Order Code RL33114

CRS Report for Congress
Received through the CRS Web

Safe Harbor for Preclinical Use of Patented Inventions in Drug Research and Development: *Merck KGaA v. Integra Lifesciences I, Ltd.*

October 7, 2005

Brian T. Yeh
Legislative Attorney
American Law Division

http://www.crsdocuments.com

Safe Harbor for Preclinical Use of Patented Inventions in Drug Research and Development: *Merck KGaA v. Integra Lifesciences I, Ltd.*

Summary

In *Merck KGaA v. Integra Lifesciences I, Ltd.*, __ U.S. __, 125 S. Ct. 2372 (2005), the United States Supreme Court unanimously held that the preclinical use of patented inventions in drug research is exempted from patent infringement claims by the "safe harbor" provision of the Patent Act, 35 U.S.C. § 271(e)(1). (Merck KGaA is a German company unaffiliated with the U.S.-based pharmaceutical company Merck & Co.) This decision potentially may help expedite the development of new medical treatments and lower the cost of some drugs for consumers.

In 2003, the U.S. Court of Appeals for the Federal Circuit had narrowly construed the safe harbor provision as protecting only clinical research activities that produce information for submission to the Food and Drug Administration (FDA) in the regulatory process. In vacating that decision, the U.S. Supreme Court ruled that the exemption applies to *all* uses of patented inventions that are "reasonably related" to the process of developing any information for FDA submission. The Court explained that, under certain conditions, the safe harbor provision is even "sufficiently broad" to protect the use of patented compounds in experiments that are not ultimately submitted to the FDA or drug experiments that are not ultimately the subject of an FDA submission. Finally, the scope of the exemption is not limited only to preclinical studies pertaining to a drug's safety in humans, but also includes preclinical data regarding a drug's efficacy, mechanism of action, pharmacokinetics, and pharmacology.

However, the Court cautioned that the exemption does not reach all experimental activity that at some point, however attenuated, may lead to an FDA approval process. For example, the safe harbor provision does not embrace basic scientific research performed on a patented compound without the intent to develop a particular drug or without a reasonable belief that the compound will cause a particular physiological effect that the researcher desires. In addition, because the matter was not at issue in the case, the Court expressly declined to decide whether or to what extent the exemption applies to patented "research tools" that are often used to facilitate general research in developing compounds for FDA submissions.

Contents

Introduction 1
Background 1
The Hatch-Waxman Act 2
The FDA Drug Approval Process 2
The Scope of Safe Harbor 3
Types Covered 3
Uses Covered 4
Merck KGaA v. Integra Lifesciences I, Ltd. 4
Facts of the Case 4
The District Court's Decision in *Integra* 6
Integra in the Federal Circuit 6
The U.S. Supreme Court's Decision in *Integra* 7
Basic Research Not Protected 8
The Standard for "Reasonable Relation" 8
An Unresolved Question: Patented Research Tools 9
Concluding Observations 10

http://www.crsdocuments.com
GalleryWatch.com

Safe Harbor for Preclinical Use of Patented Inventions in Drug Research and Development: *Merck KGaA v. Integra Lifesciences I, Ltd.*

Introduction

In *Merck KGaA v. Integra Lifesciences I, Ltd.*, __ U.S. __, 125 S. Ct. 2372 (2005), the United States Supreme Court decided, without dissent, that the patent law's safe harbor provision exempts from infringement the preclinical use of patented inventions in drug research. Without this legal immunity, pharmaceutical companies face patent infringement liability when they conduct preclinical experiments using rival companies' patented compounds. The U.S. Court of Appeals for the Federal Circuit had earlier found that the statutory exemption applied only to clinical research activity that contributes "relatively directly" to information the Food and Drug Administration (FDA) considers in approving a drug.[1] This narrow interpretation of the safe harbor provision had raised concerns that the patent law could significantly restrict the development and introduction of new medical treatments and generic drugs.

