Safe Harbor or Pirate Cove?
MERCK V. INTEGRA AND ITS SEEMING IMPACT ON INTERNATIONAL RESEARCH ACTIVITIES

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Background

To encourage the development of new pharmaceuticals, Congress amended the patent laws in 1984 to insulate pharmaceutical research from charges of infringement so long as the research is "reasonably related to the development and submission of information to the Food and Drug Administration." The safe harbor of 35 U.S.C. section271(e)(1) provides that:

> It shall not be an act of infringement to make, use, offer to sell, or sell ... a patented invention ... solely for uses reasonably related to the development and submission of information under a federal law that regulates the manufacture, use, or sale of drugs or veterinary biological products.

The courts have struggled to define the parameters of section 271(e)(1) to meet Congress's intent. Although commercial use is outside the safe harbor,[1] section 271(e)(1) has been broadly interpreted, so that,"[a]s long as the activity is reasonably related to obtaining FDA approval, the accused infringer's intent or alternative uses are irrelevant to its qualification to invoke the § 271(e)(1)(1) shield."[2] However, using a patented product to discover new clinical uses or side effects or to develop alternative products is not protected under section 271(e)(1). Likewise, selling devices for additional clinical trials after FDA approval does not fall within the safe harbor.

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In *Eli Lilly & Co. v. Medtronic, Inc.*,[3] the Supreme Court expanded the safe harbor of section 271(e)(1) to medical devices subject to FDA approval. The *Eli Lilly* Court indicated that products that undergo FDA approval, including food additives, color additives, new drugs, antibiotic drugs, and human biological products, are also eligible for the safe harbor. Class II medical devices that do not require FDA pre-market approval, a lengthy process, but merely FDA premarket notification, also fall within section 271(e)(1).

Several cases sought to determine whether section 271(e)(1) applied to uses "solely"related to or "reasonably related"to FDA approval. In *Scripps Clinic & Research Foundation v. Genetech Inc.*,[4] the safe harbor was denied where there was "a multiple purpose use of a patent invention ... where only one purpose related to FDA testing." Both *Intermedics, Inc. v. Ventritex, Co.*,[5] and *Teletronics Pacing Systems, Inc. v. Ventritex,Inc.*,[6] held that data initially developed for submission to the FDA fell under the safe harbor even where it was used for collateral activities, including testing and demonstration.

Amgen v. Hoechst Marion Roussel,[7] and *Nexcell Therapeutics Inc. v. AmCellCorp.*[8] extended section 271(e)(1) to preclinical drug discovery. *Amgen* held that Hoechst's manufacture and use of erythropoietin to develop a commercial product does not preclude the safe harbor, and "a large degree of deference to activities conducted in furtherance of FDA-approved clinical trials is appropriate."

In *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*,[9] the court found patented intermediates used to screen drugs did not infringe. The court further indicated that patents for research tools (antibodies, receptors or peptides for screening assays, cell lines, and enzymes) fell within the section 271(e)(1) safe harbor. Similarly, in *Chartex Int'l PLC v M.D. Pers. Products Corp., et al.*,[10] preclinical activities that included demonstrating patented female condoms at trade shows and evaluating consumer acceptance fell within the safe harbor.

Several cases have, nevertheless, denied section 271(e)(1) protection. *Infigen, Inc. v. Advanced Cell Tech., Inc.*,[11] where the patent in question pertained to cloning and not to a drug product or process, held that section 271(e)(1) did not apply, because the FDA does not regulate research tools.

Despite 20 years of judicial construction, confusion continues over the scope of section 271(e)(1). Recently, *Integra Life Sciences I, Ltd. v. Merck KgaA*,[12] held the safe harbor provision does not apply to *any* preclinical activities. Merck & Co., in collaboration with Scripps Research Institute, used peptides that contain certain sequences to identify for future clinical testing drugs that might inhibit angiogenesis. Integra LifeSciences, the patent(s) owner, offered Merck a license on its technology. Believing it was protected under section 271(e)(1), Merck refused the offer. Litigation ensued.

