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The Scope of the 'Safe Harbor' Provision of the Hatch-Waxman Act in View of Merck v. Integra Lifesciences

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INTRODUCTION

The impact of the Supreme Court’s decision in *Merck KGAA v. Integra Lifesciences I, Ltd.*¹ on the safe harbor provision of the Hatch–Waxman Act² is the focus of the following discussion. Thus, this paper analyzes the recent decision and proposes a new standard for determining whether Federal Drug Administration (“FDA”)–related conduct is exempt from infringement under the safe harbor. However, a thorough understanding of the section, its origins, and earlier judicial interpretations is beneficial in assessing the present scope of this important provision.

I. OVERVIEW OF THE HATCH-WAXMAN ACT

The Drug Price Competition and Patent Term Restoration Act of 1984³—also known as the Hatch–Waxman Act (the “Act”)—profoundly affected both the patent and food and drug laws and consequently, the manner in which the U.S. pharmaceutical industry operates.⁴ It attempted to strike a balance among competing interests (particularly, innovator and generic pharmaceutical companies).⁵

The Act amended the food and drug laws by, *inter alia*, creating a new procedure for approving generic drugs, which now includes antibiotics (but not biologics)—the Abbreviated New

¹ 125 S. Ct. 2372 (2005), *vacating*, 331 F.3d 860 (Fed. Cir. 2003).

² 35 U.S.C. § 271(e)(1) (2000).

³ Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98–417, 98 Stat. 1585 (codified at 15 U.S.C. §§ 68b–68c, 70b (1984); 21 U.S.C. §§ 301 et al. (1984); 35 U.S.C. §§ 156, 271, 282 (1984)).

⁴ See *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 665 (1990).

⁵ See *Allergan Inc. v. Alcon Labs., Inc.*, 324 F.3d 1322, 1325 (Fed. Cir. 2003) (explaining the benefits of the Act to both brand name and generic drug manufacturers).

Drug Application ("ANDA").⁶ It also altered the patent laws in various ways. For example, the erosion of a patent's term during FDA review is offset by extending the term for a period based on the length of agency review.⁷ In addition, the Act created a cause of action for patent infringement linked to the new ANDA procedure.⁸ It is considered a "theoretical" act of infringement to file an ANDA seeking FDA approval to market a patented drug before the pertinent patent expires.⁹ Only equitable remedies,¹⁰ whose determination was expressly assigned to the court, are available to redress such theoretical infringement.¹¹

The Act also established an exemption to infringement.¹² A patentee's competitors can usually begin marketing an otherwise infringing product only when the patent expires, or shortly thereafter.¹³ The marketing of pharmaceuticals, however, is strictly regulated by the FDA, and FDA approval can, and usually does, take years.¹⁴ Moreover, under the Federal Circuit's decision in *Roche Products, Inc. v. Bolar Pharmaceutical Co.*,¹⁵ a potential competitor could not even commence the testing required to seek FDA approval without infringing pertinent patents prior to their

⁶ *See id.*

⁷ 35 U.S.C. § 156(a)(4) (2000). *See* Pfizer Inc. v. Dr. Reddy's Labs., Ltd., 359 F.3d 1361, 1364 (Fed. Cir. 2004).

⁸ 35 U.S.C. § 271(e)(2)(A) (2000).

⁹ 35 U.S.C. § 271(e)(2)(A). *See* Allergan Inc. v. Alcon Labs., Inc., 324 F.3d at 1326. This section also covers so-called "paper NDAs" or "§ 505(b)(2) applications."

¹⁰ 35 U.S.C. § 271(e)(4) (2000). Monetary damages are only awarded if the infringer commercially manufactured, used, offered to sell, or sold an approved drug or veterinary biological product within the United States or imported such products into the United States. 35 U.S.C. § 271(e)(4)(C) (2000).

¹¹ *See* Glaxo Group Ltd. v. Apotex, Inc., No. 00 C 5791, 2001 WL 1246628, at *4 (N.D. Ill. Oct. 16, 2001); Pfizer Inc. v. Novopharm Ltd., No. 00 C 1475, 2001 WL 477163, at *3 (N.D. Ill. May 3, 2001). *See generally* Brian D. Coggio & Sandra A. Bresnick, *The Right to a Jury Trial Under the Waxman-Hatch Act*, 52 FOOD & DRUG L.J. 259 (1997); Brian D. Coggio & Timothy E. DeMasi, *The Right to a Jury Trial Under The Waxman-Hatch Act: The Question Revisted and Resolved*, 57 FOOD & DRUG L.J. 155 (2002).

¹² 35 U.S.C. § 271(e)(1) (2000).

¹³ *See* Brian D. Coggio & F. Dominick Cerrito, *The Safe Harbor Provision of the Hatch-Waxman Act: Present Scope, New Possibilities, and International Considerations*, 57 FOOD & DRUG L.J. 161, 162 (2002) [hereinafter Coggio & Cerrito, *Safe Harbor*].

¹⁴ *See generally* 21 U.S.C. §§ 301-97 (2000).

¹⁵ 733 F.2d 858 (Fed. Cir. 1984).

expiration.¹⁶ Thus, because of this prohibition, the lengthy approval process was further prolonged, and the availability of drugs was delayed.¹⁷ This ruling was not limited to generic filings, but also impacted any pharmaceutical research, including studies to prepare an NDA.¹⁸ During the FDA-approval process, however, the patentee would still enjoy market exclusivity, even though the relevant patent(s) had expired.¹⁹ Congress addressed this situation by creating the safe harbor provision, section 271(e)(1), one provision of the Hatch–Waxman Act.²⁰ Changes to the Act implemented by the FDA regulations effective August 2003, and the Medicare Prescription Drug, Improvement, and Modernization Act of 2003,²¹ did not affect the scope of the safe harbor exemption.²²

II. THE SAFE HARBOR PROVISION

Section 271(e)(1) of Title 35, United States Code, reads:

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 a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use or sale of drugs or veterinary biological products.

The section was intended to overrule the *Roche* decision and to exempt from infringement the bioequivalency testing needed to secure FDA approval of generic drugs.²³ Indeed, at one time, it

¹⁶ See *id.* at 863.

¹⁷ See Coggio & Cerrito, *Safe Harbor*, *supra* note 13, at 162.

¹⁸ See *id.*

¹⁹ See *id.*

²⁰ 35 U.S.C. § 271(e)(1) (2000). See generally *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661 (1990); Coggio & Cerrito, *Safe Harbor*, *supra* note 13.

²¹ Pub. L. No. 108–173, 117 Stat. 2206 (2003).

²² See generally Brian D. Coggio, M. Veronica Mullally, & Todd L. Krause, *Congress, FDA Address Hatch–Waxman Issues: Recent Agency Regulations and 2003 Medicare Act Clarify and Modify Generic Drug Law*, N.Y.L.J., Jan. 26, 2004, s2 (col. 1).

²³ See generally Allan M. Fox & Allan R. Bennett, *The Legislative History of the Drug Price Competition and Patent Term Restoration Act of 1984 (FDLI 1987)*.

had been argued that the section was limited to bioequivalency testing.²⁴ This interpretation was rejected, and over the ensuing years, the section has been construed very broadly.²⁵ This trend was abruptly halted by the Federal Circuit’s decision in *Integra Lifesciences I, Ltd. v. Merck KGAA*,²⁶ although the Supreme Court’s opinion vacating that decision gave the scope of the exemption a “wide berth.”²⁷

A. Early Decisions Interpreting the Safe Harbor

Early decisions addressing the safe harbor focused on the word “solely” and whether the alleged infringing “uses” related “solely” to the FDA approval process.²⁸ These decisions, particularly *Scripps Clinic*, limited the scope of the exemption,²⁹ while subsequent decisions focused on the phrase “reasonably related” and greatly expanded its scope.³⁰ In fact, conduct that is “reasonably related” to securing FDA approval does not forfeit immunity even if that conduct has additional purposes.³¹ For

²⁴ See *Scripps Clinic & Research Found. v. Genentech, Inc.*, 666 F. Supp. 1379, 1396 (N.D. Cal. 1987) (quoting H.R. REP. NO. 98–857 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647).

²⁵ See, e.g., *Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269, 1276–77 (Fed. Cir. 1993); see also *Abtox, Inc. v. Exitron Corp.*, 888 F. Supp. 6, 8–9, (Fed. Cir. 1997); *NeoRX Corp. v. Immunomedics, Inc.*, 877 F. Supp. 202, 205–06 (D.N.J. 1994); *Elan Transdermal Ltd. v. Cygnus Therapeutic Sys.*, 24 U.S.P.Q.2d (BNA) 1926, 1931–33 (N.D. Cal. 1992).

²⁶ 331 F.3d 860 (Fed. Cir. 2003).

