Merck v. Integra: Safe Harbor in Uncharted Waters?

On June 13, 2005, the Supreme Court of the United States decided Merck KGaA (“Merck”) v. Integra Lifesciences I, Ltd. (“Integra”), 545 U.S. ___ (2005). The central issue in the case concerned the safe harbor provision in 35 U.S.C. § 271(e)(1). This section creates a “safe harbor” that allows the generic companies to conduct research on patented drugs in advance of patent expiration so long as the experiments are “reasonably related” to securing regulatory approval. Without § 271(e)(1), a patent holder would get a de facto patent term extension because the generic companies could not start the testing required for the FDA approval until the patent expired, thus giving the patent holder an extension of the patent monopoly.

Section 271(e)(1) provides, in pertinent part, that “it shall not be an act of infringement to make, use, or sell 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 crux of the Merck case involved the term “reasonably related.” Specifically, the issue was how far back in the drug development process the competitor can perform otherwise-infringing experiments without incurring liability for patent infringement.1

Integra owns a series of patents related to particular peptides (“RGD peptides”), which bind certain cell surface receptors with high affinity. Working independently of Integra, a scientist at the Scripps Research Institute (“Scripps”) discovered that one of the cellular processes that the same surface receptor controls is the blood vessel growth. In theory, blocking such a receptor could halt tumor growth by depriving the tumor of the blood supply needed to grow. The Scripps researcher found that some RGD peptides could be used to effectively block the cell receptor. Therefore, these peptides were potentially valuable for the inhibition of solid tumor growth, with potential applications to cancer and many other diseases.

Recognizing the importance of Scripps’ discovery, Merck entered into an agreement with Scripps to identify possible drug candidates. The agreement set forth a 3-year timetable in which in vivo and in vitro testing of RGD peptides would occur in year one, culminating with the submission of an investigational new drug (“IND”) application to FDA in year three. Several RGD peptides were identified as potential candidates. In vivo and in vitro experiments were performed to assess their specificity, efficacy, and toxicity. Eventually, this research led to the discovery of a promising cancer drug, RGD Peptide 121974.

Integra offered Merck a license to the RGD peptide patents. After a lengthy negotiation, Merck declined. Subsequently, Integra sued Merck and Scripps for patent infringement. Among other defenses, Merck contended that the experiments in question were protected under the safe harbor provision in § 271(e)(1).

Following a jury trial in 1999, the United States District Court for the Southern District of California held that Merck infringed Integra’s patents and that § 271(e)(1) did not exempt Merck from infringing the RGD peptide patents. Merck appealed to the United States Court of Appeals for the Federal Circuit asserting, among other things, error in the District Court’s interpretation of § 271(e)(1).

In 2003, the Federal Circuit concurred with the District Court’s interpretation and affirmed the § 271(e)(1) aspect of the decision. The Federal Circuit held that the express objective of § 271(e)(1) is to facilitate the entry of safe and effective generic drugs into the market immediately upon patent expiration. The Federal Circuit’s position was that it is not in the interest of FDA to hunt for drugs that may or may not undergo clinical testing for regulatory approval. The Federal Circuit viewed Merck’s early work as “only general biomedical research,” particularly the development of a number of lead candidates simultaneously, only one of which was ultimately selected. Thus, it stated that Merck’s activities were not “reasonably related” to generating data for regulatory approval, and were not exempt from infringement liability.

The Federal Circuit did not provide any bright-line rule as to when exactly the safe harbor provision applies. It noted that the provision does not cover all stages of the drug development simply because some of the drugs will need regulatory approval some day. The best guidance provided by the Federal Circuit is that the provision does not cover exploratory research that may rationally form only a predicate for future clinical testing, which seems to
suggest at a minimum drawing a line at the commencement of clinical trials. Thus, many commentators view the Federal Circuit’s position as excluding work done for preclinical trials.

Merck subsequently petitioned the Supreme Court for certiorari. Merck argued that the safe harbor provision in § 271(e)(1) covers preclinical in vivo and in vitro studies, which encompass a wide range of animal and test-tube research that is submitted to FDA in connection with both an IND filing and the ultimate new drug application (“NDA”) filing. It also contended that the Federal Circuit erred in narrowly interpreting the provision, and stated that the undisputed evidence confirmed that the accused experiments were directed at producing data “reasonably related” to an IND application.

Integra’s brief addressed only procedural matters, and was virtually silent with respect to the interpretation of and protection under § 271(e)(1). Integra argued that the District Court’s jury instruction applied the correct legal standard, and that legally sufficient evidence supported the verdict that Merck failed to carry its burden of proof under the FDA exemption.

Close to twenty amicus briefs were filed in connection with the Merck case. Merck’s position was supported by the United States Government (the Attorney General’s and Solicitor General’s offices), the AARP, several pharmaceutical companies such as Eli Lilly, Wyeth, and Pfizer, and several biologics companies such as Genentech and Biogen. Integra’s case was supported by Applera, Isis, Invitrogen, Vaccinex, and WARP, all of which were concerned with the effect of the holding on “research tool” patents.

Of particular interest is the amicus brief for the United States. The United States government argued that the FDA exemption protects all activities that are undertaken in the course of attempting to develop a particular drug and are “reasonably related” to the development of the types of information that would be relevant to an IND or NDA. Specifically, it contended that such exemption is not limited to clinical research, and that the exemption applies when a researcher progresses beyond basic research and begins efforts to develop a particular drug.

