No. 03-1237

In the Supreme Court of the United States

MERCK KGAA,

Petitioner,

v.

INTEGRA LIFESCIENCES I, LTD., AND THE BURNHAM INSTITUTE,

Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

RESPONDENTS' BRIEF ON THE MERITS

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March 22, 2005

QUESTION PRESENTED

Whether the District Court properly instructed the jury that, to establish the affirmative defense to patent infringement set forth in 35 U.S.C. § 271(e)(1), Petitioner Merck had the burden "of proving 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 processes by which the FDA would decide whether to approve the product in question."

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INTRODUCTION

This case lies at the intersection of patent law and the drug approval process under the Federal Food, Drug, and Cosmetic Act ("FFDCA"), 21 U.S.C. § 301 *et seq.* At that intersection, patent holders have the right of way under the general rule that unauthorized uses of a patented invention constitute infringement. 35 U.S.C. § 271(a). Congress has provided, however, that where a drug manufacturer can prove that its otherwise infringing uses were "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," 35 U.S.C. § 271(e)(1) ("FDA Exemption"), such uses are exempt and patent holders must yield. Precisely because patent holders have the general right of way at this intersection, however, drug manufacturers must proceed with caution to establish their right to invoke the FDA Exemption and to avoid a collision with the rights of patent holders.

On this record, Petitioner Merck KGaA ("Merck") did not proceed with caution in the face of patent rights held by Respondents Integra Lifesciences I, Ltd. ("Integra"), and The Burnham Institute ("Burnham"). This case did not arise from a decision by Merck to perform experiments designed to satisfy FDA regulatory requirements—that work was done by Merck in Germany and is not the subject of this action. This case arose from Merck's reckless decision to hire The Scripps Research Institute ("Scripps") to embark on a basic research program to search for new drugs. The new drugs infringed pioneering patents owned by Burnham that were exclusively licensed to Integra, but Merck refused to take a license to use the inventions. Scripps, which focuses on the investigation of fundamental disease processes, was not institutionally competent to meet FDA requirements, and the preclinical data it generated had no bearing on the FDA's regulatory approval process. Merck merely used the FDA

Exemption as a pretext to shield infringing research by Scripps while performing the required FDA safety studies itself at its FDA-certified laboratories. Faced with these facts, and with Merck's witnesses discredited at trial, the jury not surprisingly concluded that Merck failed to carry its burden of proving that the infringing experiments were protected by the FDA Exemption.

In the Federal Circuit, Merck challenged the legal standard that it had proposed for the District Court's jury instruction, rather than contesting the sufficiency of the evidence under that standard. Merck argued that the FDA Exemption broadly encompasses all basic research that is a "rational predicate" to the development of data for the FDA.

Rebuffed by the Federal Circuit, Merck petitioned this Court for certiorari on the basis of the extreme legal standard it advanced in the Federal Circuit—that the FDA Exemption encompasses all basic drug research. Now that this Court has granted certiorari, Merck backpedals and disclaims the legal standard that it advanced in the Federal Circuit. Instead, Merck embraces the legal standard that it agreed to in the District Court, and vaguely seeks from this Court the sufficiency of the evidence review of the jury's verdict that it declined to seek from the Federal Circuit—even though Merck's merits brief never once uses the phrase "sufficiency of the evidence," and even though Merck's petition for certiorari never raised or even alluded to the sufficiency of the evidence supporting the jury's verdict.

Given that the parties agree that the District Court's jury instruction applied the correct legal standard, and given that Merck did not seek a sufficiency of the evidence review of the jury's verdict in its petition for certiorari, there is essentially no controversy for this Court to adjudicate. This Court should affirm the Federal Circuit's judgment affirming the

District Court's denial of Merck's renewed motion for judgment as a matter of law ("JMOL") on the FDA Exemption.

Pharmaceutical companies that seek a safe harbor under the FDA Exemption for preclinical work in their own laboratories in compliance with FDA regulations have nothing to fear from the jury verdict or the Federal Circuit opinion, properly understood. Merck's problems in this case are of its own making and are unique to it.