²⁷ *Merck KGAA v. Integra Lifesciences I, Ltd.*, 125 S. Ct. 2372, 2380 (2005).

²⁸ See, e.g., *Scripps Clinic*, 666 F. Supp. at 1395–96 (holding that use of patented compound to obtain data for FDA approval *and* to support European patent filing was infringement); see also *American Standard Inc. v. Pfizer Inc.*, 722 F. Supp. 86, 102–03 (D. Del. 1989). The Federal Circuit in *Integra LifeSciences I, Ltd. v. Merck KGAA*, 331 F.3d 860, 866 (Fed. Cir. 2003) rediscovered the term “solely.”

²⁹ *Scripps Clinic*, 666 F. Supp. at 1395–96. *But see* *Elan Transdermal Ltd. v. Cygnus Therapeutic Sys.*, 24 U.S.P.Q.2d (BNA) 1926, 1932–33 (N.D. Cal. 1992) (finding that “solely” is correctly read as modifying “uses,” not “reasonably related”). The *Elan* court specifically held that the *Scripps Clinic* decision “misconstrues the exemption.” *Id.* at 1932.

³⁰ See, e.g., *Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269, 1280 (N.D. Cal. 1991) (“Thus, Congress used this phrase to communicate its intention that the courts give parties some latitude in making judgments about the nature and extent of the otherwise infringing activities they would engage in as they sought to develop information to satisfy the FDA.”).

³¹ See *id.* at 1287–88.

example, in *Intermedics, Inc. v. Ventritex, Inc.*, the district court stated that “the inquiry is *not* generally whether the allegedly infringing party has engaged in conduct that shows that it has purposes beyond generating and presenting data to the FDA.”³² Thus, the term “solely” is not determinative.³³

B. Standard for Applying the Safe Harbor

Application of section 271(e)(1) requires a two-step analysis: (1) only infringing uses are analyzed under the section; and (2) only those infringing uses that are not “reasonably related to the development and submission of information” to the FDA are actionable.³⁴ The district court in *Intermedics* framed the following test:

Would it have been reasonable, objectively, for a party in defendant’s situation to believe that there was a decent prospect that the “use” in question would contribute (relatively directly) to the generation of kinds of information that [are] likely to be relevant in the processes by which the FDA would decide whether to approve the product?³⁵

In applying the exemption, the nature of the alleged infringing conduct, not the subjective intent of the purported infringer (*e.g.*, a profit motive), is determinative.³⁶ In *Telectronics Pacing Sys., Inc. v. Ventritex, Inc.*,³⁷ the Federal Circuit held that activities designed

³² *Intermedics*, 775 F. Supp. at 1278.

³³ In affirming, the Federal Circuit held that “[r]eliance on section 271(e)(1) is not precluded by manifestation of an intent to commercialize upon FDA approval.” *Intermedics, Inc. v. Ventritex, Inc.*, 26 U.S.P.Q.2d (BNA) 1524, 1528.

³⁴ *See Abtox, Inc. v. Exitron Corp.*, 888 F. Supp. 6, 8–9 (D. Mass. 1995); *NeoRX Corp. v. Immunomedics, Inc.*, 877 F. Supp. 202, 205–06 (D.N.J. 1994) (manufacturing product in U.S. for non–U.S. testing to generate data for foreign regulatory agencies is not protected).

³⁵ *Intermedics*, 775 F. Supp. at 1280.

³⁶ *See id.* at 1280–81 (holding that only a defendant’s actual acts, as opposed to alleged future acts, were relevant and cautioned against considering underlying motives, indirect effects, and long range consequential benefits).

³⁷ 982 F.2d 1520 (Fed. Cir. 1992) (holding that data, originally gathered for FDA submission, did not lose their protection because they were used to obtain financial backing).

to raise funds were within the safe harbor, and stated: “It would strain credulity to imagine that Congress was indifferent to the economics of developing and marketing drugs and medical devices when it enacted § 271(e)(1).”³⁸ Again, the term “solely” was not determinative.³⁹

The *Intermedics* standard was used by various courts and expressly approved by the Supreme Court in *Merck KGAA v. Integra Lifesciences I, Ltd.*⁴⁰ It is submitted, however, that a new, more precise test can be formulated based on the Court’s recent decision. This proposal is discussed in section IV, *infra*.

C. Attempts to Limit the Safe Harbor

Even before the Federal Circuit’s decision in *Integra*, some courts had limited the scope of the safe harbor. For example, in *Baxter Diagnostics Inc. v. AVL Scientific Corp.*,⁴¹ the district court found that Class I and II—as opposed to Class III—medical devices were not subject to section 271(e)(1) because the safe harbor and patent term restoration provisions (35 U.S.C. § 156) were linked.⁴² Since only patents covering Class III medical devices could be extended, only those patents (not patents covering Class I or II devices) were covered by the safe harbor.⁴³ On

³⁸ *Id.* at 1525.

³⁹ See *Chartex Int’l PLC v. M.D. Personal Prods. Corp.*, 1993 WL 306169, at *2–3 (Fed. Cir. 1993).

⁴⁰ 125 S. Ct. 2372, 2383 (2005).

⁴¹ 798 F. Supp. 612 (C.D. Cal. 1992) (holding that Class I and II devices were not subject to exemption).

⁴² *Id.* at 620. See generally James M. Flaherty, Jr., *PMA Primary: Synthesizing the 35 U.S.C. § 156 Patent Term Extension, 35 U.S.C. § 271(e)(1) Patent Infringement Exemption as Currently Applied to Medical Devices, and Medical Device Preemption Jurisprudence to Yield a Cohesive Solution Regarding Scope of Coverage*, 56 FOOD & DRUG L.J. 339 (2001) [hereinafter Flaherty, *PMA Primary*].

⁴³ *Baxter Diagnostics*, 798 F. Supp. at 618–20. In rendering its opinion, the court relied on *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 672–73 (1990), which involved Class III medical devices. *Id.*

reconsideration, the court reversed its decision.⁴⁴ Subsequent decisions also rejected this view of “class” distinction.⁴⁵

In *NeoRX Corp. v. Immunomedics, Inc.*,⁴⁶ the court denied summary judgment of non-infringement where the defendant had manufactured the patented product in the United States and shipped it overseas for testing to support foreign regulatory approval.⁴⁷ Apparently, the court found that the accused conduct lacked any link to an FDA filing and was therefore not exempt.⁴⁸ Subsequently, the court in *Biogen, Inc. v. Schering AG*,⁴⁹ relying on *NeoRX*, stated: “Biogen’s shipment of Avonex samples [the patented product] produced in the United States to foreign regulatory authorities was not related to FDA requirements or other federal law and, therefore, was outside the statutory exemption.”⁵⁰ The *Biogen* court also held that stockpiling of a drug in anticipation of FDA approval was “far more than merely do[ing] clinical trials for submission to the FDA” and thus was outside the safe harbor.⁵¹

In *Infigen, Inc. v. Advanced Cell Technology, Inc.*,⁵² Infigen alleged infringement of a patent covering a process for activating bovine oocytes for use in cloning cattle.⁵³ The court rejected the safe harbor exemption, adopted the rationale of the initial *Baxter Diagnostics* decision, and limited the type of patents embraced by section 271(e)(1):

⁴⁴ See *Baxter Diagnostics, Inc. v. AVL Scientific Corp.*, 954 F. Supp. 199 (C.D. Cal. 1996); see also *Nexell Therapeutics, Inc. v. Amcell Corp.*, 143 F. Supp. 2d 407 (D. Del. 2001).

⁴⁵ See, e.g., *Abtox, Inc. v. Exitron Corp.*, 888 F. Supp. 6, 8–9 (D. Mass. 1995), *aff’d*, 122 F.3d 1019 (Fed. Cir. 1997), *amended by* 131 F.3d 1009 (Fed. Cir. 1997); *Chartex Int’l PLC v. M.D. Personal Prods. Corp.*, 1993 WL 30619, at *2 n.2 (Fed. Cir. 1993).

⁴⁶ 877 F. Supp. 202 (D.N.J. 1994).

⁴⁷ *Id.* at 207–09.

⁴⁸ See *id.* at 209.

⁴⁹ 954 F. Supp. 391 (D. Mass. 1996).

⁵⁰ *Id.* at 397 n.1.

⁵¹ *Id.* at 396–97.

⁵² 65 F. Supp. 2d 967 (W.D. Wis. 1999); see also *PharmaStem Therapeutics, Inc. v. Viacell Inc.*, No. Civ.A. 02–148 GMS, 2003 WL 548496 (D. Del. Feb. 26, 2003) (“umbilical cord blood stem cells units are not regulated by the FDCA and therefore cannot be considered a drug” within purview of 35 U.S.C. § 271(e)(1)).