Vacating the appellate court's decision, the U.S. Supreme Court unanimously ruled that the exemption protects all uses of patented inventions that are "reasonably related" to the process of developing any information for FDA submission, which includes preclinical studies. The Court's expansive construction of the safe harbor provision "leaves adequate space for experimentation and failure on the road to regulatory approval"[2] and "provides a wide berth for the use of patented drugs in activities related to the federal regulatory process."[3]

Background

It is normally a violation of the Patent Act to use any patented invention without prior authorization of the patent owner.[4] However, a statutory exception to this general rule provides: "It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented

---

[1] Integra Lifesciences I, Ltd. v. Merck KGaA, 331 F.3d 860, 867 (Fed. Cir. 2003) (citation omitted).

[2] Merck KGaA v. Integra Lifesciences I, Ltd., __ U.S. __, 125 S. Ct. 2372, 2383 (2005).

[3] *Id.* at 2380.

[4] 35 U.S.C. § 271(a).

invention ... solely for uses reasonably related to the development and submission of information" to the United States Food and Drug Administration (FDA).[5] Thus, a party that uses a patented invention without the patent owner's permission is committing an infringing act, but if the use comes within the scope of the statutory exception, the party will not be held liable for violating the patent owner's rights.

The Hatch-Waxman Act. The statutory exception was created by the Drug Price Competition and Patent Term Restoration Act of 1984,[6] commonly known as the Hatch-Waxman Act. This legislation modified the Patent Act by creating a new section, 35 U.S.C. § 271(e), that provides "safe harbor" from infringement for pharmaceutical companies using patented inventions in their drug research and development operations.

The Hatch-Waxman Act is widely credited with encouraging and expediting the creation and availability of generic versions of approved patented drugs. Prior to its enactment, pharmaceutical companies had to wait until all relevant patents expired before undertaking the clinical research necessary to obtain FDA approval of generic equivalents.[7] Thus, an established drug's patent term was *de facto* extended beyond its expiration date by the length of the FDA regulatory process for approving the generic equivalent, which took more than two years.[8] The Hatch-Waxman Act allows generic drug manufacturers to conduct safety and effectiveness tests during the time the brand name drug's patent is still in force, often resulting in immediate introduction of a generic drug into the market upon the pioneer drug's patent expiration.[9]

The FDA Drug Approval Process. The Federal Food, Drug, and Cosmetics Act (FDCA) regulates the manufacture, use, or sale of drugs.[10] Under the FDCA, the FDA must determine that a drug is safe and effective before it can be marketed to consumers. The FDCA establishes a two-stage approval process for new drugs: an

---

[5] 35 U.S.C. § 271(e)(1).

[6] P.L. 98-417, 98 Stat. 1585 (1984), codified in 15 U.S.C. §§ 8b-68c, 70b; 21 U.S.C. §§ 301, 355, 360cc; 28 U.S.C. § 2201; and 35 U.S.C. §§ 156, 271, 282.

[7] The statutory exemption is also called the "Bolar Amendment " or "FDA exemption," since it effectively overturns the decision of the U.S. Court of Appeals for the Federal Circuit in Roche Products, Inc. v. Bolar Pharmaceutical Co., Inc., 733 F.2d 858 (Fed. Cir. 1984), which had found Bolar, a manufacturer of generic drugs, liable for infringing Roche's patented drug during the last six months of the term of the patent in its testing and investigation activities related to FDA drug approval requirements.

[8] *Roche,* 733 F.2d at 860.

[9] For more information regarding the Hatch-Waxman Act, *see* CRS Report RL30756, *Patent Law and Its Application to the Pharmaceutical Industry: An Examination of the Drug Price Competition and Patent Term Restoration Act of 1984 ("The Hatch-Waxman Act"),* by Wendy H. Schacht and John R. Thomas; and CRS Report RL32377, *The Hatch-Waxman Act: Legislative Changes Affecting Pharmaceutical Patents*, by Wendy H. Schacht and John R. Thomas.

[10] P.L. 75-717 (1938), codified in 21 U.S.C. §§ 301 et seq.