A jury found that Merck had infringed four of Integra Life Sciences' five U.S. patents. On appeal, a divided Federal Circuit panel affirmed the verdict, finding Scripps's research was not clinical testing to obtain FDA approval.[13] The court limited section 271(e)(1) to activities directly related to obtaining federal

TABLE 1

Activities Falling Within the Section 271(e)(1) Safe Harbor

- Manufacturing generic drugs, medical devices
- Preclinical, clinical, and risk-benefit assessment research
- Safety tests (even if not GLP compliant)
- Using the drug product to raise capital
- Authorizing publications in medical journals
- Exporting the patented product to evaluate manufacturing processes
- Clinical testing to comply with foreign standards
- Selling a product to international distributors
- Making an amount of the product in excess of that required for the FDA approval (i.e., stockpiling)[16]
- Characterizing the product, e.g., testing for purity and lot-to-lot variability
- Abandoning results for reasons unrelated to FDA approval
- Circulating study results to potential licensees
- Conducting consumer studies
- Selling a product to clinical investigators at a hospital
- Promoting a product to customers
- Shipping a product to a potential commercial partner

Activities Falling Outside the Section 271(e)(1) Safe Harbor

- Use of research tools
- Conducting consumer studies to evaluate consumer acceptance preclinically
- Common-law experimental use (amusement, curiosity, philosophical inquiry)
- Commercial research
- Small molecule screening

approval as "the FDA has no interest in the hunt for drugs that may or may not later undergo clinical testing for FDA approval." The majority further held that because the ultimate goal of the research was commercial, a common-law research exemption was not available. The court also recognized that expanding section 271(e)(1) to encompass drug screening would have a significant impact on the patentee's right to exclude and would "effectively vitiate the exclusive rights of patentees owning biotechnology tool patents."

Because neither activities required to file an Investigational New Drug (IND) application nor drug screening were exempted by section 271(e)(1), drug developers would have to obtain many patent licenses to develop new drugs, pursue design arounds, go off-shore, challenge in court, or they could simply use a patented invention at their own risk without permission. The decision created a divide, with the large pharmaceutical industry in opposition, smaller biotechnology companies that hold patents on research tools in favor, and research universities on either side depending on whether they were the patentee or the potential infringer. Generic drug manufacturers were also opposed, as the decision limited their ability to experiment with drugs covered by patents.

The Supreme Court granted certiorari to answer whether the use of patented inventions in preclinical research whose results are not ultimately included in a submission to the FDA are exempted from infringement by section 271(e)(1).

Broadening the Safe Harbor Provisions of Section 271(e)(1)

In June 2005 the Supreme Court reversed the Federal Circuit. Justice Scalia, writing for the Court, held that though "the contours of section271(e)(1) are not exact in every respect, the statutory text makes clear that it provides a wide berth for the use of patented drugs in activities related to the federal regulatory process." According to the court, the statute extends section 271(e)(1) to all uses of patented inventions that are "reasonably related"to the development and submission of any "information"under the FDC Act. Applying a "reasonable basis" approach, the Court stated the safe harbor necessarily includes pre-clinical studies of patented compounds that are appropriate for submission to the FDA in the regulatory process and does not exclude from the exemption information based on the phase of research in which it is developed or the particular submission in which it could be included. Therefore,

TABLE 2

Examples of Other Possible Solutions

- Create a collective licensing clearinghouse modeled on copyright permission law allowing for "fair use"
- Create "research-only" licenses with preset fees subject to a registration process
- Modify U.S. patent law to permit the penumbra of patentable subject matter to omit research tools
- Strengthen the patenting requirements for utility and nonobviousness, thereby eliminating issuance of patents that could block research
- Change the test for patent infringement by narrowing the scope to the level of disclosure, thereby substantially reducing the doctrine of equivalents[17]
- Statutorily modify Bayh-Dole to require nonexclusive licensing to interested parties or abandonment to the public domain
- Allow a period of complete exclusivity followed by a period of compulsory licensing

studies of pharmacology, toxicology, and metabolism, and even screening of compounds to identify leading candidates, fall within the safe harbor.

Although the decision answered a number of questions about the boundaries of the safe harbor, it left many questions unanswered. To the disappointment of academics and the biotechnology industry and the delight of the pharmaceutical industry, though the court decided that research not ultimately submitted to the FDA can fall under the safe harbor, thus recognizing that trial and error are part of developing drugs, the court did not decide whether section 271(e)(1) exempts research tools.

The Supreme Court vacated the Federal Circuit's decision, remanded the case, reinstated the appeal, and requested new briefs be filed consistent with the Supreme Court's decision.