⁵³ See *Infigen*, 65 F. Supp. 2d at 969.

Thus, holders of certain patents received an extended period of protection under the patent [§ 156]; in exchange, they were barred from collecting damages caused by otherwise infringing acts and by persons engaging in such acts solely for uses reasonably related to complying with FDA requirements. *See Eli Lilly*, 496 U.S. at 671, 110 S. Ct. 2683.⁵⁴

According to the court’s reading of *Eli Lilly & Co. v. Medtronic, Inc.*,⁵⁵ only patents (other than those covering generic drugs) whose terms could be extended under section 156 were subject to the safe harbor.⁵⁶

A patent holder whose patent is *ineligible* for the five-year [patent term] extension [under § 156] is *not* precluded from suing for infringement damages (except in unusual circumstances not present here, such as those involving patents pertaining to “follow-on” drug products rather than pioneers).⁵⁷

Under this reasoning, research tool patents would not be subject to the safe harbor exemption.⁵⁸ The *Infigen* court also held that the research was not exempt under the common law research exception.⁵⁹ The *Infigen* court, however, misperceived the holding in *Eli Lilly*, which did *not* limit the patents covered by section 271(e)(1) to those eligible for term extensions under section 156.⁶⁰ To the contrary, the Court recognized that in “some relatively rare

⁵⁴ *Id.* at 980. At least one commentator agrees with this limitation of the safe harbor provision. *See Flaherty, PMA Primary, supra* note 42, at 345–46.

⁵⁵ 496 U.S. 661, 672 (1990).

⁵⁶ *See Infigen*, 65 F. Supp. 2d 967, 980 (W.D. Wis. 1999).

⁵⁷ *Id.* (emphasis added).

⁵⁸ *See* Brief for the United States as Amicus Curiae Supporting Petitioner at 29–30 n.12, *Merck KGAA v. Integra Lifesciences I, Ltd.*, 125 S. Ct. 2372 (2005) (No. 03–1237) [hereinafter *Brief for the United States*]. The United States stated that this symmetry between sections 156 and 271(e)(1) was “another indication that Congress did not intend to include research tools within the scope of the inventions to which section 271(e)(1) applies.” *Id.*

⁵⁹ *See Infigen*, 65 F. Supp. 2d at 981. The Federal Circuit has held that the common law research exemption is essentially non-existent. *See also Madey v. Duke University*, 307 F.3d 1351, 1361–63 (Fed. Cir. 2002).

⁶⁰ *See Eli Lilly*, 496 U.S. at 661.

situations,” patents will not be eligible for an extension, but still be subject to the exemption of section 271(e)(1).⁶¹ Although the Court could not “readily imagine such situations,”⁶² countless possibilities do exist.

D. The Safe Harbor Is Construed Broadly

With minor exceptions, the courts have adopted an expansive reading of the safe harbor exemption. Representative of this liberal interpretation is *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*⁶³ There, Amgen sued Hoechst for infringement of Amgen’s patents on erythropoietin (EPO) and also sought a declaratory judgment that its patents would be infringed if Hoechst received FDA approval.⁶⁴ The *Amgen* court reviewed six potentially infringing activities: (1) exports of EPO; (2) purity testing; (3) manufacture of consistency batches; (4) characterization of the product; (5) viral clearance tests in Europe; and (6) radio labeling, and found that each was protected by the safe harbor.⁶⁵

As to the first category, Hoechst exported EPO to its Japanese affiliate for use as a reference in evaluating and improving its own manufacturing process.⁶⁶ Amgen contended that the shipment was not reasonably related to FDA approval because Hoechst had not sought approval of that particular process.⁶⁷ The court disagreed.⁶⁸ Since an alternative process would require FDA approval, and FDA guidelines supported the use of a reference standard from one process to evaluate an alternative process, the conduct was exempt, even though the data would not be included in Hoechst’s FDA submission.⁶⁹

⁶¹ *Id.* at 671–72.

⁶² *Id.* at 672 n.4.

⁶³ 3 F. Supp. 2d 104 (D. Mass. 1998). In reaching its decision, the *Amgen* court specifically criticized the decision in *Scripps Clinic & Research Found. v. Genentech, Inc.*, 666 F. Supp. 1379 (N.D. Cal. 1987). *Amgen* 3 F. Supp. 2d at 107–08.

⁶⁴ *Id.* at 106.

⁶⁵ *Id.* at 108–11.

⁶⁶ *Id.* at 109.

⁶⁷ *Id.*

⁶⁸ *Id.*

⁶⁹ *Id.*

In an attempt to analyze its product for purity, Hoechst conducted tests to identify pyrogens.⁷⁰ Amgen asserted that the tests were infringing since not all the resulting data would be submitted to the FDA; rather, some were actually submitted to European regulatory authorities.⁷¹ Hoechst claimed the tests were performed to confirm the purity of its EPO for use in clinical trials.⁷² The court held that even if the data obtained from the tests were insufficient for FDA purposes, the tests were nevertheless reasonably related to FDA clinical trials and thus exempt.⁷³

Hoechst's preparation of commercial-scale batches of EPO was also accused of infringement, primarily because the batches were abandoned due to lack of potency.⁷⁴ Amgen asserted that this abandonment indicated that the manufacture of these batches was not reasonably related to the FDA-approval process.⁷⁵ The court, however, held that the conduct was protected because the batches would likely lead to the generation of useful information regarding the pharmaceutical product.⁷⁶

The court held that the remaining activities were protected, even though some were not necessary to secure FDA approval.⁷⁷ For example, Amgen contended that Hoechst's worldwide efforts to gain approval for its version of EPO were not exempt.⁷⁸ The court disagreed and held that under Amgen's position, the disclosure of information obtained during clinical trials to anyone other than FDA would void the exemption.⁷⁹ Instead, the court concluded that all of Hoechst's activities challenged by Amgen were reasonably related to obtaining FDA approval. Thus, the infringement action was dismissed.⁸⁰

⁷⁰ *Id.*

⁷¹ *Id.*

⁷² *Id.* at 110.

⁷³ *Id.*

⁷⁴ *Id.*

⁷⁵ *Id.*

⁷⁶ *Id.*

⁷⁷ *Id.*

⁷⁸ *Id.*

⁷⁹ *Id.* at 110–11.

⁸⁰ The court's ruling also eliminated Amgen's right to declaratory relief because it could not establish a controversy satisfying the constitutional requirements. Although Hoechst would undoubtedly market EPO upon FDA approval and a "controversy" was

The broad scope of the exemption is also exemplified by *Wesley Jessen Corp. v. Bausch & Lomb Inc.*,⁸¹ where the court held that the safe harbor applied to post-approval clinical studies required by the FDA.⁸² There, the FDA granted Bausch & Lomb tentative approval of its extended-wear contact lens, provided it conducted a post-approval study investigating any adverse effects.⁸³ The court noted that “[n]owhere in [the] language [of the statute] . . . does Congress show an intent to limit the section 271(e)(1) exception solely to pre-approval activities.”⁸⁴ Since the FDA had required the studies, they certainly were “reasonably related to the development and submission of information” to that agency and were therefore exempt.⁸⁵

Another decision illustrating the liberal interpretation of section 271(e)(1) is *Nexell Therapeutics, Inc. v. Amcell Corp.*,⁸⁶ where the use of the patented invention in clinical trials was exempt,⁸⁷ even though the FDA had expressed concerns that the trials were not adequate for FDA submission. According to the patentee, under these circumstances, the trials could not be “reasonably related” to seeking FDA approval.⁸⁸ This argument was dismissed:

[U]nless the court is confronted with the extreme case in which either it is clear that certain otherwise infringing activities are outside the FDA approval process or the FDA

present, the court held that numerous factors militated against exercising jurisdiction at that time. First, not only was FDA approval an uncertain event, but the product or the process used by Hoechst might undergo changes that could be material to an infringement analysis, thus rendering any judgment moot. Second, because Hoechst would infringe only when its conduct exceeded the safe harbor, the court declined to upset the balance envisioned by Congress by allowing the declaratory judgment action to proceed before marketing began. *Id.* at 112–13.

⁸¹ 235 F. Supp. 2d 370 (D. Del. 2002).

⁸² *Id.* at 376.

⁸³ *Id.*

⁸⁴ *Id.* at 376.

⁸⁵ *Id.*; see also *Classen Immunotherapies, Inc. v. Biogen Idec*, 381 F. Supp. 2d 452, 455–56 (D. Md. 2005) (rejecting the argument that safe harbor “applies only to drugs which have not yet been approved by the FDA, [but it can cover] post approval activities associated with a drug that is already on the market”).

⁸⁶ 199 F. Supp. 2d 197 (D. Del. 2002).

⁸⁷ *Id.* at 202–05.

⁸⁸ *Id.* at 200.

itself affirmatively indicates that a party's activities are not reasonably related to obtaining its approval, the court will not find that accused activities that a defendant objectively believes could generate information that is likely to be relevant to the FDA approval process are not "reasonably related" to obtaining FDA approval.⁸⁹

Put simply, the court would not limit the scope of the safe harbor unless an "extreme case" was shown.⁹⁰

The broadest interpretation of section 271(e)(1) is articulated in *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*,⁹¹ where the court ruled that Bristol-Myers' drug discovery efforts using Rhone-Poulenc Rorer's ("RPR") patented intermediates to investigate and/or identify potential new drug candidates were exempt.⁹² The *Bristol-Myers* court held that all pharmaceutical research, including basic research, the synthesis of new drug candidates, their initial testing, and the determination of which drug candidates to pursue, was protected by the safe harbor.⁹³ Indeed, the court held that "[i]t would be nonsensical for the exemption to apply only in the development process after a drug candidate was identified" because infringement would necessarily occur before the protection of the safe harbor was reached.⁹⁴ As discussed *infra*, this "gap" in protection is noted in Judge Newman's dissenting opinion in *Integra Lifesciences I, Ltd. V. Merck KGAA*.⁹⁵

⁸⁹ *Id.* at 203. See also *Ino Therapeutics, Inc. v. Sensormedics Corp.*, C.A. No. 00-6033 (AET) (D.N.J. Nov. 27, 2003) Mem. Op. at 4-5 (holding sales of nitrous oxide to holders of investigational new drug applications was protected by the safe harbor).

⁹⁰ *Nexell Therapeutics* 199 F. Supp. 2d at 203.

⁹¹ No. 95 C 8833, 2001 WL 1512597 (S.D.N.Y. Nov. 28, 2001). RPR's patent claimed semi-synthetic processes for synthesizing the drug taxol and four intermediates used in preparing that drug.

⁹² *Id.* at *6.

⁹³ *Id.*

⁹⁴ *Id.* It is ironic that in many cases, a party (other than a generic) must infringe before it is eligible for protection under the safe harbor. See generally Janice M. Mueller, *No "Dilettante Affair": Rethinking the Experimental Use Exception to Patent Infringement for Biomedical Research Tools*, 76 WASH. L. REV. 1, 22-25 (2001).

⁹⁵ See *Integra Lifesciences I, Ltd. V. Merck KGAA*, 331 F.3d 860, 872-78 (Fed. Cir. 2003).

Under *Bristol-Myers*, it appeared that *all* pharmaceutical research conducted to identify new drugs was exempt.⁹⁶ In addition, since the term “patented invention” is *not* limited to patents extendable by section 156, a defendant could contend that the use of patented pipettes during drug discovery is protected by the safe harbor.⁹⁷ In view of *Merck v. Integra Lifesciences*, however, *Bristol-Myers* is not the law.

III. MERCK V. INTEGRA LIFESCIENCES

A. *The Federal Circuit Decision*

Section 271(e)(1), research tool patents, and related damages took center stage in *Integra Lifesciences I, Ltd. v. Merck KGAA*.⁹⁸ There, Integra alleged that Merck had directly infringed and induced Scripps to infringe five patents by encouraging Scripps’ tests on a target drug and related compounds.⁹⁹ Significantly, the research was conducted after Scripps had discovered that the target compound was potentially useful in treating cancer.¹⁰⁰ The defendants argued that their conduct was exempt under section 271(e)(1).¹⁰¹ The jury disagreed and returned a verdict for Integra, awarding \$15 million in damages.¹⁰² In a 2-1 decision, the Federal

⁹⁶ See *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*, No. 95 C 8833, 2001 WL 1512597, at *6. This, of course, does not include the filing of an ANDA or a paper NDA with a paragraph IV certification, either of which is an act of infringement under 35 U.S.C. § 271(e)(2).

⁹⁷ In passing, the *Bristol-Myers* court quoted one portion to the legislative history of the Act (later emphasized in *Integra Lifesciences*), which notes that the safe harbor “does not result in the total extinguishment of the patent owner rights, because the patent owner still maintains a right to exclude others from the commercial marketplace.” *Id.* at *6 n.6 (citation omitted). Quite possibly, the court may have believed that the RPR patents would be infringed and a lawsuit would be instituted when Bristol-Myers commercialized the resulting product. But the final product could well be made without using (*i.e.*, infringing) the patented intermediates. Thus, an action for infringement of the RPR patents might never be filed, and the patents might well have become commercially worthless. This same situation can apply to research tool patents.

⁹⁸ 331 F.3d 860 (Fed. Cir. 2003).

⁹⁹ *Id.* at 862–64.

¹⁰⁰ *Id.* at 863.

¹⁰¹ *Id.*

¹⁰² *Id.* at 869.

Circuit, per Judge Rader, affirmed the verdict, but vacated the award of damages and remanded the case for further consideration.¹⁰³ In its decision, the court limited the scope of section 271(e)(1) and suggested that the use of research tools, which were not even at issue in the case, in basic drug discovery was not exempt from patent infringement.¹⁰⁴ Judge Newman dissented.¹⁰⁵

The Federal Circuit opined that the Hatch–Waxman Act had two key purposes: (1) to extend the term of pharmaceutical patents to compensate for delays in the FDA approval process (section 156); and (2) to overrule *Roche v. Bolar* to ensure that the marketing of pharmaceuticals, particularly generic drugs, would not be unnecessarily delayed.¹⁰⁶ As support, the court referenced to the legislative history, which authorizes “a limited amount of testing so that generic manufactures can establish the bioequivalency of a generic substitute’.”¹⁰⁷ Despite its emphasis on generic drugs, the court noted that clinical trials were exempt under section 271(e)(1).¹⁰⁸

The court concluded that the Scripps’ research did not develop information for *submission* to the FDA, but was conducted to identify the best potential candidate for human testing.¹⁰⁹ The Supreme Court, however, indicated that this very conduct was exempt.¹¹⁰ The crux of the Federal Circuit’s decision reads:

The focus of the entire exemption is the provision of information to the FDA. Activities that do not directly produce information for the FDA are already straining the relationship to the central purpose of the safe harbor. The term “reasonably” permits some activities that are not

¹⁰³ *Id.* at 872.

¹⁰⁴ *Id.* at 871.

¹⁰⁵ *Id.* at 872.

¹⁰⁶ *Id.* at 865.

¹⁰⁷ *Id.* (quoting H.R. REP. NO. 98–857, at 8 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2692). The court also noted that the legislative history indicated that the “nature of the interference” with the rights of the patentee could not be “substantial,” but only “de minimis.”

¹⁰⁸ *Id.*

¹⁰⁹ *Id.*

¹¹⁰ *See* *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 665–78 (1990).

themselves the experiments that produce FDA information to qualify as “solely for uses reasonably related” to clinical tests for the FDA. Again, however, the statutory language limits the reach of that relationship test.

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. For instance, the FDA does not require information about drugs other than the compound featured in an Investigational New Drug application. Thus, the Scripps work sponsored by Merck was not “solely for uses reasonably related” to clinical testing for FDA.¹¹¹

The court again stressed that the purpose of the Act was to “expedite FDA approval of a generic version of a drug already on the market. . . . Therefore, the § 271(e)(1) safe harbor covers those pre-expiration activities ‘reasonably related’ to acquiring FDA approval of a drug already on the market.”¹¹² Relying on the *Intermedics* test, the court stated that the safe harbor exempts research that “‘would contribute (relatively directly)’ to information the FDA considers in approving a drug.”¹¹³ But the safe harbor does not exempt drug discovery efforts simply because the resulting product requires FDA approval.¹¹⁴ Indeed, “[t]he safe harbor does *not* reach any exploratory research that may rationally form a predicate for future FDA clinical tests.”¹¹⁵ Significantly, the Supreme Court endorsed this conclusion.¹¹⁶

Turning to research tool patents (which were not implicated by the facts as presented), the Federal Circuit noted that extending

¹¹¹ *Integra Lifesciences*, 331 F.3d at 866 (emphasis added). *But see* H.R. Rep. No. 98–857 (Pt. 1) at 45 (1984) (“A party which develops such information, but decides not to submit an application for approval, is protected as long as the development was done to determine whether or not an application for approval would be sought.”).

¹¹² *Integra Lifesciences* 331 F.3d at 867.

¹¹³ *Id.*

¹¹⁴ *Id.*

¹¹⁵ *Id.* (emphasis added).

