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The Safe Harbor Infringement Exemption Under the Hatch-Waxman Act, Finally Defined

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The safe harbor provision of the Hatch-Waxman act, *i.e.* 35 U.S.C. §271 (e)(1)², exempts from patent infringement the use of 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 . . .” The scope of protection under the safe harbor provision has been the subject of considerable uncertainty and controversy.³

An important new decision of the United States Supreme Court has replaced the uncertainty regarding the safe harbor provision with an authoritative new standard. The decision is called *Merck KGaA v. Integra Lifesciences I Ltd.*⁴ The *Merck* case reached the Supreme Court on appeal from the Court of Appeals for the Federal Circuit.⁵

The new standard announced by the Supreme Court will, in the future, be applied by all courts called upon to determine the scope of protection under the safe harbor

exemption. As will be discussed below, the Supreme Court interpreted the scope of the safe harbor provision to be more generous to the research community than did the Federal Circuit.

The Supreme Court also addressed a strong endorsement by the Federal Circuit of research tool patents. As will also be discussed below, the Supreme Court was more ambiguous about the value of such patents than was the Federal Circuit.

FACTS

Justice Scalia, writing for a unanimous Supreme Court, noted that the Federal Food Drug and Cosmetic Act (FDCA)⁶ constitutes a “Federal law which regulates the manufacture, use, or sale of drugs” under the safe harbor provision of the Hatch-Waxman Act.⁷ He began the decision by discussing the “two general stages of new-drug development” under the FDCA.

Justice Scalia noted that, under the FDCA, a drug company first submits an investigational new drug application (IND) to the United States Food and Drug Administration (FDA) in order to justify proposed clinical testing. If the clinical testing demonstrates that the drug is safe and effective for its purpose, the drug company submits to the FDA a new drug application (NDA), and requests a license to sell the drug to the public.⁸

The respondents in the Supreme Court

case, Integra LifeSciences I, Ltd. and the Burnham Institute (collectively, Integra), own five patents that cover peptides containing the sequence Arg-Gly-Asp, known as RGD peptides.⁹ The petitioner, Merck KGaA,¹⁰ sponsored research at the Scripps Research Institute conducted by Dr. David Cheresh in order to discover drugs that inhibit angiogenesis for use as anti-cancer agents.

Dr. Cheresh conducted experiments *in vitro* and in animals with RGD peptides, which were provided by Merck. The purpose of these experiments was to evaluate the efficacy, specificity, toxicity and pharmacokinetics of various RGD peptides as angiogenesis inhibitors, and to elucidate their mechanisms of action.¹¹ Scripps selected one of the peptides as the most promising candidate for testing in humans. The National Cancer Institute filed an IND for the selected peptide.¹²

DISTRICT COURT TRIAL

Integra filed a patent infringement suit against Merck, Scripps, and Dr. Cheresh in the District Court for the Southern District of California.¹³ Integra alleged that Merck infringed, and induced others to infringe, Integra’s patents by supplying the RGD peptides to Scripps, and that Dr. Cheresh and Scripps infringed the patents by using the RGD peptides in the angiogenesis experi-

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ments described above.¹⁴ Merck argued, *inter alia*, that the safe harbor provision of the Hatch-Waxman Act exempted the experiments at Scripps from infringement.¹⁵

After the trial, the district court, with the consent of the parties, gave the following instruction to the jury regarding the standard for determining the scope of exemption from patent infringement under the safe harbor provision:¹⁶

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. (emphasis added).

This instruction to the jury was consistent with a long line of previous district court and Federal Circuit opinions regarding the scope of the safe harbor provision.¹⁷ The loose and liberal language of the standard, which can be seen from the highlighted words in the quote above, provides a relatively broad scope for the safe harbor exemption. The broad scope favors the ability of researchers to investigate new drugs without fear of liability from existing patents.

Despite the generous scope accorded by the district court to the safe harbor exemption, the jury found that Merck had failed to show its activities were protected from infringement. The district court denied Merck's motion for judgment as a matter of law, and held:¹⁸

... that the evidence was sufficient to show that "any connection between the infringing Scripps' experiments and FDA review was insufficiently direct to qualify for the (safe harbor exemption)."

