

FREEDOM TO RESEARCH: ROOM FOR TRIAL AND ERROR  
IN DRUG DEVELOPMENT AFTER *MERCK KGAA v.*  
*INTEGRA LIFESCIENCES I, LTD.*

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I. INTRODUCTION

Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984,<sup>1</sup> commonly known as the Hatch-Waxman Act, to expedite the introduction of pharmaceutical drugs to the market.<sup>2</sup> The Act introduced an exception to the general rule of patent infringement,<sup>3</sup> defined as the unauthorized manufacture, use, offer for sale, or sale of a patented invention during the patent term.<sup>4</sup> The exception, codified at 35 U.S.C. § 271(e)(1), modifies the general rule by providing that “[i]t shall not be an act of infringement to make, use, offer to sell, or sell within 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 drug . . . .”<sup>5</sup> The § 271(e)(1) exception shields testing conducted to obtain regulatory approval under the Federal Food, Drug, and Cosmetic Act (FDCA).<sup>6</sup> To fall under the safe harbor provision of § 271(e)(1), otherwise infringing conduct must reasonably relate to the process of developing and submitting information for obtaining drug regulatory approval.<sup>7</sup> When the connection between conduct and regulatory approval grows too attenuated, the conduct does not fall under the exception and is, therefore, infringing.

In *Merck KGaA v. Integra Lifesciences I, Ltd.*,<sup>8</sup> the United States Supreme Court faced the question of whether the use of a patented invention in preclinical research is sufficiently “reasonably related” to the drug regulatory approval process to fall within the safe harbor of

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1. Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended in scattered sections of 15, 21, 28, and 35 U.S.C. (2000)).

2. MARTIN J. ADELMAN ET AL., CASES AND MATERIALS ON PATENT LAW 391 (2d ed. 2003).

3. *Merck KGaA v. Integra Lifesciences I, Ltd.*, 125 S. Ct. 2372, 2376–77 (2005).

4. 35 U.S.C. § 271(a) (2000).

5. *Id.* § 271(e)(1).

6. *Merck*, 125 S. Ct. at 2377.

7. 35 U.S.C. § 271(e)(1).

8. *Merck*, 125 S. Ct. 2372.

§ 271(e)(1).<sup>9</sup> Integra Lifesciences I, Ltd. (Integra) filed an infringement action against Merck KGaA<sup>10</sup> (Merck) for its use of Integra's patented compounds in preclinical research, the results of which were not "ultimately included in a submission to the Food and Drug Administration."<sup>11</sup> The Supreme Court adopted a broad interpretation of the § 271(e)(1) exception and held that the safe harbor provision applied, absolving Merck of liability for patent infringement.<sup>12</sup>

## II. BACKGROUND

### A. A Brief Overview of the Drug Regulatory Approval Process

Unlike other patented inventions, a patented drug<sup>13</sup> must receive regulatory approval from the Food and Drug Administration (FDA) before it is approved for sale in the United States.<sup>14</sup> To receive approval, a drug developer must prove that its proposed drug is safe and effective by generating and submitting data for review to the FDA's Center for Drug Evaluation and Research.<sup>15</sup> The FDA's regulatory oversight ensures that all new drugs conform to the agency's standards for quality, safety, and effectiveness prior to reaching consumers in the United States.<sup>16</sup>

The FDCA requires applicants to submit data to the FDA at two general stages in the course of new drug development.<sup>17</sup> The first stage occurs when an applicant submits an investigational new drug application (IND) to obtain clearance for clinical testing of a potential drug on humans.<sup>18</sup> Before clinical testing on humans can begin, an applicant must generate preclinical laboratory data and explain in the IND why such data justify testing in humans.<sup>19</sup> In a process called "review," the FDA evaluates the data submitted by the applicant.<sup>20</sup> Review at the preclinical stage serves to protect the safety of human volunteer test subjects and to

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9. *Id.* at 2376–77.

10. Merck KGaA of Germany should not be confused with U.S. pharmaceutical company Merck & Co., Inc.

11. *Merck*, 125 S. Ct. at 2376.

12. *Id.* at 2383–84.

13. Here, the term "drug" refers to the subject matter regulated by the Food and Drug Administration and includes pharmaceuticals, medical devices, and biological products. *See generally* CTR. FOR DRUG EVALUATION & RESEARCH, U.S. DEP'T OF HEALTH & HUMAN SERVS., 2004 REPORT TO THE NATION: IMPROVING PUBLIC HEALTH THROUGH HUMAN DRUGS 1 (2005), available at <http://www.fda.gov/cder/reports/rtn/2004/rtn2004.pdf> [hereinafter CDER, IMPROVING PUBLIC HEALTH].

14. *See id.*

15. *Id.*

16. *Id.*

17. *Merck*, 125 S. Ct. at 2377.

