Drug Discovery Tools and the Clinical Research Exemption from Patent Infringement

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Authors’ Note: Since we wrote the following article, the Court of Appeals for the Federal Circuit handed down its decision in Integra LifeSciences I, Ltd. v. Merck KGAA, Nos. 02-1052 and 02-1065) (Fed. Cir. June 6, 2003). The Court affirmed the holding of the District Court for the Southern District of California that the clinical research exemption from patent infringement, codified in 35 USC §271(e)(1), does not reach the Scripps-Merck drug screening activities that infringe Integra’s patent. According to the CAFC, the exemption does not “globally embrace all experimental activity that at some point, however attenuated, may lead to an FDA approval process. The safe harbor does not reach any exploratory research that may rationally form a predicate for future FDA clinical trials” (Integra, slip op. at 10). Policy considerations supporting the decision include a concern that “expansion of §271(e)(1) to include the Scripps-Merck [preclinical] activities would effectively vitiate the exclusive rights of patentees owning biotechnology tool patents” (Integra, slip op. at 11).

However, on the issue of damages, the CAFC reversed, on the grounds that the record evidence does not adequately support the jury’s $15 million “reasonable royalty” award to Integra. On remand, the Court instructed the district court to consider various factors in arriving at a proper damage award, including the presence or absence of stacking royalties for research tools (see Integra slip op. at 17–18).

INTRODUCTION

The clinical research exemption from patent infringement permits experimentation with patented inventions, such as drugs and medical devices, by exempting from infringement those activities that are reasonably related to seeking regulatory approval from the federal government. The intent of the exemption is to facilitate competitor development of alternatives or generic forms of a patented invention that can enter the market immediately on expiration of the patent.

An unsettled legal question is how far upstream in the research process the exemption reaches. The technological platforms of a significant number of biotechnology companies are based on drug discovery tools. There has been much debate concerning whether wide-scale patenting of so-called research tools stifles research and impedes development of therapeutically beneficial products. Patents covering drug discovery platforms may constitute one of only a few assets an emerging company has and may be essential for raising capital and leveraging alliances. A legal setting whereby the clinical research exemption from patent infringement is deemed to reach, for example, a pharmaceutical company’s unauthorized preclinical use of an emerging company’s patented drug discovery tool, may therefore prove problematic for a significant segment of the industry.

Provided here is a discussion of the clinical research exemption from patent infringement and the current legal uncertainty concerning the extent to which the exemption reaches preclinical activities. This discussion is followed by comments concerning the potential impact of the exemption on certain companies in the drug discovery industry.

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THE UNCERTAIN LEGAL SETTING

In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act, also known as the Hatch-Waxman Act, to address two unintended distortions of the 17-year patent term caused by the requirement that certain products receive regulatory approval prior to marketing. First, because the patent term clock runs without regard to the regulatory approval process, the period of time the holder of a patent covering a regulated drug had potential market exclusivity was significantly reduced. The early years of the patent term were lost to the patent holder because regulatory approval takes years to obtain. In contrast, the second distortion favored the patent holder at the end of the patent term. Prior to enactment of the Act, making, using, or selling a patented invention constituted patent infringement even if the activity was solely for the purpose of conducting tests and developing information necessary to obtain regulatory approval. Because competitors could not, without infringing, commence activities necessary for regulatory approval until after a patent had expired, a de facto period of market exclusivity for the patent holder extended beyond the patent term.

The Act attempted to eliminate the first distortion by providing a patent term extension for up to 5 years to compensate a patent owner for marketing time lost to the approval process. The second distortion was addressed with the clinical research exemption from patent infringement, the so-called safe harbor provision. This provision has been interpreted broadly by the Supreme Court and the Court of Appeals for the Federal Circuit (CAFC), exempting from patent infringement, not only drugs, but also medical devices and seemingly commercial activities bearing only a tangential relationship to the regulatory approval process. However, there is conflicting guidance in the judicial case law concerning the harbor’s depth. As discussed below, significant uncertainty exists concerning whether the clinical research exemption from patent infringement reaches preclinical activities such as drug screening and development.

While the Supreme Court and CAFC have not yet had occasion to render decisions clarifying how far upstream in the research process the exemption

2 At the time of enactment of the Act in 1984, the term of a U.S. patent was 17 years from the date of grant. The patent laws were subsequently amended to provide that a U.S. patent “shall be for a term beginning on the date on which the patent issues and ending 20 years from the date on which the application for the patent was filed in the United States or, if the application contains a specific reference to an earlier filed application . . . from the date on which the earliest such application was filed.” 35 USC 154(a)(2).
3 The decision of the CAFC in Roche Prods., Inc. v. Bolar Pharmaceutical Co, was a key factor in bringing about the enactment of the Act. In that case, the court held that experimental use defense to patent infringement did not cover the “limited use of a patented drug for testing and investigation strictly related to FDA drug approval requirements during the last 6 months of the term of the patent.” Roche Prods., Inc. v. Bolar Pharmaceutical Co., 733 F.2d 858 at 861 (Fed. Cir. 1984), cert. denied, 469 U.S. 856 (1984).
4 However, there is conflicting guidance in the judicial case law concerning the harbor’s depth. As discussed below, the Supreme Court and CAFC have not yet had occasion to render decisions clarifying how far upstream in the research process the exemption

even though it used its clinical trial data for more than FDA approval. Telectronics Pacing Systems Inc. v. Ventritex Inc., 982 F.2d 1520, 25 USPQ 2d (BNA) 1196 (Fed. Cir. 1992). Specifically, the court found that the defendant’s activities—presenting clinical trial data at a cardiology conference; reporting clinical trial progress to investors, analysts, and journalists; and describing clinical trial results in a private fund-raising memorandum—fell under the category of dissemination of data developed for FDA approval. Id. at 1524. The court noted that the “disclosure of clinical trial data cannot, in and of itself, constitute an infringing activity.” Id. Similarly, in Intermedics, Inc. v. Ventritex Inc., the U.S. District Court for the Northern District of California held that the defendants’ allegedly infringing activities were all reasonably related to obtaining FDA approval for its implantable defibrillator and therefore were protected by §271(e)(1). Intermedics, Inc. v. Ventritex Inc., 775 F. Supp. 1269, 20 USPQ 2d 1422 (N.D. Cal. 1991). The activities there included: (1) the manufacture of several hundred defibrillators for use in clinical trials; (2) sales of the defibrillators to U.S. hospitals for use in clinical trials; (3) sales of defibrillators to international distributors to obtain regulatory approval to export them for clinical trials conducted abroad; (4) testing of the defibrillators abroad; and (5) demonstrations of the defibrillators at trade shows. Id. at 1431. And in NeoRx Corp. v. Immunomedics, Inc., the U.S. District Court for New Jersey held that the §271(e)(1) exemption is not lost even if it turns out that some of the otherwise-infringing activities failed to generate information in which the FDA was interested or generated more data than turned out to be necessary to secure FDA approval. NeoRx Corp. v. Immunomedics, Inc., 877 F. Supp. 202, 31 USPQ 2d 1423, 1432 (D.N.J. 1994).
reaches, two lower court decisions have dealt with this issue. The first case involved Advanced Cell Technology’s (ACT’s) use of Infigen’s patented method for parthenogenic activation of bovine oocytes in cloning experiments. ACT argued that because the purpose of those experiments was ultimately to develop transgenic cattle capable of producing a product requiring Food and Drug Administration (FDA) approval prior to marketing, the clinical research exemption from patent infringement applied, and there was no infringement. The District Court for the Western District of Wisconsin disagreed. According to the court, an earlier Supreme Court decision required a symmetrical reading of the patent term extension and clinical research exemption provisions of the Hatch-Waxman Act. In other words, according to the Court, an exemption from infringement should be recognized only for activities falling under patents eligible for term extension. Because a patent covering oocyte activation methods is not eligible for term extension, the district court opined that the lawsuit was not precluded under the clinical research exemption.

In contrast, in a later case, the District Court for the Southern District of New York held that Bristol-Myers Squibb’s (BMS’s) use of Rhone-Poulenc Rorer’s (RPR’s) patented Taxol intermediates for the purpose of generating analogs fell under the safe harbor and was exempt from infringement. In reaching this conclusion, the court rejected RPR’s argument that the safe harbor applies only to research occurring after a drug candidate has been selected or filed with the FDA. The court reasoned that use of patented intermediates is reasonably related to an FDA application and thus exempt from patent infringement:

even though each such use of the patented intermediates may not directly yield information that could be submitted to the FDA, but relates to a preliminary activity that may facilitate or be useful in generating information that could be submitted to the FDA.

The court explicitly adopted the argument advanced by BMS that:

It would be nonsensical for the exemption to apply only in the development process after a drug candidate was identified, or after a drug candidate was actually filed with the FDA. If so, the exemption would never be reached because the underlying preliminary research and development work could not be undertaken.

The issue is currently before the Federal Circuit in Integra LifeSciences I, Ltd. v. Merck KGAA, a case with potentially far-reaching consequences for the biotechnology industry. At issue are patents owned by Integra LifeSciences directed to RGD peptides, an amino acid sequence involved in cell adhesion, and to two receptors on the surface of cells, $\alpha_v\beta_3$ and $\alpha_v\beta_5$, by which cells attach the RGD sequence.

Specifically, a scientist at The Scripps Research Institute determined that blocking the $\alpha_v\beta_3$ receptor could inhibit angiogenesis and, hence, tumor growth. Recognizing the commercial potential for angiogenesis inhibitors, Merck entered into a research agreement with Scripps whereby scientists at Scripps would screen hundreds of RGD peptides supplied by Merck using the $\alpha_v\beta_3$ and $\alpha_v\beta_5$ cell-surface receptors to identify potential drug candidates. Neither Merck nor Scripps had a license under the Integra patents to use either RGD peptides or the $\alpha_v\beta_3$ and $\alpha_v\beta_5$ receptors.

Integra filed suit against Merck and Scripps for patent infringement, alleging that Scripps directly infringed, and Merck induced infringement of, Integra’s patents by using the RGD peptides and the $\alpha_v\beta_3$ and $\alpha_v\beta_5$ cell-surface receptors in the course of Merck’s research program. As one of its defenses,
Merck asserted that the allegedly infringing activities were exempt from infringement under the §271(e)(1) clinical research exemption. The jury returned a verdict for Integra, finding that Scripps and its scientists directly infringed and that Merck willfully infringed and induced Scripps’ infringement of the asserted patents.14

Merck filed a post-trial motion for judgment as a matter of law that all of the drug discovery research was exempt from infringement under §271(e)(1) and that no reasonable jury could have concluded otherwise.15 Essentially, Merck argued that the exemption applies “‘because the [drug screening] results inform and will lead to clinical trials, which, in turn, would produce data that would be submitted to the FDA even if the data from the accused research had not itself been submitted to the FDA.’”16 The district court disagreed, finding that the evidence was sufficient to uphold the jury verdict. Specifically, the court focused on whether the research experiments conducted by Scripps were of the type that would be required to support an IND or NDA application at the FDA. The court concluded that “any connection between the infringing Scripps experiments and FDA review was sufficiently indirect to qualify for the exemption.”17

The case is currently before the CAFC on cross appeals filed by the parties. Merck reiterated on appeal its argument that all of the preclinical drug screening experiments conducted by Scripps are exempt, as a matter of law, from infringement under §271(e)(1).18 In its briefs, Merck acknowledges that the issue of how much of the drug development process falls within the exemption has not been addressed but contends that the legislative history of §271(e)(1) favors a broad interpretation of the statute.19 Specifically, Merck contends that “Congress must have intended the phrase ‘uses reasonably related to the development and submission of information’ to the FDA to encompass drug development research that serves as a rational predicate to generating information for submission to the FDA, including any tests conducted to determine whether to proceed with a drug candidate.”20 Citing the decision of the district court in Bristol-Myers Squibb, Merck asserts that to construe the exemption more narrowly would be “nonsensical” and “would seem to negate Congress’s intent to have new drugs come to market without delay upon expiration of a patent.”21

Integra, for its part, contends that the “rational predicate” test advanced by Merck would dramatically expand the scope of the §271(e)(1) exemption and result in any and all research in the chain of events that could ultimately lead to development of any drug requiring FDA approval being exempt from infringement. According to Integra, such a test is inconsistent with a plain reading of the statute and clearly contrary to Congressional intent.22

**POTENTIAL IMPACT ON THE DRUG DISCOVERY INDUSTRY**

How the CAFC decides Integra could have far-reaching implications for the drug discovery industry, particularly for emerging companies having research tools as their platform technology. The National Institutes of Health has defined the term “research tool” to encompass, in its broadest sense, the “full range of resources that scientists use in the laboratory.”23 Thus, the term is considered to include cell lines, monoclonal antibodies, reagents, animal models, growth factors, combinatorial chemistry libraries, drugs and drug targets such as receptors, clones and cloning tools such as PCR, methods, laboratory equipment and machines, databases, and computer software. Id. To the researcher in the laboratory, such products are considered means to an end—a tool for developing a new therapeutic or diagnostic product or simply for conducting academic research. To the provider of such research tools, however, they are a valuable end product for sale to

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14 Id. at 2–4.
16 Id. at 18.
19 Id. at 43.
20 Id. at 45–46.
21 Id. At 46.
22 Brief for Plaintiffs-Cross-Appellants at 8–9, Integra LifeSciences I, Ltd. v. Merck KGAA, Nos. 02-1052 and 02-1065 (Fed. Cir. Nov. 21, 2001)
customers and a significant business asset. Numerous biotechnology companies have been formed on the basis of a drug discovery platform as the core technology. A quick search of the Internet provides several sites listing several hundred U.S. companies focused on drug discovery for disease therapeutics.

The court’s rationale in the BMS case and the arguments advocated by Merck in the Integra v. Merck appeal echo the sentiment expressed by some that patents on drug discovery tools stifle research and innovation. Several commentators have argued that research tool patenting has hindered research tool dissemination. Screening, developing, and producing a therapeutic product involves myriad techniques and methods, each of which may be the subject of third-party patent protection. Thus, it has been argued that the number of licenses to upstream research tools required to produce a therapeutic or diagnostic product may be prohibitive.

One example given is that of a company wanting to develop a DNA microarray of single nucleotide polymorphisms (SNPs) having to seek licenses from numerous different SNP owners. Of additional concern to some is the so-called reach-through royalty, which requires paying a royalty on downstream commercial products developed through the use of a patented drug discovery tool. Proposals offered to overcome these perceived problems focus primarily on expanding the common law experimental use exemption—which currently exists only as a very narrow exemption—judicially narrowing the scope of research tool patents through more stringent interpretation of the patent laws, or amending Title 35 of the United States Code to expressly exempt from infringement use of a patented invention in “research or experimentation.”

Of course, a legal environment that facilitates,
rather than inhibits, drug development is in the public interest. Whether this is best achieved by significantly diluting the value of patents directed to drug discovery tools is, however, questionable. As argued by another commentator, “experience shows that patents on inputs [e.g., drug discovery tools] generally do not prevent the production of outputs [e.g., diagnostic or therapeutic products].” Industry statistics seem to support this assertion. For example, the number of approved biotechnology medicines and vaccines has increased seven-fold in the past 10 years despite the fact that the total number of biotechnology-related patents granted in the U.S. each year has tripled over the same period. Further, “the ability for patents to bring immense amounts of, and diversity in, sources of funding and other resources to the basic biological research community is recognized as a critical factor in the great success the community has enjoyed since 1980.” Indeed, within the drug discovery industry, emerging companies having research tools as their primary assets are often the most reliant on strong patent protection for survival. These companies view patents, not only as being critical for raising venture capital, but also as necessary to leverage alliances with other companies. Such alliances can increase the efficiency of product development by combining, for example, a small company’s innovative drug discovery platform with an established company’s drug development capability and know-how. Because many biotechnology companies do not have the expertise or resources to develop drugs themselves, seeking customers for their drug discovery tools constitutes a critical business strategy. Of those companies able to enter clinical trials on their own, at least in the case of genomic and proteomic companies, many have substantially more drug targets than they could possibly develop. Customers are sought for those targets not developed in-house to help defray costs. If the terms of any license sought are too onerous, potential licensees would seek out or develop alternatives, such as licensing a competing research tool or designing around the patent. Thus, for companies having research tools as their core technological platform, using patents to stifle competition by inhibiting the dissemination of the tool is probably not a luxury they can afford.

With respect to big pharma, however, it is true that there is less incentive to seek customers for internally developed drug discovery tools. In contrast to the rest of the industry, an established pharmaceutical company is likely to be fully capable of exploiting an internal research tool itself to develop therapeutic or diagnostic products. However, it does not follow that public access would be increased by significant dilution of the value of research tool patents. Instead, the absence of meaningful patent protection for drug discovery tools may lead to an increase in trade secrets, which, of course, is the antithesis of public dissemination.

An often-overlooked factor in the research tool debate is that one seeking to assert a patent directed to a research tool against a potential infringer already faces an uphill battle. The first hurdle is proving infringement. Where the potential infringer is manufacturing and selling the research tool itself, proof of infringement is a relatively straightforward matter. However, where the infringing conduct involves secretly using the tool in the course of an internal drug discovery program, infringement will be much more difficult to establish. In such circumstances, a therapeutic product sold by the potential infringer may provide no clue as to how it was developed.
Even if infringement is established, one faces a second, potentially greater, hurdle: proof of damages. The measure of damages recoverable for patent infringement is provided for by statute. The Supreme Court has interpreted “damages” to mean “the difference between [the patentee’s] pecuniary condition after the infringement, and what his condition would have been if the infringement had not occurred.” Where the infringer is a company that sells a competing (albeit infringing) research tool, the calculation of damages could be based on the sales that the patent owner would have had but for the sale of the infringing research tool. However, the patent owner’s case for damages is much more difficult to establish where the infringer does not market the research tool itself but rather sells a therapeutic or diagnostic product developed using the tool. In such a case, it is unlikely that the research tool company has a competing therapeutic or diagnostic product on the market. Moreover, that company must show that “but for” the infringing use of the research tool, the infringer would not have made the sales of the therapeutic or diagnostic product that it made. Depending on the nature of the research tool, this could be very difficult.

Even if the research tool company is unable to prove lost profits, it is still entitled to recover a reasonable royalty for the infringing use. In effect, this sets a minimum level of compensation to which the research tool owner is entitled. To the extent there is an established royalty rate in the industry for similar research tools, it will likely be applied to determine the damages. However, research tools in the biotechnology industry often lack an established royalty rate. Although the courts have, in some instances, imposed a reach-through royalty that extends to revenues generated from the sale of the therapeutic or diagnostic products generated from the infringing use of the research tool, the prospect for this is very uncertain and depends on a number of factors, including the nature of the research tool, the market for it, and the availability of non-infringing alternatives. Thus, the hurdles faced by a research tool patent owner in seeking compensation for infringement can be significant.

CONCLUSION

Drug discovery tools constitute the technological platform for a number of companies in biotechnology. Where a competitor is secretly using a research tool to screen for drugs, the patent holder already faces significant hurdles when attempting to establish infringement and damages. It has nonetheless been suggested that the value of drug discovery tool patents should be diluted through statutory amendment or by expanding the experimental use exemption from patent infringement. In *Integra v. Merck*, which is currently awaiting a decision by the CAFC, drug discovery tool patents face yet another attack in the form of the clinical research exemption from patent infringement. It is possible that the CAFC will decide *Integra* on other grounds and avoid the issue altogether or decide the issue but fail to elaborate on the exact boundaries of the exemption. However, should the CAFC adopt the rule set forth by the Southern District of New York in *Bristol-Myers Squibb*, drug discovery tool patent holders may be left with little recourse when attempting to assert their patent rights against competitors.

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42 See 35 USC §284, which states: “Upon finding for the claimant the court shall award the claimant damages adequate to compensate for the infringement, but in no event less than a reasonable royalty for the use made of the invention by the infringer, together with interest and costs as fixed by the court.” 35 USCA §284 (2001) (emphasis added).
45 See Donald R. Ware, Research tool patents: judicial remedies, 30 AIPLA Q. J. 267, 282–296 (2002).