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Hatch-Waxman Safe Harbor Construed in 'Merck v. Integra'

The U.S. Supreme Court in June 2005 issued its much-anticipated decision in *Merck KGaA's*¹ (*Merck*) nearly decade-long battle with *Integra Lifesciences Ltd.* (*Integra*) over the scope of the "Hatch-Waxman Safe Harbor."²

The Court vacated the U.S. Court of Appeals for the Federal Circuit's decision in favor of *Integra* and remanded for further proceedings, but left unanswered many questions that initially drew the attention of the pharmaceutical, biotech and patent communities and led to 19 amicus filings, including an appearance by the Bush administration.

The ultimate issue in the case is whether certain preclinical experiments conducted by the *Merck* defendants in the mid-1990s on potential new drug candidates infringed upon several of *Integra's* patents directed to "RGD" peptides. *Merck* claims those tests were reasonably related to generating data for an Investigatory New Drug application (IND) and therefore exempt under the Hatch-Waxman Safe Harbor. *Integra* claims *Merck's* use of the patented peptides is not covered by the safe harbor because the experiments were not "solely for uses reasonably related to the development and submission of information" to the FDA. 35 USC §271(e)(1). The Federal Circuit's decision was welcomed by some in the biotech community who fear an expansive interpretation of the safe harbor would destroy the value of so-called "research tools," which are useful early in the drug development process, but often unnecessary at the marketing stage or once a lead drug candidate has been identified. Innovator drug companies, on the other hand, lamented the Federal Circuit's decision as one that would impede new drug development efforts in the United States.

Patented Compounds Exempt

In a unanimous decision, the Supreme Court held that the Hatch-Waxman Safe Harbor exempts the use of patented compounds from claims of infringement so long as there is a reasonable basis for believing that the experiments will produce the types of information that are relevant to an FDA submission. *Merck KGaA v. Integra Lifesciences I, Ltd.*, 2005 US LEXIS 4840 (June



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13, 2005). The decision removes some of the fog created by the language in the Federal Circuit's opinion, which called into question the application of the safe harbor to preclinical testing and to innovator, as opposed to generic, drug developers. However, the Court did not resolve some important questions asked by many who followed the case.

Merck claims those tests were reasonably related to generating data for an Investigatory New Drug application and therefore exempt under the Hatch-Waxman Safe Harbor.

Part of the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act), the Hatch-Waxman Safe Harbor provides:

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. 35 USC §271(e)(1) (emphasis added).³

Applications Expedited

One principal goal of Congress in enacting the safe harbor was to expedite the preparation,

submission and review of generic drug applications. Prior to its enactment, the groundwork to support such an application could not begin until the expiration of applicable drug patents. This had the effect of extending the term of drug patents.

However, §271(e)(1) is not on its face limited to generic drugs, and prior to the *Integra* case, courts generally construed the statute to embrace activities other than those associated with generic drugs or clinical stage testing. Before *Integra*, the most important decision construing the safe harbor was *Eli Lilly v. Medtronic*, 496 US 661 (1990), where the Supreme Court held the safe harbor extends to medical devices, despite the fact that §271(e)(1) does not refer specifically to medical devices. See also *Intermedics, Inc. v. Ventritex, Co.*, 775 F.Supp 1269, 1285 (NDCal 1991), aff'd, 991 F.2d 808 (Fed. Cir. 1993) (safe harbor covers preclinical tests necessary to obtain safety certification of medical devices); *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc. et al.*, 2001 USDist LEXIS 19361 (SDNY 2001) (safe harbor covers the use of patented intermediates to synthesize new drug compounds for preclinical testing). The Federal Circuit's *Integra* decision seemed to reverse this trend and more narrowly construe the safe harbor.

Integra owns a series of patents covering short amino-acid sequences, known as peptides, including the sequence "RGD," and methods of using the peptides to regulate cellular healing. *Integra's* predecessor, *Telios*, believed the peptides could be used to stimulate healing but was never able to develop a successful drug of its own.

The *Merck* defendants independently discovered that inhibition of cellular adhesion can suppress angiogenesis and believed this could lead to a treatment for cancer. They screened a number of potential peptide candidates and then entered into an agreement (the Scripps-Merck agreement) to fund and conduct experiments to gather information to support an Investigatory New Drug application (IND) for EMD 66203 or a derivative thereof. An IND is a regulatory filing required by the FDA at the preclinical stage of new-drug development. The FDA considers the applicant's IND based on preclinical data to determine whether to allow the requisite clinical testing in humans to support an application to market a new drug (NDA). *Merck* used the patented peptides in its experiments, but had not marketed any of the patented inventions when *Integra* filed suit against

Merck for patent infringement or when the jury rendered its verdict.

In affirming the jury verdict in *Integra's* favor, Judge Randall Rader wrote for a divided Federal Circuit panel that relied heavily on the perception that the safe harbor was crafted for generic drug applicants. Judge Rader appeared to interpret the safe harbor to exclude experiments related to preclinical testing and those generating data that were not actually submitted to the FDA.