STATEMENT OF THE CASE

The FFDCA's Two-Stage Drug Approval Process

Because the issue in this case is whether Merck has carried its burden of proving that the Scripps experiments were "reasonably related" to the drug approval process, Integra begins with a review of that process. The FFDCA and its implementing regulations establish a two-stage regulatory approval process for new drugs in the United States. The first stage involves an "Investigational New Drug" ("IND") application; the second stage involves a "New Drug Application" ("NDA").

The Role of "Preclinical" and "Clinical" Data in the FDA Drug Approval Process

In the drug approval process, there are two types of drug testing: "preclinical" and "clinical." "Preclinical" testing means testing in test tubes or other artificial settings (*in vitro*) or in living animals. *See* FDA, *Pre-Clinical Research*, http://www.fda.gov/ cder/handbook/preclin.htm. "Clinical" tests or trials, on the other hand, means tests involving human beings. *See* 21 C.F.R. § 312.3(b).

The FDA distinguishes between the use of preclinical and clinical data in the drug approval process. As discussed

below, the FDA reviews preclinical data that has been obtained from laboratories certified as compliant with the FDA's "Good Laboratory Practices" to determine whether a drug candidate is safe enough to proceed to clinical trials. The clinical trials are the basis for further testing on safety, and additionally, efficacy—i.e., does the drug perform as intended with respect to the condition treated? The FDA distinguishes between preclinical and clinical data in the drug approval process:

> The purpose of preclinical work—animal pharmacology/toxicology testing—is to develop adequate data to undergird a decision that it is reasonably safe to proceed with human trials of the drug. Clinical trials represent the ultimate premarket testing ground for unapproved drugs. During these trials, an investigational compound is administered to humans and is evaluated for its safety and effectiveness in treating, preventing, or diagnosing a specific disease or condition. The results of this testing will comprise the single most important factor in the approval or disapproval of a new drug.

FDA, *Clinical Studies (Overview)*, http://www.fda.gov/cder/handbook/clinstud.htm.

Although preclinical data is used to assess safety, it is not used to assess efficacy. There is only one narrow situation—not present in this case—where the FDA may consider preclinical data for efficacy purposes. That circumstance arises where "human efficacy studies are not ethical or feasible." 21 C.F.R. § 314.600.

The IND Stage: The FDA Considers Safety and Not Efficacy

A party seeking approval to market a new drug compound must first seek permission from the FDA to begin clinical trials on human beings. *See* 21 U.S.C. § 355(i)(2). An applicant for permission to conduct clinical trials on human beings with a new drug compound must provide:

> (A) information on design of the investigation and adequate reports of basic information, certified by the applicant to be accurate reports, *necessary to assess the safety of the drug for use in clinical investigation*; and (B) adequate information on the chemistry and manufacturing of the drug, controls available for the drug, and primary data tabulations from animal or human studies.

Id. (emphasis added). Section 355(i)(2) focuses on safety, and does *not* require any submission with respect to a drug candidate's efficacy.[1] Section 355(i)(2)'s omission of "efficacy" or "effectiveness" is telling, in that the concept of "efficacy" is found frequently and prominently in the FFDCA's drug approval provisions. *See, e.g.*, 21 U.S.C. § 355(i)(1) (requiring the FDA to promulgate regulations permitting qualified experts "to investigate the safety and effectiveness" of non-approved drugs for approval purposes).

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[1] Remarkably, Merck cites Section 355(i)(2) and 21 C.F.R. § 312.23 for the proposition that "the preclinical phase involves the development of information to satisfy the FDA that the drug is *sufficiently effective* and safe to justify testing as an [IND] in human clinical trials." Merck Br. at 7 (emphasis added). As demonstrated from the statutory text quoted above, nothing in Section 355(i)(2) supports Merck's "*sufficiently effective*" assertion. As demonstrated further below, 21 C.F.R. § 312.23 does not require preclinical data showing effectiveness.

The FDA's implementing regulation for Section 355(i)(2) requires that the sponsor of a drug candidate submit an IND to the FDA before clinical trials may begin. *See* 21 C.F.R. § 312.20. If the FDA does not object to the proposed clinical trials within 30 days of submission of the IND, such trials may proceed. *See* 21 C.F.R. § 312.40(b).

