

## Merck v. Integra: the Supreme Court's Interpretation of the § 271(e)(1) Safe Harbor Provision on Patent Infringement

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### Abstract

*The safe harbor provision on patent infringement, 35 U.S.C. § 271(e)(1), creates an exemption from patent infringement for use of a patented invention that is reasonably related to development and submission of information for FDA submission. The Supreme Court in Merck v. Integra held that the exemption extends to preclinical studies of patented compounds that are appropriate for submission to the FDA in the regulatory process. The decision will likely create significant impact on drug research and development. This article provides a historical context of the § 271(e)(1) safe harbor, an analysis of Merck v. Integra, and a discussion on potential implications of the Supreme Court decision.*

On June 13, 2005, the Supreme Court of the United States issued the landmark decision Merck KGaA v. Integra Lifesciences I, Ltd.<sup>1</sup> In an unanimous opinion, the Court broadly interpreted the scope of the safe harbor provision, 35 U.S.C. § 271(e)(1), which creates an exemption from patent infringement for 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 Court held that the exemption extends to preclinical studies of patented compounds that are appropriate for submission to the FDA in the regulatory process. This includes both preclinical data pertaining to the safety of drugs in humans, and preclinical studies related to a drug’s efficacy, mechanism of action, pharmacology, and pharmacokinetics.

The Court vacated a decision by the Federal Circuit, which had limited the § 271(e)(1) exemption to research activities that supply information for submission to the FDA. The Court opined that the exemption does not categorically exclude either experimentation on drugs that are not ultimately the subject of an FDA submission or use of patented compounds in experiments that are not ultimately submitted to the FDA.

Although the Supreme Court in Integra has not clearly delineated the contours of the safe harbor, its decision will likely create significant impact on drug research and development. This article provides a historical context of the § 271(e)(1) safe harbor and an analysis of the Integra case, in order to facilitate understanding of the contours of the § 271(e)(1) safe harbor and the significance of the Supreme Court’s Decision.

### Background of the § 271(e)(1) safe harbor

35 U.S.C. § 271(e)(1) was enacted as part of the Drug Price Competition and Patent Term Restoration Act of 1984, popularly known as the Hatch-Waxman Act. The Act was enacted to address unique problems caused by delays in the FDA approval process for drugs. Because pioneer drug developers have to go through the lengthy FDA approval process in order to bring their new drug products to the market, a large portion of their patent terms were sacrificed to the FDA approval process, which significantly shortened the length of the effective patent

terms. On the other hand, generic drug developers have to go through the same FDA approval process before the generic drugs can be brought to the market. As a consequence, there was no immediate competition from generic drugs after the patent for the pioneer drug expired, and the patent holder continued to enjoy de facto market exclusivity after its patent has expired. In an attempt to address such dual distorting effects of regulatory approval requirements, Congress enacted the Hatch-Waxman Act.

The Hatch-Waxman Act has two titles. Title I provides an abbreviated New Drug Approval (“NDA”) procedure whereby generic drug firms can introduce copies of the pioneer drugs to the market place without repeating expensive and lengthy clinical trials. Title II of the Act modified the Patent Code by providing both a safe harbor provision to the general prohibition against patent infringement and a patent term extension provision. The patent term extension provision in Title II of the Hatch-Waxman Act is encoded in 35 U.S.C. § 156, which permits an extension of the original term of a patent if certain mandatory conditions are met. The safe harbor provision of the Hatch-Waxman Act was encoded in 35 U.S.C. § 271(e)(1), which allows development of generic drugs prior to the expiration of the patent. Through the enactment of the statute, Congress hoped to minimize the amount of time between the expiration of a patent on a brand name drug and the availability of approved generic drug equivalent.

Despite of the specific legislative intent, the language of § 271(e)(1) seems very broad. It in pertinent part, 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 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 . . .