¹¹⁶ *Merck KGAA v. Integra Lifesciences I, Ltd.*, 125 S. Ct. 2372, 2383 (2005).

section 271(e)(1) to cover Scripps’ research “would effectively vitiate the exclusive rights of patentees owning biotechnology tool patents” and would certainly not be a “*de minimis* encroachment on the rights of the patentee.”¹¹⁷ Thus, *Bristol–Myers*, which is not even mentioned in the court’s opinion, is clearly not the law.¹¹⁸

In her dissent, Judge Newman opined that the common law research exemption should exempt early pharmaceutical research, and section 271(e)(1) should protect further developmental efforts until commercialization.¹¹⁹ Otherwise, infringing research is necessary, and this would create a “gap” before the safe harbor exemption was reached.¹²⁰ Her concerns were not limited to pharmaceutical research; she was disturbed that technological progress¹²¹ would be hampered if all research, particularly basic research, were potentially infringing.¹²²

¹¹⁷ *Integra Lifesciences*, 331 F.3d at 867.

¹¹⁸ The court vacated the damages award because it was not clear that the lower court properly analyzed the hypothetical negotiation *before* the infringement began. Indeed, the value of a license could be “dramatically different” at a later date. In determining the amount, the court noted that the level of risk associated with the technology should be assessed, as well as a party’s inability to predict success, and the number of patent licenses necessary to conduct the research (“patent stacking”). *Id.* at 870–71. In particular, the Federal Circuit stated that the royalty would be lower if negotiated at the beginning of the research, rather than closer to product launch. On remand, Integra was awarded \$6.375 million as damages. *Integra Lifesciences I, Ltd. v. Merck KGAA*, 96 CV 1307–B (AJB) 2004 WL 2284001, *1 (S.D. Cal. Sept. 7, 2004). Unfortunately, the methodology used to determine the amount did not relate to research tool patents. *See generally* Donald Ware, *Research Tool Patents: Judicial Remedies*, 30 AIPLA Q.J. 267 (2002); Michael J. Stimson, *Damages for Infringement of Research Tool Patents: The Reasonableness of Reach Through Royalties*, 2003 STAN. TECH. L. REV. 3 (2003).

¹¹⁹ *Integra Lifesciences*, 331 F.3d at 875.

¹²⁰ *Id.* at 875–77.

¹²¹ *See id.* at 875–77. “[T]he patent system both contemplates and facilitates research into patented subject matter, whether the purpose is scientific understanding or evaluation or comparison or improvement.” *Id.* at 875.

¹²² *See id.* Since, in many areas of technology, technical information is *not* published apart from patents, how can the technology be studied, improved or “design[ed] around,” if such efforts constitute patent infringement? If these efforts were prohibited, why then, according to Judge Newman, must patents comply with the written description and best mode requirements? Certainly, when the patents expire 17–20 years later, the disclosures would be ancient. Judge Newman posits that these requirements indicate that contemporaneous (non–infringing) experiments are contemplated, *i.e.*, the patented invention is not placed “on ice” and protected from further study for years. *Id.*

According to Judge Newman, when basic research ends and commercial development begins, the common law research exemption expires.¹²³ In this case, however, the developmental work was protected by section 271(e)(1).¹²⁴ While she agreed with the limited origins of the section, she recognized that its scope had been extended;¹²⁵ she agreed, however, that it did not reach back down the chain of experimentation to cover basic research.¹²⁶ According to her, however, those research efforts should be exempt under the common law research exemption.¹²⁷ Judge Newman's opinion seemingly ignores *Madey v. Duke University*,¹²⁸ which would indicate that Scripps' early research efforts were not protected by the common law research exemption, although the district court had ruled otherwise.¹²⁹

As to research tools, Judge Newman differentiated between the use of a tool to conduct research and research on the tool itself.¹³⁰ Research "on" the tool should be exempt, but the use of a tool "for the purpose for which it was made" infringes.¹³¹ Under Judge Newman's view, if a research tool, e.g., an assay, is used to identify new drug candidates—the "purpose for which it was made"—that conduct should infringe.¹³² Unfortunately, the relationship between research tool patents and the safe harbor exemption was not addressed by the Supreme Court.¹³³

¹²³ *Id.* at 876.

¹²⁴ *Id.*

¹²⁵ *Id.* at 877.

¹²⁶ *Id.*

¹²⁷ *Id.* at 878.

¹²⁸ 307 F.3d 1351 (Fed. Cir. 2002).

¹²⁹ *See id.* at 1352.

¹³⁰ *Integra Lifesciences*, 331 F.3d at 877–78.

¹³¹ *Id.* at 878 n.10 (citing *Madey v. Duke Univ.*, 307 F.3d 1351 (Fed. Cir. 2002)).

¹³² *Id.*

¹³³ *See Merck KGAA v. Integra Lifesciences I, Ltd.*, 125 S. Ct 2372, 2382 n.7 (2005) (quoting Judge Newman's dissent: 331 F.3d at 878, "Use of an existing tool in one's research is quite different from study of the tool itself").

B. The Arguments Before the Supreme Court

Before the Supreme Court, Merck stressed the dire public policy ramifications of the Federal Circuit’s decision.¹³⁴ Indeed, unless the decision was reversed:

The patent holder would be able to bar all laboratory tests using the compound—or, as in this case, any structurally similar compound. . . . Drug innovators and researchers will have to sit on their hands awaiting patent expiration before *starting* to conduct the battery of experiments necessary to qualify a potentially path-breaking new drug. . . . Consequently, the patent holder will enjoy a de facto patent-term extension, while potential treatment for innumerable diseases and conditions will be denied to patients for a decade or more after all patents expire.¹³⁵

The brief summarized the preclinical testing necessary for an IND to demonstrate that Scripps’ research was exempt.¹³⁶ Since it did not need to establish that all drug discovery efforts were exempt to prevail, Merck stressed that the alleged infringing conduct “reflected a shift from basic discovery to inquiry into how this particular structure would work as a drug.”¹³⁷ Thus, once screening ends, and “a particular structure” shows promise, efforts to optimize that drug by experiments on “related drugs” is exempt as long as “the experiment relates to a topic that is of interest to the FDA.”¹³⁸ According to Merck, a “world of difference [exists] between basic exploratory research or screening of untested structures in test tubes and the drug optimization and preclinical research [necessary in an IND].”¹³⁹ The Supreme Court followed this generalized approach in stating that “basic scientific research” is not exempt under the safe harbor.¹⁴⁰

¹³⁴ See Brief for Petitioner at 41–43, *Merck KGAA v. Integra Lifesciences I, Ltd.*, 125 S. Ct. 2372 (No. 03–1237) [hereinafter *Brief for Petitioner*].

¹³⁵ *Id.* at 4.

¹³⁶ *Id.* at 7.

¹³⁷ *Id.* at 13.

¹³⁸ *Id.* at 39.

¹³⁹ *Id.* at 40.

¹⁴⁰ See *Merck KGAA v. Integra Lifesciences I, Ltd.*, 125 S. Ct. 2372, 2382 (2005). Although research tool patents were “not at issue,” the danger to such patents, according

Integra contended that only preclinical studies directed to safety—not efficacy—conducted in accordance with the FDA’s “Good Laboratory Practices” were exempt.¹⁴¹ Since Scripps’ tests did not satisfy this requirement, they were irrelevant to the FDA approval process.¹⁴² In support of its position, Integra cited FDA regulations requiring that preclinical tests on safety be included in an IND application, but such regulations did not require any tests on the drug’s efficacy.¹⁴³ Similarly, tests on related compounds are relevant to safety, not efficacy, and thus are not within the exemption unless performed under GLP, and Scripps’ tests were not.¹⁴⁴ In particular, efforts to identify “the best drug candidate to subject to future clinical testing” do not generate information for the FDA because the tests are not on the final product.¹⁴⁵ Accordingly, Scripps’ research was not exempt.¹⁴⁶

In its reply, Merck argued that the exemption could apply even before Scripps settled upon the optimum structure.¹⁴⁷ Rather, “[s]ince the tweaking to optimize structure is an essential part of the preclinical process,” such research must be protected.¹⁴⁸

Setting the stage for the Supreme Court’s decision, Merck noted that application of the exemption entails two inquiries—one temporal and one substantive.¹⁴⁹ First, how far along the drug development process must research be before the exemption applies?¹⁵⁰ Second, what categories of information (*i.e.*, types of research) are relevant to the FDA’s regulatory role?¹⁵¹ As shown

to Merck, would be “limited,” and therefore, this consideration had “little bearing” on Congressional intent regarding the safe harbor. *Brief for Petitioner, supra* note 134, at 33, 41, 43.

¹⁴¹ Respondents’ Brief on the Merits at 4, *Merck KGAA v. Integra Lifesciences I, Ltd.*, 125 S. Ct. 2372 (2005) (No. 03–1237).

¹⁴² *Id.* at 24.

