MERCK KGAA v. INTEGRA LIFESCIENCES I, LTD.: GREATER RESEARCH PROTECTION FOR DRUG MANUFACTURERS

SAMUEL RUBIN*

In *Merck KGaA v. Integra Lifesciences I, Ltd.*,[1] Merck KGaA (Merck) sought protection under a statutory exemption[2] from claims of patent infringement brought by Integra Lifesciences.[3] The Supreme Court addressed whether the use of patented inventions during preclinical research infringed the patent-holders' rights if the results were not submitted to the Food and Drug Administration (FDA).[4] The Court held unanimously that a statutory safe-harbor provision contained in 35 U.S.C. § 271(e)(1) "extend[ed] to all uses of patented inventions that are reasonably related to the development and submission of *any* information under the [Federal, Food, Drug, and Cosmetic Act]."[5] The Court's interpretation of the safe-harbor provision broadened protection for those engaged in drug research at a substantial cost to patent-holders.

I. BACKGROUND

In 1988, Merck began funding research conducted by Dr. David A. Cheresh at the Scripps Research Institute.[6] Dr. Cheresh discovered that certain arginine-glycine-aspartate (RGD) peptides were an effective angiogenesis inhibiter. Angiogenesis, the process by which

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* 2006 J.D. Candidate, Duke University School of Law.

1. Merck KGaA v. Integra Lifesciences I, Ltd., 545 U.S. ___ (2005); 125 S. Ct. 2372 (2005).
2. Hatch-Waxman Act, 35 U.S.C. § 271(e)(1) (1994).
3. Respondents and the Burnham Institute co-owned the patented material peptides. *Merck*, 125 S. Ct. at 2377.
4. *Id.* at 2376.
5. *Id.* at 2380 (citing Eli Lilly v. Medtronic, Inc., 496 U.S. 661, 665–69 (1990)).
6. Both the Scripps Institute and Dr. Cheresh were dismissed from the initial patent infringement suit. *Id.*

new blood vessels sprout from existing blood vessels,[7] plays a critical role in the spread of disease.[8] Dr. Cheresh succeeded in reversing tumor growth in chicken embryos by using RGD peptides that were patented by Integra but provided to him by Merck.[9]

In 1995, Merck entered into an agreement with Dr. Cheresh and Scripps to fund further testing of the patented RGD peptides. The research was designed to identify the most promising candidate for submission of an investigational new drug ("IND") application to the FDA; however, some of the research on patented peptides would not result in the submission of the IND application. From 1995 to 1998, Dr. Cheresh conducted experiments on the RGD peptides provided by Merck.

Integra sought to license the patented RGD peptides to Merck until negotiations broke off in the spring of 1996.[10] In November of that year, Merck began to push its peptides through the regulatory process, and it shared its research with the National Cancer Institute, which agreed to sponsor clinical trials.[11] In July 1996, Integra sued Merck, Scripps, and Dr. Cheresh for patent infringement in the Southern District of California. Integra sought damages from Merck for providing the patented peptides and an injunction to stop both Dr. Cheresh and Scripps from using the patented peptides to conduct further angiogenesis research.[12] Merck denied infringement and invoked protection under both Section 271(e)(1) and a common-law research exemption to patent infringement claims.[13]

II. BROADENING THE SAFE-HARBOR PROVISION OF SECTION 271(E)(1)

Section 271(e)(1) provides that "[i]t shall not be an act of infringement to . . . use . . . a patented invention . . . solely for uses

7. *Id.* at 2378.
8. *Id.*
9. *Id.*
10. Integra Lifesciences I, Ltd. v. Merck KGaA, 331 F.3d 860 (Fed. Cir. 2003).
11. *Merck*, 125 S. Ct. at 2379.
12. *Id.* The suits against Dr. Cheresh and Scripps were dismissed by the District Court on post-trial motion. *Id.* at 2380.
13. *Id.* at 2379. The opinion is limited to discussion of Section 271(e)(1). The district court found that the common-law research exemption barred claims of infringement for pre-1995 research, but questions of fact remained as to whether Section 271(e)(1) barred claims for post-1995 research.

reasonably related to the development and submission of information under a Federal law which regulates the . . . use . . . of drugs."[14] Although the Federal Circuit found that the Section 271(e)(1) safe harbor applied only to clinical testing that was absolutely necessary to supply required information to the FDA, the Supreme Court held that "[Section] 271(e)(1)'s exemption from infringement extends to all uses of patented inventions that are reasonably related to the development and submission of *any* information under the [Federal Food, Drug, and Cosmetic Act]."[15]

