason.