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THE SUPREME COURT TILTS TOWARD DRUG DEVELOPERS

Drug Discovery After Merck v. Integra

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Introduction

The Supreme Court generally gives wide berth to the Federal Circuit in patent cases. Despite sharp discord on the Federal Circuit itself and consternation among the district judges on the fundamental topic of patent claim interpretation, the Supreme Court has remained on the sidelines. In one area, however, the Supreme Court has been vigilant. Twice now the Court has interceded on the interpretation of a patent statute relating to new drug development.

In a unanimous decision, the Supreme Court in Merck v. Integra broadly construed the safe harbor provision of the Hatch-Waxman Act to make it more difficult to enforce patents against drug developers. Vacating a decision from a divided panel of the Federal Circuit, the Supreme Court held that the safe harbor extends to “all uses of patented inventions that are reasonably related to the development and submission of any information under the FDCA.” The impact of this decision may be marred, however, by loose ends not addressed by the Court and by the Court’s approval of an unfortunately vague jury instruction.

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1 The open disagreement within the Federal Circuit on claim interpretation was displayed again recently in the dissent by Judges Meyer and Newman in the en banc decision in Phillips v. AWH Corp., 415 F.3d 1303 (Fed. Cir. 2005). “What we have wrought is the substitution of a black box, as it so pejoratively has been said of the jury, with the black hole of this court. Out of this void we emit ‘legal’ pronouncements by way of ‘interpretive necromancy’; these rulings resemble reality, if at all, only by chance.” Phillips, 415 F.3d at 1330 (note omitted). “Eloquent words can mask much mischief. The court’s opinion today is akin to rearranging the deck chairs on the Titanic — the orchestra is playing as if nothing is amiss, but the ship is still heading for Davey Jones’ locker.” Phillips, 415 F.3d at 1334-35.

2 See Hon. Kathleen M. O’Malley, Hon. Patti Saris, & Hon. Ronald H Whyte, The Law, Technology and the Arts Symposium: The Past, Present and Future of the Federal Circuit: A Panel Discussion: Claim Construction from the Perspective of the District Judge, 54 CASE W. RES. L. REV. 671 (Spring 2004) (“[T]here seems to be a changing perspective on how to do claim construction,” Judge Saris, p. 678; “I have jokingly said that perhaps litigants should want to be on the losing side at the district court level because there appears to be a presumption at the CAFC that district court judges generally get claim construction wrong.” Judge O’Malley, p. 680; “If the reversal rate is as high as some claim, the easiest thing to do is figure out what your decision is and then write the opposite,” Judge Whyte, p. 680.).

3 The Supreme Court’s last foray into patent claim interpretation was Markman v. Westview Instruments, Inc., 517 U.S. 370, 116 S. Ct. 1384 (1996), where the Court affirmed the Federal Circuit, holding that the interpretation of patent claims is an issue of law to be decided by the judge. In two other recent cases, the Supreme Court has dealt with the scope of patent claims for purposes of the doctrine of equivalents. Festo Corp. v. Shoketsu Kinzoku Kogyo, 535 U.S. 722, 122 S. Ct. 1831 (2002); Warner-Jenkinson Co. v. Hilton Davis Chem. Co., 520 U.S. 17, 117 S. Ct. 1040 (1997). In none of these cases did the Supreme Court address the central issues of claim interpretation that are now dividing the Federal Circuit and confusing the district judges — how to construe the meaning of terms appearing in claims, and the relationship between the claims, the specification and the file history, for purposes of interpreting the claims.

4 The Supreme Court previously construed 35 U.S.C. § 271(e)(1) in Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661, 110 S. Ct. 2683 (1990). See discussion infra notes 29-32 and accompanying text. A third drug case was taken by the Court while this article was in press. See Laboratory Corp. of Am. V. Metabolite Lab. Inc., (docket 04-607).

5 Merck KGaA v. Integra Lifesciences I, Ltd., 125 S. Ct. 2372, 162 L. Ed. 2d 160 (2005).

6 Merck KGaA. 125 S. Ct. at 2380 (emphasis in original).
I. Background

As of 1984, the patent and pharmaceutical regulatory statutes were out of sync. All new drugs, both generic and brand-name, were subject to the same rigorous FDA safety and effectiveness testing—arguably a wasted effort for copycat generic drugs. Patents applicable to new drugs would often issue long before the drugs were approved for sale by the FDA, thereby effectively wasting a portion of market exclusivity at the beginning of the patent term. At the same time, as a result of the Federal Circuit's decision in the *Roche v. Bolar* case, parties interested in making and selling generic drugs could not begin FDA testing until the patent for the brand name drug expired without the risk of being sued for infringement. This resulted in a *de facto* extension of the patent term beyond that set by law.

Congress dealt with these problems in “The Drug Price Competition and Patent Term Restoration Act,” more commonly known as the “Hatch-Waxman Act.” The purpose of Hatch-Waxman was to strike a balance between the competing interests of brand-name and generic drug manufacturers by providing incentives to produce new drugs, while offering quick FDA approval for low cost generic drugs. Hatch-Waxman created a faster approval process for generic drugs, allowing generic manufacturers to file an “Abbreviated New Drug Application” (“ANDA”), supported only by showing that the generic drug is “the same” as or “bioequivalent” to an already approved drug. This allowed the providers of generics to by-pass the full FDA safety and effectiveness process and thereby bring less expensive versions of brand name drugs to market sooner.

Hatch-Waxman also provided a “safe harbor” against patent infringement, effectively overruling the *Roche* decision, which held that clinical tests conducted by generic manufacturers before patent expiration were infringing. Hatch-Waxman amended the statutory definition of patent infringement to exclude activity “reasonably related” to submitting information to the FDA. As a consequence, the FDA approval for generic drug applications now more closely coincides with patent expiration, enabling generics to reach the market more quickly.

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11 *Roche*, 733 F.2d at 858.

In exchange for allowing faster generic drug approvals, the Act established patent term extensions for innovator drugs to offset the term used up during the approval process. There are some limits to the extension: it cannot exceed five years, nor can the period between product approval and patent expiration exceed fourteen years. The patentee must also act with “due diligence” throughout the regulatory period. This means they must not delay FDA review, and anyone can challenge an extension on that basis.

The Act also provides a dispute resolution procedure. The ANDA rules offer four routes for marketing of generic drugs. Three routes, called Paragraph I, Paragraph II, and Paragraph III certifications, apply to ANDA filings that do not involve challenges to patents. Through these routes, multiple generics can enter the market at the same time, creating a very competitive market. To date, 94% of more than eight thousand ANDA applications filed have used this route for ANDA filing.

The fourth route is called a Paragraph IV certification. It applies when patent protection has not expired, and the generic drug maker claims that either the patent is invalid or its product does not infringe the patent. Paragraph IV certifications are desirable because the first to file one becomes eligible for 180 days of market exclusivity, during which time the FDA will not review any other generic drug application. However, the rules also provide that filing a Paragraph IV certification with the FDA is an infringing act. This allows the patentee an opportunity to sue the generic manufacturer for patent infringement and obtain an automatic thirty month stay on FDA approval activities.

Recently the Act was amended to close perceived loopholes. For example, patentees are required to list each patent related to a given drug in the FDA publication called “Approved Drug Products with Therapeutic Equivalence Evaluations,” commonly known as the “Orange Book.” Prior to the amendments to the Act, patentees were required to file notice of a patent in the Orange Book. Notice of additional patents could be later filed in the Orange Book, gaining

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14 35 U.S.C. § 156 (c)-(d).

5 Chi.-Kent J. Intell. Prop. 127
the opportunity for additional stay periods. Under the amendments to the Act, only a single automatic stay is allowed.22

The amendments also give generic companies the ability to seek the de-listing of patents that are inappropriately listed in the Orange Book, such as drug packaging, drug metabolites, and intermediate forms of a drug.23 They also clarify that multiple 180-day exclusivity periods will be given if multiple applicants file on the same day,24 and that the exclusivity period will be lost if marketing is not timely pursued.25

II. The Safe Harbor of 35 U.S.C. § 271(e)(1)

The provision of the Act intended to permit infringement-free FDA-related research and testing is an amendment to the statute defining infringement, 35 U.S.C. § 271, by adding a new subpart “(e)(1),” which provides in pertinent part:

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 any 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 or veterinary biological products.26

As stated above, this statute was prompted by the result in Roche v. Bolar. In that case, a generic drug manufacturer acquired a small quantity of a patented compound to obtain data needed for a New Drug Application to be filed with the FDA. The patent covering the compound was within six months of expiration, but the patent holder nonetheless sued for infringement and sought a temporary restraining order (“TRO”) to enjoin the testing. After granting the TRO requested by Roche, the trial court subsequently ruled on the merits in favor of

22 See, e.g., FDA Generic Drugs Final Rule Questions and Answers summarizing the rule changes, at http://www.fda.gov/oc/initiatives/generics/qna.html (last visited January 4, 2006). See also, 21 CFR 314.94(a)(12)(vi) (2005iv) (“If a patent on the listed drug is issued and the holder of the approved application for the listed drug does not submit the required information on the patent within 30 days of issuance of the patent, an applicant who submitted an abbreviated new drug application for that drug that contained an appropriate patent certification before the submission of the patent information is not required to submit an amended certification.”).

23 See, e.g., FDA Generic Drugs Final Rule Questions and Answers summarizing the rule changes, at http://www.fda.gov/oc/initiatives/generics/qna.html (last visited January 4, 2006). See also, 21 U.S.C. § 355(j)(C)(ii)(I) (“If an owner of the patent or the holder of the approved application under subsection (b) of this section for the drug that is claimed by the patent or a use of which is claimed by the patent brings a patent infringement action against the applicant, the applicant may assert a counterclaim seeking an order requiring the holder to correct or delete the patent information submitted by the holder under subsection (b) of this section on the ground that the patent does not claim either — (aa) the drug for which the application was approved; or (bb) an approved method of using the drug.”).

24 21 U.S.C. § 355(j)(5)(B)(iv)(II)(bb) (“As used in this subsection, the term "first applicant" means an applicant that, on the first day on which a substantially complete application containing a certification described in paragraph (2)(A)(vii)(IV) is submitted for approval of a drug, submits a substantially complete application that contains and lawfully maintains a certification described in paragraph (2)(A)(vii)(IV) for the drug.”).

25 21 U.S.C. § 355(j)(5)(D) (“the term "forfeiture event", with respect to an application under this subsection, means the occurrence of any of the following: (I) Failure to market . . . ”).

26 35 U.S.C § 271(e)(1).
the accused infringer Bolar, on the basis that the accused activity was not infringing because it was *de minimis* and experimental. A prompt appeal was taken and the Federal Circuit sided with the patent holder. The court rejected arguments that the activity was *de minimis* or that it constituted non-infringing experimental use, and ruled that the FDA-necessitated testing constituted infringing “use” of the patented invention under 35 U.S.C. § 271(a). The safe harbor provision of § 271(e)(1) was tailored to overrule *Roche* by carving activities reasonably related to FDA approval out of the definition of infringement.

Section 271(e)(1) was initially reviewed by the Supreme Court in *Eli Lilly v. Medtronic*, wherein the Court considered the distinction between drugs and medical devices. In *Eli Lilly*, the issue was whether activities undertaken by Medtronic in the course of FDA-related testing of an implantable cardiac defibrillator were covered by the safe harbor of § 271(e)(1). Justice Scalia authored the opinion for the majority of a divided Court. Relying on the purpose of § 271(e)(1) in the context of the other aspects of Hatch Waxman, the majority in *Eli Lilly*, ruled in favor of Medtronic. Although it found the statute inelegantly drafted, the Court held that the statute applies to the entirety of any Federal Act, at least some portion of which regulates drugs. Because the FDCA is such an Act and because the FDCA regulates medical devices as well as drugs, the majority in *Lilly* reasoned that the protection of §271(e)(1) applies to FDA-related testing of medical devices as well as drugs.

Not long after *Eli Lilly*, the Federal Circuit further broadened the safe harbor in *Telectronics v. Ventritex*. The issue was whether data could be used for business purposes in addition to FDA uses, and still maintain protection under § 271(e)(1). In that case, the accused infringer, Ventritex, had conducted clinical trials of its implantable defibrillator pursuant to an Investigational Device Exemption from the FDA, and used the results of the clinical trials to raise investment money. Ventritex had reported on the results of their clinical testing to

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27 *Roche*, 733 F.2d at 860-61.
28 The Federal Circuit has taken a very dim view of the *de minimis* defense to patent infringement. *Embrex Inc. v. Service Eng’g Corp.*, 216 F.3d 1343, 1352-53 (Fed. Cir. 2000), Rader, J. concurring (“Since its inception, this court has not tolerated the notion that a little infringement – *de minimis* infringement – is acceptable or not infringement at all...[T]he statute leaves no leeway to excuse infringement because the infringer only infringed a little.”).
30 Dissenting Justices Kennedy and White would have limited the safe harbor of §271(e)(1) to drugs, not including medical devices, based on what they considered a literal reading of the statute. *Eli Lilly*, 496 U.S. at 679-80, 110 S. Ct. at 2693.
31 “No interpretation we have been able to imagine can transform §271(e)(1) into an elegant piece of statutory draftmanship. To construe it as the Court of Appeals decided, one must posit a good deal of legislative imprecision; but to construe is as petitioner would, one must posit that and an implausible substantive intent as well.” *Id.* at 679, 110 S. Ct. at 2693.
32 *Id.*
34 *Telectronics*, 982 F.2d at 1521.
investors and analysts, and had included a description of the clinical testing and the results in a private placement memorandum sent to potential investors.\textsuperscript{35}

The patent holder, Telectronics, argued that using the clinical testing for fund raising activities was unrelated to FDA reporting requirements, and that by such unrelated use, the activities “lost” their otherwise exempt status under § 271(e)(1).\textsuperscript{36} The Federal Circuit ruled that the safe harbor was not impaired by the fact that the exempt activities were used for “fundraising and other business purposes.”\textsuperscript{37}

In \textit{AbTox Inc. v. Exitron Corp.}, the Federal Circuit addressed the issue of whether the § 271(e)(1) infringement exemption applies to different classes of medical devices.\textsuperscript{38} In \textit{AbTox}, the device at issue was a plasma sterilizer, which is a Class II medical device.\textsuperscript{39} In contrast, the device that had been at issue in \textit{Eli Lilly}, an implantable cardiac defibrillator, was a Class III device. Class II devices, unlike Class III devices, can be marketed without advance FDA approval.\textsuperscript{40} There is an FDA approval process for Class II devices, but it is “by no means comparable” to the pre-market approval necessary for Class III devices.\textsuperscript{41} Also, Class III devices are eligible for patent term extensions under 35 U.S.C. § 156, whereas Class II devices are not.

Judge Rader, writing for the panel in \textit{AbTox}, noted that the rationale for the Supreme Court’s ruling in \textit{Eli Lilly} was not applicable to Class II devices.\textsuperscript{42} Nonetheless, he felt constrained to follow the broad holding of \textit{Eli Lilly} and the Federal Circuit ruled the safe harbor applicable to all classes of medical devices.\textsuperscript{43}

