When is patent infringement not patent infringement? *Merck v Integra* and the 'safe harbour'

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Abstract

The Supreme Court recently ruled on the scope of the patent infringement 'safe harbour' of 35 U.S.C. §271(e)(1), which was passed by Congress in 1984 to allow generic drug manufacturers to test their drugs before the expiration of the patents that covered the drugs. The scope of the safe harbour has been interpreted by the courts to be much broader than that, and the Supreme Court confirmed the breadth of the exemption. The Supreme Court did not, however, address the application of the safe harbour to research tools, an issue of vast commercial importance. This paper traces the history of the safe harbour and the *Merck* v *Integra* decision, and explains the current state of the law and where the law may be going.

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INTRODUCTION

The patent infringement 'safe harbour', originally designed to allow generic drug companies to test drugs for bioequivalence before patent expiration so that the generic form could be marketed as soon as the patent did expire, has been closely watched since its enactment by Congress in 1984. Recently, the Supreme Court considered the safe harbour in *Merck v Integra,* 125 S. Ct. 2372 (2005);[1] The Supreme Court's decision clarified certain aspects of the safe harbour, but left substantial questions about research tools open for further decisions by other courts or action by Congress.

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HATCH–WAXMAN ACT & 35 U.S.C. §271(E)(1)

In 1984, the United States Congress enacted the Drug Price Competition and Patent Term Restoration Act, also known as the Hatch–Waxman Act, as a compromise between research-oriented manufacturers and production-oriented generic manufacturers. The Act has three principal parts to support the development of generic versions of off-patent drugs, while balancing the rights of patent holders: patent term extension, Abbreviated New Drug Application (ANDA) filing, and a research exemption 'safe harbour'. First, the Act provides a patent term extension of up to 5 years to compensate patent holders for time lost in regulatory review. Second, the Act created ANDAs, which allow generics to piggyback on the clinical research of branded pharmaceuticals. By allowing generic drug manufacturers to incorporate the safety and efficacy data from an approved product, the generic manufacturers can avoid the time and

expense of the extensive clinical trial period. The third provision, a patent infringement safe harbour established under 35 U.S.C. §271(e)(1), allows one to use a patented invention to conduct experiments needed to obtain Food and Drug Administration (FDA) approval without being liable for patent infringement. On this safe harbour, the statute simply states that '[i]t 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'.

Although only 16 words, the clause 'solely for uses reasonably related to the development and submission of information under a Federal law' has been litigated dozens – perhaps hundreds – of times, including two trips to the Supreme Court. The issue is almost always the boundaries of the safe harbour protection. The 'solely for' part of the statutory language can be used to interpret the provision narrowly such that the exemption only applies if the patented invention is used in clinical testing of a patented drug to supply information for an ANDA. In contrast, the 'reasonably related' part of the statutory language can be used to interpret the provision broadly such that the exemption applies if the patented invention is used anywhere on the road from drug discovery to regulatory review.

MERCK V INTEGRA – THE UNDERLYING DISPUTE

Because courts only make decisions in the context of actual disputes between actual parties, and because court decisions are limited to the disputes before them, it is important to understand the underlying dispute in the *Merck v Integra* lawsuit. In that case, Integra owned five patents related to a short tri-peptide segment of fibronectin: arginine–glycine–aspartic acid ('the RGD peptide'). The RGD peptide has been shown to inhibit angiogenesis, the process of generating new blood vessels, by blocking membrane receptors on certain cells. Angiogenesis has been identified as potentially important in tumour growth, diabetic retinopathy, rheumatoid arthritis, psoriasis and inflammatory bowel disease. Dr. Cheresh at the Scripps Research Institute independently discovered that blocking certain receptors on the cell membrane inhibits angiogenesis. Under an agreement with Merck, researchers at Scripps conducted preclinical tests for the identification and development of potential drug candidates. Notably, these experiments did not supply information for submission to the FDA, but instead identified the best drug candidate to subject to future clinical testing under FDA processes.

Integra learned of the Scripps–Merck agreement and believed that the RGD-related research infringed its five patents. After Merck declined a licensing opportunity, Integra sued Merck, Scripps and Dr. Cheresh for patent infringement. Integra's complaint alleged that Merck willfully infringed and induced others to infringe its patents by supplying the RGD peptide to Scripps, and that Dr. Cheresh and Scripps infringed the same patents by using the RGD peptide in experiments. In response, Merck asserted that the work with Scripps fell under the safe harbour provision of 35 U.S.C. §271(e)(1).

THE TRIP THROUGH THE COURTS (AND IT IS NOT DONE YET)

At trial, the Judge gave the jury the following instructions regarding the safe harbour:

> 'To prevail on this defense, [Merck] must prove by a preponderance of the evidence that it would be objectively reasonable for a party in [Merck's] and Scripps' situation to believe that there was a decent prospect that the accused activities would contribute, relatively directly, to the generation of the kinds of information that are likely to be relevant in the processes by which the FDA would decide whether to approve the product in question… [Merck] does not need to show that the information gathered from a particular activity was actually submitted to the FDA'.

The jury found that the preclinical Merck–Scripps experiments were not protected by §271(e)(1) because the testing was not sufficiently directly related to the submission of information to the FDA. Integra was awarded damages of US$15m.

Merck appealed to the Federal Circuit, the court in Washington, DC that hears all appeals from patent cases in the United States. Two of the three judges on the panel of the Federal Circuit, Judges Rader and Prost, agreed with the trial court that Merck's activities did not fall within the safe harbour, and that the safe harbour 'does not globally embrace all experimental activity that at some point, however attenuated, may lead to an FDA approval process'.[2] The majority went further, explaining a narrow view of the safe harbour that it 'does not reach any exploratory research that may rationally form only a predicate for future FDA clinical tests'. Thus, concluded the majority, the expansion of the research exemption to include the Scripps–Merck activities would 'effectively vitiate the exclusive rights of patentees owning biotechnology tool patents. After all, patented tools often facilitate general research to identify candidate drugs, as well as downstream safety-related experiments on those new drugs'. Judge Newman, the presiding judge on the panel, dissented from the Federal Circuit decision.

In support of its opinion, the majority turned to the legislative intent of the Hatch–Waxman Act. The decision explained that the express objective of the Act was to facilitate the immediate entry of safe, generic drugs into the marketplace upon expiration of a drug patent, and that the exemption was narrowly tailored so that §271(e)(1) would have only a tiny impact on a patentee's exclusionary rights. The court concluded that 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', and was therefore not encompassed by the exemption. The court further noted that '[t]he FDA has no interest in the hunt for drugs that may or may not later undergo clinical testing for FDA approval'.

Even with its focus on legislative intent, the Federal Circuit left open many questions regarding the scope of the safe harbour. First, the decision did not address whether it was Merck's role as a pioneer drug manufacturer or simply the nature of its activities that prohibited its experiments from invoking the safe harbour. Second, the court did not consider whether only clinical research could fall within the safe harbour, or whether the safe harbour could also reach preclinical research. Third, the decision did not address whether experimental activities that are not ultimately submitted to the FDA are protected. Additionally left untouched was the issue of whether the use of patented research tools is included within the safe harbour of §271(e)(1). These questions remained when the Supreme Court granted certiorari.

Merck then appealed to the Supreme Court, which agreed to review the case. The Supreme Court disagreed with the Federal Circuit, deciding that the safe harbour provision of §271(e)(1) is to be interpreted broadly and that the 'exemption from infringement extends to all uses of patented inventions that are reasonably related to the development and submission of *any* information under… Federal law'. Further, the Supreme Court specifically said that '[t]his necessarily includes *preclinical* studies of patented compounds that are appropriate for submission to the FDA in the regulatory process' (emphasis added in italics).

In an attempt to define the statutory boundaries of §271(e)(1), the Supreme Court held that the 'reasonably related' requirement does not categorically exclude (1) experimentation on drugs that are not ultimately the subject of an FDA submission, and (2) the use of patented compounds in experiments that are not ultimately submitted to the FDA. Finally, despite the Supreme Court's broad reading of the statute, it refused to comment on the safe harbour's application to research tools. In the final footnote, the Court remarked: 'we… 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.' Although the research tool issue was

not the focus of the case before reaching the Supreme Court, the Court's comment that 'Respondents have never argued the RGD peptides were used at Scripps as research tools, and it is apparent from the record that they were not' seems to overstate the facts. The patented RGD peptides were, for instance, used by Merck as positive control in certain experiments. Certainly this type of use should be considered using the compounds as 'research tools.'