18. *Id.*

19. *Id.*

20. CDER, IMPROVING PUBLIC HEALTH, *supra* note 13, at 1.

ensure the quality and integrity of the data gathered.<sup>21</sup> Once an IND application is approved, clinical testing on humans may proceed.<sup>22</sup> If the clinical tests show that the investigational drug is effective and safe for human use, an applicant may then proceed to the second stage of new drug development by submitting a new drug application (NDA) for final market approval.<sup>23</sup> The FDA conducts one final review to determine whether the drug effectively serves its intended purpose and whether its health benefits outweigh its risks.<sup>24</sup> Only drugs that survive the lengthy FDA regulatory approval process receive permission for sale in the United States.<sup>25</sup>

*B. The Interplay Between Regulatory Approval and Patent Law Prior to Passage of the Hatch-Waxman Act*

Prior to passage of the Hatch-Waxman Act, the lengthy FDA regulatory review process distorted the patent term for drugs by delaying both the introduction of newly patented drugs to consumers and the entry of competitors' generic drugs to the market following the expiration of a patent.

At the beginning of a drug's patent term, the drug regulatory review period effectively shortens the time in which a patentee may enjoy an exclusive right to market and sell a patented drug.<sup>26</sup> The federal patent law "grant[s] to the patentee . . . the right to exclude others from making, using, offering for sale, or selling the invention throughout the United States"<sup>27</sup> for a term of twenty years from the patent application filing date.<sup>28</sup> Although the clock on a patent term begins to run as soon as the patent application is filed,<sup>29</sup> a patent holder must wait for FDA regulatory approval before selling the drug to consumers<sup>30</sup> and thereby loses any potential financial benefit at the beginning of a drug's patent term. As the clock for the patent term runs, the patentee may prevent others from using its patented drug, but the patentee itself is prevented from commercially marketing or using the drug while it is undergoing FDA regulatory review.<sup>31</sup>

At the tail end of a drug's patent term, the interplay between the regulatory review process and patent law results in an extension of the

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21. *See id.*

22. *See id.*

23. *See id.* (citing 21 U.S.C. § 355(b)(1) (2000)).

24. *See* CDER, IMPROVING PUBLIC HEALTH, *supra* note 13, at 1.

25. *See id.*

26. *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 669–70 (1990).

27. 35 U.S.C. § 154(a)(1) (2000).

28. *Id.* § 154(a)(2).

29. *See id.* § 154(a)(1); *see also Eli Lilly*, 496 U.S. at 669–70. Inventors, including drug pioneers, typically file their patent applications without delay. *See Eli Lilly*, 496 U.S. at 669.

30. *Eli Lilly*, 496 U.S. at 669–70.

31. *See* 35 U.S.C. § 271(a).

period of market exclusivity beyond the term of the patent.<sup>32</sup> As with newly patented drugs, a competitor's generic copy of a name-brand drug is subject to FDA regulatory review before it is approved for sale in the United States.<sup>33</sup> Before the Hatch-Waxman Act, patent law prohibited competitors from generating data for FDA regulatory approval of a generic drug during the patent term of its name-brand counterpart.<sup>34</sup> Producers of generics were forced to wait for a drug patent to expire because use of a patented drug "to derive FDA required test data" constituted an act of patent infringement.<sup>35</sup> The FDA review period, coupled with patent law requirements, thus delayed market entry of generic versions of a patented drug.<sup>36</sup>

### C. History of the § 271(e)(1) Experimental Use Safe Harbor

#### 1. Common Law Experimental Use Exception

Prior to codification of the experimental use exception in § 271(e)(1), a limited experimental use exception existed in common law. The common law experimental use defense originated in *Whittemore v. Cutter*,<sup>37</sup> in which Justice Story, riding circuit, wrote, "[I]t could never have been the intention of the legislature to punish a man, who constructed [a patented] machine merely for philosophical experiments, or for the purpose of ascertaining the sufficiency of the machine to produce its described effects."<sup>38</sup>

However, in *Roche Products, Inc. v. Bolar Pharmaceutical Co.*, the Federal Circuit held that use prior to a brand-name drug's patent expiration date, even for purposes of obtaining quick approval for a generic, did not fall within the common law experimental use exception.<sup>39</sup> Thus, the competitor's testing of patented compounds to obtain FDA regulatory approval for a generic drug constituted patent infringement. As stated by the court, "[U]nlicensed experiments conducted with a view to the adaptation of the patented invention to the experimenter's business is a violation of the rights of the patentee to exclude others from using his patented invention."<sup>40</sup> Congress overruled the holding of *Roche* in 1984 by enacting the Hatch-Waxman Act.<sup>41</sup>

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32. *Eli Lilly*, 496 U.S. at 670.

33. See CDER, IMPROVING PUBLIC HEALTH, *supra* note 13, at 1.

34. *Eli Lilly*, 496 U.S. at 670.

35. *Roche Prods., Inc. v. Bolar Pharm. Co.*, 733 F.2d 858, 863 (Fed. Cir. 1984).

36. *Eli Lilly*, 496 U.S. at 670.

37. 29 F. Cas. 1120 (C.C.D. Mass. 1813) (No. 17,600); see also *Roche*, 733 F.2d at 862.

38. *Whittemore*, 29 F. Cas. at 1121.

39. See *Roche*, 733 F.2d at 863.

40. *Id.*

41. 5 DONALD S. CHISUM, CHISUM ON PATENTS § 16.03[1][d] (2004).