¹⁴³ *Id.* at 5–8.

¹⁴⁴ *Id.* at 9, 37–38.

¹⁴⁵ *Id.* at 27.

¹⁴⁶ *Id.* at 27–28.

¹⁴⁷ Reply Brief for Petitioner at 1, *Merck KGAA v. Integra Lifesciences I, Ltd.*, 125 S. Ct. 2372 (No. 03–1237) [hereinafter *Reply Brief for Petitioner*].

¹⁴⁸ *Id.*

¹⁴⁹ *Id.* at 5.

¹⁵⁰ *Id.*

¹⁵¹ *Id.* at 5–6.

below, the Supreme Court addressed both questions. It could be argued, however, that the answer to the second inquiry is much clearer than that to the first.

C. *The Supreme Court Decision*

Justice Scalia, who had authored the Court's decision in *Eli Lilly v. Medtronic*, delivered the opinion for a unanimous Court.¹⁵² The Court vacated the Federal Circuit's decision and remanded the case so that the evidence could be reviewed under the standard set forth in the jury instructions, which the Court expressly endorsed.¹⁵³ After summarizing the general legal principles, the Court detailed the alleged infringing research.¹⁵⁴ These facts—as specifically articulated by the Court—are a useful backdrop in interpreting the scope of the safe harbor in light of the Court's legal pronouncements.

In 1988, Merck funded Scripps' research on angiogenesis, a process by which new blood vessels emanate from existing vessels.¹⁵⁵ In 1994, Scripps succeeded in reversing tumor growth using, *inter alia*, a cyclic RGD peptide provided by Merck under a research agreement.¹⁵⁶ In 1995, based upon this early success, Merck entered a new agreement to fund further research by Scripps, including *in vitro* and *in vivo* testing of RGD peptides, to identify a "primary candidate" for clinical testing.¹⁵⁷ Scripps conducted additional experiments on RGD peptides supplied by Merck (EMD 66203 and two closely related derivatives) to evaluate their suitability "as potential drug candidates."¹⁵⁸ The tests measured "the efficacy, specificity, and toxicity of the particular peptides . . . and evaluated their mechanism of action

¹⁵² Merck KGAA v. Integra Lifesciences I, Ltd., 125 S. Ct. 2372 (2005).

¹⁵³ *Id.* at 2384.

¹⁵⁴ *Id.* at 2377–79.

¹⁵⁵ *Id.* at 2377–78.

¹⁵⁶ *Id.* at 2378. One of the patented peptides was used as a control in certain experiments, but this conduct was not specifically address by the Federal Circuit or the Supreme Court.

¹⁵⁷ *Id.*

¹⁵⁸ *Id.*

and pharmacokinetics in animals.”¹⁵⁹ Based upon these tests, Scripps decided that EMD 121974 was “the most promising” candidate to evaluate in humans.¹⁶⁰ On July 18, 1996, as the Merck/Scripps collaboration was continuing, Integra filed suit for patent infringement.¹⁶¹ The issue at trial focused on whether the post-1995 research fell within the safe harbor exemption.¹⁶²

The Court initially stated that “the statutory text [of § 271(e)(1)] makes clear that it provides a *wide berth* for the use of patented drugs in activities related to the federal regulatory process.”¹⁶³ Furthermore, the “exemption from infringement extends to all uses of patented inventions that are reasonably related to the development and submission of *any* information under the FDCA.”¹⁶⁴ Lower court decisions interpreting the scope of the safe harbor will undoubtedly be guided by its “wide berth” of protection.¹⁶⁵ Just how wide will be determined on a case-by-case basis. The Court’s decision, however, can be conveniently parsed to answer discreet questions related to the scope of the exemption. This analysis follows.

1. Generic v. Branded Products

The safe harbor is not limited to the preparation of generic (“ANDA”) applications.¹⁶⁶ Rather, it includes NDAs, BLAs, and so-called paper-NDAs (§ 505(b)(2) applications).¹⁶⁷ As the Court stated:

[Congress] did [not] create an exemption applicable only to the research relevant to filing an ANDA for approval of a generic drug. Rather, it exempted from infringement *all*

¹⁵⁹ *Id.* Somewhat later, in November 1996, Merck initiated a formal project to guide one of the RGD peptides (EMD 85189) through regulatory approval. Merck later switched focus to EMD 121974. *Id.* at 2379.

¹⁶⁰ *Id.* at 2378.

¹⁶¹ *Id.* at 2379.

¹⁶² *Id.*

¹⁶³ *Id.* at 2380 (emphasis added).

¹⁶⁴ *Id.*

¹⁶⁵ *See, e.g.,* Classen Immunotherapies, Inc. v. Biogen Idec, 381 F. Supp. 2d 452, 456 (D. Md. 2005).

¹⁶⁶ *See, e.g.,* Merck KGAA v. Integra Lifesciences I, Ltd., 125 S. Ct. 2372, 2383 (2005).

¹⁶⁷ *See id.*

uses of patented compounds “reasonably related” to the process of developing information for submission under *any* federal law regulating the manufacture, use, or distribution of drugs.¹⁶⁸

The Federal Circuit opinion had caused some confusion on this point.

2. Clinical Trials v. Preclinical Tests

Addressing the issue raised by the petition for certiorari, the Court held that the safe harbor exemption is *not* limited to clinical trials, but can encompass preclinical tests.¹⁶⁹ As the Court stated:

[The exemption] necessarily includes *preclinical* studies of patented compounds that are appropriate for submission to the FDA in the regulatory process. There is simply no room in the statute for excluding certain information from the exemption on the basis of the phase of research in which it is developed or the particular submission [INDA v. NDA] in which it could be included.¹⁷⁰

. . . .

[T]he FDA requires that applicants include in an IND summaries of the *pharmacological, toxicological, pharmacokinetic, and biological qualities of the drug in animals*. . . . The primary (and, in some cases, only) way in which a drug maker may obtain such information is through *preclinical* in vitro and in vivo studies.¹⁷¹

Unfortunately, the Court did not explain what studies are “appropriate for submission.”¹⁷² Ironically, the Court also held that an FDA submission is not necessary for the exemption to apply.¹⁷³ Regardless, the holding demonstrates (clearly shows)

¹⁶⁸ *Id.*

¹⁶⁹ *Id.* at 2380.

¹⁷⁰ *Id.* (emphasis added) (footnote omitted).

¹⁷¹ *Id.* at 2381 (emphasis added).

¹⁷² *Id.* at 2380.

¹⁷³ *Id.* at 2382.

that the types of research potentially included within safe harbor protection are quite broad.¹⁷⁴

3. Safety v. Efficacy Tests

In rejecting Integra's argument that only preclinical safety tests are exempt from Section 271(e)(1)'s safe harbor protection, the Court held that preclinical tests evaluating either a drug's safety or efficacy are potentially subject to the safe harbor.¹⁷⁵

[T]he FDA does not evaluate the safety of proposed clinical experiments in a vacuum; rather, as the statute and regulations reflect, it asks whether the proposed clinical trial poses an "unreasonable risk." . . . Accordingly, the FDA directs that an IND must provide sufficient information for the investigation to "make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial." . . . Such information necessarily includes preclinical studies of a drug's efficacy in achieving particular results.¹⁷⁶

In addition, preclinical tests (*e.g.*, safety, efficacy, mode of action, etc.) need *not* be performed under good laboratory practice requirements to come within safe harbor.¹⁷⁷ Integra's argument that preclinical studies (other than safety) must comply with these standards was rejected.¹⁷⁸

[T]he FDA's requirement that preclinical studies be conducted under "good laboratory practices" applies only to experiments on drugs "to determine their safety." . . . The good laboratory practice regulations do not apply to preclinical studies of a drug's efficacy, mechanism of action, pharmacology, or pharmacokinetics. Second, FDA regulations do not provide that even safety-related experiments not conducted in compliance with good laboratory practices regulations are not suitable for

¹⁷⁴ *Id.*

¹⁷⁵ *Id.* at 2381.

¹⁷⁶ *Id.* (quoting 21 C.F.R. § 312.22(a) (2005)).

¹⁷⁷ *Id.* at 2381–82.

¹⁷⁸ *Id.*

submission in an IND. Rather, such studies must include "a brief statement of the reason for the noncompliance."¹⁷⁹

Thus, *all* preclinical trials are potentially exempt under the safe harbor regardless of their compliance with good laboratory practice.

4. Submission Of Data To The FDA

The use of patented compounds in experiments which generate data that are not submitted to the FDA may still come within the safe harbor.¹⁸⁰

[T]he use of a patented compound in experiments that are not themselves included in a "submission of information" to the FDA does not, standing alone, render the use infringing. The relationship of the use of a patented compound in a particular experiment to the "development and submission of information" to the FDA does not become more attenuated (or less reasonable) simply because the data from that experiment are left out of the submission that is ultimately passed along to the FDA.¹⁸¹

Indeed, it would seem beyond dispute that test results need not be submitted for the exemption to apply, especially since the Court's opinion focuses on this particular issue.