The FDA's requirements for the contents of an IND can only be understood in the context of the three phases of clinical trials that may occur if the IND is not disapproved by the FDA. Phase 1 studies are relatively limited and closely-monitored trials on fewer than 100 persons to "determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, *and, if possible, to gain early evidence on effectiveness.*" 21 C.F.R. § 312.21(a)(1) (emphasis added). Phase 2 studies usually involve no more than several hundred persons to evaluate the effectiveness and safety of the drug *Id.* § 312.21(b). Phase 3 studies are "intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug." *Id.* § 312.21(c).

Just as Section 355(i)(2) of the FFDCA focuses on safety-related data for seeking approval to conduct clinical trials, the FDA regulation outlining "[g]eneral principles of the IND submission" also focuses exclusively on safety: "[The] FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety." 21 C.F.R. § 312.22(a). Thus, in terms of data actually submitted to the FDA in an IND, only safety-related data are relevant to the decision to begin Phase 1 clinical testing. While efficacy information is relevant to a subsequent IND submission for Phases 2 and 3 of the clinical trials, such effi-

cacy data are derived from the Phase 1 and 2 tests conducted on human beings, not from the Phase 1 preclinical data.[2]

The FDA's regulation governing the content of the IND submission further confirms that the FDA reviews preclinical data in the IND for the safety of the human subjects in Phase 1 of the clinical testing. That regulation requires the IND submission to include "[a]dequate information about *pharmacological* and *toxicological* studies of the drug involving laboratory animals or in vitro, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations." 21 C.F.R. § 312.23(a)(8); *see also* A PRACTICAL GUIDE TO FOOD AND DRUG LAW AND REGULATION 96 (K. Piña and W. Pines eds., 1998); Addendum, page 8a.

The FDA requires applicants for an IND to submit either preclinical data generated in compliance with well-defined Good Laboratory Practices ("GLP") or a statement of reasons for noncompliance. 21 C.F.R. § 312.23(a)(8)(iii). GLP requirements apply to all "nonclinical studies," which are defined as "in vivo or in vitro experiments in which test articles are studied prospectively in test systems under laboratory conditions *to determine their safety.*" 21 C.F.R. § 58.3 (emphasis added). In practice, applicants for an IND are expected to meet GLP requirements. *See* HOW TO WORK WITH THE FDA: TIPS FROM THE EXPERTS 2 (W. Pines ed., 2000).

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[2] *See* E. WHITMORE, DEVELOPMENT OF FDA-REGULATED MEDICAL PRODUCTS 45 (2004) ("The drug company must first convince the FDA that the drug is reasonably safe *to use in humans to evaluate safety and efficacy* in clinical trials. This is established through preclinical (that is, nonhuman) laboratory testing, including testing in animals.") (emphasis added)

The FDA's Interest in Related Compounds Is Limited to Safety Considerations

Merck asserts that by regulation an IND requires "information not only on the particular compound proposed, but also, as relevant, on 'related drugs.'" Merck Br. at 48 (citing 21 C.F.R. § 312.23(a)(5)(v)). Section 312.23(a)(5)(v) requires that the Investigator's Brochure include "a description of possible risks and side effects to be anticipated on the basis of prior experience with the drug under investigation or with related drugs." Thus, related compounds are relevant only to the issue of safety, and then only for the Investigator's Brochure, not the IND itself. The IND itself does not require any *preclinical* data on other compounds, although it does require information of "risks of particular severity or seriousness anticipated on the basis of . . . prior studies in humans with the drugs or related drugs." 21 C.F.R. § 312.23(a)(3)(iv)(f).

Grounds for Disapproval of an IND

Under the FFDCA, the FDA may disapprove an IND and thus bar Phase 1 clinical trials by issuing a "clinical hold." 21 U.S.C. § 355(i)(3)(A). Such a clinical hold may be issued when "the drug involved represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation." *Id.* § 355(i)(3)(B). Nothing in the statute requires consideration of efficacy; instead, the focus is on risk to the subjects of the trial.

Similarly, Section 355(i)(3)(B)'s implementing regulation does not include efficacy data as a basis upon which to issue a clinical hold. 21 C.F.R. § 312.42(b) (stating that grounds for imposition of a clinical hold include, *inter alia*, (i) "unreasonable and significant risk of illness or injury"); *see also* FDA, *Phase 1 Clinical Studies*, http://www.fda.gov/cder/handbook/phase1.htm.