Courts encountering the § 271(e)(1) issue have consistently interpreted the statute broadly. In *Eli Lilly & Co. v. Medtronic, Inc.*,<sup>2</sup> the Supreme Court held that the term “patented invention” in the statute was not limited to patented drugs, but rather encompasses class III medical devices, which typically will go through the same lengthy FDA approval process.<sup>3</sup> The Federal Circuit in the *Abtox* case has taken one step further, finding that the statute applies to all kinds of patented medical devices.<sup>4</sup> Because most of the § 271(e)(1) cases involve either patented drugs or patented medical devices, it was not clear whether the term “patented invention” also encompasses inventions other than drugs and medical devices, such as research tools. The Southern District Court of New York in the *Bristol-Myers* case answered the question affirmatively, holding that the term “patented invention” refers

to all kinds of inventions, including a patented intermediate compound used for screening of new drug candidates.<sup>5</sup> The Western District Court of Wisconsin in the *Infigen* case, on the other hand, had refused to read the statute as broad as to encompass a patented method for making transgenic cows for milk production.<sup>6</sup>

Another term in the statute courts have analyzed was the term “solely for uses reasonably related.” Earlier cases have relied heavily on the legislative history of the statute and limited the application of § 271(e)(1) to use of an invention for the sole purpose of obtaining FDA approval.<sup>7</sup> More recent cases, however, have essentially ignored the term “solely” in the statute and focused on the inquiry of whether the allegedly infringing use is “reasonably related” to development and submission of information to the FDA.<sup>8</sup> Most courts have adopted a test provided in the Northern District Court of California in the *Intermedics* case (the “Intermedics test”), which indicated that the appropriate question to ask is:

Would it have been reasonable, objectively, for a party in defendant’s situation to believe that there was a decent prospect that the “use” in question would contribute (relatively directly) to the generation of kinds of information that was likely to be relevant in the process by which the FDA would decide whether to approve the product.<sup>9</sup>

Applying this test, courts have found a lot of activities “reasonably related” to development and submission of information to the FDA, and thus exempt under the § 271(e)(1) safe harbor. These include, for example, use of patented medical devices for collecting data prior to submission of an FDA application and preclinical studies that were not submitted to the FDA.<sup>10</sup> The Southern District Court of New York in the *Bristol-Myers* case went even further, holding that use of patented intermediate compound in screening for new drugs fall under the § 271(e)(1) safe harbor. There was thus clearly a trend towards a broad interpretation to the § 271(e)(1) safe harbor provision prior to the *Integra* case.

### Background of Merck KGaA v. Integra Lifesciences I, Ltd. (“Integra”)

*Integra* involves a short tripeptide segment of fibronectin (“the RGD peptide”) that mediates interaction between fibronectin and a cell surface receptor integrin during angiogenesis, a process essential for tumor growth. In the late 1980’s, Dr. David Cheresch at the Scripps Research Institute (“Scripps”) discovered that blocking integrin receptors on the cell surface inhibits angiogenesis, thereby showing promise in cancer therapy. In 1988, Merck KGaA (“Merck”, a German company

unrelated to Merck & Co. in the United States), entered into an agreement with Scripps to fund research for identifying potential drug candidates that might inhibit angiogenesis. This research led to the discovery of a cyclic RGD peptide (EMD 66203) as a potential drug candidate. In 1995, Merck and Scripps entered into a second agreement 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.<sup>11</sup> The agreement contemplated commencing clinical trials with a drug candidate within three years. From 1995 to 1998, Scripps scientists conducted several *in vivo* and *in vitro* experiments on EMD 66203 and two other closely related cyclic RGD peptides. The tests measured the efficacy, specificity, and toxicity of the cyclic RGD peptides as angiogenesis inhibitors, and evaluated their mechanism of action and pharmacokinetics in animals.<sup>12</sup> An Investigational New Drug (“IND”) application for one of the cyclic RGD peptides, EMD121974, was filed with the FDA in 1998.<sup>13</sup>

In July 1996, Integra Lifesciences I, Ltd. (“Integra”), owner of several patents on RGD peptides, sued Merck for patent infringement.<sup>14</sup> Merck responded that its work with Scripps fell under the § 271(e)(1) safe harbor. At trial, the jury found Merck liable for patent infringement, and further that Merck had failed to show that its post-1995 activities were exempted by § 271(e)(1).<sup>15</sup> In a post-trial motion, the district court denied Merck’s motion for judgment as a matter of law, reasoning that there was sufficient evidence to support the jury’s finding on the § 271(e)(1) issue. Merck appealed.

