Patented Compounds Reasonably Related to Process of Developing Information for Submission to FDA are Exempt From Patent Infringement—*Integra Life Sciences v. Merck*, 496 F.3d 1334 (Fed. Cir. 2007).

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The development of pharmaceutical drugs is a rapidly growing industry. The government has consistently been involved in pharmaceutical research, development, and manufacturing and patenting. The Food and Drug Administration (FDA) regulates the industry and ensures the best scientific development for production in United States' drug companies. In *Integra Life Science v. Merck*, the Federal Circuit Court of Appeals implements the Supreme Court's statutory interpretation of the FDA's safe harbor provision and considers when research may amount to patent infringement. The Court held that experiments must be reasonably related to research that, if successful, could be submitted to the FDA for continued research and clinical trials in order to avoid patent infringement.

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1 * See Christian Howlett, Congressional Budget Office, *Research and Development in the Pharmaceutical Industry*, (Oct.2006), available at http://www.cbo.gov/ftpdocs/76xx/doc7615/10-02-DrugR-D.pdf. The research and development of drugs is an all consuming process that costs millions of dollars. Id. The research and development of drugs is an all consuming process that costs millions of dollars. Id. Since 1990 total spending on health related drugs and research has tripled. Id.

2 Id. The Federal government spent over $25 billion on research and development of health related drugs in 2005. Id. Federal spending helps encourage companies to do the right research to develop the best life sustaining and life saving drugs. See Howlett, supra note 1.

3 See The Food and Drug Administration: About the Food and Drug Administration, at http://www.fda.gov/opacom/hpview.html (last visited February 2, 2008). The FDA is responsible for protecting public health and safety and therefore has high standard of scientific research. Id.

4 496 F.3d 1334, 1336 (Fed. Cir. 2007).

5 Id. The court on remand implements the Supreme Court's rules and holding and finds that there was no infringement because Merck's use fell under the statutory exemption. Id.
infringement.\footnote{Id. at 1348. The Court construed this exception so that research must be reasonably related but considers that the very nature of the industry is one where experiments must fail before they are successful. \textit{Id}.}

The litigation commenced when Integra Life Sciences (Integra), the plaintiff in this suit, claimed that the defendants infringed on several patents.\footnote{Integra Life Sciences, 496 F.3d at 1336. The five patents in the suit relate to peptides that contain the RGD sequence of amino acids. \textit{Id}. These inventions can demonstrate cell interactions such as cell blocking, cell attachment and disrupting cell attachment. \textit{Id}.} The defendants, Merck and Scripps Research Institute (Scripps), collaborated research efforts with Dr. David Cheresh on the inhibition of angiogenesis.\footnote{Id. Scripps is a non-profit, public benefit corporation which employs Cheresh as a tenured professor at the Immunology Department. Integra Life Sciences v. Merck, 50 U.S.P.Q.2d 1846 (S.D. Cal. 1999). Cheresh’s research is extremely advanced in the fields of proteins and cell membranes and allegedly discovered that growth of new blood cells can be inhibited. \textit{Id}. Angiogenesis is the formation and differentiation of blood vessels. See Miriam Webster Online Dictionary Medline Plus: Angiogenesis, at http://www2.merriam-webster.com/cgi-bin/mwmmednlm?book=Medical&va=angiogenesis (last visited Jan. 31, 2008). The development of these blood vessels is a critical factor in several diseases such as cancer, diabetes and arthritis. \textit{Integra}, 496 F.3d at 1336. Dr. Cheresh discovered that angiogenesis is affected by blocking cell surface receptors and depriving them of blood. \textit{Id}. In 1994, Merck provided Cheresh with a peptide that was effective in inhibiting angiogenesis. \textit{Id}.}