This case presents the question whether uses of patented inventions in preclinical research, the results of which are not ultimately included in a submission to the [FDA], are exempted from infringement by 35 U.S.C. § 271(e)(1).¹⁸²

Obviously, the Court did not require an FDA "submission" for the exemption to apply.¹⁸³

¹⁷⁹ *Id.* (quoting 21 C.F.R. § 58.3(d)).

¹⁸⁰ *Id.* at 2383.

¹⁸¹ *Id.*

¹⁸² *Id.* at 2376.

¹⁸³ *Id.* at 2383.

5. Tests on Non-Submitted Compounds

The Court held that the safe harbor is *not* limited to tests on the specific compound that is the subject of an FDA submission.¹⁸⁴ Thus, “drug optimization” or “tweaking” (to use Merck’s terms) can be exempt and therefore a final drug candidate need not be identified before the exemption can apply.¹⁸⁵ This aspect of the Court’s ruling is particularly significant to pharmaceutical companies. It does not follow . . . that § 271(e)(1)’s exemption from infringement categorically excludes . . . experimentation on drugs that are *not* ultimately the subject of an FDA submission.¹⁸⁶

[E]ven at late stages in the development of a new drug, scientific testing is a process of *trial and error*. In the vast majority of cases, neither the drug maker nor its scientists have any way of knowing whether an initially promising candidate will prove successful over a battery of experiments. That is the reason they conduct the experiments. Thus, to construe § 271(e)(1), as the Court of Appeals did, not to protect research conducted on patented compounds for which an IND is not ultimately filed is effectively to limit assurance of exemption to the activities necessary to seek approval of a generic drug[.]¹⁸⁷

. . . .

Properly construed, § 271(e)(1) leaves adequate space for *experimentation and failure* on the road to regulatory approval: 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”

¹⁸⁴ *Id.* at 2382.

¹⁸⁵ *Reply Brief for Petitioner, supra* note 147, at 1.

¹⁸⁶ *Id.* at 2382 (emphasis added).

¹⁸⁷ *Id.* at 2382–83 (emphasis added).

to the “development and submission of information under . . . Federal Law.”¹⁸⁸

It is clear that the safe harbor is *not* limited to experiments on a single drug candidate.¹⁸⁹ Indeed, from 1995–98, Scripps conducted *in vitro* and *in vivo* research on multiple RGD peptides¹⁹⁰ supplied by Merck. These experiments focused on EMD 66203 and two closely related derivatives and were designed to evaluate the “suitability of each of the peptides as potential drug candidates.”¹⁹¹ “The tests measured the efficacy, specificity, and toxicity” of the candidates as well as “their mechanism of action and pharmacokinetics” with the purpose of selecting the “most promising candidate “for clinical trials”¹⁹². These “optimization” studies were not exempt under the Federal Circuit’s ruling.¹⁹³

The scope of the safe harbor, however, does have limits. For example, the Supreme Court did not “quibble” with the Federal Circuit’s holding that “the exemption ‘does not globally embrace all experimental activity that at some point, however attenuated, may lead to an FDA approval process’.”¹⁹⁴ If one assumes that “basic scientific research” as defined by the Court is not exempt (discussed *infra*), the key issue is how much “trial and error,” albeit on “potential drug candidates,” is exempt from infringement? It would seem that research specifically directed to a limited class of drug candidates, *e.g.*, those sharing a common structure, or those operating *via* the same pathway, to determine the “best candidate” might well be exempt. The more limited the “class,” the more likely the research will be exempt.

6. Basic Scientific Research

“Basic scientific research,” as that term is defined by the Supreme Court, is “surely not ‘reasonably related to the

¹⁸⁸ *Id.* at 2383 (quoting 35 U.S.C. § 271(e)(1) (2000) (emphasis added)).

¹⁸⁹ *See id.* at 2383.

¹⁹⁰ *Id.* at 2378.

¹⁹¹ *Id.*

¹⁹² *Id.*

¹⁹³ *Id.* at 2382.

¹⁹⁴ *Id.* (quoting *Integra Lifesciences I, Ltd. v. Merck KGAA*, 331 F.3d 860, 867 (Fed. Cir. 2003)) (citation omitted).

development and submission of information' to the FDA" and thus is not within the safe harbor.¹⁹⁵

The Federal Circuit concluded that the exemption "does not globally embrace all experimental activity that at some point, however attenuated, may lead to an FDA approval process."¹⁹⁶

We do not quibble with [this] statement. Basic scientific research on a particular compound, performed without the intent to develop a particular drug or a reasonable belief that the compound will cause the sort of physiological effect the researcher intends to induce, is surely not "reasonably related to the development and submission of information" to the FDA.¹⁹⁷

A few key questions remain: What constitutes "basic scientific research"? In particular, what is considered research "on a particular compound"? What constitutes a "reasonable belief"? Moreover, during so-called basic research, scientists usually "inten[d] to develop a particular drug."¹⁹⁸ Otherwise, he or she would not engage in the research-at-issue. But does this "intent" exempt all drug discovery efforts? The specific facts in *Merck* should be considered in answering these questions. There, the alleged infringing research had progressed significantly by 1995—the point in time when the parties disputed whether the safe harbor became applicable.¹⁹⁹ At that time, the number of potential drug candidates was limited, and the preclinical research focused on selecting the "most promising candidate" for testing in humans.²⁰⁰ This conduct is certainly not what many would consider "basic scientific research."

Since the Supreme Court relied heavily on the views expressed in the U.S. government's amicus curiae brief, it is noteworthy that the government took the position that once a "researcher begins

¹⁹⁵ *Id.* (quoting 35 U.S.C. § 271(e)(1)) (2000)).

¹⁹⁶ *Id.* (quoting *Integra Lifesciences*, 331 F.3d at 867).

¹⁹⁷ *Id.* (emphasis added).

¹⁹⁸ *Id.*

¹⁹⁹ *See id.* at 2379.

²⁰⁰ *See id.* at 2378.

attempting to develop a substance with specific characteristics in order to achieve a specific objective, the research is protected.”²⁰¹ In support of its position, the government quoted an FDA guideline that “[m]any drugs . . . are introduced into development based on knowledge of in vitro receptor binding properties”²⁰² As to screening, the government proposed the following:

“[S]creening” of compounds for use in a particular drug, including testing designed to compare the effects of different compounds is reasonably related to the development and submission of information to the FDA because it allows the researcher to identify the appropriate compound or compounds to submit. The court of appeals’ contrary view would eviscerate the exemption with respect to non-generic drugs, because a researcher would always have to conduct infringing tests before its work would qualify for the exemption.

. . . .

. . . As long as a scientist is working on developing a particular drug . . . the number of compounds screened has nothing to do with whether the screening was reasonably related to the development and submission of information to the FDA. Instead, it reflects the luck (or intuition) of the scientist, or the difficulty of the task.²⁰³

It would appear that the Supreme Court, at least implicitly, rejected the government’s broad interpretation of the safe harbor, as is reflected in the Court’s exclusion of “basic scientific research” from the exemption.²⁰⁴

²⁰¹ *Brief for the United States*, *supra* note 58, at 17.

²⁰² *Id.* at 12 (quoting FDA, Guidance for Industry Exposure–Response Relationships—Study Design Data Analysis, and Regulatory Applications 3 (Apr. 2003), available at <http://www.fda.gov/cber/gdlns/exposure.htm>).

²⁰³ *Id.* at 18–19.

²⁰⁴ See *Merck KGAA v. Integra Lifesciences I, Ltd.*, 125 S. Ct. 2372, 2382 (2005). The American Intellectual Property Law Association [hereinafter AIPLA] argued that “early drug discovery activity” conducted “merely to identify promising candidates for further study” is not within the safe harbor. Brief for AIPLA as Amicus Curiae in Support of Neither Party at 2, *Merck KGAA v. Integra Lifesciences I, Ltd.*, 125 S. Ct. 2372 (2005) (No. 03–1237) [hereinafter *Brief for AIPLA*].

7. Research Tool Patents

No definitive answer on the status of such patents vis-à-vis the safe harbor was provided. In a footnote, the Court stated:

We therefore need not—and do not—express a view about whether, or to what extent, § 271(e)(1) exempts from infringement the use of “research tools” in the development of information for the regulatory process.²⁰⁵

In that same footnote, the Court cited Judge Newman’s dissenting opinion that the “[u]se of an existing tool in one’s research is quite different from the study of the tool itself.”²⁰⁶ Thus, in view of the footnote, the fact that the Integra patents were viewed by Court as product patents, and that the alleged infringement was the use of the patented peptides as products rather than as tools, any conclusions regarding research tool patents are dicta. Regardless, the Federal Circuit has recognized that it is “obliged to follow . . . clearly articulated Supreme Court dicta.”²⁰⁷ Of course, whether dicta is “clearly articulated” is yet another question.