The Court concluded that Section 271(e)(1) "necessarily" included preclinical study of patented compounds as long as the studies were "appropriate" steps in preparing an IND application.[16] The Court reasoned that limiting application to clinical trials would effectively limit application of the safe-harbor provision to submissions to the FDA of abbreviated new drug applications (ANDAs) for generic drugs already approved for market, because those would be the only drugs that could possibly already be in clinical trials.[17] Such a limited reading of the statute was seemingly foreclosed by *Eli Lilly & Co. v. Medtronic, Inc.*, in which the Supreme Court determined that Section 271(e)(1) applied to all inventions, not drug-related inventions alone.[18]

Despite its concession that Section 271(e)(1) applied to drugs in preclinical as well as clinical trials, Integra nevertheless argued that protection should not extend to preclinical studies relating to the drug's efficacy, mechanism of action, or pharmacokinetics.[19] In fact, Integra sought to narrow the safe-harbor provision to preclinical research to determine the safety of the drug in humans, arguing that safety is the only data the FDA is—or should be—interested in when

14. 35 U.S.C. § 271(e)(1).

15. *Merck*, 125 S. Ct. at 2380 (citing Eli Lilly v. Medtronic, Inc., 496 U.S. 661, 665–69 (1990)) (emphasis in original).

16. *Id.*

17. *Id.* at 2383 ("Thus, to construe 271(e)(1), as the Court of Appeals did . . . is effectively to limit assurance of the exemption to the activities necessary to seek approval of a generic drug.").

18. Eli Lilly v. Medtronic, Inc., 496 U.S. 661, 665 (1990); *see also* Tanuja V. Garde, *Supporting Innovation in Targeted Treatments: Licenses of Right to NIH-Funded Research Tools*, 11 MICH. TELECOMM. & TECH. L. REV. 249, 264 (2005) (stating that the Supreme Court possibly granted certiorari in *Merck* because the Federal Circuit's limited construction of Section 271(e)(1) "arguably conflict[ed] with the Supreme Court's decision in *Eli Lilly & Co. v. Medtronic, Inc.*, which held that the statutory exemption is not limited to generic drugs but also covers medical devices").

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

an IND is submitted.[20] The Supreme Court rejected these arguments, finding that though safety is the primary concern of the FDA, it is not its only concern.[21]

III. IMPACT AND CONCLUSION

Merck KGaA v. Integra Lifesciences I, Ltd. broadened the application of Section 271(e)(1) with respect to: (i) the phase of the research, (ii) the scope of the research, and (iii) the result of the research. After *Merck*, the safe-harbor provision can be used to shield drug manufacturers from liability for (i) using patented materials both before and after clinical trials have been approved by the FDA, (ii) conducting research beyond issues pertaining to human safety, and (iii) failing to submit an IND to the FDA on research that used the patented compounds.[22] The case reflected a pro-development and concomitant anti-property-right policy, acknowledging that in reality, scientific testing is a process of "trial and error," and the safety of proposed clinical experiments cannot be evaluated "in a vacuum."[23]

Merck has already had an impact on pending patent litigation, and it is likely to affect the future of research exemptions. As a result of the decision, drug companies will be able to conduct research on patented inventions free from threat of liability for infringement reasonably related to submission to the FDA. In fact, some have suggested this will foster greater efficiency in the drug industry.[24] Aside from the effect *Merck* will have on pending patent litigation, the expansive scope of the new formulation reaches back to encompass the infant stages of research. As such, the decision in *Merck* weakens protection for so-called research tools, which are

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20. *Id.*

21. Integra also argued that Merck should be denied protection under Section 271(e)(1) for failure to comply with FDA's "good laboratory practices." *Id.* at 2380. The Court rejected this argument, noting that "good laboratory practice" rules apply only to safety and not to preclinical studies of a drug's efficacy. *Id.* Moreover, the Court stated that Merck's non-compliance with "good laboratory practice" would not necessarily preclude submission of an IND to the FDA. *Id.*

22. *See, e.g.*, Dennis Crouch, *Merck v. Integra: Supreme Court Reverses, Broadens Statutory Experimental Use Safe Harbor*, PATENTLY-O: PATENT LAW BLOG, June 14, 2005; *see also* Yann Joly, *Integra v. Merck: The Resurrection of the American Research Exemption?*, CENTRE FOR INTELLECTUAL PROPERTY POLICY, June 2005, *available at* http://www.cipp.mcgill.ca/db/news/00000025.pdf.