A divided panel of the Federal Circuit affirmed the district court’s finding of liability.<sup>16</sup> The court held that the § 271(e)(1) safe harbor does not reach back down the chain of experimentation to embrace any exploratory research that may rationally be a predicate for future FDA clinical tests. Because the Scripps work was “not clinical testing to supply information to the FDA, but only general biomedical research to identify new pharmaceutical compounds,” the court found that the safe harbor does not apply. The court reasoned that the FDA had no interest in the “hunt” for drugs that may or may not later undergo clinical testing for FDA approval.<sup>17</sup> The court also reasoned that if the safe harbor exemption were expanded to include Merck’s activities, it would “effectively vitiate the exclusive rights of patentees owning biotechnology research tool patents.”<sup>18</sup>

### The Supreme Court’s Opinion

The Supreme Court granted certiorari on the issue of “whether uses of patented inventions in preclinical researches, 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>19</sup> In an unanimous opinion written by Justice Scalia, the Supreme Court vacated the decision by the Federal Circuit and ruled that § 271(e)(1) safe harbor extends to preclinical studies of patented compounds that are appropriate for submission to the FDA.

At the outset, the Court stated that the statute provides a wide berth for the use of patented drugs in activities related to the federal regulatory process. The Court found it apparent from the statutory text that the exemption extends to “all uses of patent inventions that are reasonably related to the development and submission of any information under the [Food, Drug, and Cosmetic Act].”<sup>20</sup> The Court indicated that there was simply no room in the statute for excluding certain information from the exemption on the basis of either the phase of research in which it is developed or the particular submission in which it could be included.

The Court rejected Integra’s argument that the only information that is of interest to the FDA at the IND submission stage is information pertaining to the safety of the drug in humans, finding that the FDA’s interest in information gathered at the preclinical stage is not so constrained. The Court reasoned that, although the regulation provides that the agency’s “primary objectives in reviewing an IND are . . . to assure the safety and rights to subjects,” the evaluation cannot be carried out in a vacuum, but rather requires comparison of the risks and benefits associated with the proposed clinical trials. This, according to the Court, would necessarily include a review of preclinical studies of a drug’s efficacy in achieving particular results.

The Court further rejected Integra’s argument that § 271(e)(1) should not apply because the experiments in question were not conducted in conformity with the FDA’s “good laboratory practice” regulations. The Court reasoned that the good laboratory practice regulations apply only to experiments on drugs to determine their safety, not to preclinical studies on a drug’s efficacy, mechanism of action, pharmacology, or pharmacokinetics. The Court further indicated that even noncompliant safety-related studies are submissible to the FDA, so long as the reason for noncompliance is provided.

The Court stated that it did not “quibble” with the Federal Circuit’s assertion that the § 271(e)(1) exemption “does not globally embrace all experiment activities that at some point, however attenuated, may lead to an FDA approval process.”<sup>21</sup> It added that basic research on a particular compound, performed without the intent to develop a particular drug or without a reasonable belief that the compound will cause the sort of physiological effect that the researcher intends to

induce, would not fall under the safe harbor. On the other hand, the Court held that the § 271(e)(1) safe harbor is not categorically inapplicable to either (1) experimentation on drugs that are not ultimately the subject of an FDA submission, or (2) use of patented compounds in experiments that are not ultimately submitted to the FDA. The Court reasoned that, in reality, even at late stages in the development of a new drug, scientific testing is a process for trial and error. Thus, to construe § 271(e)(1) as the Federal Circuit did is to effectively limit assurance of exemption to the activities necessary to seek approval of a generic drug, since this is the only situation where one can know at the outset that a particular compound will be the subject of an eventual application to the FDA. Similarly, the Court pointed out that it is not always clear to parties setting out to seek FDA approval exactly what kinds of information will be required in order to gain FDA approval.

The Court held that the term “reasonably related” in the statute should be broadly interpreted, and discussed how to determine whether use of a patented compound is reasonably related to the development and submission of information to the FDA:

Properly construed, § 271(e)(1) leaves adequate space for experimentation and failure on the road to regulatory approval: At least where a drug maker 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).<sup>22</sup>

The Court stated that the standard set forth in the jury instruction at the trial of this case was consistent with the Court’s construction of the statute, and remanded the case for a determination of sufficiency of the evidence supporting a jury’s finding of no § 271(e)(1) exemption.