## 2. *The Hatch-Waxman Act: Codification of an Experimental Use Exception*

The Hatch-Waxman Act created the statutory experimental use exception of § 271(e)(1) as part of a complex legislation package<sup>42</sup> designed to address the interplay between producers of new drugs and producers of generic drugs.<sup>43</sup> The purpose of the package was to resolve distortions in the drug patent term and to speed generic drugs to market.<sup>44</sup> The provisions of the Hatch-Waxman Act not only created an exemption for activities related to obtaining regulatory approval under § 271(e)(1) but also amended the FDCA and various patent laws in other significant ways. For example, in addition to the experimental use exception, the Hatch-Waxman Act extended the patent term for drugs subject to delays in regulatory review, created the Abbreviated New Drug Application (ANDA) for expedited review of generic drugs, and established a new infringement remedy for patent holders against competitors who file an ANDA during the patent term.<sup>45</sup>

Introduced by § 202 of the Hatch-Waxman Act,<sup>46</sup> the § 271(e)(1) safe harbor provision allows competitors to engage in otherwise infringing conduct if the conduct is “solely” related to securing federal drug regulatory approval.<sup>47</sup> The exception applies to conduct that is “reasonably related to the development and submission of information” under the federal drug regulation laws.<sup>48</sup> The decision of the Supreme Court in *Merck* expanded the reach of § 271(e)(1) by broadly interpreting the scope of the exception.

### III. THE DECISION

#### A. *Background of the Case*

##### 1. *The Patents in Suit*

Integra and its co-plaintiffs own the five patents<sup>49</sup> involved in *Merck*, which relate to the mechanism of cell adhesion.<sup>50</sup> In cell adhesion, cells

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42. *Id.*

43. ADELMAN ET AL., *supra* note 2, at 391.

44. *See* Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661, 669–70 (1990).

45. CHISUM, *supra* note 41, § 16.03[1][d].

46. Pub. L. No. 98-417, tit. 2, sec. 202, 98 Stat. 1585 (1984) (codified as amended at 35 U.S.C. § 271(e)(1) (2000)).

47. 35 U.S.C. § 271 (e)(1) (2000).

48. *Id.*

49. The patents implicated in *Merck* were U.S. Patent No. 4,988,621 (filed Dec. 10, 1987); U.S. Patent No. 4,792,525 (filed June 17, 1985); U.S. Patent No. 5,695,997 (filed June 2, 1995); U.S. Patent No. 4,879,237 (filed May 24, 1985); and U.S. Patent No. 4,789,734 (filed Aug. 6, 1985). *Merck KGaA v. Integra Lifesciences I, Ltd.*, 125 S. Ct. 2372, 2377 (2005). For simplicity, I refer to these co-owned patents as Integra’s patents.

form tissues by adhering to each other and to a non-cellular component of tissue called the extracellular matrix.<sup>51</sup> Two proteins known as “integrin” and “fibronectin” are involved in this process of cell adhesion.<sup>52</sup> Integrin is a receptor located on the surface of a cell that recognizes and attaches to fibronectin, an extracellular protein.<sup>53</sup> Fibronectin serves as an anchor, securing cells to the extracellular matrix.<sup>54</sup> Cell adhesion may support wound healing, prevent rejection of prosthetic devices, and promote the growth of new blood vessels.<sup>55</sup> All five of Integra’s patents concern a short tri-peptide sequence, known as the “RGD peptide,” of fibronectin.<sup>56</sup> The inventors also isolated an integrin receptor, called the  $\alpha_v\beta_3$  receptor, which interacts with the patented RGD peptide in the cell adhesion process.<sup>57</sup>

## 2. Merck’s Preclinical Research

In *Merck*, the experimental use of RGD peptides for preclinical cancer research was funded by Merck and conducted by Dr. David Cheresh at the Scripps Research Institute (Scripps).<sup>58</sup> Dr. Cheresh’s research focused on angiogenesis, the process by which new blood vessels form from preexisting blood vessels in the body.<sup>59</sup> Angiogenesis plays a key role in tumor growth by supplying blood and nutrients that allow tumors to grow and spread to other parts of the body.<sup>60</sup> In addition to its role in solid tumor cancers, angiogenesis also is implicated in diseases such as diabetic retinopathy and rheumatoid arthritis.<sup>61</sup> Substances that block angiogenesis potentially could form a basis for the treatment of cancer and other diseases.<sup>62</sup>

Dr. Cheresh’s team at Scripps identified two substances that inhibit angiogenesis, one of which was an RGD peptide.<sup>63</sup> Both substances studied by the Scripps researchers operated by blocking  $\alpha_v\beta_3$  receptors<sup>64</sup> and arrested tumor growth by halting the formation of blood vessels

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50. *Id.* at 2377.

51. See BRUCE ALBERTS ET AL., *MOLECULAR BIOLOGY OF THE CELL* 1080 (4th ed. 2002).

52. See *id.* at 1103, 1113.

53. *Id.* at 1113.

54. *Id.* at 1103.

55. *Integra Lifesciences I, Ltd. v. Merck KGaA*, 331 F.3d 860, 863 (Fed. Cir. 2003).

56. *Id.* at 862.

57. *Id.*

58. *Merck KGaA v. Integra Lifesciences I, Ltd.*, 125 S. Ct. 2372, 2377 (2005).

59. *Id.* at 2377–78.