\textsuperscript{35} \textit{Id.}
\textsuperscript{36} \textit{Id.} at 1523.
\textsuperscript{37} \textit{Id.} at 1525 (“By permitting the testing and regulatory approval process to begin well before a controlling patent had run its course, Congress must have intended to allow competitors to be in a position to market their products as soon as it was legally permissible…. If Congress intended to make that more difficult, if not impossible, by preventing competitors from using, in an admittedly non-infringing manner, the derived test data for fund raising and other business purposes, it would have made that intent clear. The statute contains no such provision.”).
\textsuperscript{38} \textit{AbTox Inc. v. Exitron Corp.}, 122 F.3d 1019, 1029 (Fed. Cir. 1997).
\textsuperscript{39} The Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. §§ 301-395 (1994), classifies medical devices in three categories. Class I devices present no unreasonable risk of illness or injury and are subject to only “general controls.” Class II devices are potentially more harmful than Class I devices. Class II devices may be marketed without advance FDA approval, but they must comply with FDA performance regulations known as “special controls.” Class III devices, which cannot be marketed without advance FDA approval, are devices which either “present a potential unreasonable risk of illness or injury” or are “purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health.” See discussion in \textit{Abtox}, 122 F.3d at 1028, citing \textit{Medtronic, Inc. v. Lohr}, 518 U.S. 470, 477, 116 S. Ct. 2240, 2246 (1996).
\textsuperscript{40} \textit{Abtox}, 122 F.3d at 1028.
\textsuperscript{41} \textit{Id.}
\textsuperscript{42} \textit{Id.} at 1029.
\textsuperscript{43} “Ultimately, this court must follow the Supreme Court’s broader holding, which remains in force despite a potential conflict with its own narrower reasoning.” \textit{Id.}
The case law, therefore, from both the Supreme Court and the Federal Circuit, had taken a uniformly broad approach to interpreting § 271(e)(1). The courts had held that the safe harbor of Hatch-Waxman was applicable to all classes of medical devices as well as drugs, whether or not FDA pre-approval was necessary, and that the erstwhile infringing activity, rendered non-infringing by the statute, could be used for marketing, fundraising and other business purposes.

III. Merck v. Integra

An issue left unresolved by the cases and the statute itself was the scope of activity protected by the safe harbor of 35 U.S.C § 271(e)(1). The statutory language, “solely for uses reasonably related to the development and submission of information [to the FDA],” leaves room for debate. To understand the debate requires some understanding of the drug screening process.

Generally speaking, potential drugs are screened in a protein assay to identify those chemicals that provide a desired change in protein activity. These screens are called “High Throughput Screening” or “HTS” because typically hundreds of thousands of different chemicals are tested in the screen. Chemicals that produce the desired change in protein activity are called “leads.” Once a “lead” compound is identified, it usually must be optimized for solubility, toxicology, and the like, before being declared an official drug “candidate.” Candidates then undergo clinical testing, and the lucky winner to survive that obstacle course eventually becomes an FDA approved drug.

Although not addressed by either the Federal Circuit or the Supreme Court, the scope of activities subject to the safe harbor had been interpreted broadly by the district courts in recent decisions. District courts in Massachusetts, the Southern District of New York, and Delaware had found the safe harbor of § 271(e)(1) applicable to pre-clinical development of new drugs. This trend was reversed by the Federal Circuit in the Integra v. Merck case.

Beginning in 1988, Merck KGaA (Merck) funded research on angiogenesis by a scientist, Dr. David Cheresh, at the Scripps Research Institute (Scripps). Angiogenesis, the process of growing new blood vessels, plays a critical role in several diseases including solid tumor cancers, diabetic retinopathy, and rheumatoid arthritis. Dr. Cheresh discovered that by blocking special molecules called “integrins” on the surface of cells, he could stem the growth of new blood vessels. Initially, Dr. Cheresh used a monoclonal antibody in his angiogenesis research, but later he began using a peptide called EMD 66203, which was provided to him by Merck.
EMD 66203, which is covered by Integra's patents, is a specific variant of the "RGD" peptide—a three amino acid peptide containing arginine-glycine-aspartate that had been looped round so that the front end joined the back end and was thus "cyclized." The cyclic RGD binds to the integrins on the cell surface, thus blocking the growth of new blood vessels and making the peptide useful to slow tumor growth. Dr. Cheresh’s discoveries were published in medical journals and in the general media in 1994.

Merk’s initial agreement to fund Dr. Cheresh’s angiogenesis research was set to expire in July 1995. Merck entered into a new three-year agreement with Scripps in February 1995, providing for in vitro and in vivo testing of RGD peptides, and calling for submission of an Investigation New Drug application (IND) to the FDA in the third year. It was agreed that once a primary candidate for clinical testing was “in the pipeline,” Merck would perform the toxicology tests necessary for FDA approval.

Dr. Cheresh focused on the EMD 66203 peptide and two closely related derivatives called EMD 85189 and EMD 121974. Dr. Cheresh tested the efficacy, specificity, and toxicity of the three peptides as angiogenesis inhibitors, including testing in animals. He ultimately determined that EMD 121974 was the best candidate for testing in humans, and an IND was eventually filed in 1998.

However, Integra sued Merck, Scripps and Dr. Cheresh for patent infringement in July of 1996 in the Southern District of California. The complaint alleged that Merck induced infringement of Integra’s patents by supplying the RGD peptide to Scripps, and that Scripps and Dr. Cheresh infringed by using the RGD peptide in their angiogenesis experiments. The defendants contended that they did not infringe and that in any event the accused activities were protected by the common law research exception and by the FDA exception codified at 35 U.S.C. § 271(e)(1).