Accordingly, the court found Merck guilty of patent infringement, and awarded *Integra* damages of fifteen million dollars.¹⁹

FEDERAL CIRCUIT APPEAL

Merck appealed the district court decision to the Federal Circuit. In order to understand the significance of the Supreme Court deci-

sion, it is necessary to review the Federal Circuit decision, there referred to as *Integra v. Merck*. The Federal Circuit stated the issue in *Integra* as:²⁰

... whether the §271(e)(1) Safe Harbor reaches back down the chain of experimentation to embrace development and identification of new drugs that will, in turn, be subject to FDA approval.

The Federal Circuit's interpretation of the scope of the safe harbor exemption in *Integra* was narrower than that of the consensus of previous district court and Federal Circuit decisions referred to above,²¹ including the district court decision the Federal Circuit was reviewing. In particular, the Federal Circuit stated that the safe harbor provision:²²

... does not, for instance, expand the phrase 'reasonably related' to embrace the development of new drugs because those new products will also need FDA approval. Thus (the safe harbor provision) simply does not globally embrace all experimental activity that at some point, however attenuated, may lead to an FDA approval process. The safe harbor does not reach any exploratory research that may rationally form a predicate for future FDA clinical tests.

The Federal Circuit emphasized how narrowly it viewed the safe harbor provision by suggesting that it might exempt from patent infringement only those activities "...reasonably related to acquiring FDA approval of a drug already on the market." Such an interpretation would, in effect, limit the exemption to activities of generic drug companies seeking approval of an ANDA.²³

Since the Federal Circuit in *Merck* construed the safe harbor exemption more narrowly than did the district court, the Federal Circuit easily affirmed the district court decision that Merck's activities were not exempt from patent infringement.²⁴

Perhaps the most significant part of the Federal Circuit decision was that relating to the harm done to research tool patents by a broad exemption under the safe harbor provision. The Federal Circuit entered the heated debate regarding such patents decisively on the side of being able to protect research tools. Thus, the Federal Circuit attempted to justify its narrow scope of exemption under the safe harbor provision on the basis that:²⁵

... expansion of (the safe harbor provision) to include (Merck's) activities would effectively vitiate the exclusive rights of patentees owning biotechnology tool patents. After all, patented tools often facilitate general research to identify candidate drugs, as well as downstream safety-related experiments on those drugs...

Thus, exaggerating (the safe harbor provision) out of context would swallow the whole benefit of the Patent Act for some categories of biotechnological inventions. Needless to say, the 1984 Act was meant to reverse the effects of *Roche*²⁶ under limited circumstances, not to deprive entire categories of inventions of patent protection.

SUPREME COURT DECISION

Merck appealed the Federal Circuit decision to the Supreme Court. Justice Scalia, writing for a unanimous court, stated the issue as follows:²⁷

This case presents the question 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 (the safe harbor provision).

The Supreme Court made clear that it construed the safe harbor exemption more broadly than did the Federal Circuit. In fact, Justice Scalia stated that he considered the loose and liberal jury instruction quoted above from the district court decision "...to be consistent with, if less detailed than, the construction of (the safe harbor exemption) that we adopt today."²⁸

For example, Justice Scalia expressly rejected the suggestion of the Federal Circuit, mentioned above,²⁹ that the safe harbor exemption is limited to activities of generic drug companies seeking approval of an ANDA.³⁰ Quite the contrary.

Justice Scalia emphasized that the safe harbor exemption covers a wide range of pre-clinical as well as clinical studies. He noted, for example, that the FDA requires drug companies to include in an IND summaries of the pharmacological, toxicological, pharmacokinetic, and biological qualities of potential drugs in animals. He reasoned that

such information is obtained through pre-clinical *in vitro* and animal studies.³¹

In its *Merck v. Integra* decision, the Supreme Court articulated the most detailed and authoritative standard to date for determining the line between experiments that qualify under the safe harbor exemption and those that do not. The standard, according to the court, “. . . provides a wide berth for the use of patented drugs in activities related to the federal regulatory process,”³² and “...leaves adequate space for experimentation and failure on the road to regulatory approval.”³³

Justice Scalia stated the new standard most definitively as follows:³⁴

At least where 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.” §271(e)(1).