In 1988, Merck agreed to support Cheresh with funding for his research and, in return, Scripps granted Merck an option to license future inventions stemming from his research.\footnote{Id. at 1336. The companies hoped to conduct medical testing on human subjects within three years. \textit{Integra}, 496 F.3d at 1336.} Then, in 1995, a new agreement allowed Merck to increase Cheresh’s funding.\footnote{Id. Federal law requires a drug to be approved before it can be shipped within the United States. \textit{See U.S. Federal Drug Administration: Drug Applications, at http://www.fda.gov/cder/regulatory/applications/ind_page_1.htm#Introduction (last visited Jan. 31, 2008). Usually, experimenters will want to have a drug tested in a few states which requires it be shipped within the United States. \textit{Id}. In order for this to happen, the FDA must grant a legal exemption for the drug to be shipped beyond the state’s borders. \textit{Id}. The FDA grants this exemption through the IND allowing the drug to be tested in several different states. \textit{Id}. The preclinical development determines of the product is reasonably safe for initial use in humans and if the drug warrants commercial development. \textit{See U.S. Federal Drug Administration: Drug Applications, http://www.fda.gov/cder/regulatory/applications/ind_page_1.htm#Introduction (last visited January 31, 2008). If the drug satisfies these elements, then the experimenters must}

The clinical trials conducted by Cherish require the approval from the FDA, which can be obtained through an Investigational New Drug Application (IND).\footnote{Id. at 1336. The development of these blood vessels is a critical factor in several diseases such as cancer, diabetes and arthritis. \textit{Integra}, 496 F.3d at 1336. Dr. Cheresh discovered that angiogenesis is affected by blocking cell surface receptors and depriving them of blood. \textit{Id}. In 1994, Merck provided Cheresh with a peptide that was effective in inhibiting angiogenesis. \textit{Id}.}
Along with Merck, Cheresh and other individuals at Scripps conducted the experiments that are charged with infringement. In October 1998, the National Cancer Institute sponsored clinical trials of the peptide Merck and Scripps had chosen.

In 1996, Integra filed suit against Merck, Scripps, and Cheresh for patent infringement. In their defense, Merck claimed that this early scientific research was not patent infringement because of the common law research exemption. Merck’s second defense was that the studies were conducted in furtherance of drug development and future clinical trials that are exempt from infringement under the FDA Safe Harbor Exemption.

show that the drug will not expose people to unreasonable risk even when used in early clinical trials. There are three different IND types: Investor IND, Emergency IND and Treatment IND. In Investigator IND, a physician conducts the experiments and submits the drug to the IND process to study an unapproved drug or consider an already approved drug for a new use or use on a new and different patient population. In an Emergency IND, the FDA authorizes the use of an experimental drug if there is not enough time to submit to a regular IND. See U.S. Federal Drug Administration: Drug Applications, at http://www.fda.gov/cder/regulatory/applications/ind_page_1.htm#Introduction (last visited Jan. 31, 2008). Treatment IND allows experimental drugs to receive clinical testing for immediately life threatening conditions.

Integra, 496 F.3d at 1336. They conducted various experiments using peptides and concluded peptide EMD121974 had the best properties for future development. Id.

Id.; see also National Cancer Institute: Angiogenesis Inhibitors in Clinical Trials, at http://www.cancer.gov/clinicaltrials/developments/anti-angio-table (last visited Jan. 31, 2008). The National Cancer Institute’s highest priority is cancer research and treatment. Id. Their goal is to provide patients of all financial means the best treatment possible. Id.; see also National Cancer Institute: The Nation’s Investment at http://plan.cancer.gov/ (last visited Mar. 20, 2008).


This issue was not before the jury at the district court level and therefore all subsequent judgments do not determine the validity of this issue. Integra Life Science v. Merck, 331 F.3d 860 (Cal. 2003). On appeal, Merck did not claim that the common law exception should even apply to any of the patents considered by the jury. Id.