"Investigational New Drug" (IND) application and a "New Drug Application" (NDA).[11]

The drug manufacturer must file an IND with the FDA after the company has identified, through preclinical testing on animals and in test tubes, chemical compounds that appear to have beneficial therapeutic effects. The IND is a request for authorization to conduct clinical (human) testing, and it must contain information and data from the preclinical studies that justify the proposed clinical trial.[12]

Once the FDA approves the IND, the drugmaker can commence clinical studies. If these studies demonstrate that a new drug is reasonably safe and effective for use, the drugmaker is required to submit a NDA.[13] The NDA must include data from preclinical and clinical studies. After extensive review of the NDA, the FDA issues final approval or denial of the application for manufacturing and selling the new drug to the public.[14]

The Scope of Safe Harbor

The Patent Act's safe harbor provision has often been compared to the "fair use" defense in copyright law, since it immunizes from liability otherwise infringing acts in order to advance compelling public policy interests. The legislative history of the Hatch-Waxman Act provides the basis for this analogy: "Just as we have recognized the doctrine of fair use in copyright, it is appropriate to create a similar mechanism in the patent law. That is all this bill does."[15] Despite this deceptively simple language of purpose, the safe harbor provision has been the subject of confusion and litigation for many years following its enactment. For over two decades, federal courts struggled to define the breadth and contours of the exemption, particularly concerning the types and uses of patented invention covered by the safe harbor.

Types Covered. As for the types of covered patented invention, the United States Supreme Court in *Eli Lilly & Co. v. Medtronic, Inc.* expansively interpreted § 271(e)(1) to include not only drug and veterinary products, but also medical devices

---

[11] 21 U.S.C. § 355(i). Generic drug companies may file an abbreviated new drug application (ANDA) with the FDA. 21 U.S.C. § 355(j). An ANDA must reveal that the generic product has the same active ingredients as, and is bioequivalent to, a prior approved brand name drug. Also, in its ANDA, the generic drug manufacturer may rely upon the safety and efficacy data of the original drug manufacturer.

[12] 21 U.S.C. § 355(i)(1)(A).

[13] 21 U.S.C. § 355(b)(1).

[14] For more information concerning the FDA drug approval process, *see* CRS Report RL32797, *Drug Safety and Effectiveness: Issues and Action Options After FDA Approval,* by Susan Thaul, and CRS Report RL30989, *The U.S. Drug Approval Process: A Primer*, by Blanchard Randall IV.

[15] H.Rept. 98-857 (II) at 30, 98th Cong., 2d Sess. (1984), *reprinted in* 1984 U.S.C.C.A.N. 2686, 2714.

that are subject to pre-market approval by the FDA.[16] The *Eli Lilly* Court determined that "[t]he phrase 'patented invention' in § 271(e)(1) is defined to include all inventions, not drug-related inventions alone."[17] The Court opined that if Congress had wanted the safe harbor to cover only generic drugs, "there were available such infinitely more clear and simply ways of expressing that intent."[18] As written, § 271(e)(1) applies to the "entire statutory scheme of regulation,"[19] including "medical devices, food additives, color additives, new drugs, antibiotic drugs, and human biological products."[20]

Uses Covered. Concerning the protected uses of a patented invention, a long disputed issue was what kind of research in the drug development process qualified for the exemption: basic research, preclinical research, or clinical studies. These three stages of drug development are described as follows: basic research involves the testing of thousands of compounds to discover any biological activity relevant to understanding the cause of a disease; the preclinical stage involves more focused research on a smaller group of chemical compounds in the hopes of finding the best candidate for clinical development; and clinical studies are the testing of the drug on human subjects in preparation for FDA approval.[21] Following its interpretive lead in *Eli Lilly,* the Supreme Court in *Merck KGaA v. Integra Lifesciences I, Ltd. ("Integra")* ruled that § 271(e)(1) immunizes from infringement both preclinical and clinical use of patented inventions in the drug research and development process.