The defendants moved for summary judgment, contending that all the accused activities since at least September 1995 were covered by the safe harbor of § 271(e)(1). Integra argued

50 Before the Supreme Court, *Merck KGaA* did not contest that the EMD 66203 peptide was covered by the Integra patents. 125 S. Ct. at 2378, n. 3. Integra had performed the original research that identified RGD as the important part of a cell surface protein that promoted cell adhesion, and had obtained five patents related to the RGD peptide. *Integra v. Merck KGaA*, 2003 U.S. App. LEXIS 27796, **3-4. 51 *Merck KGaA*, 125 S. Ct. at 2378.

52 *Id.*

53 *Id.*

54 *Id.*

55 *Id.*

56 *Id.*

57 U.S. Pat. Nos. 4,988,621 ("the ‘621 patent"), 4,792,525 ("the ‘525 patent"), 5,695,997 ("the ‘997 patent"), 4,879,237 ("the ‘237 patent"), and 4,789,734 ("the ‘734 patent").

58 *Merck KGaA*, 125 S. Ct. at 2379.

59 *Id.*
that the motion should be denied on the basis that § 271(e)(1) applies only to applications for generic drug versions of FDA-approved “pioneer” drugs already in the marketplace.\(^6\) The trial court, citing *Eli Lilly* and *AbTox*, ruled that § 271(e)(1) is not limited to testing for generic drugs.\(^6\) and noted that at least one District Court had applied § 271(e)(1) to an IND application.\(^6\) However, despite holding that the defendants’ conduct was “eligible for the § 271(c)(1) exception,” the trial court found that material issues still existed as to “when defendants’ conduct became exempt,” and the motion for summary judgment was denied.\(^6\)

The case proceeded to jury trial before District Senior Judge James M. Fitzgerald of the District of Alaska, sitting in the Southern District of California. At the conclusion of the evidence, the court ruled that, with one exception, Merck’s pre-1995 activities were covered under the common-law research exemption.\(^6\) The court ruled, however, that whether the post-1995 activities fell within the protection of § 271(e)(1) must be submitted to the jury, who returned a verdict finding that the defendants infringed four of the asserted patents, and that the activities were not protected by § 271(e)(1).\(^6\) Fifteen million dollars in damages were awarded against Merck, the only defendant against whom damages were sought.\(^6\) Post-trial, the judge dismissed Scripps and Dr. Cheresh, but entered judgment against Merck on the jury verdict of infringement and damages.\(^6\)

On appeal, a divided panel comprised of Judges Rader, Prost, and Newman, with Judge Rader writing for the majority and Judge Newman dissenting, affirmed the judgment of infringement.\(^6\) Judge Rader’s opinion for the panel majority took a decidedly narrow view of the scope of activities protected by § 271(e)(1). He relied heavily on the legislative history as showing an intention to facilitate generics to enter the market for sale of patented drugs upon expiration of the patent.\(^6\) He quoted a House Committee report describing the protected pre-market activity as “a limited amount of testing so that generic manufacturers can establish the bioequivalency of a generic substitute,” and he concluded that “the express objective of the 1984 Act was to facilitate the immediate entry of safe, effective generic drugs into the

\(^6\) Id. at *9.
\(^6\) Id. at *10, citing NeoRX Corp. v. Immunomedics, Inc., 877 F. Supp. 202, 204 (D.N.J. 1994).
\(^6\) Id. at *13.
\(^6\) Merck KGaA, 125 S. Ct. at 2379. The ruling of the trial court applying the common law research exception to Dr. Cheresh’s pre-1995 activities does not appear to comport with the limited scope of that exception as held in *Madey v. Duke Univ.*, 307 F.3d 1351 (Fed. Cir. 2002). That ruling was apparently not challenged on appeal, but the theory was abandoned by the defendants, probably as a result of the *Madey* case.
\(^6\) Merck KGaA, 125 S. Ct. at 2379.
\(^6\) Id.
\(^6\) The basis for the post-trial dismissal of Scripps and Dr. Cheresh is not indicated in the published opinions of this case. Prior to trial, Integra had limited its request for relief against those two parties to declaratory relief. *Integra*, 331 F.3d 860 at 863.
\(^6\) The Federal Circuit reversed the damages award and remanded the case for a recalculation of damages. Id at 872.
\(^6\) Id. at 865.
marketplace upon expiration of a pioneer drug patent.” In this case, none of the factors noted by Judge Rader in the legislative history were present: Merck and Scripps were not generic drug manufacturers, their activities were not aimed at quickly bringing a generic version of a patented drug to market upon expiration of a patent, and the activity itself was much more basic than bioequivalency testing. Plainly, Judge Rader believed that neither the parties nor the activities they were engaged in were the intended beneficiaries of the safe harbor.

Judge Rader framed the issue as whether the statute “reaches back down the chain of experimentation to embrace development and identification of new drugs that will, in turn, be subject to FDA approval.” While acknowledging the Eli Lilly holding that the statute is not limited to generics, Judge Rader stated that, because the focus is on the provision requiring the transfer of information to the FDA, applying the statute to “[a]ctivities that do not directly produce information for the FDA . . . already strain[s] the relationship to the central purpose of the safe harbor.” He termed the statute a “de minimis encroachment on the rights of the patentee.” Although the opinion did not state precisely where in the “chain of experimentation” the statutory protection commences, it rejected an interpretation that “would encompass drug development activities far beyond those necessary to acquire information for FDA approval of a patented pioneer drug already on the market.”

