Keywords: **Section 271(e)(1) exemption, preclinical research, reasonably related, common law research exemption.**

Summary: **Preclinical research that is not included in an FDA submission can be exempt from patent infringement under 35 U.S.C. § 271(e)(1) if the drug maker has a reasonable basis for believing that the research, if successful, would be appropriate to include in an FDA submission.**

Integra LifeSciences I Ltd. v. Merck KGaA
83 U.S.P.Q.2d 1673 (Fed. Cir. 2007)
Decided July 27, 2007

I. Facts

Integra LifeSciences sued Merck, the Scripps Research Institute, and Dr. David Cheresh for patent infringement in the Southern District of California. Integra owns five patents related to a tripeptide sequence known as the "RGD peptide." The RGD peptide "promotes cell adhesion by attaching to $\alpha_V\beta_3$ integrins, [which are] receptors commonly located on the outer surface of certain endothelial cells."

Beginning in 1988, Dr. Cheresh, a researcher with Scripps participating in a joint venture with Merck, began researching techniques to fight cancer and other diseases by blocking the formation of new blood vessels from existing vessels. In 1994, Dr. Cheresh succeeded in reversing tumor growth in chicken embryos using an RGD peptide provided by Merck. In November 1996, Merck initiated the formal FDA review process so that it could eventually begin human trials on one version of Dr. Cheresh's tumor fighting RGD peptide.

Earlier in 1996, however, Integra charged that Merck, Scripps, and Dr. Cheresh had willfully infringed their patents by using the RGD peptide in Dr. Cheresh's cancer treatment experiments. Merck, Scripps, and Dr. Cheresh responded that their actions did not infringe Integra's patents, and that even if they did, they were protected by the common law research exemption before 1995, and by 35 U.S.C. § 271(e)(1) from 1995 onward.

At the conclusion of the trial, the district court held that Merck's pre-1995 actions were protected by the common law research exemption but left the question regarding the Section 271(e)(1) exemption to the jury. The relevant jury instruction read in part that "[t]o prevail on this defense Merck must prove … that it would be objectively reasonable for a party in Merck's and Scripps' situation to believe that there was a decent prospect that the accused activities would contribute, relatively directly, to the generation of the kinds of information that are likely to be relevant in the process by which the FDA would decide whether to approve the product in question."

The jury found that Merck, Scripps, and Dr. Cheresh had infringed Integra's patents and awarded damages of $15 million. In response to post-trial motions, the district court dismissed Integra's suit against Dr. Cheresh and Scripps, but denied Merck's motion for a judgment as a matter of law ("JMOL") and affirmed the jury's damage award.

Merck appealed to the Court of Appeals for the Federal Circuit. The Federal Circuit affirmed the district court's denial of Merck's JMOL motion, holding that the experimentation "was not clinical testing to supply information to the FDA, but only general biomedical research." And, as

such, Dr. Cheresh's research was not *solely* for uses reasonably related to an FDA submission, as required by Section 271(e)(1).

Merck appealed to the Supreme Court, which granted certiorari to review the Court of Appeals' construction of Section 271(e)(1). In 2005, the Supreme Court held that the safe harbor created by 35 U.S.C. § 271(e)(1) "exempted from infringement all uses of patented compounds 'reasonably related' to the process of developing information for submission" to the FDA. The Supreme Court explained that "reasonably related" includes uses of the compound in research conducted after the biological mechanism and physiological effect of a candidate drug have been recognized, and that, if successful, would be appropriately included in a submission to the FDA.

The Supreme Court vacated the denial of Merck's JMOL motion and remanded the case back to the Federal Circuit to determine whether the evidence presented at trial was sufficient to support the jury's verdict in light of the new construction of Section 271(e)(1).

II. Issue

Were Merck's research activities reasonably related to the development of information that could be submitted to the FDA?

III. Discussion

Yes – The Federal Circuit focused on applying the Supreme Court's interpretation of 35 U.S.C. § 271(e)(1) to the facts presented by Merck and Integra. The Supreme Court held that Section 271(e)(1) exempts from infringement *all uses* that are "reasonably related" to the process of developing information for submission.

The Federal Circuit first examined 16 experimental categories that were undisputedly performed by Merck (and the co-defendants). These experiments were categorized by Merck as having to do with efficacy, mechanism of action, pharmacokinetics, pharmacology, and safety.

Integra reiterated, as it had before the Supreme Court to no avail, that more than half of the experiments performed by Merck had nothing to do with either human safety or efficacy and, thus, were not properly within the scope of the § 271(e)(1) exemption. However, since the Supreme Court had interpreted the statute to encompass experiments directed towards "efficacy, mechanism of action, pharmacology, or pharmacokinetics," which Integra conceded were the types of experiments at issue, this argument was not persuasive.

The key fact, according to the Federal Circuit, was that "all of the challenged experiments were performed after the discovery that a cyclic RGD peptide inhibited angiogenesis." This knowledge provides a bright line that distinguishes "research" or "discovery" (that may not fall within the exemption) from experiments directed towards "efficacy, mechanism of action, pharmacology, or pharmacokinetics" that do.

Finally, the parties and the majority agreed with the Supreme Court that this case did not involve "research tools" and, thus, did not provide an opportunity for the Federal Circuit to decide whether research tools fall within the scope of the § 271(e)(1) exemption.

IV. Dissent

Judge Rader's dissent was primarily directed towards the fact that the case did not address research tools and his opinion that the Federal Circuit was interpreting the Supreme Court decision far too broadly in excluding research tools from consideration. Judge Rader argued that claims from both the '237 and '734 patents should have been construed by the Federal Circuit in order to more properly determine whether or not these patents were directed to research tools. The Federal Circuit's decision, merely to apply the Supreme Court's Merck decision without explicating its application to the claims of each patent-in-suit or remanding for the District Court to make fact-finding determinations in view of the Supreme Court's interpretation of § 271(e)(1) could have the effect of weakening patent protection for research tools. According to Judge Rader, "universities and independent researchers will have to understand that their work on research tools is likely to amount only to a charitable (but nondeductible) gift to the pharmaceutical industry."