In a footnote, the Court declined to address the issue of research tools. The Court stated that Integra had “never argued the RGD peptides were used at Scripps as research tools, and it is apparent from the record that they were not.”<sup>23</sup> Accordingly, the Court found it unnecessary to 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>24</sup>

### Interpreting § 271(e)(1) in the Post-Integra Era

The Supreme Court has clarified that the § 271(e)(1) safe harbor protection is not limited to research conducted in clinical trials, and may encompass preclinical studies. The Court further clarified that the preclinical studies that can be exempt under § 271(e)(1) may include both preclinical data pertaining to the safety of drugs in humans and studies related to a drug’s efficacy, mechanism of action, pharmacology, and pharmacokinetics. The fact that preclinical studies are not conducted under “good laboratory practices” set forth in the FDA’s regulations does not disqualify the activities from the safe harbor exemption. The Court also ruled that experimentation on drugs that are not ultimately the subject of an FDA submission, or use of patented compounds in experiments that are not ultimately submitted to the FDA, may be exempt under § 271(e)(1), as long as there is a reasonable basis to believe that the experiment will produce the type of information that is relevant to an FDA submission.

The Court acknowledged that, at some point, the relationship between the experimental activities and the FDA approval process may be too attenuated to warrant an exemption under § 271(e)(1). It has not, however, provided guidance as to how far upstream in the research development process § 271(e)(1) reaches. Notably, the Court stated that the jury instruction at trial, which adopted the “Intermedics test,” was “consistent” with its decision. Because most cases prior to Integra adopted the “Intermedics test,” it is likely that future courts encountering the § 271(e)(1) issue will continue to rely on cases prior to the Integra for guidance.

The Court explicitly declined to address the question of whether use of research tools can be protected by the § 271(e)(1) safe harbor. By its terms, § 271(e)(1) applies only to use of “a patented invention.” Various amicus briefs filed with the Court, including the Solicitor General’s brief, suggested that patented research tools do not fall within the scope of § 271(e)(1) because they are not “patented inventions” within the meaning of the statute. Notably, although the Court did not express an opinion on the meaning of “patented invention” in the statute, it focused primarily on the situation where the patented invention used by the alleged infringer is the actual or potential subject of FDA regulatory review. Thus, one could certainly argue that, after Integra, § 271(e)(1) remains inapplicable to the use of patented research tools, because most research tools are used as tools to study or develop other compounds for FDA regulatory review, rather than being the subject of FDA regulatory review themselves. This is consistent with the longstanding views of most in the scientific and legal community and with the Solicitor General’s suggestion in its amicus brief. Indeed, even Merck

acknowledged in its brief to the Court that “it is not at all clear that use of the research tool would be exempt.”<sup>25</sup>

## Conclusion

Section 271(e)(1), which is part of the 1984 Drug Price Competition and Patent Term Restoration Act, also known as the Hatch-Waxman Act, was originally designed to expedite FDA approval of generic versions of patented drugs by allowing generic drug manufacturers to perform developmental work and bioequivalency testing prior to patent expiration. Despite this narrow legislative intent, courts prior to *Integra* had broadly interpreted the statute. The Supreme Court in *Integra* confined its decision to correcting the Federal Circuit’s erroneously narrow interpretation of the safe harbor. It has not delineated the contours of the safe harbor. It thus remains to be seen how future courts will define the reach of § 271(e)(1) following *Integra*.

## Reference:

1. 2005 U.S. LEXIS 4840 (U.S. June 13, 2005).
2. U.S. 661 (1990).
3. The FDA classifies medical devices into three categories (classes I, II, and III) based on the risk posed by their uses. Class III medical devices pose the highest risk and are subject to the most rigorous premarketing approval requirements. Class I and class II medical devices involve less risk and are subjected only to expedited approval process.
4. *Abtox, Inc. v. Exitron Corp.*, 122 F.3d 1019 (Fed. Cir. 1997).
5. *Bristol-Myers Squibb v. Rohne-Poulenc Rorer, Inc.*, 2001 U.S. Dist. LEXIS 19361 (S.D.N.Y. Nov. 27, 2001).
6. *Infigen, Inc. v. Advanced Cell Technology, Inc.*, 65 F.Supp. 2d 967 (W.D. Wis. 1999).
7. See, e.g., *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 231 U.S.P.Q. (BNA) 978 (N.D. Cal. 1986); *American Standard v. Pfizer*, 722 F. Supp. 86 (D. Del. 1989).
8. See, e.g., *Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269 (N.D. Cal. 1991); *Teletronics Pacing Systems, Inc. v. Ventritex, Inc.*, 982 F.2d 1520 (Fed. Cir. 1992); *Wesley Jessen Corp. v. Bausch & Lomb, Inc.*, 235 F. Supp. 2d 370 (D. Del. 2002).
9. *Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269 (N.D. Cal. 1991).
10. *Abtox, Inc. v. Exitron Corp.*, 122 F.3d 1019 (Fed. Cir. 1997); *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 3 F.Supp. 2d 104 (D. Mass. 1998).
11. *Integra Lifesciences I, Ltd. v. Merck KGaA*, 2003 U.S. App. LEXIS 27796, at \*5 (Fed. Cir. June 6, 2003).
12. These activities include, for example, receptor binding assays to investigate the efficacy and specificity of structure