The panel majority characterized the activities of the defendants as “general biomedical research to identify new pharmaceutical compounds,” and outside the scope of § 271(e)(1). The Federal Circuit seemed to identify the Scripps-Merck research as mere drug “identification,” because they tested three compounds, and only selected one for further study, stating: “The Scripps-Merck experiments did not supply information for submission to the United States Food and Drug Administration (FDA), but instead identified the best drug candidate to subject to future clinical testing under the FDA processes.”

There is also language in the opinion suggesting that the exemption does not include “pre-clinical” research, such as animal research. This is significant because animal studies are the basis for clinical studies in humans. Under the panel majority’s interpretation of the statute,

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70 Id. at 865-866.
71 Id. at 867-868.
72 Id. at 866.
73 Id.
74 Id. at 867.
75 Id.
76 Integra, 331 F.3d 860 at 866 (“In this case, the Scripps work sponsored by Merck was not clinical testing to supply information to the FDA, but only general biomedical research to identify new pharmaceutical compounds. The FDA has no interest in the hunt for drugs that may or may not later undergo clinical testing for FDA approval.”).
77 Id.
78 “This court has not considered the question arising in this case, namely, whether the pre-clinical research conducted under the Scripps-Merck agreement is exempt from liability for infringement of Integra’s patents under § 271(e)(1).” Id.
new drugs could never get past the first three years of pre-clinical testing to get to human testing without risking patent infringement, injunction and/or damages.

The Federal Circuit panel’s decision in Merck was clearly a retrenchment. Although the decision did not expressly limit the safe harbor to generic drugs, the opinion left open how, if at all, the safe harbor could apply to activity in preparation for a New Drug Application. Although the court acknowledged the substantial burden posed by the cumulative number of licenses a drug developer may be required to obtain,79 a result of the panel’s decision would be to increase that number. The panel’s decision also served to disadvantage drug companies in the United States in comparison to those in certain foreign countries, where more patent protection for drug research is available.80

The importance of the Federal Circuit’s narrow construction of the testing covered by the safe harbor of § 271(e)(1) is heightened by the unavailability of the common law “research use defense.” In the distant past, there was an exception to patent infringement where the use was for research or purely experimental purposes. In 1813, Justice Story in Whittemore v. Cutter first articulated a research use exception, using the now anachronistic term “philosophical” instead of scientific. Justice Story stated, “it could never have been the intention of the legislature to punish a man, who constructed such a [patented] machine merely for philosophical experiments, or for the purpose of ascertaining the sufficiency of the machine to produce its described effects.”81 Although mere dictum, this observation provided the impetus for judicial recognition of an experimental use defense.

While this defense had been rarely used and was modest in its application, the Federal Circuit nevertheless signaled its effective demise in Madey v. Duke,82 decided a year before the Integra case. In Madey, the court held the research use exception only applies when activity is not in furtherance of the alleged infringer’s legitimate business, but must be “solely for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry.”83 Thus, the court remanded the case, suggesting that Duke University might not qualify for the defense, even though it was a non-profit research institution because it was furthering legitimate business purposes, including “educating and enlightening students and faculty . . . [and increasing] the status of the institution and lure lucrative research grants, students and faculty.”84 Under such a high standard, it is unlikely that any enterprise can qualify for the experimental use defense, making the Merck case and the scope of the § 271(e)(1) exception even more important.

Merck was denied rehearing and rehearing en banc in the Federal Circuit, prompting a petition for writ of certiorari in the Supreme Court, which was granted.85 The Court vacated the

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79 Id. at 871.
83 Madey, 307 F.3d at 1362.
84 Id.
Federal Circuit’s decision and in doing so, took a very different approach to the interpretation of § 271(e)(1). Justice Scalia, writing for a unanimous court, rejected the view taken by Judge Rader, which had focused on the statute as directed toward the generic drug approval process.

Pulling no punches, Justice Scalia described the Federal Circuit’s statement that the FDA “had no interest in the hunt for drugs that may or may not later undergo clinical testing for FDA approval” as “disregard[ing] ... reality.” He directly rejected two basic premises of the Federal Circuit’s opinion: “Congress did not limit § 271(e)(1)’s safe harbor to the development of information for inclusion in a submission to the FDA; nor did it create an exemption applicable only to the research relevant to filing an ANDA for approval of a generic drug.” He also rejected the idea that animal testing is not included in the exemption.

The Supreme Court construed § 271(e)(1) broadly as providing safe harbor for “all uses of patented inventions that are reasonably related to the development and submission of any information under the FDCA.” Although the Court did not say exactly where “on the road to regulatory approval” the protection of § 271(e)(1) begins, the Court did provide the following guidance:

At least where a drug-maker has a reasonable basis for believing that a patented compound may work, through a particular biological process, to produce a particular physiological effect, and uses the compound in research that, if successful, would be appropriate to include in a submission to the FDA, that use is ‘reasonably related’ to the ‘development and submission of information under ... Federal law’ ...

The Court also made clear that the test for protection under the statute does not necessarily include a requirement that the results of experiments with a patented compound be included in a submission to the FDA. The Court accepted the proposition that, especially during the preclinical stage, it will not always be clear what kinds of information and in what quantities, will be needed to win FDA approval.