60. *Angiogenesis*, WIKIPEDIA: THE FREE ENCYCLOPEDIA (May 20, 2006), <http://en.wikipedia.org/wiki/Angiogenesis>.

61. *Merck*, 125 S. Ct. at 2378.

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

63. *Merck*, 125 S. Ct. at 2378. Dr. Cheresh received his supply of RGD peptide from Merck. *Id.* The other anti-angiogenic substance, a monoclonal antibody, was developed by Dr. Cheresh himself. *Id.*

64. *Id.*

needed to support tumor expansion.<sup>65</sup> Results from animal testing indicated that the anti-angiogenic substances shrank tumors and prevented their spread.<sup>66</sup> Based on the results of the study, researchers hoped that findings from the study could unlock new therapies to combat cancerous tumors and other diseases in humans, though, at that time, studies had yet to be conducted to confirm the safety and effectiveness of the substances in humans.<sup>67</sup>

Recognizing the therapeutic value of Dr. Cheresch's results, Scripps and Merck entered into a new agreement in 1995, whereby Merck pledged to fund further research by Dr. Cheresch to identify and develop new drug candidates from RGD peptides and other substances that blocked angiogenesis.<sup>68</sup> Part of the agreement called for testing the RGD peptide EMD 66203 and its derivatives to identify the best candidate for clinical testing in humans and thereafter to "perform the toxicology tests necessary for FDA approval to proceed to clinical trials."<sup>69</sup> Merck agreed to produce the RGD peptides and supply them to Scripps for testing.<sup>70</sup> The parties contemplated identification of the candidate and submission of an IND application to the FDA in three years.<sup>71</sup> The Scripps team, under Dr. Cheresch's direction, conducted *in vitro* and *in vivo* experiments on EMD 66203 and its derivatives, EMD 85189 and EMD 121974, and ultimately chose EMD 121974 as the primary candidate for drug development.<sup>72</sup>

After identifying a primary candidate in 1996, the parties commenced formal procedures for gaining regulatory approval in the United States and Europe.<sup>73</sup> Subsequently, in 1998, the National Cancer Institute agreed to sponsor clinical trials of EMD 121974 and filed the necessary IND application with the FDA.<sup>74</sup>

### B. History of the Case

In 1996, Integra learned of the agreement between Merck and Scripps and subsequently filed suit.<sup>75</sup> Initially, Integra contacted Merck and offered to license its RGD peptide-related patents, but after the

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65. Lawrence K. Altman, *Scientists Report Finding a Way to Shrink Tumors*, N.Y. TIMES, Dec. 30, 1994, at A1.

66. *Id.*

67. *Id.*

68. *See Merck*, 125 S. Ct. at 2378.

69. *Id.*

70. *Id.*

71. *Id.* An IND application is required to secure approval from the FDA to begin testing of potential drug candidates on humans. The clearance is necessary to protect the safety of test participants and to ensure the integrity of the data collected. *See supra* Part II.A.

72. *Merck*, 125 S. Ct. at 2378.

73. *Id.* at 2379.

74. *Id.* (citing *Integra Lifesciences I, Ltd. v. Merck KGaA*, 331 F.3d 860, 874 (Fed. Cir. 2003) (Newman, J., dissenting)).

75. *See id.*

parties failed to reach an agreement, Integra filed an infringement suit against Merck, Scripps, and Dr. Cheresch, seeking damages from Merck and a declaratory judgment against Scripps and Dr. Cheresch.<sup>76</sup> The defendants asserted that their conduct did not infringe Integra's patents and, furthermore, that the common law research exception and the § 271(e)(1) statutory exception protected the experiments.<sup>77</sup>

### 1. *The District Court Decision*

The district court found that the common law research exception shielded most of the defendants' activities prior to 1995, but the case was brought before a jury to determine whether the defendants' post-1995 activities fell under the § 271(e)(1) exception.<sup>78</sup> The § 271(e)(1) safe harbor shields activities "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."<sup>79</sup> The district court instructed the jury regarding § 271(e)(1) as follows:

To prevail on this defense, [Merck] must prove by a preponderance of the evidence that it would be objectively reasonable for a party in [Merck's] and Scripps' situation to believe that there was a decent prospect that the accused activities would contribute, relatively directly, to the generation of the kinds of information that are likely to be relevant in the processes by which the FDA would decide whether to approve the product in question.<sup>80</sup>

The jury found that the experiments were not sufficiently related to FDA review to qualify for protection under the § 271(e)(1) exception and awarded damages of \$15 million to Integra.<sup>81</sup>

### 2. *The Federal Circuit Decision*

On appeal, a divided Federal Circuit panel affirmed the district court's ruling that the defendants' preclinical research activity was too attenuated from FDA review to qualify for the § 271(e)(1) exception.<sup>82</sup> The majority viewed the research sponsored by Merck as "general biomedical research to identify new pharmaceutical compounds" rather than "clinical testing to supply information to the FDA."<sup>83</sup> Because Merck included only one of the three RGD peptides identified as

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

77. *Merck*, 125 S. Ct. at 2379.

78. *Id.*

79. 35 U.S.C. § 271(e)(1) (2000).

80. *Merck*, 125 S. Ct. at 2379.

81. *Id.* at 2380.