Merck KGaA v. Integra Lifesciences I, Ltd.

Facts of the Case. Integra Lifesciences I, Ltd. ("Integra") is a pharmaceutical company that owns five patents related to a sequence of three amino acids, arginine, glycine, and aspartic acid (the "RGD peptide"), which promotes cell adhesion by attaching to receptors on cell surface proteins called integrins.[22] Scientists working for Telios Pharmaceuticals, Inc. discovered that the RGD peptide had potential use in promoting wound healing and biocompatibility of prosthetic devices, prompting Telios to obtain patents for the RGD peptide compositions and methods. However, after failing to develop a viable commercial product, Telios sold the patents to Integra.[23]

---

[16] 496 U.S. 661 (1990).

[17] *Id.* at 665.

[18] *Id.* at 667.

[19] *Id.* at 666.

[20] *Id.* at 674.

[21] James N. Czaban & Nishita Doshi, *Supreme Court Applies Broad Interpretation of Bolar Amendment to Protect Innovative Drug Research From Claims of Patent Infringement,* 70 PAT., TRADEMARK, & COPYRIGHT J. (BNA) 1726 (June 24, 2005).

[22] *Integra*, 331 F.3d at 862-63.

[23] *Id.* at 873 (Newman, J., dissenting).

In the mid-1980s, Dr. David Cheresh at the Scripps Research Institute ("Scripps"), a non-profit corporation that conducts biochemical research, discovered that blocking integrin receptors using the RGD peptide inhibited angiogenesis, a process by which new blood vessels sprout from existing vessels. Angiogenesis plays a critical role in the spread of many diseases, including cancerous tumor growth, diabetic retinopathy, and rheumatoid arthritis.[24]

Merck KGaA ("Merck"),[25] a German pharmaceutical corporation unaffiliated with the U.S.-based pharmaceutical company Merck & Co., was interested in developing this discovery into a drug to control angiogenesis. In 1988, Merck entered into an agreement with Scripps to provide funding for Dr. Cheresh's research, in exchange for Scripps granting Merck an option to license future discoveries arising from his research.[26] In 1994, Dr. Cheresh succeeded in reversing tumor growth in chicken embryos using a RGD peptide identified as EMD 66203, which had been provided by Merck. This peptide was covered by Integra's patent.[27]

Due to Dr. Cheresh's breakthrough achievement, Merck and Scripps entered into a new collaboration agreement in September 1995 to fund the "necessary experiments to satisfy the biological bases and regulatory (FDA) requirements for the implementation of clinical trials" with EMD 66203 or a derivative thereof.[28] Dr. Cheresh then proceeded to conduct *in vivo* and *in vitro* experiments on EMD 66203 and two derivatives of it, EMD 85189 and EMD 121974, in order to evaluate each peptide as potential drug candidates. These "tests measured the efficacy, specificity, and toxicity of the particular peptides as angiogenesis inhibitors, and evaluated their mechanism of action and pharmacokinetics in animals."[29] Based on these tests, in November 1996 Merck's pharmaceutical steering committee selected EMD 85189 for pre-clinical development; in April 1997, Merck switched to EMD 121974 as its most promising candidate for clinical testing.[30] In October 1998, Merck reached an agreement with the National Cancer Institute (NCI) to sponsor the clinical trials, and later that year, the NCI filed an IND application with the FDA for EMD 121974.[31]

---

[24] *Id.* at 863.

[25] *See* Merck is Not the Same as Merck, *available at* [http://www.merck.de/servlet/PB/menu/1014710/index.html].

[26] Telios Pharms., Inc. v. Merck KGaA, 1997 U.S. Dist. LEXIS 24187, Case No. 96-CV-1307 (S.D. Cal., Sept. 9, 1997), at *3.

[27] *Integra,* 125 S. Ct. at 2378 n.3.

[28] *Integra,* 331 F.3d at 863.