Whether accused conduct is exempt should *not* depend on whether a “research tool” is used to conduct the alleged infringing research. Rather, the determination should be based on whether the conduct itself is within the safe harbor. If the conduct is not exempt, the exemption will not apply. If the conduct is exempt,

²⁰⁵ *Merck KGAA*, 125 S. Ct. at 2382 n.7.

²⁰⁶ *Integra Lifesciences I, Ltd. v. Merck KGAA*, 331 F.3d 860, 878 (Fed. Cir. 2003). Section 271(e)(1) uses the term “patented invention” and makes no distinction between the types of patents covered by the exemption. 35 U.S.C. § 271 (e)(1) (2003). The legislative history of § 271(e)(1), however, supports an argument differentiating between research tool patents and other types of patents. *See supra* discussion in notes 99 and 109. The AIPLA asserted that “[h]igh-throughput screening techniques” are not exempt because “[t]heir principal goal is the identification of candidates. . . [for] further testing . . .” *Brief for AIPLA, supra* note 204, at 20. Similarly, the Biotechnology Industry Organization [hereinafter BIO] maintained that its “members generally, though not uniformly, agree that screening large numbers of compounds not known or reasonably expected to have a particular effect . . . is rarely if ever within the ambit of the Section 271(e)(1) safe harbor.” *Brief for BIO as Amicus Curiae in Support of Neither Party at 14, Merck KGAA v. Integra Lifesciences I, Ltd.*, 125 S. Ct. 2372 (2005) (No. 03–1237).

²⁰⁷ *Independent Ink, Inc. v. Ill. Tool Works, Inc.*, 396 F.3d 1342, 1351 (Fed. Cir. 2005).

however, the mere fact that a research tool patent is involved should not automatically preclude application of the safe harbor. For example, if a tool is used merely to confirm the results of a clinical trial, an argument exists that the activity is exempt. Of course, hypotheticals yielding unforeseen results, such as using patented pipettes during clinical trials can be envisioned. Does such conduct infringe? Would it matter whether the patented pipettes were absolutely necessary to confirm the results of the clinical trials? Regardless, since the types of conduct covered by the safe harbor exemption were broadened by the Court, the rights of research tool patentees were diminished correspondingly.²⁰⁸

IV. A PROPOSED “TEST” FOR APPLYING THE SAFE HARBOR

In limiting the scope of the safe harbor, the Court noted that “[b]asic scientific research on a particular compound, performed without the intent to develop a particular drug or a reasonable belief that the compound will cause the sort of physiological effect the research intends to induce is surely not” within the safe harbor.²⁰⁹ However, the provision does exempt conduct:

[W]here a drugmaker 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 FDA²¹⁰

In differentiating what is protected from what is not, the following standard emerges: before the safe harbor applies, the researcher must have a “reasonable belief” or “a reasonable basis for believing” that the particular compound, or compounds, being

²⁰⁸ The government raised the possibility that research tool patents are not covered by the § 271(e)(1) safe harbor, in which case the exemption provided by the safe harbor would never apply to such patents, and all unauthorized uses of research tools would be infringing. See *Brief for the United States*, *supra* note 58, at 28–29. This view has not been accepted.

²⁰⁹ *Merck KGAA*, 125 S. Ct. at 2382.

²¹⁰ *Id.* at 2383.

tested will produce a “particular physiological effect.”²¹¹ This formulation is consistent with the Federal Circuit’s statement, approved by the Supreme Court, that “the exemption ‘does not globally embrace all experimental activity that at some point, however attenuated, may lead to an FDA approval process.’”²¹² The second requirement the Court imposed, that the resulting information “be appropriate”²¹³ for FDA submission, is seemingly unnecessary.²¹⁴ If the resulting information were required by the FDA, or if it could be submitted, even if not actually required, a stronger argument could be made that the safe harbor applies to the accused conduct.

If this “test” is applied to the facts in *Merck*, the result is clear. Based upon their earlier research, Scripps’ scientists had a “reasonable belief” or “reasonable basis for believing” that the “particular compounds” being tested would cause “the sort of physiological effect” they were investigating.²¹⁵ The alleged infringing research was designed to evaluate “the suitability of each of the peptides as potential drug candidates.”²¹⁶ The research, as summarized by the Supreme Court, was not “general biomedical research to identify new pharmaceutical compounds,” as characterized by the Federal Circuit.²¹⁷ Rather, it was performed with “a reasonable belief that the compound[s] will cause the sort of physiological effect the research intends to induce. . . .”²¹⁸

The jury instructions approved by the Supreme Court were based on those used in *Intermedics*.²¹⁹ They read:

²¹¹ See *id.* at 2382–83.

²¹² *Id.* at 2382 (quoting *Integra Lifesciences I, Ltd. v. Merck KGAA*, 331 F.3d 860, 878 (Fed. Cir. 2003)).

²¹³ *Id.* at 2383. The first requirement, that the drug work “through a particular biological process,” would seem to be unnecessary as well, except to the extent that such information would assist in forming a “reasonable belief” that the candidate compound would produce a particular physiological effect. *Id.*

²¹⁴ See discussion *supra* Part IV.C.4.

²¹⁵ See *Merck KGAA*, 125 S. Ct. at 2382–83.

²¹⁶ *Id.* at 2378.

²¹⁷ *Integra Lifesciences I, Ltd. v. Merck KGAA*, 331 F.3d 860, 866 (Fed. Cir. 2003).

²¹⁸ *Merck KGAA*, 125 S. Ct. at 2382.

²¹⁹ *Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269 (N.D. Cal. 1991).

To prevail on this [§ 271(e)(1)] defense, the [defendant] must prove by a preponderance of the evidence that it would be objectively reasonable for a party in [defendant's] . . . 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."

. . . .

[Defendant] does not need to show that the information gathered from a particular activity was actually submitted to the FDA.²²⁰

The *Intermedics* test involves interpreting the terms "reasonable," "objectively," "decent prospect," "relatively directly," and "information . . . likely to be relevant."²²¹ The test is inherently ambiguous, even though the resulting information need not be submitted to the FDA. The Supreme Court's decision supports an alternative instruction that focuses on whether there is a "reasonable basis for believing" that the compound(s) at issue will produce a "particular physiological effect" and, if so, whether the information obtained from the research would be "appropriate" for an FDA submission. As previously noted, the "submission" prong of the test may well be unnecessary.

The Supreme Court's formulation is more precise than that in *Intermedics*. Certainly, its application, which focuses primarily on the "reasonable belief" of the researcher, is more direct, since the types of protectable information (e.g., safety, efficacy, pharmacology, toxicology, pharmacokinetics, metabolism, mechanism of action, etc.) will usually not be determinative. This formulation is broader than one based on the Federal Circuit's *Integra* decision, but significantly narrower than one based on *Bristol-Myers v. Rhone Poulenc Rorer*.²²² It clearly exempts the

²²⁰ *Merck KGAA*, 125 S. Ct. at 2379 (citation omitted).

²²¹ *Intermedics*, 775 F. Supp. at 1280.

²²² No. 95 C 8833, 2001 WL 1512597 (S.D.N.Y. Nov. 28, 2001).

research at issue in *Merck v. Integra*, but would not exempt “basic scientific research” as the Supreme Court has defined this term.

CONCLUSION

The Supreme Court’s decision in *Merck v. Integra Lifesciences* answers a number of questions regarding the scope of the safe harbor provision. Where the decision does not provide a clear answer, such as, for example, on the question of what constitutes “basic scientific research,” the formulation the decision proposes provides more predictability than the present *Intermedics* standard. Even more certainty, however, may be forthcoming. On August 17, 2005, the Federal Circuit, having received the certified judgment of the Supreme Court, returned the case to the original merits panel, and set dates for the filing of new briefs “with particular attention [to be] paid to the Supreme Court decision.”²²³ Significantly, the “court *sua sponte* allow[ed] amicus briefs.”²²⁴ The Federal Circuit may thus soon answer the questions that the Supreme Court did not address fully; and in particular, reach a determination as to the applicability of the safe harbor exemption to “basic scientific research” and research tools.

²²³ *Integra Lifesciences I, Ltd. v. Merck KGAA*, Nos. 02–1052, 02–1065, 2005 WL 1965928, at *1 (Fed. Cir. Aug. 17, 2005).

²²⁴ *Id.*