The NDA Stage: Safety and Efficacy

If all three phases of clinical trials succeed, an applicant then files an NDA pursuant to 21 U.S.C. § 355(b), to include "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use." 21 U.S.C. § 355(b)(1)(A). Thus, in contrast to the FFDCA provision governing the IND, which speaks only in terms of safety, *see id.* § 355(i)(2), the FFDCA provision governing the NDA expressly requires data on *both* safety and efficacy.

Similarly, the NDA regulations and the FDA website state that NDA data is reviewed for both safety *and* efficacy. *See* 21 C.F.R. § 314.2 ("The purpose of this part [governing NDA] is to establish an efficient and thorough drug review process in order to: (a) facilitate the approval of drugs shown to be safe and effective; and (b) ensure the disapproval of drugs not shown to be safe and effective."); *Clinical Studies (Overview)*, *supra* ("An NDA must provide sufficient information, data, and analyses to permit FDA reviewers to reach several key decisions, including[w]hether the drug is safe and effective for its proposed use(s), and whether the benefits of the drug outweigh its risks.").

Finally, while the regulations do contain a provision requiring the submission of "nonclinical" data as part of the NDA, 21 C.F.R. § 314.50(d)(2), the regulations define "nonclinical" as referring to preclinical data relating to *safety*. 21 C.F.R. § 58.3(d). Thus, the regulations clarify that the preclinical data are relevant at the NDA stage only for *safety* purposes (aside from in the few cases encompassed by the narrow exception noted above).

The Patents in Suit

In the 1980s, two scientists at Burnham, Drs. Erkki Ruoslahti and Michael Pierschbacher, made a series of pioneering discoveries concerning the mechanism by which cells attach and detach from proteins that form the extracellular matrix in the body. Tr. 333–43. First, they made the surprising discovery that out of the thousands of amino acid combinations that form the extracellular matrix proteins, a sequence of only three amino acids (referred to as "RGD") constitutes the site where cells attach to these proteins. Tr. 824–26. Second, they used synthetic peptides containing the RGD attachment site as a tool to isolate the cellular structures that bind to that site, which turned out to be cell surface proteins with the characteristics of a receptor. Tr. 346–47.

Drs. Ruoslahti and Pierschbacher then identified other members of what turned out to be a genetically-related family of cell surface receptors, previously unknown, that bind to the RGD attachment site. Tr. 350. These cell surface receptors, called integrins, are enormously important because they control myriad cellular functions and processes. In effect, Drs. Ruoslahti and Pierschbacher discovered the key (the RGD sequence) to a lock (the integrin cell surface receptors) that controls a wide range of cellular activity. These discoveries by Drs. Ruoslahti and Pierschbacher spawned an explosion of scientific research related to RGD peptides and integrins. Tr. 362–65, 369, 370–75.

Four patents at issue were granted for these pioneering discoveries.[3] Claim 1 of U.S. Patent No. 4,789,734 (the "'734 Patent") claims a composition containing a cell surface receptor that binds to the RGD attachment site. S.A. 14.

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[3] A fifth patent, U.S. Patent No. 4,988,621 (the "'621 Patent"), also covered certain aspects of these inventions; it is not at issue here.

That claim encompasses the $\alpha_v\beta_3$ receptor.[4] Claims 4 and 8 of U.S. Patent No. 4,879,237 (the "'237 Patent") claim methods for detaching animal cells from a substrate. S.A. 16–17. The asserted claims of these patents would not be infringed by the manufacture or sale of the RGD peptide drug composition for which Merck seeks FDA approval. They are useful only as biomedical research tool patents.

Claim 8 of U.S. Patent No. 4,792,525 (the "'525 Patent") claims the composition of non-naturally occurring RGD-containing peptides that have cell attachment activity. S.A. 12. Claims 15 through 18 of U.S. Patent No. 5,695,997 (the "'997 Patent") claim various methods for blocking cell surface receptors. S.A. 19. These claims would be infringed by sale or use of Merck's proposed RGD product.