Justice Scalia attempted to draw a sharp line between the kinds of experiments that satisfy the new standard for safe harbor exemption, and basic research, which does not. Thus, he contrasted the above definition of pre-clinical research with the following definition of basic research³⁵ :

Basic 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, is surely not “reasonably related to the development and submission of information” to the FDA.

The Supreme Court has finally provided the medical research community and the courts with an authoritative standard for distinguishing the kind of research that qualifies under the safe harbor exemption, and the kind of research that does not. The case was remanded to the district court for reconsideration consistent with the newly announced standard.³⁶ The district court’s reconsideration, as well as future cases, will reveal just how sharp the distinction drawn by Justice

Scalia will prove to be.

Justice Scalia addressed the statement by the Federal Circuit regarding the protection of research tools in a footnote.³⁷ As mentioned above, the Federal Circuit suggested that a narrow construction of the safe harbor provision is necessary to avoid depriving research tool patents of their value.³⁸

Justice Scalia was more ambivalent about, and appeared to be less sympathetic to, research tool patents than was the Federal Circuit. He noted that Merck did not argue that the RGD peptides were used at Scripps as research tools. Therefore, he declined to express a view “. . . about whether, or to what extent, (the safe harbor exemption) exempts from infringement the use of ‘research tools’ in the development of information for the regulatory process.”³⁹

It is not clear what effect the Supreme Court’s ambivalence will have on the strong endorsement of research tool patents made in the Federal Circuit’s *Integra v. Merck* decision. See above. Justice Scalia appeared to be inclined to wait for a more appropriate case to address this issue.


It should be noted, however, that the safe harbor provision, at least literally, broadly exempts from patent infringement the use of “a patented invention.”⁴⁰ There is no suggestion in the literal language of the safe harbor provision that different classes of inventions are to be treated differently. Therefore, it is difficult to speculate how an exception will be made for the class of inventions deemed to constitute research tools.

Moreover, the safe harbor provision already contains an explicit exception for the class of inventions relating to certain “new animal drug or veterinary biological product(s).”⁴¹ Therefore, it may be difficult to argue that congress intended an implicit exception for a different class.

Nevertheless, it is interesting, and possibly significant, that the Supreme Court expressly declined to rule out such an exception. See above.⁴² (“We therefore need not - and do not - express a view about whether, or to what extent, (the safe harbor exemption) exempts from infringement the use of ‘research tools’ in the development of information for the regulatory process.”)⁴³

The *Merck v. Integra* decision gave Justice Scalia a second opportunity to give a broad

interpretation to the safe harbor exemption of the Hatch-Waxman Act. In 1990, he held in *Eli Lilly v. Medtronic*⁴⁴ that the safe harbor exemption was not limited to drugs, and covered medical devices as well.

It is interesting to note that Justice Scalia appears to have mellowed somewhat with time. When he first considered the safe harbor provision in *Eli Lilly* in 1990, he stated: “No interpretation we have been able to imagine can transform §271(e)(1) into an elegant piece of statutory draftsmanship.”⁴⁵ Fifteen years later, in *Merck v. Integra*, his criticism was more subdued and less sarcastic: “[T]he contours of this provision are not exact in every respect.”⁴⁶ 