In short, the Supreme Court demolished the rough equivalence that the Federal Circuit had attempted to make between the safe harbor of § 271(e)(1) and generic drug testing. The Supreme Court interpreted the statute as applying to “any” testing “reasonably related” to the

86 Merck KGaA, 125 S. Ct. 2372, 162 L. Ed. 2d 160 (2005).
87 Id. at 2382.
88 Id. at 2383.
89 Id. at 2381.
90 Id. at 2380 (emphasis in original).
91 Id. at 2383.
92 Id.
93 Id.
94 Id.
FDA approval process, even where the data is not ultimately submitted to the FDA (as in the case of a failed drug lead or candidate).95

Aside from the main part of the Supreme Court’s decision, which addresses § 271(e)(1) substantively, one aspect of this decision that may have significant and unforeseen practical importance in future trials is the Court’s comments on the jury instruction, an issue not discussed in the Federal Circuit’s opinion. The trial court’s instruction to the jury is reprinted in its entirety in the Supreme Court’s decision:

To prevail on this defense, [petitioner] must prove by a preponderance of the evidence that it would be objectively reasonable for a party in [petitioner’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.

Each of the accused activities must be evaluated separately to determine whether the exemption applies.

[Petitioner] does not need to show that the information gathered from a particular activity was actually submitted to the FDA.96

It is relatively rare for the Supreme Court to deal with jury instructions. But, almost in passing, the Supreme Court expressly approved the above instruction as consistent with the Court’s holding in this case.97 Because the Court has now blessed this instruction, it is likely to have great weight with district judges fashioning jury instructions in future cases under this statute.

The immediate result of the Court’s approval of the jury instruction is that there is no need for a new trial, and the issue on remand to the Federal Circuit will be the sufficiency of the evidence to support the jury’s verdict, applying the law as stated in the instruction and as explained in more detail in the Supreme Court’s opinion.98

95 "It does not follow from this, however, that § 271(e)(1)’s exemption from infringement categorically excludes either (1) experimentation on drugs that are not ultimately the subject of an FDA submission or (2) use of patented compounds in experiments that are not ultimately submitted to the FDA. Under certain conditions, we think the exemption is sufficiently broad to protect the use of patented compounds in both situations." "Id. at 2382.

96 "Id. at 2379.

97 "T]he evidence presented at trial has yet to be reviewed under the standards set forth in the jury instruction, which we believe to be consistent with, if less detailed than, the construction of § 271(e)(1) that we adopt today." "Id. at 2384.

98 "We decline to undertake a review of the sufficiency of the evidence under a proper construction of § 271(e)(1) for the first time here. Accordingly, we vacate the judgment of the Court of Appeals and remand the case for proceedings consistent with this opinion." "Id. at 2384. On remand, the Federal Circuit issued an order returning the case to the same panel and providing a schedule for new briefs to be filed “with particular attention paid to the Supreme Court decision.” "Integra LifeSciences I, Ltd. v. Telios Pharm., Inc., 02-1052,-1065, United States Court of Appeals for the Federal Circuit, Order dated August 17, 2005. Somewhat surprisingly, the order sua sponte invited amicus briefs. Ordinarily amicus briefs are filed to address issues of law and policy that may be of interest to a constituency beyond the parties to the case. In this instance, now that the Supreme Court has decided the important
By approving the jury instructions in this case, the Supreme Court may have sown the seeds of difficulties in future cases. The instruction does inform the jury that to be covered by the statute it is not necessary that the information resulting from the activity was actually submitted to the FDA. However, aside from that one point, the instruction does not really provide clear guidance to a jury. For example, the phrases “decent prospect,” “contribute, relatively directly,” and “likely to be relevant” are vague, awkward, and will lead to jury confusion.

The Supreme Court took pains in *Merck v. Integra* to set forth, in broad and strong language, the meaning of this important statute to a jury. However, the meaning of the statute will boil down to what is stated in the jury instruction. Unfortunately, the approved jury instruction does not match in force or clarity the substantive discussion in the Court’s decision. This means that the hard decisions in future cases may have to be made by the trial judge in either summary judgment rulings or in post-trial JMOL rulings, or by the Federal Circuit on appeal.

**IV. Drug Discovery after *Merck v. Integra***

Drug companies can be relieved that any experiments conducted after “lead” identification appear to be exempt from infringement, so long as they can be shown to be related to the submission of information to the FDA. This includes both clinical and pre-clinical testing. The multimillion dollar question, however, is how far back on the “road to regulatory approval” does the exemption extend? It is clear that it extends past clinical to pre-clinical testing, but does it go all the way back, for example, to drug discovery or to High Throughput Screening (HTS)?

The Supreme Court’s *Merck v. Integra* opinion suggests that it might. The Court stated that “[i]n the statute for excluding certain information from the exemption on the basis of the phase of research in which it is developed.”

Interestingly, the U.S. government agrees with this viewpoint. As stated in their amicus brief:

A researcher could not, however, settle on a particular compound unless it had already run tests on that compound that revealed it to be the best candidate for use in the drug. Thus, “screening” of compounds for use in a particular drug . . . is reasonably related to the development and submission of information to FDA because it allows the researcher to identify the appropriate compound or compounds to submit.\(^9\)

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\(^9\) The Supreme Court left no doubt that preclinical testing can fall within the infringement safe harbor: “We thus agree with the Government that the use of patented compounds in preclinical studies is protected under § 271(e)(1) as long as there is a reasonable basis for believing that the experiments will produce ‘the types of information that are relevant to an IND or NDA.’” *Brief of United States as Amicus Curiae 23.* *Merck KGaA,* 125 S. Ct. at 2383-84.