[29] *Integra,* 125 S. Ct. at 2378. Efficacy means how well a drug can be expected to work in curing a disease; mechanism of action is how it achieves those results; pharmacokinetics is the rate at which a drug is absorbed into and eliminated from the bloodstream; and toxicity is the negative side effects of the drug at different dosages. Brief for Petitioner Merck KGaA at 12-13, *Merck KGaA v. Integra Lifesciences I, Ltd.,* 125 S. Ct. 2372 (2005) (No. 03-1237).

[30] *Telios Pharms.,* 1997 U.S. Dist. LEXIS 24187, at *5.

[31] *Integra,* 331 F.3d at 873 (Newman, J., dissenting).

When Integra became aware of Merck's agreement with Scripps to conduct angiogenesis research for commercial purposes, Integra offered Merck the opportunity to purchase licenses to use its patented RGD peptides. In July 1996, after Merck had declined the offer, Integra sued Merck, Scripps, and Dr. Cheresh, seeking monetary damages for Merck's alleged patent infringement and a declaratory judgment against Scripps and Dr. Cheresh.[32] In defense, Merck asserted that its actions involving the RGD peptides came within the common-law research exemption[33] and the statutory safe harbor afforded by § 271(e)(1).

The District Court's Decision in *Integra*. At the conclusion of trial, the U.S. District Court for the Southern District of California dismissed Integra's claim for declaratory judgment and held that the common-law research exemption protected Merck's pre-1995 use of the RGD peptides.[34] However, the court found that a question of fact remained as to whether Merck's post-1995 actions fell within the scope of the § 271(e)(1) safe harbor. The district court instructed the jury that, for Merck to prevail on the safe harbor defense, it must prove by a preponderance of the evidence that it was objectively reasonable for the company to believe that "there was a decent prospect" that the experiments "would contribute, relatively directly," to the generation of information likely to be relevant to the drug approval regulatory process.[35]

The jury found Merck liable for infringing Integra's patents and that Merck had failed to show that § 271(e)(1) protected its post-1995 research activities. The jury awarded damages of $15 million in royalties. In response to post-trial motions, the district court dismissed Integra's suit against Scripps and Dr. Cheresh, but affirmed the jury's monetary award, explaining that there was substantial evidence to show that the connection between the experiments and FDA review was "insufficiently direct to qualify for the [§ 271(e)(1) exemption]."[36]

***Integra* in the Federal Circuit.** In June 2003, a divided panel of the Court of Appeals for the Federal Circuit affirmed the district court's determination as to liability but reversed the court's refusal to modify the damages award.[37] The panel majority found that safe harbor does not "reach any exploratory research that may

---

[32] *Id.* at 863.

[33] The common-law research exemption is a limited, judge-made exception to the patentee's right to exclude. Its historic foundations arise from Whittemore v. Cutter, 29 Fed. Cas. 1120, 1121 (C.C.D. Mass. 1813), in which Justice Story stated, "it could never have been the intention of the legislature to punish a man, who constructed such a machine merely for philosophical experiments..." Courts have recognized the use of this exemption for research that has no commercial purpose. *Integra,* 331 F.3d at 874-75 (Newman, J., dissenting).

[34] *Integra,* 125 S. Ct. at 2379.

[35] *Id.*

[36] *Id.* at 2380.

[37] On remand, the District Court reduced the award to $6.375 million, on the calculated basis of $1.5 million per year as a reasonable royalty between the infringement period August 1994 and November 1998. *Integra*, 2004 WL 2284001, at *11 (S.D. Cal. Sept. 7, 2004).

rationally form only a predicate for future FDA clinical tests."[38] In confining the § 271(e)(1) exemption to research activities that contribute "relatively directly" to information "reasonably related" to clinical testing for the FDA, the appellate court stated:

> In this case, the Scripps work sponsored by Merck was not clinical testing to supply information to the FDA, but only general biomedical research to identify new pharmaceutical compounds. The FDA has no interest in the hunt for drugs that may or may not later undergo clinical testing for FDA approval.[39]