82. *Id.*

83. *Integra Lifesciences I, Ltd. v. Merck KGaA*, 331 F.3d 860, 866 (Fed. Cir. 2003).

potential drug candidates<sup>84</sup> in its submission to the FDA, the majority refused to apply the exception under § 271(e)(1) to absolve Merck of infringement liability.<sup>85</sup> The majority concluded that “[t]he FDA has no interest in the hunt for drugs that may or may not later undergo clinical testing for FDA approval.”<sup>86</sup> The majority further explained that “§ 271(e)(1) simply does not globally embrace all experimental activity that at some point, however attenuated, may lead to an FDA approval process.”<sup>87</sup> In the majority’s view, expanding the exception to cover all stages of new drug development would ignore the fact that the § 271(e)(1) safe harbor was originally enacted to expedite approval of generic versions of drugs already on the market, not to assist in the development of new drugs.<sup>88</sup> Furthermore, the majority cautioned that a broad reading of § 271(e)(1) might “effectively vitiate the exclusive rights of patentees owning biotechnology tool patents . . . . [because] these patented tools would only supply some commercial benefit to the inventor when applied to general research.”<sup>89</sup> Judge Newman dissented from the majority’s construction of the experimental use exception.<sup>90</sup>

### C. *The Supreme Court’s Holding*

The United States Supreme Court granted certiorari to determine “whether uses of patented inventions in preclinical research, the results of which are not ultimately included in a submission to the Food and Drug Administration (FDA), are exempted from infringement by 35 U.S.C. § 271(e)(1).”<sup>91</sup> In a unanimous decision, the Court held that the § 271(e)(1) safe harbor extends to protect use of patented inventions in *all* preclinical studies where a reasonable basis exists for believing that the experiments will lead to the development of a particular drug or produce the types of information that are “appropriate for submission to the FDA in the regulatory process.”<sup>92</sup>

The Court based its decision on the plain language of § 271(e)(1), which provides a wide exemption for activities “reasonably related to the development and submission of information under a Federal law which regulates the use . . . of . . . drugs.”<sup>93</sup> Because the FDCA is a federal law that regulates the use of drugs by requiring submission of information to the FDA for drug regulatory approval, submission of information to the

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84. Merck identified RGD peptides EMD 66203, EMD 85189, and EMD 121974 as potential drug candidates but included only EMD 12974 in its submission to the FDA. *Merck*, 125 S. Ct. at 2378.

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

86. *Id.*

87. *Id.* at 867.

88. *Id.*; see also *supra* Part II.C.2.

89. *Integra*, 331 F.3d at 867.

90. *Id.* at 873.

91. *Merck KGaA v. Integra Lifesciences I, Ltd.*, 125 S. Ct. 2372, 2376 (2005).

92. *Id.* at 2380.

93. *Id.* (quoting 35 U.S.C. § 271(e)(1) (2000)).

FDA qualifies for the § 271(e)(1) safe harbor provision.<sup>94</sup> According to the plain language of the statutory text, an activity that generates “*any* information under the FDCA” falls within the scope of the exemption.<sup>95</sup> The Court refused to exclude information from the protection of § 271(e)(1) simply “on the basis of the phase of research in which it is developed or the particular submission in which it could be included.”<sup>96</sup>

Merck’s alleged infringing conduct involved experiments conducted at the preclinical stage of new drug development. During the preclinical stage, applicants generate and submit laboratory data to the FDA in an IND application to request approval for clearance to test the investigational drug in humans.<sup>97</sup> The primary goal of the IND application process is to “assure the safety and rights” of participants in clinical trials.<sup>98</sup> Even though Merck failed to focus its preclinical experiments solely on drug safety, and did not include all of the experimental results in a submission to the FDA, the Supreme Court concluded that Merck’s experimental use of a patented invention fell under the protection of § 271(e)(1).<sup>99</sup>

#### *1. § 271(e)(1) Does Not Confine Protected Preclinical Research to Evaluation of Drug Safety*

Although Integra acknowledged that § 271(e)(1) granted a wide scope of protection, it argued that, at the preclinical stage, only information concerning the safety of the drug in humans was reasonably related to regulatory approval of the drug.<sup>100</sup> Because Merck’s preclinical research included screening tests for potential drug candidates unrelated to the evaluation of drug safety, Integra maintained that Merck’s activities exceeded the scope of information reasonably related to obtaining regulatory drug approval and should not qualify for protection under § 271(e)(1).<sup>101</sup> The Court, however, declined to restrict the § 271(e)(1) exemption only to those experiments designed to collect data concerning drug safety.<sup>102</sup>

The FDA review of an IND application assesses more than the safety characteristics of a drug. In an IND application, applicants must also include information on “the pharmacological, toxicological, pharmacokinetic, and biological qualities of the drug in animals.”<sup>103</sup> Moreover, the FDA considers the therapeutic value of a drug in treating

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94. *Id.* at 2377.

95. *Id.* at 2380.

96. *Id.*

97. *See supra* Part II.A.

98. *Merck*, 125 S. Ct. at 2381.

99. *Id.* at 2382–83.

100. *Id.* at 2381.