Collectively, these patented inventions cover not only the compositions of RGD peptides with cell attachment activity and the cell surface receptors to which they bind, but also three distinct ways to manipulate cell interaction with the extracellular matrix: (1) promotion of cell attachment by use of an RGD peptide ('525 Patent); (2) blocking cell attachment ('997 Patent); and (3) disrupting existing cell attachment ('237 Patent). Tr. 361. All of these compositions and methods, regardless of whether they cover a drug product, are useful as tools for biomedical research. This use of RGD peptides to isolate the integrin receptors is a good example of the value of the inventions as research tools.

Drs. Ruoslahti and Pierschbacher founded Telios Pharmaceuticals in June 1987. Tr. 375. Burnham's RGD patents were exclusively licensed to Telios.

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[4] The term $\alpha_v\beta_3$ is pronounced "alpha-v-beta-3."

Dr. Cheresh's Discovery That the Integrin $\alpha_v\beta_3$ Controls Angiogenesis

In April 1994, following the path blazed by Drs. Ruoslahti and Pierschbacher, Dr. David Cheresh, a scientist at Scripps, published a paper in *Science* demonstrating that one of the cellular processes controlled by the integrin $\alpha_v\beta_3$ is angiogenesis, the growth of blood vessels. Tr. 1063. Specifically, Dr. Cheresh demonstrated that blocking the $\alpha_v\beta_3$ receptor would inhibit angiogenesis in tumors, depriving them of the blood supply they need to grow. *Id.*

This discovery showed that any one of three types of entities known to block the $\alpha_v\beta_3$ receptor—antibodies, synthetic RGD peptides, or organic molecules that "mimic" the cell attachment activity of the RGD sequence—could be used as a drug therapy that inhibits the growth of solid tumors. Tr. 1080–81. Dr. Cheresh characterized this work as his "major discovery," stating, "That was when we knew what we had." J.A. 190.

Dr. Cheresh's *Science* publication described the use of an antibody to block the $\alpha_v\beta_3$ receptor. Tr. 1063. Subsequently, in December 1994, Dr. Cheresh published a second paper in which he used an RGD peptide for the same purpose. That peptide, denominated 66209, had been provided to him by Merck. In a previous paper, it had been shown that 66203 blocked the $\alpha_v\beta_3$ receptor. Tr. 1072–75.

Merck Imports Infringing Compounds for Scripps' Use and Induces Scripps to Infringe

After learning of Dr. Cheresh's discovery, Merck expressed interest in negotiating a sponsored research agreement with him and Scripps to investigate $\alpha_v\beta_3$ inhibitors. Merck was not interested in pursuing work on antibodies, but

it was interested in research on the two other classes of potential $\alpha_v\beta_3$ inhibitors: RGD peptides and organic molecules that mimic the RGD cell attachment activity. Tr. 1103, 1115–16. Merck had not then decided on what $\alpha_v\beta_3$ inhibitor it would focus its development efforts. On April 13, 1995, Merck's head of Preclinical Research and Development, Dr. Jan Sombroek, wrote to Dr. Cheresh that "Merck will take care of toxological studies once we have defined a product for the pipeline. Pharmacokinetica, pharmacodynamics and biodistribution studies will routinely be performed at our institute in Grafing, unless we ask you to help us because of capacity problems." J.A. 126–27.

In August 1995, Merck and Scripps executed a research funding agreement for the use of peptide and organic molecule inhibitors of $\alpha_v\beta_3$. Dr. Cheresh testified, "[A]t that time we were really searching for an ideal drug candidate." Tr. 1092. To that end, Scripps used RGD peptides as positive controls to assess the anti-angiogenic properties of non-RGD organic molecule mimetics. Tr. 1091, 1092–94. The agreement provided Merck funding to Dr. Nicoloau, a Scripps scientist charged with developing organic molecule mimetics to be tested. This funding of Dr. Nicoloau and testing of his newly developed non-RGD organic compounds were important parts of Merck's strategic objective in funding Scripps' research. Docket No. 1027, Ex. 9, at 91.