Furthermore, the court expressed concern that construing the safe harbor provision more expansively "would effectively vitiate the exclusive rights of patentees owning biotechnology tool patents," since patented research tools are often used in general research to identify candidate drugs and experiments on those drugs.[40]

On January 7, 2005, the U.S. Supreme Court granted *certiorari* to review the court of appeals' interpretation of the safe harbor provision.[41]

The U.S. Supreme Court's Decision in *Integra*

The question presented to the Supreme Court was "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)."[42] In a unanimous opinion written by Justice Scalia, the Court vacated the judgment of the Federal Circuit and held that the § 271(e)(1) safe harbor protected the preclinical use of patented compounds "as long as there is a reasonable basis for believing that the experiments will produce 'the types of information that are relevant to an IND or NDA'" submission to the FDA.[43]

The Court explained:

> [W]e think it apparent from the statutory text that § 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 FDCA. ... This necessarily includes preclinical studies of patented compounds that are appropriate for submission to the FDA in the regulatory process. There is simply no room in the statute for excluding certain information from the exemption on the basis of the phase of research in which it is developed or the particular submission in which it could be included.[44]

---

[38] *Integra,* 331 F.3d at 867.

[39] *Id.* at 866-67.

[40] *Id.* at 868.

[41] *Integra,* 125 S. Ct. 823 (2005).

[42] *Integra,* 125 S. Ct. at 2376.

[43] *Id.* at 2383-84 (citation omitted).

[44] *Id.* at 2380 (emphasis in original) (citations omitted).

The Court rejected Integra's argument that the scope of the safe harbor is limited only to preclinical studies pertaining to the safety of a drug in humans.[45] Since the FDA requires an IND to be filed *before* human trials can begin, IND applications must include summaries of a drug's efficacy, pharmacokinetics, pharmacology, and toxicological effects in animals.[46] This data would necessarily have to be developed in preclinical studies — information that is "reasonably related" to an FDA submission and thus covered by § 271(e)(1).[47]

The Court further disagreed with Integra's claim that Merck's preclinical research is disqualified from safe harbor protection because the experiments were not conducted in conformity with the FDA's "good laboratory practices" (GLP) regulations. Two reasons supported the Court's reasoning: first, the FDA's GLP regulations concerning preclinical studies apply only to experiments on drugs "to determine their safety," and not to studies of a drug's efficacy, mechanism of action, pharmacology, or pharmacokinetics; second, even non-GLP compliant safety-related studies are suitable for submission in an IND, when such studies are accompanied by a reason for the noncompliance.[48]

Basic Research Not Protected. The Court placed an outer limit to the safe harbor provision by endorsing the Federal Circuit's conclusion that the exemption does not reach all experimental activity that at some point, however attenuated, may lead to an FDA approval process.[49] For example, safe harbor does not embrace basic scientific research performed on a patented compound without the intent to develop a particular drug or without a reasonable belief that the compound will cause a particular physiological effect that the researcher desires.[50] Thus, the boundary line between unprotected basic research and protected preclinical research is reached when a scientist discovers that a patented compound produces a "particular" physiological effect through a "particular" biological process.[51]

The Standard for "Reasonable Relation". In denying safe harbor protection for Merck's preclinical activities, the Federal Circuit had relied upon the fact that the "Scripps-Merck experiments did not supply information for submission to the [FDA], but instead identified the best drug candidate to subject to future clinical testing under the FDA processes."[52] The Supreme Court dismissed the appellate court's narrow interpretation of the "reasonably related" requirement in § 271(e)(1). Such a construction, the Court explained, "disregards the reality that ... scientific testing is a process of trial and error," and that "neither the drugmaker nor

---

[45] *Id.* at 2381 ("We do not understand the FDA's interest in information gathered in preclinical studies to be so constrained.")

[46] 21 C.F.R. § 312.23(a)(5).

[47] *Integra,* 125 S. Ct. at 2381.

[48] *Id.* at 2382 (citations omitted).

[49] *Id.*

[50] *Id.*

[51] *Id.* at 2383.