In its unanimous decision, the Court sided with Merck, setting aside the Federal Circuit’s holding and remanding the case for further proceedings. Citing its previous decision in Eli Lilly, the Court made it clear from the outset that based on the statutory text, “§ 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,” (emphasis in original) and that “[t]his necessarily includes preclinical studies of patented compounds that are appropriate for submission to the FDA in the regulatory process.” It rejected the suggestion from the Federal Circuit’s opinion that § 271(e)(1) is “limited to research conducted in clinical trials.” (emphasis in original). The Court held that § 271(e)(1) applies to preclinical in vitro and in vivo studies intended to obtain information on the pharmacological, toxicological, pharmacokinetic, and biological qualities of the drug in animals. Citing the amicus brief for the United States, the Court concurred with the government that such use is protected under § 271(e)(1) so long as the drugmaker reasonably believes that the experiments will produce information relevant to an IND or NDA submission.

What does this holding mean? In its discussion, the Court broadly interpreted the § 271(e)(1) safe harbor provision with a narrow focus on the use of “patented compounds.” Is a “patented compound” one that could be the subject of an FDA application, or is it broader than that? The only conceivable scenario suggested by the Court where § 271(e)(1) does not apply is where the basic research is being performed without the intent to develop a drug or without a “reasonable belief” that the compound would cause the sort of physiological effect intended. By not providing any guidance on what
constitutes a “reasonable belief” or what “patented compounds” encompass, the Court seemingly allows the drug companies tremendous leeway and flexibility to start investigating new therapies with “patented compounds.”

Another interesting issue is the focus of the opinion on “patented drugs” and “patented compounds.” “Method” patents are not discussed in the opinion, at least suggesting that method patents may not be subject to the “safe harbor” protection. This may give method claims an added value boost as part of a patent portfolio.

Finally, the Court left open application of the Merck case to “research tool” patents. “Research tools” are generally defined as devices, compounds, and methods that are used in drug development but are not themselves drugs. Examples could include devices such as protein synthesizers, cell surface receptors of disease pathways that will be used to identify antibodies or small molecule drugs, or particular methods of high throughput screening. Extending the “safe harbor” protection to these types of patents could effectively vitiate their value. The Court stated in the already famous “Footnote 7” that neither party argued that the RGD peptides were research tools, and thus “we therefore need not—and do not—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.” The Court also cited Judge Newman’s dissent in the Federal Circuit’s opinion, stating that “[u]se of an existing tool in one’s research is quite different from study of the tool itself.” Judge Newman’s general position was two-fold: first, that the common law research exemption should be expanded to cover the basic, exploratory research; and second, that § 271(e)(1) should not apply to “research tools,” drawing a distinction between “experimenting on a patented invention” and “experimenting with a patented invention.”

Interestingly, several commentators have already taken the position that the Court’s decision will have a negative impact on research tool patents. On the other hand, Invitrogen immediately declared that the Court’s ruling will not have a material effect on patented research tools. The fact that the Court did not settle this issue is troubling. On remand, the Federal Circuit is unlikely to address it. The uncertainty surrounding the applicability of § 271(e)(1) to “research tools” is likely to remain, at least until the Federal Circuit provides further guidance in a suitable case.

The Authors

Robin Silva
San Francisco
(415) 544-7010
silva@robinderby.com
A partner and patent biotech lawyer in the Intellectual Property group, Robin’s legal practice is centered on IP portfolio strategic development, management and counseling in domestic and international issues with an emphasis in emerging biotechnology companies.

Zheng Bao
San Francisco
(415) 781-1989
bao@zheng@dorsey.com
A summer associate in the Patent group, Zheng just completed his first year of law school at Duke University School of Law. Prior to law school, Zheng worked for eight years as a chemist. He is also a registered patent agent.

Trademark, Copyright & Brand Management Group

Elizabeth Buckingham, Minneapolis
612.343.2178
buckingham.elizabeth@dorsey.com

Patent Group

Lee Osman, Denver
303.629.3434
osman.lee@dorsey.com

IP Litigation Group

Peter Lancaster, Minneapolis
612.340.7811
lancaster.peter@dorsey.com

Tucker Trautman, Denver
303.629.3409
trautman.tucker@dorsey.com

For further information regarding our intellectual property law practice, please contact any group leader.

Dorsey & Whitney offices that offer intellectual property services

Denver
Des Moines
Hong Kong
London
Minneapolis
New York
Palo Alto
San Francisco
Seattle

To receive this newsletter by email or to change your address, please contact:

Toni Byard, Minneapolis
612.340.7824
byard.toni@dorsey.com

Visit us on the Internet at www.dorsey.com

INTELLECTUAL PROPERTY UPDATE | Volume 5, Number 2
Dorsey & Whitney is a full-service international law firm with core practices in the areas of intellectual property, corporate securities and finance, M&A, international law and complex litigation.

©2005 Dorsey & Whitney LLP. This newsletter is published for general information purposes only. Views herein are deemed of general interest and should not necessarily be attributed to Dorsey & Whitney LLP or its clients. This newsletter does not establish or continue an attorney-client relationship with Dorsey & Whitney LLP. The contents should not be construed as legal advice or opinion. If you have any questions, you are urged to contact a lawyer concerning your specific legal situation. For further information, please contact one of the lawyers listed on the previous page.

Dorsey & Whitney LLP
Suite 1500
50 South Sixth Street
Minneapolis, MN 55402-1498