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JUSTICES TO REVIEW PATENT SAFE HARBOR

Ruling could have big impact on drugs, biotech.



By Marcia Coyle

STAFF REPORTER

WASHINGTON—A different kind of “drug war” will play out this month in the U.S. Supreme Court in a potentially landmark patent challenge with huge implications for the role of the biomedical and biotechnology industries in the development of new drugs.

Drug manufacturing giants, such as Eli Lilly & Co., generic manufacturers, such as Eon Labs Inc., biotechnology companies and patent practitioners and scholars have chosen sides in *Merck KGAA v. Integra*

LifeSciences, No. 03-1237, which will be argued on April 20.

The *Merck* case basically asks the justices to determine how far down the chain of research and experimentation into new drugs does a federal safe harbor statute reach to protect drug manufacturers from liability for patent infringement.

Some lower courts have interpreted the exemption broadly, protecting many infringing acts, but the appellate court in the *Merck* case said the exemption did not reach early drug research and experimentation.

Merck, accused by *Integra* of violating its

patents on short amino acid sequences—so-called RGD peptides—in research involving tumor growth, lost at trial in which a jury subsequently imposed \$15 million in damages, and on appeal to the U.S. Court of Appeals for the Federal Circuit.

If the Federal Circuit’s view of the scope of the safe harbor statute prevails, *Merck* warns that potential treatments for “innumerable diseases and conditions” will be denied to patients for a decade or more after patents related to drug research expire.

The core of the safe harbor exemption is about being able to use patented inventions as a basis for newly developed drugs or

generics, said Merck's high court counsel, E. Joshua Rosenkranz, a shareholder in Heller Ehrman White & McAuliffe's New York office.

"Our view is Congress struck the balance and the balance is between the right of a patent holder to exploit its patent commercially and the rights of innovators simply to conduct the experiments necessary to get a head start on the very lengthy FDA approval process in a world where, if they have to sit on their hands until a patent expires, the patent holder gets a de facto extension of a decade or more," said Rosenkranz.

But drug companies seeking the federal safe harbor "have nothing to fear" from the jury verdict or Federal Circuit opinion, "properly understood," according to Integra LifeSciences Holdings Corp.'s court papers.

Merck's problems are of its own making, said Integra's high court counsel, Mauricio Flores, a partner in McDermott, Will & Emery's Irvine, Calif., office.

"I don't think Congress set out to solve the general problem—if there is a problem—of balancing patent rights against biomedical research," said Flores. "The policy of the [patent] law—a policy actually reflected in the Constitution—is it's important in all fields of endeavor to give people the incentive to disclose their discoveries, and that is just as applicable to biomedical research as it is to any field."

Infringing use?

The Merck case actually has its roots in the 1980s, when two scientists made discoveries concerning the mechanism by which cells attach and detach from proteins that form the extracellular matrix in the body.

As Integra explains in its brief, those scientists, in effect, discovered the key—the RGD sequence of three amino acids—to a lock—integrin cell surface proteins that act



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**—U.S. Court of Appeals
for the Federal Circuit**



as a receptor—that controls a wide range of cellular activity.

The RGD tri-peptides bind to the integrin molecules on a cell's surface. Because of that binding capacity, the RGD peptides can manipulate cell activities, affecting cell adhesion and blood vessel growth. Integra owns the patents on several RGD tri-peptides.

In 1994, David Cheresch of the Scripps Research Institute found that one of the cellular processes controlled by the integrin



E. JOSHUA ROSENKRANZ:
*Congress balanced inventors'
and patent holders' rights.*

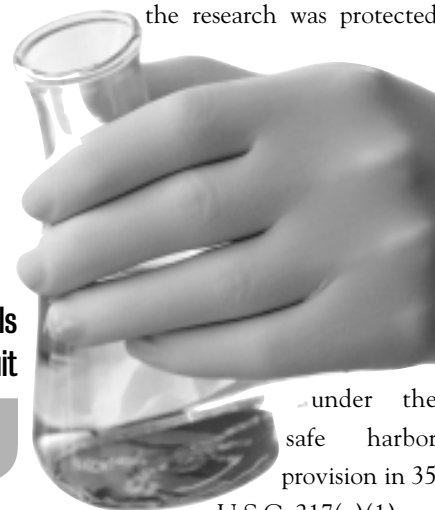
molecules is the growth of blood vessels. Blocking that integrin receptor, he demonstrated, inhibited tumor growth by depriving them of the blood supply they needed to enable them to grow.

He also found that some RGD peptides could block the integrin receptor and could be used as a drug therapy to inhibit the growth of solid tumors, with application to cancer and many other diseases. Merck began funding

Cheresch's research into the RGD peptides, and in the mid-1990s, they found a promising cancer drug, RGD peptide 121974.