Integra, 496 F.3d at 1336. Merck claims that under the FDA’s safe harbor provision, 35 U.S.C. §271(e)(1), their research is exempt and does not infringe in Integra’s patent. Id. 35 U.S.C. §271(e)(1) defines the safe harbor provision against patent infringement as:

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 (other than a new animal drug or veterinary biological product (as those terms are used in the Federal Food, Drug and Cosmetic Act and the Act of March 4, 1913) which is primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology or other processes involving site specific genetic manipulation techniques) 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 or veterinary biological
The trial court found that Merck had infringed upon several of the patents being held by the plaintiffs and further held that the defendants were not protected by the safe harbor exemption.\textsuperscript{17} Merck filed a timely appeal; however, the Court of Appeals affirmed, holding that Scripps's work was not clinical testing for purposes of providing information to the FDA but rather was general research to consider new pharmaceutical options and compounds.\textsuperscript{18}

The issue was then taken to the Supreme Court.\textsuperscript{19} The Supreme Court held that the use of all patented compounds reasonably related to the process of developing information for submission to the FDA is exempt from infringement.\textsuperscript{20}

The Supreme Court remanded the case to the Court of Appeals to determine the statutory interpretation and law in this case.\textsuperscript{21} On remand, the court reversed the rulings of the District Court and of the Court of Appeals and held there was not enough evidence to sustain the jury verdict and judgment.\textsuperscript{22} The Court held the challenged experiments met the 'reasonably related' criteria and that, if the research was in fact successful, it would be included in the IND submission to the FDA.\textsuperscript{23}
Pharmaceutical patent infringement litigation is a growing field and the issues litigated before the courts represent the conflict between advancing and encouraging research and development (R&D) and preserving the rights of the patent owner—the original designer and developer. Pharmaceutical patent infringement occurs when "whoever without authority makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent. . . ." Under federal law, drug makers are obliged to submit research data to the FDA at two different stages. The first stage requires drug companies and manufacturers to receive authorization from the FDA to conduct clinical trials on humans through an IND application. The IND application must explain the preclinical testing, including animal testing, and must justify the proposed clinical testing and experimentation. The second stage requires companies to submit a New Drug Application (NDA) to market a new drug, which requires full reports and disclosure of the testing to show whether the drug is safe and effective in use. Only the first stage

26 Merck, 545 U.S. at 196. 21 U.S.C. §301 allows the Federal Food, Drug and Cosmetic Act (FDCA) which was enacted by federal law to regulate the manufacture, use or sale of drugs. Id. The act was passed in response to a pediatric drug in Tennessee that failed and ultimately lead to the death of over 100 people. U.S. Food and Drug Administration: The 1938 Food, Drug and Cosmetic Act, at http://www.fda.gov/oc/history/historyoffda/section2.html (last visited Feb. 15, 2008). The terrible tragedy created a surge of public outcry and forced the bill through Congress and Franklin Roosevelt signed the bill into law in 1938. Id. The FDA now had control over cosmetics and medical devices. Id. Drugs had to be labeled with directions for safe use and all drugs were required to receive pre-market approval. Id. Manufacturers were required to prove to the FDA that the drugs were safe before being put on the open market. U.S. Food and Drug Administration: The 1938 Food, Drug and Cosmetic Act, at http://www.fda.gov/oc/history/historyoffda/section2.html (last visited Feb. 15, 2008).
28 Merck, 545 U.S. at 196; see also 21 U.S.C §355(g)(1)(a). The IND application must contain all of the necessary information from the preclinical testing. Merck, 545 U.S. at 196.
29 Merck, 545 U.S. at 196; see also U.S. Federal Drug Administration: New Drug Application (NDA) Process, at http://www.fda.gov/cder/regulatory/applications/nda.htm#Introduction (last visited Feb. 15, 2008). The NDA is the way drug companies get approval to market and sell drugs in the US. Id. The NDA allows the FDA to consider whether the drug is safe and effective, if the benefits outweigh the risks, if the labeling is appropriate, and whether the manufacturing methods maintain the drugs purity, identity, strength and quality. Id. Drug companies that want to market a generic drug must file an Abbreviated New Drug Application
of FDA approval is at issue in this case.\textsuperscript{30}