Thus, the Scripps research funded by Merck was not limited to RGD peptides. Tr. 1115. Nor was this Merck-funded research strictly limited to the search for an RGD or non-RGD organic compound that blocks the $\alpha_v\beta_3$ receptor. The Merck-funded research was also designed generally to strengthen the "scientific foundation" of the basic approach of blocking the $\alpha_v\beta_3$ receptor to inhibit angiogenesis in tumors. Tr. 1128. As explained by Dr. Cheresh, "[The] idea is to have three separate structural distinct compounds do the

same thing, and that really bolsters the notion that $\alpha_v\beta_3$ is the thing you want to target, whether you do it with a peptide, whether you do it with an antibody, whether you do it with an organic molecule." Tr. 1128–29. Identifying organic molecules that mimic cell attachment activity would enable Scripps to obtain broader patent claims. Tr. 1129.

Under the 1995 agreement, Merck, not Scripps, took responsibility for conducting the expensive experiments necessary to assess toxicity and pharmacokinetics under the FDA's "Good Laboratory Practices" requirements. Merck Br. at 14. As an institution dedicated to basic research aimed at discovering the principles that underlie disease, Tr. 3208, Scripps lacked the expertise and facilities necessary to comply with the GLP requirements for nonclinical research related to safety.

Merck Refuses to Purchase a License from Telios

When Dr. Pierschbacher read Dr. Cheresh's December 1994 article describing the use of an RGD peptide to inhibit angiogenesis, he realized that Scripps' work had passed beyond the basic research stage and had advanced to the point where commercial drug possibilities were being explored. Tr. 416–17. Dr. Pierschbacher also realized that people at Merck with whom he was already in contact were interested in using an RGD peptide as a cancer drug. Tr. 417–19.

Dr. Pierschbacher and others at Telios unsuccessfully tried to convince Merck to work with an RGD compound that Telios was developing. Telios later made clear that, regardless of whether Merck went ahead with Scripps or with Telios, Merck would have to obtain a license to Telios's RGD patents. Tr. 450. At a final meeting with Dr. Pierschbacher in Germany, Merck announced that it had no in-

terest in licensing any rights from Telios and was terminating negotiations. Tr. 450–51.[5]

The District Court Action

Unable to negotiate a license agreement with Merck, Telios and Burnham brought this patent infringement action against Merck in the U.S. District Court for the Southern District of California in 1996. J.A. 10. Integra joined the action as a plaintiff when it acquired Telios's patent rights. (Hereinafter, the plaintiffs are referred to collectively as "Integra.") The suit alleged that Merck, Scripps, and Dr. Cheresh either directly infringed or induced the infringement of five U.S. patents by importing the infringing RGD peptides into the United States and by contracting for their infringing use in evaluating potential drug candidates and general biomedical experiments. *See* Compl., Docket No. 1.

Merck, Scripps, and Dr. Cheresh answered that the experiments at issue were exempt from infringement liability under either the common law research exemption or the FDA Exemption, 35 U.S.C. § 271(e)(1). Under Merck's theory, any research to identify or develop a drug subject to FDA approval would be exempt from patent infringement liability.

Early in the case, Merck moved for partial summary judgment on the FDA Exemption with respect to one of the patents at issue. The District Court agreed with Merck that the FDA Exemption encompassed activities reasonably related to the submission of information for an IND application but denied the motion, finding that triable issues of fact ex-

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[5] Merck asserts that Telios *conditioned* a license upon an agreement from Merck to provide support for developing unrelated drugs, *see* Merck Br. at 21, but that is incorrect. The page Merck cites does not support the assertion.

isted as to whether the Scripps experiments beginning in September 1995 were exempt under the FDA Exemption. J.A. 33–44. The District Court based this ruling in part on inconsistencies in the testimony of Dr. Cheresh and Merck employees. J.A. 37–44.

Before submitting the case to the jury, the District Court partially granted Merck's Rule 50(a) motion for judgment as a matter of law and ruled that all pre-1995 experiments (with the exception of a single experiment performed in August 1994) were exempt under the common law research doctrine. Tr. 3369–91. Integra did not appeal this ruling.[6]

The District Court found that issues of fact precluded judgment as a matter of law that the remaining 180 Scripps experiments conducted from 1994–1998 were covered by the FDA Exemption. Tr. 3391. Accordingly, the District Court submitted the 180 experiments conducted from 1994–1998 to the jury to resolve the factual dispute over whether the FDA Exemption's "reasonable relationship" test was met. The court adopted an instruction that applied a legal standard on which *both* parties agreed and had derived from *Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269 (N.D. Cal. 1991), *aff'd without op.*, 991 F.2d 808 (Fed. Cir. 1993).[7] The instruction adopted by the District Court incorporated the legal standard proposed by Merck:[8]

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[6] The District Court also dismissed the case against Scripps and Dr. Cheresh. The Federal Circuit affirmed this ruling. *See* P.A. 6, 23.