change; angiogenesis/chick CAM assays for inhibition of blood vessel formation in chick embryo when vessel growth is artificially induced; angio-matrigel experiments to investigate inhibition of artificially induced vascularization in mice; cell adhesion assays by spectrophotometric measurement of inhibition of cell attachment to protein; chemotaxis studies to study the effect of various peptides on cell migration over extracellular matrix fibers; use of chick embryos; fluorescent-activated cell sorting to study the effect on the receptor-ligand binding reaction; vascularization of the retina and induced arthritis of the joints, studies with mice and rabbits; chi CAM assays to study angiogenesis associated with tumor transplantation and growth in chick embryos; and tumor growth in SCID-mice or nude mice.

13. The IND submission was excluded from evidence at trial.
14. *Integra* unsuccessfully sought to license the patents to Merck prior to the lawsuit.
15. The district court held, with one exception, that Merck’s pre-1995 activities were protected by the common law research exemption. That holding was not challenged.
16. 2003 U.S. App. LEXIS 27796.
17. *Id.* at \*15. The Federal Circuit relied heavily on the legislative history of the statute, which shows Congressional intent to facilitate immediate entry of generic drugs into the market place. Several months later, however, the court issued an errata order, clarifying that it did not rule that the safe harbor was limited to activities related to the approval of generic drugs.
18. *Id.* at \*18.
19. 2005 U.S. LEXIS 4840, at \*4.
20. *Id.* at 15 (originally emphasized).
21. *Id.* at \*22-23.
22. *Id.* at \*25.
23. *Id.* at \*22, n7. Actually, over the same period, Scripps also used the RGD peptide as a positive control during studies of some organic mimetics designed to block integrin in a manner similar to the RGD peptides.
24. *Id.*
25. Brief of Merck, at 41-42.

## Translational research in the development of modern medicine

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## Introduction

The total US healthcare spending in 2004 reached \$1.8 trillion, representing 15% of the GDP. It is expected to increase to about \$3.6 trillion by 2014. Although the medical expense skyrocketed, the rate of cancer-related mortality has not changed significantly since the 1980s. The diseases that impact US healthcare spending most are chronic. More than half of the medical expense has been spent on the treatment of chronic diseases such as cancer. Standard clinical endpoints such as survival, illness-free survival and/or symptom-free interval may take decades to be assessed. This review article will address the possible resolutions through the implement of translational research in academia institutes and biopharmaceutical industry. The goal of translational research is productive testing and validation of new therapeutic modalities or diagnostic and prognostic markers<sup>(1)</sup>.

## History and current status

### *Traditional uni-directional medicine R&D*

Traditionally, the pharmaceutical R&D and clinical organizations tend to work in silos. The discovery scientists discovered and refined chemical structures to create drug-like molecules, tested them in cellular and animal models, and then passed them along to the clinical organization for testing in humans. Once the compound was thrown over the fence, there was very little interaction between R&D scientists and clinicians. The flow of information remained strictly uni-directional.

### *NCI’s developmental therapeutic program*

The concept of translational research was first mentioned at NCI’s Rapid Access to Intervention Development (RAID) program. It is designed to assist translation to the clinic of novel anticancer therapeutic interventions, either synthetic, natural product, or biologic, arising in the academic community. Applications to RAID are brief with 20 pages or less in length, and should clearly outline the resources required to ready the proposed therapeutic agent for clinical trials<sup>(2)</sup>.

### *NIH RAID Pilot program (Rapid Access to Interventional Development)*

In 2004, the National Institutes of Health (NIH) established a pilot program called the NIH-RAID Pilot (Rapid Access to Interventional Development), similar to the National Cancer Institute’s (NCI) RAID program, to make available, on a competitive basis, certain critical resources needed for the development of new small molecule therapeutic agents. This program, part of the translational research component of re-engineering the clinical research enterprise, will use resources of NCI’s Developmental Therapeutics Program. In the program’s pilot phase, animal efficacy studies, and synthesis of recombinant proteins, monoclonal antibodies or reagents for gene therapy will not be supported.

The main goal of the Roadmap is to identify major opportunities and gaps in