In 1984, Congress enacted an exemption to the patent rule which, as amended, became 35 U.S.C. §271(e)(1).\textsuperscript{31} The exemption relates to all uses of the already patented invention that reasonably relate to the development and submission of any information under the FDCA.\textsuperscript{32} However, the statute does not require that the research be accepted by the FDA because the statute is not narrowly construed and leaves room for experimentation and, consequently, the failure of experiments.\textsuperscript{33}

The Court in \textit{Integra Life Sciences v. Merck} applied the Supreme Court’s reasoning and determined that the defendants did not infringe on the plaintiff’s patent when they used the patented compounds in its own research.\textsuperscript{34} The Court reasoned that Merck’s experiments and research, if successful, would be includable in a submission to the FDA for clinical testing; therefore, the statutory exemption is satisfied.\textsuperscript{35}

Applying the Supreme Court’s reasoning, the court on remand held that Merck’s experiments and research could reasonably be included in an FDA submission (ANDA) but do not have to make an independent showing that the drug is safe. \textit{Merck}, 545 U.S. at 196.

\textsuperscript{30} See generally, \textit{Integra}, 496 F.3d at 1334.

\textsuperscript{31} \textit{Merck}, 545 U.S. at 195. Congress passed the Drug Price Competition and Patent Term Restoration Act ("DPCPTR") in 1984 which was enacted in response to growing concern over R&D advancement and the necessity for a certain level of designer protection. Pub. L. No. 98-417, Title II, 98 Stat. 1585 (1984); see also 180 A.L.R. Fed. 487. These sections were codified as 21 U.S.C. §355 and 35 U.S.C. §271(e)(1994). \textit{Id.} The relevant statute, 35 U.S.C. 271(e)(1) was designed to allow aspects of patented drugs to be used if they reasonably relate to the submission of information to the FDA. Harvard Law School, Mapping the Contours of The Experimental Use Exemption: 35 U.S.C. x 271(e)(1)’s Past, Present, and Future, 3, available at http://leda.law.harvard.edu/leda/data/234/Concannon__Sarah_paper_00.pdf (last visited Mar. 31, 2008). This aspect of the statute is an exemption and creates a safe harbor provision which allows experimentation if it is reasonably related to research that may be submitted to the FDA. \textit{Id.}

\textsuperscript{32} \textit{Merck}, 545 U.S. at 202.

\textsuperscript{33} \textit{Id.} at 207. The Court has acknowledged that the exemption is not narrowly construed and “allows all uses of patented compounds ‘reasonably related’ to the process of developing information for submission under \textit{any} federal law regulating the manufacture, use or distribution of drugs.” \textit{Id.} at 206-07. The court holds the exemption allows for experimentation to fail and as long as the company has a reasonable basis for believing the use of the patented compound will work, they are within the statutory exemption. \textit{Id.} at 207.

\textsuperscript{34} 496 F.3d 1334 (Fed. Cir. 2007); see also \textit{Merck}, 545 U.S. at 207 (holding exemption broad enough to include all use of patented compounds if reasonably related to developing information for submission to FDA).

\textsuperscript{35} \textit{Integra}, 496 F.3d at 1348.
and the fact that the experiments were not successful did not per se lead to a violation of the statute by the defendants. The statutory exemption, which allows drug makers to use patents if they are reasonably related to research to be submitted to the FDA, does not mandate that all experiments and research be successful to the point of submission. Further, the statute recognizes that research must often fail before it can succeed; this recognition is the impetus behind the exemption. Specifically, the purpose is to promote the advancement of life saving drugs through research and experimentation subject to the approval of the FDA. Experiments are necessary during all stages of research and investigation and are necessary for medical advancement and innovation.

The Court in this case diligently followed the reasoning and analysis set out by the Supreme Court. The Court explained that the information does not need actual submission to the FDA in order to be exempt from patent liability because with scientific experimentation there are always uncertainties and failures. The Court seems to give credence to the very nature of the industry: in order to have human advancement and scientific success, the pharmaceutical industry must have leeway to build upon the success of others within the industry.