[52] *Integra,* 331 F.3d at 865-66.

its scientists have any way of knowing whether an initially promising candidate will prove successful over a battery of experiments."[53] Thus, under certain conditions, the Court noted that the safe harbor provision is "sufficiently broad" to protect the use of patented compounds in experiments that are not ultimately submitted to the FDA or drug experiments that are not ultimately the subject of an FDA submission.[54]

The Court announced a standard for construing § 271(e)(1)'s reasonable relation requirement in a way that "leaves adequate space for experimentation and failure on the road to regulatory approval":

> 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."[55]

An Unresolved Question: Patented Research Tools. Research tools are defined as "tools that scientists use in the laboratory, including cell lines, monoclonal antibodies, reagents, animal models, growth factors, combinatorial chemistry and DNA libraries, clones and cloning tools (such as PCR), methods, laboratory equipment and machines."[56] Smaller biotechnology companies and universities that invent research tools are concerned that a broader construction of § 271(e)(1) encompassing these tools will deprive them of licensing fees that they collect from larger pharmaceutical firms.[57] Moreover, some companies rely on such fees for their financial existence, since many of these research tools have little commercial value beyond usage in drug research.[58] The Federal Circuit in *Integra* had specifically identified this potential negative consequence for patented research tools, in its support for a more limited safe harbor:

> [T]he context of this safe harbor originally keyed its use to facilitating expedited approval of patented pioneer drugs already on the market. Extending § 271(e)(1) to embrace all aspects of new drug development activities would ignore its language and context with respect to the [Hatch-Waxman Act] in an attempt to

---

[53] *Integra,* 125 S. Ct. at 2383.

[54] *Id.* at 2382. The legislative history of § 271(e)(1) supports this reasoning: "A party which develops [information for the FDA regulatory process], but decides not to submit an application for approval, is protected [by the safe harbor] as long as the development was done to determine whether or not an application for approval would be sought." H.Rept. 98-857 (I) at 45, 98th Cong., 2d Sess. (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647, 2678.

[55] *Integra,* 125 S. Ct. at 2383 (citing § 271(e)(1)).

[56] *Integra,* 331 F.3d at 874 n.4 (citing *Sharing Biomedical Research Resources: Principles and Guidelines for Recipients of NIH Research Grants and Contracts,* 64 Fed. Reg. 72090, 72092 n.1 (Dec. 23, 1999)).

[57] David Savage & Denise Gellene, *High Court Boosts Drug Research; Justices Say Companies Are Free to Use Patented Compounds in Developing Medicines. Analysts Say Ruling May Hurt Some Biotech Firms,* L.A. TIMES, June 14, 2005, at C1.

[58] *Id.*

> exonerate infringing uses only potentially related to information for FDA approval. Moreover, such an extension would not confine the scope of § 271(e)(1) to *de minimis* encroachment on the rights of the patentee. For example, expansion of § 271(e)(1) to include the Scripps-Merck activities would effectively vitiate the exclusive rights of patentees owning biotechnology tool patents. Thus, exaggerating § 271(e)(1) out of context would swallow the whole benefit of the Patent Act for some categories of biotechnological inventions. Needless to say, the [Hatch-Waxman Act] was [not] meant ... to deprive entire categories of inventions of patent protection.[59]

In its amicus curiae brief submitted to the Supreme Court, the U.S. Government suggests that § 271(e)(1) does not apply to patented research tools.[60] The Government's brief explains that the safe harbor section, by its own terms, applies only to "a patented invention." The Patent Act defines the term "invention" to mean any "invention or discovery," "*unless* the context otherwise indicates."[61] The brief asserts that the context of § 271(e)(1) indicates that Congress may not have intended to include patented research tools within the scope of the safe harbor exemption. Since most research tools are used to study or develop other compounds for submission to the FDA regulatory approval process, rather than being themselves the subject of FDA regulatory review, it is plausible to conclude that research tools are not "patented inventions" within the meaning of the statute.[62]

In *Integra,* the Supreme Court expressly declined to decide whether or to what extent the exemption applies to patented research tools since the matter was not at issue in the case. The Court explained that Integra had never argued that the RGD peptides were used by Merck/Scripps as research tools, "and it is apparent from the record that they were not."[63] Thus, without a definitive judicial determination from the Court, the use of patented research tools in drug research and development may or may not fall under the § 271(e)(1) exemption from infringement. Such uncertainty over the patent rights of makers of research tools could serve as a source of continued confusion and litigation in this area.