ENDNOTES

1. Hoffmann & Baron, LLP. The opinions expressed in this article are solely the current opinions of the author, and not necessarily those of Hoffmann & Baron, LLP; any of its attorneys or agents; any of its clients; and not necessarily even the future opinions of the author.
2. Officially called the Drug Price Competition and Patent Term Restoration Act of 1984, §202, 98 Stat. 1585, as amended.
3. See, for example, Lawrence B. Ebert, “In Favor of the Federal Circuit Position in *Merck v. Integra*,” J. Pat. Trademark. Off. Soc’y., 1011 (April, 2005); Brian Coggio, “The Safe Harbor Provisions of the Hatch Waxman Act: Present Scope, New Possibilities, and International Considerations,” 57 Food Drug L.J. 161 (2002).
4. 125 S.Ct. 2372, 74 U.S.P.Q.2d 1801 (June 13, 2005).
5. *Integra v. Merck*, 331 F.3d 860 (Fed. Cir. 2003).
6. Ch. 675, 52 Stat. 1040, as amended, 21 U.S.C. §301 *et seq.*
7. *Merck v. Integra*, 74 U.S.P.Q.2d at 1802.
8. *Id.* at 1803.
9. U.S. Patent Nos. 4,988,621, 4,792,525, 5,695,997, 4,879,237, and 4,789,734.
10. Merck KGaA is located in Darmstadt, Germany, and is not affiliated with Merck & Co., Inc. of Whitehouse Station, New Jersey.
11. *Merck v. Integra*, 74 U.S.P.Q.2d at 1804.
12. *Id.*
13. In response to a post-trial motion, the district court dismissed the suit against Dr. Cheresch and Scripps. *Id.* at 1805.
14. *Id.* at 1804.
15. *Id.*
16. *Id.* at 1804-1805.
17. *Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269, 1277 (N.D. Cal. 1991), aff’d without opinion, 991 F.2d 808 (Fed. Cir. 1993); *Elan Transdermal Ltd. v. Cygnus Therapeutics Systems*, 24 U.S.P.Q.2d 1926, 1931-1932 (N.D. Cal. 1992); *Teletronics Pacing Sys. Inc., v. Ventritex, Inc.*, 982 F.2d 1520, 1525 (Fed. Cir. 1992); *Elan Transdermal Ltd. v. Cygnus Therapeutics Systems*, 24 U.S.P.Q.2d 1926, 1931-1932 (N.D. Cal. 1992); *Abtox, Inc. v. Exitron Corp.*, 122 F.3d 1019, 1028 (Fed. Cir. 1997); *Bristol-Myers Squibb Company v. Rhone Poulenc Rorer, Inc.*, 2001 U.S. Dist. LEXIS 19361 (S.D.N.Y. 2001).

18. *Merck v. Integra*, 74 U.S.P.Q.2d at 1805.
19. The damages were reduced to 6.375 million dollars on remand from the Federal Circuit. *Id.* at n.5.
20. *Integra v. Merck*, 331 F.3d at 865.
21. See discussion around, and citations in, footnote 17, above.
22. *Integra v. Merck*, 331 F.3d at 867.
23. *Id.*
24. *Id.* at 868.
25. *Id.*
26. Refers to *Roche v. Bolar*, 221 USPQ 937 (Fed. Cir. 1984). In *Roche*, the Federal Circuit held that the use of a chemical compound protected by a patent in a clinical trial constituted patent infringement. One of the purposes of the Hatch-Waxman Act was to overrule the *Roche* decision.
27. *Merck v. Integra*, 74 U.S.P.Q.2d at 1802.
28. *Id.* at 1808.
29. See discussion above around footnote 23.
30. *Merck v. Integra*, 74 U.S.P.Q.2d at 1807.
31. *Id.* at 1805 and 1806.
32. *Id.* at 1805.
33. *Id.* at 1807.
34. *Id.*
35. *Id.*
36. *Id.* at 1808.
37. *Id.* at 1807, n7.
38. See discussion above around footnote 25.
39. *Merck v. Integra*, 74 U.S.P.Q.2d at 1807, n7.
40. 35 U.S.C. §271(e)(1).
41. *Id.*
42. See discussion above around footnote 39.
43. *Merck v. Integra*, 74 U.S.P.Q.2d at 1807, n7.
44. 496 U.S. 661 (1990).
45. *Eli Lilly v. Medtronic*, 496 U.S. at 679 (1990).
46. *Merck v. Integra*, 74 U.S.P.Q.2d at 1805.

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