101. *Id.*

102. *Id.*

103. *Id.*

a serious disease when weighing the “risks and the benefits associated with the proposed clinical trials.”<sup>104</sup> In general, the FDA tolerates more safety risks for drugs that have greater potential for treating major diseases when making its determination on whether to allow clinical trials in humans.<sup>105</sup> For those reasons, the Court concluded that preclinical testing of an experimental drug to obtain information not related to safety qualifies as information necessary for regulatory submission to the FDA.<sup>106</sup> Therefore, the Court held that non-safety related experiments at the preclinical stage of drug development fell within the § 271(e)(1) exception.

*2. The § 271(e)(1) Exception Applies to Drugs and Experiments Not Ultimately Submitted to the FDA for Regulatory Approval*

The Supreme Court also held that the § 271(e)(1) safe harbor applied to the use of patented inventions in (1) studies concerning a potential drug, even when that drug is later not submitted for FDA consideration, and (2) experiments, the results of which are not ultimately included in a submission to the FDA.<sup>107</sup> Even though the Court agreed with the Federal Circuit that “the exemption ‘does not globally embrace all experimental activity that at some point, however attenuated, may lead to an FDA approval process,’”<sup>108</sup> the Supreme Court took exception with the Federal Circuit’s narrow interpretation of the § 271(e)(1) safe harbor because such an interpretation ignores “the reality that . . . scientific testing is a process of trial and error.”<sup>109</sup> Instead, the Court favored an interpretation of § 271(e)(1) that “leaves adequate space for experimentation and failure on the road to regulatory approval.”<sup>110</sup>

The Supreme Court also criticized the Federal Circuit’s construction of § 271(e)(1), which precludes protection for drugs not submitted to the FDA, as unduly restrictive.<sup>111</sup> A new drug must pass a series of tests before it can reach a stage of drug development that requires submission

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104. *Id.*

105. *Id.*

106. *Id.* Additionally, Integra contended that Merck’s activities did not qualify for the §271(e)(1) exemption because the experiments conducted did not comply with the FDA’s “good laboratory practices regulations.” *Id.* at 2381–82. Once again, the Court disagreed, finding that information is not excluded from the safe harbor provision merely because an applicant did not conduct tests according to the FDA’s “good laboratory practices” standards. *Id.* at 2382. The Court explained that the “good laboratory practices” standard applies only to tests conducted to evaluate safety, and, furthermore, even safety tests that do not conform to “good laboratory practices” may be included in an IND submission to the FDA, so long as the applicant provides an explanation for its failure to comply. *Id.* at 2382. Merck’s failure to comply with FDA “good laboratory practices” therefore did not disqualify its experiments from the § 271(e)(1) exception.

107. *Id.* at 2382.

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

109. *Id.*

110. *Id.* at 2383.

111. *Id.*

of information to the FDA.<sup>112</sup> The Federal Circuit's interpretation effectively would have limited the safe harbor exception to experiments on generic drugs and excluded newly developed drugs.<sup>113</sup> Such limitations would have arisen because it is only with a generic drug, where the active ingredient is known and previously approved, that a drug developer would know with certainty that the drug could be included successfully in a submission to the FDA.<sup>114</sup> By contrast, for a newly developed drug, where the active ingredient is untested and unproven, the Federal Circuit's interpretation would have denied a drug developer protection if the drug developer had pursued a promising drug that ultimately failed to pass experiments designed to collect information for FDA submission.<sup>115</sup> The Court refused to turn the protection of § 271(e)(1) into a game of Russian roulette for new drug developers. Relying on the statutory text of § 271(e)(1), which broadly covers "all uses of patented compounds 'reasonably related' to the process of developing information for submission under *any* federal law regulating . . . drugs,"<sup>116</sup> the Court found that the language of the statute protects all experiments on a drug for which a drug developer "has a reasonable basis for believing that a patented compound may work . . . to produce a particular . . . effect," not just research relating to the approval of generic drugs.<sup>117</sup> Since a drug must pass a series of tests before it reaches the FDA, it is not surprising that courts should avoid reading the § 271(e)(1) safe harbor "so narrowly as to render [its] stated protection of activities leading to FDA approval for all drugs illusory."<sup>118</sup>

For the same reasons, the Supreme Court also held that "the use of a patented compound in experiments,"<sup>119</sup> the results of which are not included in a submission to the FDA, "does not, standing alone, render the use infringing."<sup>120</sup> The uncertainties of new drug development, especially at the preclinical stage, limit a drug developer's ability to anticipate at the outset which experiments will be required to secure FDA approval.<sup>121</sup> Protection under the safe harbor rule does not evapor-

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112. *See id.*

113. *Id.*

114. *Id.*

115. *See id.*

116. *Id.* (quoting *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 674 (1990)).