Concluding Observations

The original legislative intent behind the Hatch-Waxman Act that created § 271(e)(1) was to facilitate the introduction of a generic drug upon the patent expiration of the brand name drug. However, as the Supreme Court explained in the *Eli Lilly* case that broadened § 271(e)(1) beyond generic drugs to the entire statutory scheme of FDA regulation:"[I]t is not the law that a statute can have no effects which are not explicitly mentioned in its legislative history."[64]

---

[59] *Integra,* 331 F.3d at 867.

[60] Brief for United States as *Amicus Curiae*, at 29, *Merck KGaA v. Integra Lifesciences I, Ltd.,* 125 S. Ct. 2372 (2005) (No. 03-1237).

[61] 35 U.S.C. § 100(a) (emphasis added).

[62] Brief for United States as *Amicus Curiae*, at 29.

[63] *Integra,* 125 S. Ct. at 2382 n.7.

[64] *Eli Lilly,* 496 U.S. at 669 n.2 (quoting Pittston Coal Group v. Sebben, 488 U.S. 105, 115 (continued...)

The consequences of the Supreme Court's decision in *Integra* are significant. Some observers argue that if the Federal Circuit's opinion had not been vacated, its narrow interpretation of the patent law's safe harbor potentially would have created a chilling effect on the development of innovative, pioneer drugs and new generic drugs. Limiting § 271(e)(1) to only clinical research appears contrary to the objectives of the Hatch-Waxman Act: If a drug manufacturer could not perform the preclinical studies needed to obtain FDA approval to conduct clinical studies, "the [§ 271(e)(1)] exemption would never be reached because the underlying preliminary research and development work could not be undertaken" without risking patent infringement liability.[65]

The Supreme Court's more expansive construction of § 271(e)(1) avoids this result. Since "it will not always be clear to parties setting out to seek FDA approval for their new product exactly which kinds of information, and in what quantities, it will take to win that agency's approval," the safe harbor provision is needed to immunize certain preclinical studies that use patented compounds.[66] The Court also provided an articulated standard for courts, scientists, drug companies, and patent holders to follow concerning the scope of § 271(e)(1) coverage: Safe harbor applies if there is a reasonable basis to believe that the preclinical experiments will produce information that is relevant to an IND or NDA submission with the FDA. Failure to meet this standard would constitute infringing conduct not exempted by § 271(e)(1). By unanimous opinion, the *Integra* Court has emphatically clarified that preclinical use of patented compounds in pharmaceutical research is not categorically unprotected and can qualify for the patent law's safe harbor as long as it comes within this enunciated standard.

However, the *Integra* Court left unresolved the issue of whether research tools come within the scope of the safe harbor exemption. It is important to note that *Integra* does not affect the validity and value of patented research tools when they are employed in basic research or for purposes unrelated to an FDA submission.[67] Yet the unauthorized use of research tools in the development of information for the FDA regulatory process may constitute infringing conduct or could be exempted by the patent law's safe harbor. This legal uncertainty raises concerns about the enforceability of research tool patents in this circumstance. Unless or until the Supreme Court answers this question in a future case, Congress may desire to clarify § 271(e)(1)'s applicability to research tools.

---

[64] (...continued)
(1988)).

[65] Brief for United States as *Amicus Curiae*, at 14 (quoting Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc., 2001 WL 1512597, at *6 (S.D.N.Y. Nov. 28, 2001)).

[66] *Integra,* 125 S. Ct. at 2383 (citation omitted).

[67] Brief for United States as *Amicus Curiae*, at 30.