Although a win for Merck, the Supreme Court did *not* rule that Merck's activities fell within the safe harbour. Instead, the Supreme Court specifically approved of the instruction that had originally been given to the jury that Merck had to prove 'that it would be objectively reasonable' for it 'to believe that there was a decent prospect that the accused activities would contribute, relatively directly, to the generation of the kinds of information that are likely to be relevant in the processes by which the FDA would decide whether to approve the product in question' and that Merck did 'not need to show that the information gathered from a particular activity was actually submitted to the FDA'. The Supreme Court remanded the case for further consideration by the Federal Circuit.

WHERE DOES MERCK STAND NOW?

After the Supreme Court's decision, the parties submitted additional written briefing to the Federal Circuit, and the Federal Circuit heard oral argument on 5th June, 2006. Despite the Supreme Court's specific and deliberate refusal to reach the issue, the oral argument focused almost exclusively on research tools. Judge Rader even called it the 'central issue we're going to be dealing with here'. Judge Rader went on: 'until footnote [7] in the Supreme Court's opinion, you did not have a research tool exemption. Now, apparently, under the footnote, you've got one'. Seeing this as a change in the law, during oral argument, Judge Rader seemed inclined to remand the case to the district court to determine whether Integra's patented compounds were used as research tools and, if so, if Merck's use was protected by the §271(e)(1) exemption.

Attempting to avoid the research tool issue, Merck argued that its activities were exempt from infringement under the Supreme Court's 'bright line' interpretation that experiments fall within the safe harbour 'at the time frame where the drug maker has a reasonable basis for believing that the compound may work through a particular biological process to produce a particular physiological effect'. Judge Newman was not sympathetic to this argument and retorted 'it's not a very bright line, is it?'

For its part, Integra argued that the jury instructions were consistent with the Supreme Court's ruling and that the Federal Circuit should therefore defer to the jury's factual finding that Merck's experiments were not exempt. Judge Rader was equally unsympathetic to this argument, questioning at one point 'A cavalry charge into the artillery rarely works. The Supreme Court has fired a pretty heavy volley of artillery here. Are you sure you shouldn't use your cavalry otherwise?'

In a situation rarely seen in litigation, Merck and Integra agreed that the Federal Circuit should not address the research tool issue. After oral arguments, both parties submitted supplemental letters urging the court *not* to decide the issue of whether Merck's use of Integra's patented compounds fell outside the safe harbour based on whether they were used as 'research tools.' Merck argued that it would be improper to address the research tool issue because Integra never made this argument in the district court, Federal Circuit, or Supreme Court. Integra agreed with Merck and argued that the research tool question should be answered in a case in which the issue has been 'squarely raised and thoroughly vetted' in the trial court.

WHAT ARE RESEARCH TOOLS, AND WHY DO WE CARE SO MUCH ABOUT THEM?

To state the obvious, research tools are tools that scientists use to conduct research. In theory, they range from pipettes and test

tubes, to the Nobel Prize winning polymerase chain reaction ('PCR'), novel receptors that allow screening techniques for finding compounds useful for treating disease, cell lines, monoclonal antibodies, animal models, combinational chemistry, and DNA libraries. Logically, even potential drug compounds themselves are research tools when they are candidates in tests that screen for therapeutic usefulness.

So why does this matter? It matters because, especially in the life sciences field, research tools themselves can be the culmination of a long and innovative development process. Entire companies are built around, not the *use* of research tools, but the *invention* and sale of them. For example, Applied Biosystems and Rosetta Inpharmatics (a subsidiary of Merck) are businesses focused primarily on the commercialisation of research tools.

Moreover, in the life sciences field, it is also possible – indeed, likely – that many uses of those research tools will be somewhere along the process of getting information to the FDA. For those tools – such as biomarkers, gene sequences or receptors – that are reasonably straightforward to replicate (once highly trained scientists are armed with the disclosure and roadmap of a patent), it is easy to envision widespread use of patented research tools with limited consequences. This would destroy any profit motive for the research tool innovators.