\(^10\) *Id.* at 2380 (emphasis added).

Moreover, interpreting the statute to include HTS could be considered to be consistent with FDA practice. For example, the FDA has a procedure called a “Screening IND” that permits a manufacturer to present multiple variants of a drug in a single IND, with a view toward researching “a number of closely related drugs to choose the preferred compound or formulation.” Thus, to the extent that drug companies choose to use the screening IND application and submit the HTS results for several promising leads, they might thereby strengthen their argument that HTS is included in the safe harbor.

The issue of whether HTS should be covered by the safe harbor was debated in the amicus briefs filed with the Supreme Court. For example, the American Intellectual Property Law Association (AIPLA) amicus brief argued that “[h]igh-throughput screening techniques . . . should not be considered ‘reasonably related’ to the development of information for the FDA.” AIPLA contended that the FDA is concerned with safety and effectiveness, and noted that the screening IND is only for closely related molecules. As noted by the Federal Circuit, “exaggerating § 271(e)(1) out of context would swallow the whole benefit of the Patent Act for some categories of biotechnological inventions.”

The Integra case does not squarely present the issue of whether § 271(e)(1) applies to HTS. Scripps began with the known RGD peptide and merely improved that peptide by cyclizing it for use as a drug and by making other minor modifications. Arguably, the Scripps research was more akin to the lead “optimization” experiments performed once a lead is identified in a HTS. Thus, although the case has been remanded for further consideration in light of the proper interpretation of the statute, the decision on remand by the Federal Circuit is not likely to provide much guidance on the question of how far back in the drug screening process the safe harbor goes.

The question of the scope of the FDA infringement exception is important to consumers, research-based drug companies, the biotechnology industry, and even the American economy. The possibility of patent infringement or reach-through royalties serves to raise drug prices, which are felt by many consumers to be too high already. Further, in an environment of patent litigation and uncertain damages, drug companies may move their research facilities offshore, a

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104 AIPLA Brief at 20.
105 AIPLA Brief at 14.
107 A “reach-through royalty” is a royalty on a downstream product, rather than on the patented product per se. As an example, a royalty on a drug that was discovered with the use of a patented product, such as a patented protein or gene, would be called a reach-through royalty.
108 Cf. Although expensive, medicine is a fraction of the cost of surgery.
trend already seen as drug companies open screening facilities in the Far East.\textsuperscript{109} As the research moves, so do jobs. Pharmaceutical research is a $33 billion industry\textsuperscript{110} that directly employs more than 310,000 people.\textsuperscript{111} Further, as research moves, so does the American technical edge over other countries.\textsuperscript{112}

An overly broad reading of § 271(e)(1) could also be a serious blow to the biotechnology industry—a $30 billion a year industry that has produced some 160 drugs and vaccines, has another 370 biotech products in clinical trials, and employs almost 200,000 people.\textsuperscript{113} A safe harbor broad enough to reach initial HTS studies could potentially erode the value of many genomic patents, whose main worth may lie in screening uses for the genes and proteins claimed therein.

**Conclusion**

Although it is now clear that the FDA safe harbor is not restricted to generic drugs, and that it includes animal as well as human studies, the precise boundary of the safe harbor has yet to be determined. The answers will have to be provided in future cases. The handling of those future cases may be more problematic than the Supreme Court intended, as a consequence of the poorly drafted jury instructions approved by the Court.

As a practical matter, we can expect drug companies to begin including screening data in their IND submissions in an attempt to push the limits of the safe harbor to the very beginning of the drug discovery process. Meanwhile, biotech patent owners who might feel stymied by the result in *Merck v. Integra*, may turn to Congress, attempting to have the boundaries of the § 271(e)(1) exemption clarified by amendment. At the same time, research and non-profit organizations may potentially seek to have the common law research use defense codified in a more substantial and enhanced form from the vestige remaining after the *Madey* decision.

\textsuperscript{109} *Bayer AG v. Housey Pharms., Inc.* 340 F.3d 1367, 1368 (Fed. Cir. 2003) (establishing that it is possible to import drugs discovered in overseas screening because the § 271(g) restriction on importation covered “products” not information). See also, Nancy Evans, *Offshore Drug Development May be Necessary to Control Cost* (March 2004), at http://www.gsb.stanford.edu/news/headlines/2004healthcareconf.shtml (“Between 1990 and 2000, the number of clinical trials abroad jumped from 271 to 4,458, and the number of countries involved more than tripled — from 22 to 79.”).


\textsuperscript{112} See also, Nancy Evans, *Offshore Drug Development May be Necessary to Control Cost* (March 2004), at http://www.gsb.stanford.edu/news/headlines/2004healthcareconf.shtml (last visited January 4, 2006) (“Forty to 60 percent of postdocs in the United States are from the PRC and Taiwan. In 10 years, there will be a reverse brain drain in U.S. biotech. The people who will be leaving are the same people who are doing our best research here.” (quoting Fred Volinsky, managing director of RCT BioVentures).

The research use exceptions to patent infringement, both as stated in § 271(e)(1) or as provided in judge-made law, will continue to be politically charged, because the result will ultimately affect drug prices. Thus, a careful delineation of the boundaries of the safe harbor is important to all members of the community—drug manufacturers and consumers alike.