117. *Id.*

118. *Id.*

119. *Id.*

120. *Id.*

121. *Id.*

ate merely because the experiment is not ultimately included in a submission to the FDA. So long as a drug developer has “a reasonable basis for believing that the experiments will produce ‘the types of information that are relevant to [an FDA submission],’” the use of patented compounds in preclinical experiments falls under the protection of § 271(e)(1).<sup>122</sup>

#### IV. IMPACT OF THE CASE

##### *A. Effect of the Supreme Court’s Broad Interpretation of the § 271(e)(1) Exception*

###### *1. Impact on Drug Research*

The Supreme Court’s broad reading of § 271(e)(1) in *Merck* opens the door to greater use of patented inventions in research directed at drug development. Indeed, one possible effect of *Merck* is to encourage research that may lead to the discovery of new drugs. First, the Court’s ruling assures drug researchers that experimentation involving an invention during its patent term will not incur infringement liability, so long as the researchers believe from the outset that the experiments will likely lead to information that supports a submission to the FDA.<sup>123</sup> As a result, drug researchers are free to develop improvements on patented potential drug candidates during the patent term. Researchers also may use a patented invention in research conducted to discover new and unclaimed uses for the invention, as in *Merck*, where the defendants applied a peptide useful for cell adhesion to the treatment of cancerous tumors.<sup>124</sup> Areas of research once avoided by drug developers due to fears of patent infringement liability may now attract renewed attention and funding.

Second, the Supreme Court also recognized the inevitability of trial and error in scientific research and ruled that the § 271(e)(1) safe harbor protection applied even if the research ultimately yielded disappointing results.<sup>125</sup> Consequently, a drug developer need not adopt an overly cautious research approach to ensure protection under § 271(e)(1). The ruling in *Merck* eliminates the risk of losing the safe harbor protection because of a decision to follow a line of research aimed at an ultimately unsuccessful drug candidate. As a result, *Merck* should encourage experimentation that may not otherwise have been pursued because of

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122. *Id.* at 2383–84 (quoting Brief for the United States as Amicus Curiae Supporting Petitioner at 18, *Merck KGaA v. Integra Lifesciences I, Ltd.* 125 S. Ct. 2372 (2005) (No. 03-1237), 2005 WL 429972).

123. *Id.* at 2383.

124. *Id.* at 2377–78.

125. *Id.* at 2383.

the uncertainty of securing immunity from infringement liability. Research thus may proceed for drug candidates that are likely, but not guaranteed, successes.

## 2. *Impact on Patent Holders*

While *Merck* may encourage more innovation and experimentation in drug development, the decision also has some negative implications for patent holders. Specifically, patentees will no longer be assured the right to exclude others from using a patented invention to engage in drug development activities during the patent term. The impact of this is twofold. First, researchers may not rely on patent protection to reserve areas of drug research for themselves. Other researchers need not wait for a patent term to expire or be required to obtain permission from the patentee before initiating studies using a patented invention in drug development. A patentee engaged in research on a patented drug invention thus should expect to encounter competition from other researchers, since *Merck* prevents patentees from blocking others' research activities by threatening to bring an infringement action. Patentees who sit on their inventions, therefore, may lose rights to patented improvements on the underlying invention. Competition, then, may encourage a patentee to engage in continued development of the invention, stay abreast of colleagues' developments in the field, and spur new drug discoveries.

The second impact of *Merck* on patentees occurs in the area of patent licensing. Under certain circumstances, *Merck* eliminates the previous obligation<sup>126</sup> on drug researchers to obtain a license for use of a patented invention. For activities that fall under the § 271(e)(1) safe harbor, a drug developer may forgo securing a license from the patentee and paying royalties to use the patented invention. There is no need to obtain a license when the safe harbor already shields the actor from infringement liability. As a result, the licensing of patented inventions used in drug development will likely decline.

## 3. *Limitations on the Reach of § 271(e)(1)*

The *Merck* decision gives the § 271(e)(1) exception full force by shielding uses of patented inventions in activities leading to the federal regulatory approval of drugs. However, the requirement that drug developers have a "reasonable basis for believing" that the experiments will lead to the development of a particular drug or produce the types of information needed for FDA regulatory approval constrains the broad reach of the exception.<sup>127</sup> A drug developer that uses a patented

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126. In *Merck*, a failed negotiation for a license on the patent preceded the infringement suit. *Integra Lifesciences I, Ltd. v. Merck KGaA*, 331 F.3d 860, 863 (Fed. Cir. 2003).

127. *Merck*, 125 S. Ct. at 2383.

invention cannot claim the protection of § 271(e)(1) if it has no “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.”<sup>128</sup> “Basic scientific research” with no aim towards drug development is excluded from the protection of § 271(e)(1).<sup>129</sup> *Merck* thus shifts the focus of the analysis for determining the applicability of § 271(e)(1) from whether the use of a patented invention is ultimately included in an FDA submission to whether the experimenter believed that its use would yield results suitable for submission to the FDA when it initiated use of a patented invention.<sup>130</sup>

*B. Issues Left Unresolved by the Supreme Court Decision in Merck*

*1. Whether the § 271(e)(1) Exception Applies to Use of Patented Research Tools*

The Supreme Court declined to address whether the § 271(e)(1) exception applies to the use of patented research tools in experiments aimed at generating information for regulatory drug approval. As the Court explained, “Respondents have never argued the RGD peptides were used at Scripps as research tools, and it is apparent from the record that they were not . . . . We therefore need not—and do not—express a view about whether, or to what extent, § 271(e)(1) exempts from infringement the use of ‘research tools’ in the development of information for the regulatory process.”<sup>131</sup> A “research tool” is defined as “a product or method whose purpose is use in the conduct of research, whether the tool is an analytical balance, an assay kit, a laser device . . . or a biochemical method such as the PCR.”<sup>132</sup> The Supreme Court, citing Judge Newman’s dissenting opinion from the Federal Circuit, distinguished the use of the product or method as a “research tool” from the “study” of the product or method itself.<sup>133</sup> The experiments funded by *Merck* studied patented RGD peptides in an effort to develop the peptides themselves as drug candidates; the experiments in question did not employ the peptides as tools to aid in the study of other compounds.<sup>134</sup> Accordingly, the Court concluded that *Merck* did not raise an issue concerning the application of the § 271(e)(1) exception to “research tools.”<sup>135</sup>

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128. *Id.* at 2382.