Research tool innovators have many strategies to respond to this possibility. One, of course, would be to convince the courts to address the issue, and rule that the use of a patented invention as a research tool would not be within the safe harbour. Many, many companies have argued this quite fiercely in amicus curiae briefs to the Federal Circuit. These so-called 'amicus' briefs (or 'friend of the court' briefs) are submitted by non-parties to bring issues and arguments to the attention of a court. Amicus in support of Integra have argued that the safe harbour should not be applied to research tools because the tools are not the subject of the relevant FDA filing. In contrast, the US Government filed an amicus brief in support of Merck, arguing that the Federal Circuit 'erred by artificially narrowing the statutory exemption in an effort to protect research tools.' Of the almost 20 amicus briefs that were filed in connection with this case, the Supreme Court only cited the one submitted by the United States in support of Merck.

Other questions for consideration for research tool innovators, depending on the nature of the tool and the business model of the company include:

- is the invention police able?
- are there contractual limitations that will help?
- is the research tool easy to copy?

Business strategies that research tool innovators can therefore consider include:

- The risk of the use of the tool being held to be within the safe harbour must be factored in during negotiations with a potential licensee.
- The possibility of using trade secret, as opposed to patent, protection should be considered if the tool is appropriate for trade secret protection.
- Field-of-use restrictions may be helpful.
- 'Reach-through royalties' may be a way to value research tools.
- Focusing patent filings in countries with no research safe harbour and where research is likely may be helpful for certain kinds of companies.

WHAT'S NEXT?

Even without the final word – or at least the next word – from the Federal Circuit, trial courts have continued to address other disputes that raise safe harbour issues, doing their best to apply the guidance set out in the Supreme Court's decision. For instance, in *Classen Immunotherapies v Biogen IDEC*, 381 F.Supp. 2d 452 (D. Md., 2005), the patents involved methods for evaluating the safety of vaccine administration schedules. The defendants, who collected post-approval information to submit to the FDA, argued that the safe harbour protected their activities. Although not yet ruling for certain that the safe harbour applied, the trial court allowed

this defense to go forward, ruling that the Supreme Court's decision did not bar the safe harbour merely because the accused infringement was post-FDA approval. And in *Third Wave v Stratagene*, 381 F. Supp. 2d 891, the trial court, again in a pre-trial ruling, explained its refusal to dismiss a case because of the safe harbour with a seemingly narrower view of the safe harboor:

> 'I am not convinced that a remote desire to obtain FDA approval for products 'using the [invention]' is sufficient to satisfy the 'reasonably related standard. Defendant's construction of § 271(e)(1) would read the term 'reasonably' out of the provision, granting immunity to any testing no matter how remotely related to a hypothetical submission to a federal agency. Moreover, § 271 provides exemption 'solely for uses reasonably related to the development and submission of information' to federal regulatory agencies; defendant's CEO testified that its testing was motivated 'in part' by a desire to obtain FDA approval'.

No trial courts have yet attempted to reach the research tool issue.

CONCLUSION

It seems that the Federal Circuit is poised to address the issue of whether research tools are categorically excluded from the safe harbour. Whether that issue will be reached in the next opinion in *Merck v Integra* is unclear. One possibility is that the Federal Circuit will send the case back to the trial court with instructions to address this issue and develop the factual record about whether and how the patented compounds were used as research tools.

Outside the research tool controversy, the Supreme Court's decision makes the safe harbour issue intensely factual. Researchers will be well served by keeping this in mind during their research. If sued for infringement, a researcher will have to prove to a jury that he or she had a 'reasonable basis for believing' that the results could be submitted to the FDA. 'Papering' the record with contemporaneous documentation will be much preferred by juries over after-the-fact testimony. It may also be helpful to deliberately and strategically perform experiments that produce information that could be submitted to the FDA.

Perhaps the most important thing to realise is that the Supreme Court's decision did not draw very many bright lines. This area of law will continue to develop and evolve, and neither patentees nor accused infringers should assume a 'sure thing' for the more controversial applications of the safe harbour-like research tools and attenuated preclinical studies.

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References

1. The Supreme Court's opinion is available online on its website at http://a257.g.akamaitech.net/7/257/2422/13jun20051230/www.supremecourtus.gov/opinions/04pdf/03-1237.pdf (last visited Sept. 14, 2006).
2. *Integra v Merck*, 331 F. 3d 860 (Fed. Cir. 2003).