Since the Supreme Court decision, several cases have been decided that pertain to section 271(e)(1). In *Classen Immunotherapeutics, Inc. v. Biogen IDEC*,[14] a federal court in Maryland considered whether patent research protocols directed to vaccine administration, for which FDA approval was not sought, and research that was clearly postapproval were included under the safe harbor. The court ruled such activity was reasonably related to the "development and submission of information" to the FDA.

In another case, *Third Wave Tech. v. Strategene Corp.*,[15] the Court ruled that the safe harbor did not apply to "start-up" research to detect nucleic acids for which there was only a "remote desire" to obtain FDA approval.

Impact and Conclusion

The issue is now whether the Supreme Court's ruling places patented inventions into the hands of would-be infringers under the guise of public interest, thereby violating both the intent of patent law and the constitutional rights of patent holders under the Takings Clause of the Fifth Amendment. Has the decision tilted the balance between monopoly and public policy? Premarket approval is not mutually exclusive of commercial interest. Universities and nonprofits conduct research both to generate revenues and for the greater common good. Is "partially reasonably related" tantamount to "reasonably related"?

Is the section 271(e)(1) exemption capable of consistent application in adiverse range of situations? Table 1 lists activities that fall within or outside the safe harbor. Table 2 lists examples of possible solutions.

In the wake of *Integra*, companies involved in pharmaceutical research need to examine their activities to ensure they are protected. Premarket research activities conducted by generic manufacturers, like bioequivalency testing for Abbreviated New Drug Applications and branded generic submissions, would still appear to qualify for the safe harbor exemption. It is important to note that researchers will need to contemporaneously document actual research activities and be prepared to demonstrate that such activities are "reasonably related" to the submission of "information"to the FDA. Experiments will need to be performed that produce information that at least "could" be submitted to the FDA.

The question remains regarding the common law experimental use exemption; that is, exempting from infringement the use of a patent for amusement, philosophical inquiry, or curiosity that has no commercial purpose.

Will confusion over the ruling lead to research moving offshore? In as much as many countries overseas have broad, codified, clear provisions for experimental use, will this decision result in research moving offshore to avoid liability in the United States?

Where does the decision leave research tools? Will research tool patents be applied for in countries where research occurs, such as China and India, but there is no safe harbor?

Certainly there will be more litigation now that the court has left research tools exposed. And, finally, is there a need for statutory reform of the experimental use doctrine, to make it like the fair use exemption in copyright law? That is, should legislation exempt public research institutions and basic research laboratories from patent infringement claims? Whether by legislation or by decisions in the courts, the research exemption must remain viable to ensure continued global progress in the sciences and useful arts.◆

Endnotes

1. American Standard, Inc. v. Pfizer, Inc., 722 F. Supp. 86 (D. Del. 1989).
2. *See* Abtoc, Inc. v. Exitron Corp., 122 F.3d 1019, 1030 (Fed. Cir. 1997).
3. 496 U.S. 661 (1990).
4. 231 U.S.P.Q. (BNA) 978, 979 (N.D. Cal. 1986).
5. 775 F. Supp. 1269, 1272 (N.D. Cal. 1991), *aff'd without opinion*, 991 F.2d 808 (Fed. Cir. 1993).
6. 19 U.S.P.Q.2d (BNA) 1960 (N.D. Cal. 1991), *aff'd*, 982 F.2d 1520 (Fed. Cir. 1992).
7. 3 F. Supp. 2d 104 (2002).
8. 199 F. Supp. 2d 197 (2002).
9. No. 95 Civ. 8833, 2001 WL 1512597 (S.D.N.Y 2001).
10. 5 F.3d 1505 (Fed. Cir. 1993).
11. 65 F. Supp. 2d 967 (W.D. Wis. 1999).
12. 331 F.3d 860 (Fed. Cir. 2003).
13. 331 F.3d 860, 865-67 (Fed. Cir. 2003).
14. 381 F. Supp. 2d 482 (D. Md. 2005).
15. 381 F. Supp. 2d 891 (W.D. Wis. 2005).
16. *But see* Biogen v. Schering AG, 954 F. Supp. 391 (D. Mass. 1996) (stockpiling interferon in anticipation of imminent FDA approval to market same does not fall under the § 271(e)(1) exception).
17. Shawn C. Troxler, *Biotechs Beware: Safe Harbor No More?* 5 N.C.J.L. & TECH. 59, 76 (2003).

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