The Courts' efforts to promote scientific advancement are evident throughout the Supreme Court's decision and the remanded decision in the Court of Appeals. It is evident that on policy grounds the Court is promoting scientific advancement and construing and interpreting the statute to allow for medical and scientific advancement and innovation.

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36 Id. at 1339.
37 Id. The Court acknowledges that the nature of the research industry mandates that some experiments will fail before they can ultimately succeed. Id. Not every experiment becomes patentable material. Integra, 496 F.3d at 1348.
38 Id.
39 Id., 496 F.3d at 1348.
40 See id. (stating Court recognizes legislative purpose of encouraging development of new drugs).
41 See Merck, 545 U.S. at 202. The Supreme Court explained all that is required for the statutory exemption is that the used compound be reasonably related to information which could be submitted to the FDA. Id.
42 Merck, 545 U.S. at 206. Additionally, the Court has held that just because that aspect is left out of the FDA submission does not mean there was patent infringement. Id.
43 See Merck, 545 U.S. at 206.
44 See Integra, 496 F.3d at 1348. The Court of Appeals on remand applied the Supreme Courts reasoning and concluded that Merck's use of the compound was reasonably related to information that could be submitted to the FDA. Id. By allowing the use of such compounds, the Court is essentially promoting scientific advancement and the furtherance of medical advancements and technology. Id.
advancement. By allowing the exemption to apply to any information that could reasonably be included in an FDA submission of research findings even when the research utilizes the patented materials, the Court is allowing companies to use compounds and determine the necessity for submission based on scientific extermination without violating or infringing on patents.

Of note, the Supreme Court did not mention the impact this patent exemption may have on researchers who want to have their materials and experiments protected by patents. For example, this exemption may deter researchers from conducting life-saving experiments for fear that their hard work would be wasted because it would no longer be protected by patent law. Furthermore, drug companies may have a difficult time finding financial backing for drug experiments that will not survive patent protection. The Court may have considered these consequences when making its decision, but nonetheless decided that the health benefits of using patents with FDA submissions outweighed the industrial impact.

The Court of Appeals for the Federal Circuit applied the Supreme Court's reasoning and determined if Merck's use of Integra's patented compounds constituted patent infringement, or if Merck's use was within the statutory exemption because it was reasonably related to information, that could possibly be submitted to the FDA for approval in clinical trials. The Court concluded that Merck's use of the compounds did not constitute patent infringement because the information could have been

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45 Id. The Court appeared to place an emphasis on the promotion of life saving drugs and avoided hindering medical advancement through patent law. See Integra, 496 F.3d at 1348.
46 See id. This allows companies to confidently use many variations of compounds without patent infringement. Id.
47 See Merck, 545 U.S. at 206-08. The Court did not acknowledge the impact this will have on a researcher's motivation to conduct experiments that may later be infringed upon. Id.
48 See Merck, 545 U.S. at 206-08. A researcher may not feel inclined to conduct experiments and create life saving drugs if their work is not going to be protected by patent law. See id.
49 See generally, Merck, 545 U.S. 195. The drug companies may feel discouraged and may decide to limit their research on patents that will satisfy the exemption. Id. The Supreme Court may have left out this information because they wanted to speculate how the exemption will impact the drug market and healthcare in the United States before creating new law about the impact of the exemption. Id.
50 See Merck, 545 U.S. at 206-08. It is likely that the life saving consequences of the exemption outweigh the financial impacts on large drug companies. Id. Although this balance was not expressly explained in the court's decision, it is a reasonable inference because of the competing interests at play within this case, namely the advancement of medical technology against the need for patent protection. See id.
51 Integra, 496 F.3d at 1347.
submitted to the FDA for approval.\textsuperscript{52} Furthermore, the Court explained that the nature of the exemption affords companies the inevitability of failure and the possibility that the information would not be submitted.\textsuperscript{53}

\textsuperscript{52} Id. at 1348.

\textsuperscript{53} See Merck, 545 U.S. at 202 (stating the Court has acknowledged that experiments failure of experiments before success is inevitable).