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

24. Joly, *supra* note 22, at 3.

products or methods "whose purpose is use in the conduct of research."[25]

In the five months since the Supreme Court decided *Merck*, several courts have grappled with its impact on pending litigation. In *Classen v. Biogen*,[26] a federal district court applied *Merck* to dismiss claims of patent infringement against drug manufacturers for conducting research on patented inventions.[27] However, the broadened interpretation is not limitless. Decisions in the wake of *Merck* have required something more than "a remote desire to obtain FDA approval for products [as] sufficient to satisfy the 'reasonably related standard.'"[28]

Another criticism of the broad application of Section 271(e)(1) suggests that the majority did not give adequate attention to the "*solely* for uses reasonably related to submission under a Federal law" language contained in the text of Section 271(e)(1).[29] For instance, the court in *Third Wave Technologies, Inc. v. Stratagene*[30] focused on the word "solely" when it noted that partial desire to submit to the FDA was an insufficient ground for invocation of the Section 271(e)(1) exemption.[31]

Merck not only broadened protection for drug manufacturers under Section 271(e)(1), it will likely also affect the law of research exemptions by providing decreased protection to holders of research tool patents. Although the Court in *Merck* expressly avoided the research-tool exemption issue, application of the safe-harbor provision to pre-clinical trials allows the provision to reach back much farther than the Federal Court's interpretation of the exemption would have.[32]

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25. *Integra Lifesciences v. Merck KGaA*, 331 F.3d 860 (Fed. Cir. 2003) (Newman, J. dissenting) *corrected by* 2003 U.S. App. LEXIS 27796, *50 (July 10, 2003).

26. Classen Immunotherapies, Inc. v. Biogen IDEC, 381 F. Supp. 2d 452 (D. Md. 2005).

27. *Id.* at 455-56.

28. Third Wave Techs., Inc. v. Stratagene Corp., 381 F. Supp. 2d 891, 913 (D. Wis. 2005).

29. *See* Lawrence Ebert, *One Response to Merck v. Integra*, Sept. 25, 2005, *available at* http://madisonian.net/archives/2005/06/14/merck-v-integra/ (last visited Nov. 8, 2005) ("Although a strict constructionist, Justice Scalia did not analyze the word 'solely' in 271(e)(1). However, by allowing that the jury instruction in *Merck v. Integra* was not inconsistent with the Supreme Court decision, Justice Scalia generated a mechanism to re-introduce 'solely.'").

30. *Third Wave Techs., Inc.*, 381 F. Supp. 2d at 913.

31. *See id.* (finding testimony from CEO that testing was "motivated 'in part' by a desire to obtain FDA approval" insufficient grounds to invoke protection under Section 271(e)(1)).

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

One critic has even suggested that broadening of the statutory provision in *Merck* demonstrates favoritism towards the protection of research within the drug industry above other industries.[33] In this regard, the statutory exception is a revitalization of research protection for drug manufacturers who lost the common law exception in *Madey v. Duke University*.[34] In *Madey*, the Federal Circuit significantly narrowed the common-law experimental-use exemption to include only those acts that are "solely for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry."[35] After *Madey*, if the infringer's act can be said to be "in furtherance of the infringer's legitimate business purpose," the act is not protected under the common-law experimental-use exemption.[36]

There is widespread agreement that the Supreme Court has made the status of research tool patents unclear.[37] Practitioners agree that by avoiding the issue of a research tool patent exemption in *Merck*, the Court invited future litigation on the precise issue of whether 271(e)(1) exempts use of patented research tools from patent infringement.[38] Irving N. Feit, a patent specialist, has noted that use of the words "patented invention" and specific exclusion from protection of animal and veterinary products in Section 271(e)(1) suggests that there is no indication that the Court will treat research tool patents as a separate class of inventions.[39] Although the Court's decision in *Merck* leaves the door open for future litigation as to the precise impact Section 271(e)(1) will have on research exemptions, *Merck*

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33. Garde, *supra* note 18, at 266 ("[B]roadening the statutory exemption while at the same time leaving the common-law experimental use exemption in its limited form suggests that only in the drug development industry is research more important than patent rights on other technologies, including, possibly even research tools.").

34. Madey v. Duke Univ., 307 F.3d 1351 (Fed. Cir. 2003), *cert. denied*, 539 U.S. 958 (2003); *see also* Joly, *supra*, note 22, at 3.

35. *Madey*, 307 F.3d at 1362.

36. *Id.*

37. *See, e.g.*, Garde, *supra* note 18, at 262 ("By ['failing to differentiate between experimenting on and experimenting with patented technology'] the availability of the exemption is now uncertain for research tools"); Crouch, *supra* note 22 ("Rather than settling the law the Court appears to have created an unfortunate uncertainty regarding the value of patents covering research tools."); Irving N. Feit, *The Safe Harbor Infringement Exemption Under the Hatch-Waxman Act, Finally Defined*, INTELLECTUAL PROPERTY TODAY, Aug. 2005, at 28, *available at* http://www.iptoday.com/pdf_current/Feit_Proof%203.pdf. ("It is not clear what effect the Supreme Court's ambivalence will have on the strong endorsement of research tool patents made by the Federal Circuit's *Integra v. Merck* decision.").

38. *See, e.g.*, Crouch, *supra* note 22; Feit, *supra* note 37, at 28.

39. Feit, *supra* note 37, at 28.

marks a commitment by the Court to a policy of broadening protection in drug research and development, even at a substantial cost to patent-holders.