[7] The Federal Circuit had previously approved the *Intermedics* standard. *See Telectronics Pacing Sys., Inc. v. Ventritex, Inc.*, 982 F.2d 1520, 1525 n.5 (Fed. Cir. 1992). District courts have consistently applied *Intermedics* in construing Section 271(e)(1). *See, e.g., Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 3 F. Supp. 2d 104, 108 (D. Mass. 1998).

[8] *See* Docket No. 992, at 14. Although the District Court adopted Merck's proposed *legal standard* for the instruction, the District Court

(continued...)

> To prevail on this defense, Merck must prove by a preponderance of the evidence 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 processes by which the FDA would decide whether to approve the product in question.

J.A. 57. The verdict form emphasized Merck's burden of proof as to the FDA Exemption. The verdict form provided: "Has Defendant Merck KGaA met its burden of proving by a preponderance of the evidence that all of the accused activities are covered by the FDA Exemption?" J.A. 62.[9]

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did not adopt the entirety of Merck's proposed instruction. Hence, Merck filed objections to the jury instructions. Those objections are not material to the legal standard to which Merck agreed. Indeed, Merck failed to appeal those objections to the Federal Circuit or to note those objections in its certiorari petition or its merits brief.

[9] Merck objected to the jury verdict form and sought an experiment-by-experiment determination of the FDA Exemption, but the District Court overruled the objection, finding that "there wasn't enough support in either the underlying evidence or in final summations upon which the jury could make an adequate and competent decision" on an experiment-by-experiment basis. J.A. 456. Merck later filed a motion for a new trial based on the verdict form, but the District Court correctly denied the motion. The District Court ruled that "the verdict form used was adequate to obtain a jury determination of all factual issues essential to judgment." Docket No. 1135 at 3 (citing *In re Haw. Fed. Asbestos Cases*, 871 F.2d 891, 894 (9th Cir. 1989)). Merck notes its objection in its merits brief to this Court, Merck Br. at 22, but fails to assert any legal error in the District Court's overruling of the objection. Merck also failed to challenge the verdict form in its appeal to the Federal Circuit. Moreover, Merck's certiorari petition failed to raise this issue.

The jury found that Merck willfully infringed and induced infringement of each of the patents in suit. J.A. 63. Applying the legal standard proposed by Merck, the jury found that Merck did not carry "its burden of proving by a preponderance of the evidence that all of the accused activities are covered by the FDA Exemption." J.A. 62. The jury awarded Integra $15,000,000 in damages for Merck's infringing activities. J.A. 62. The District Court entered an amended final judgment on October 6, 2000. P.A. 45–46.

Merck then filed a renewed JMOL motion under Federal Rule of Civil Procedure 50(b) with respect to its affirmative defense under the FDA Exemption. The District Court denied this motion, finding that the record evidence was sufficient to uphold the verdict. P.A. 47–50. Merck also filed a motion for a new trial based on the FDA Exemption. The District Court denied the motion, finding that "there was ample evidence for both the court and the jury to determine that the FDA Exemption did not apply to this action. The clear weight of the evidence supports the verdict, and Merck's arguments do not present grounds for granting a new trial." Docket No. 1135 at 2.

The Federal Circuit Appeal

On appeal to the Federal Circuit, Merck argued that the FDA Exemption encompasses "drug development research that serves as a rational predicate to generating information for submission to the FDA, including any tests conducted to determine whether to proceed with a drug candidate." Merck C.A. Br. at 45. In effect, Merck challenged the legal standard in the jury instruction, even though Merck had agreed with the substance of that instruction, thereby waiving any objection under Federal Rule of Civil Procedure 51.

Rather than rejecting (as waived) Merck's newly-raised challenge to the legal standard found in the jury instruction,