129. *Id.*

130. *See id.* at 2382–83.

131. *Id.* at 2382 n.7 (citations omitted).

132. *Integra Lifesciences I, Ltd. v. Merck KGaA*, 331 F.3d 860, 878 (Fed. Cir. 2003).

133. *Merck*, 125 S. Ct. at 2382 n.7 (citing *Integra*, 331 F.3d at 878 (Newman, J., dissenting)).

134. *See id.* at 2378–79.

135. *Merck*, 125 S. Ct. at 2382 n.7.

Whether the use of research tools falls under the § 271(e)(1) exception remains an issue for a future decision. On the one hand, if the Court's deference to the plain language of § 271(e)(1) in *Merck* is any indication, a future judgment may interpret the safe harbor to include research tools. The plain language of § 271(e)(1) states that activities employing "a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates . . . drugs" shall not be considered "acts of infringement."<sup>136</sup> While the subject matter of exempted experiments must be of a kind submitted for regulatory approval, a "patented invention" used in such experiments need not be limited to those inventions requiring regulatory drug approval. The statutory language does not explicitly confine the term "patented invention" to any specific type of invention.<sup>137</sup> On the other hand, the Court's endorsement of Judge Newman's view may hint at a different result. The Court may determine that studies of patented inventions themselves fall under the § 271(e)(1) exception, while deployment of patented inventions as tools to aid in the study of another objective falls outside of the exception. Under such a distinction, the use of "research tools" in the development of information for regulatory submission would not receive protection under § 271(e)(1).

## 2. *Status of the Common Law Research Exception*

The Supreme Court in *Merck* also did not express a view on the common law research exception.<sup>138</sup> The § 271(e)(1) exception does not apply outside the context of development of information for regulatory drug submission; as such, experimental use of a patented invention in another context may yet incur infringement liability.<sup>139</sup> Judge Newman, dissenting from the Federal Circuit majority, espoused recognizing "the exemption for research conducted in order to understand or improve upon or modify the patented subject matter, whatever the ultimate goal."<sup>140</sup> She explained that an expanded research exception is in harmony with patent law's bargain of limited exclusivity in exchange for public disclosure because

[t]he patent statute requires full disclosure of the invention . . . . Such details would be idle and purposeless if this information cannot be used for 17–20 years. Indeed, there would be little value in the requirement of the patent law that patented information must be removed from secrecy in consideration of the patent right

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136. 35 U.S.C. § 271(e)(1) (2000).

137. *See id.*

138. *See generally Merck*, 125 S. Ct. at 2382.

139. *Id.*

140. *Integra Lifesciences I, Ltd. v. Merck KGaA*, 331 F.3d 860, 876 (Fed. Cir. 2003).

to exclude, if the information is then placed on ice and protected from further study and research investigation.<sup>141</sup>

However, the Federal Circuit has strictly limited the common law research exception in previous decisions such as *Madey v. Duke University*<sup>142</sup> and *Roche Products, Inc. v. Bolar Pharmaceutical Co.*<sup>143</sup> Until an appeal reaches the Supreme Court concerning the issue of the common law research exception, the status of experimental use of patented inventions outside the context of § 271(e)(1) remains precarious.

## V. CONCLUSION

In *Merck KGaA v. Integra Lifesciences I, Ltd.*, the Supreme Court interpreted the § 271(e)(1) safe harbor to encompass the use of patented inventions in preclinical drug research. In the context of such research, the use of patented inventions is exempted from infringement provided that the experimenter has a reasonable basis to believe from the outset that its work will result in information for submission to the FDA. The Court recognized that trial and error is inherent in scientific research and acknowledged the reality that experiments occasionally fail. Even when a new drug developer pursues a path that results in failure, protection from patent infringement liability does not terminate under § 271(e)(1). As long as a drug developer has an end in mind, disappointing results will not rob it of the benefit of the exception.

Ultimately, the Court's broad construction of the § 271(e)(1) research exception will further drug research by encouraging new drug development during the term of a patented invention. Researchers need not wait until the end of the term of a patented invention to explore avenues for improvements or new uses for a patented invention. Ultimately, the outcome of *Merck* remains faithful to the original purpose of the Hatch-Waxman Act: to expedite the market entry of newly developed drugs.

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141. *Id.* at 875.

142. 307 F.3d 1351 (Fed. Cir. 2002) (concluding that a university's use of a patented laser constituted infringement).

143. 733 F.2d 858 (Fed. Cir. 1984) (concluding that use of a patented invention for the purpose of generating information for a submission to the FDA constituted infringement). The decision in *Roche* prompted Congress to enact the § 271(e)(1) exception. *See supra* note 41 and accompanying text.