Merck, according to Integra, refused

to obtain a license to the RGD peptides now owned by Integra. In 1996, Integra sued Merck, Scripps and Cheresch for patent infringement. Merck claimed that the research was protected



under the safe harbor provision in 35 U.S.C. 217(e)(1).

The safe harbor statute generally exempts from infringement those activities "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 products."

In its decision on Merck's appeal of its loss at trial, the Federal Circuit noted that Congress had two goals in enacting the safe harbor statute in 1984. Congress, it said, wanted to increase the patent term as compensation to the patent holder who had to undergo a protracted regulatory approval period before enjoying market exclusivity. And, the court said, Congress wanted to eliminate the de facto patent term extension that patent holders received because generic drug companies had to wait for patents to expire before they could conduct the otherwise infringing research needed to develop data for regulatory approval.

The 1984 act allowed generic drug manufacturers to do research and experimentation on patented drugs so that the generic drug could be marketed as soon as the relevant patents had expired.

The limitation in the safe harbor is that the infringing research must be "solely for purposes reasonably related to the

development and submission of information under Federal law." In *Merck*, the Food and Drug Administration (FDA) is the key agency.

The battle in the Supreme Court is over the meaning of "reasonably related."

The Federal Circuit essentially said that the safe harbor exemption would protect activities that would contribute relatively directly to information the FDA considers for drug approval—the standard used by the trial court in *Merck*. It does not protect all activity in the research and development chain, the court said, simply because it may lead to an FDA approval process.

The appellate panel said, "The FDA has no interest in the hunt for drugs that may or may not later undergo clinical testing for FDA approval." And, it added, "The safe harbor does not reach any exploratory research that may rationally form a predicate for future FDA clinical tests."

To read the exemption more broadly, the court said, would destroy patent rights held by a whole class of patentees owning biotechnology-tool patents. Biotechnology tools are a method or device that is very useful in the drug development process but does not encompass the actual final product.

The court held that Merck's activity was not exempt from infringement liability because it was preclinical research that did not supply information for submission to the FDA. Merck, the court said, simply had identified a drug candidate that would be subject to future clinical testing for FDA approval.

Testing reasonably related

In the high court, Merck argues that the safe harbor protects the critical stages of drug design and preclinical

experiments—which were done in this case—but not basic research or preliminary screening of structures never shown to affect the target. And all of the experiments at issue produced information the FDA considers in an investigational new drug application.



MAURICIO FLORES: *Integra's counsel says Merck's problems are its own making.*

"There's a gray area between basic research and drug development or preclinical research," said Heller Ehrman's Rosenkranz. "When you are in that gray area, it may well be a jury question. Our argument is we are well beyond that gray area. We are beyond that Eureka moment. We found the drug. Integra said Merck knew it was sitting on a gold mine.

"Merck had a drug candidate that shrank tumors in animal models," he added. "It had a known structure, a target, a disease, an effect on that disease, and it understood the mechanism by which the drug candidate affected disease."

The Bush administration is supporting Merck and has filed a brief saying the Federal Circuit erred in limiting the safe harbor to clinical research and excluding preclinical research.

"The exemption begins to apply once a researcher has progressed beyond basic research, developed a concept for a drug, and begun attempting to develop that drug," said the solicitor general.

Eli Lilly, supporting Merck, appears to go a step beyond the government's position in arguing that virtually every experiment is reasonably related to FDA approval.

Ruling itself at issue

What the Federal Circuit held is actually disputed by the parties. Integra contends the appellate court did not exclude preclinical research from the exemption, merely Merck's preclinical experiments.

"I think it's fair to say the solicitor

general's brief believes it is wrong to categorically exclude preclinical experiments from the scope of the exemption," said McDermott Will's Flores. "We don't think the solicitor general is correctly interpreting what the Federal Circuit did, but we do agree that preclinical experiments as a category are eligible for the exemption. We think the particular experiments at issue here do not satisfy the 'solely for uses reasonably related' standard."

Integra, which is backed in the high court by biotech tool makers and others, argues that Scripps focuses on investigation of fundamental disease processes, was not institutionally competent to meet FDA requirements, and generated preclinical data that had no bearing on the FDA approval process.

Integra charges that Merck "merely used the FDA exemption as a pretext to shield infringing research by Scripps."

The Federal Circuit, it contends, affirmed the district court's legal standard—a standard that Merck had proposed as a jury instruction—and there is no controversy before the justices.

Merck, said Flores, "has backed away" from its position when it petitioned for high court review. At that point, he said, the company argued that the safe harbor exemption encompasses all basic drug research that is a "rational predicate" to the development and submission of information to the FDA.

"The solicitor general does not endorse that theory," said Flores. "I think Merck now is trying to avoid an open conflict. I think Merck's brief is really focused on the general idea that it's bad policy to apply patents to biomedical research. That's the real thrust of Merck's argument."

A decision is expected by July.

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