The majority also found that to expand the safe harbor to include the Merck experiments would "effectively vitiate the exclusive rights of patentees owning biotechnology research tools." *Integra Lifesciences I, Ltd. v. Merck KGaA*, 2003 USApp LEXIS 27796, *18 (Fed. Cir. June 6, 2003) vacated by *Integra*, 2005 USLEXIS 4840. In dissent, Judge Pauline Newman argued that Merck's actions were protected either under the common-law research exemption⁴ or the Hatch-Waxman Safe Harbor. Judge Newman noted the illogic of a rule that protects the earliest activity under the common-law research exemption and the downstream clinical testing under the Hatch-Waxman Safe Harbor while creating "an intervening kind of limbo" for preclinical activities. *Id.* at *48.

Supreme Court Decision

The language of the Federal Circuit's opinion in *Integra* raised a number of important questions, including:

1. Is the safe harbor limited to generic drugs?
2. If not limited to generics, is it limited to later stage clinical testing to support an NDA or can it also cover preclinical testing to support an IND?
3. If not limited to clinical testing, how far down the chain of drug development does the safe harbor reach?
4. Does the safe harbor protect preclinical testing for purposes other than generating safety data?
5. Does the safe harbor protect experimental activities, if the resultant data is never submitted to the FDA?
6. Does the common-law research exemption cover any of the Merck experiments at issue?
7. Do the *Integra* patents claim biological research tools and is the use of patented research tools within the safe harbor or common law research exemption?

These and other issues prompted 19 amicus filings. Some saw the potential for the Federal Circuit's decision to increase the cost and slow the pace of drug development, as well as to increase the ultimate price of new drugs to consumers. Others feared that an expansive interpretation of the Hatch-Waxman Safe Harbor, or the common-law research exemption, would permit drug developers to infringe with impunity patents on biological research tools and destroy the incentive to develop the tools necessary to identify new drug candidates in the first place. Cognizant of the potential importance of the case, the Solicitor General appeared by invitation of the Court and supported Merck.

The parties themselves agreed that many of the

questions raised by the numerous amicus filings were not properly before the Court. Merck did not rely on the common-law research exemption as a defense to infringement.⁵ *Integra* did not contend it was entitled to an exception to the Hatch-Waxman Safe Harbor for patented research tools. Further, Merck, *Integra* and the Solicitor General agreed that the Hatch-Waxman Safe Harbor is not limited to generic drugs or clinical testing alone, despite language in the Federal Circuit's opinion that suggests otherwise.

The principal issues disputed by the parties were:

- 1) whether the safe harbor reaches far enough down the chain of drug development to exempt from infringement the particular kinds of preclinical testing conducted by Merck;
- 2) whether preclinical data other than safety data qualifies for the safe harbor; and
- 3) whether information not ultimately submitted to the FDA is covered by the safe harbor.

The Court rejected the notion that the Hatch-Waxman Safe Harbor is limited to generic drug development or clinical stage activities. The Court noted that §271(e)(1) applies to uses of patented inventions that are reasonably related to the development and submission of any information to the FDA and concluded:

This [information] necessarily includes preclinical studies of patented compounds.... 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 in which it could be included. *Integra*, 2005 U.S. LEXIS 4840 at *16-17.

The Court also found that the safe harbor is not limited to preclinical safety testing. Relying on the government's brief on behalf of the FDA, the Court reasoned that the FDA in evaluating an IND for a particular drug must weigh the potential benefits and risks associated with human clinical trials and, therefore, must consider information other than safety-related data, including information related to efficacy, mechanism of action, pharmacokinetics or pharmacology. *Id.* at *19-20.

The Court also rejected the proposition that the safe harbor includes only activities related to compounds or experimental data that are ultimately the subject of an FDA submission. *Id.* at *23-25. Justice Antonin Scalia explained, "One can know at the outset that a particular compound will be the subject of an eventual application to the FDA only if the active ingredient in the drug being tested is identical to that in a drug that has already been approved." *Id.* at *24. Applying such a narrow interpretation of §271(e)(1), therefore, would effectively limit the safe harbor exemption to those activities necessary to seek approval of a generic drug—a result that is contrary to the text of the statute. *Id.*

Finally, before remanding, the Court offered additional guidance on the proper scope of the safe harbor:

At least where 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 FDA,

that use is "reasonably related" to the "development and submission of information under...Federal law." *Id.* at *25 (citation omitted). The Court made clear, however, that the safe harbor does not reach "[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..." *Id.* at *23.

Unanswered Questions

The Federal Circuit will now determine on remand whether substantial evidence supports the jury's verdict of infringement in view of the Supreme Court's clarification of the scope of the safe harbor. However, a number of questions of more general interest remain.

For example, the standard articulated by the Court does not make clear what constitutes a "reasonable basis for believing that a compound will work, through a particular biological process, to produce a particular physiological effect." Nor does it explain how one can get to that point without infringing to take advantage of the safe harbor. The Court's statements concerning basic research indicate the safe harbor does not necessarily insulate all steps in the new drug development chain. The Court was also silent on the potential application of the common-law research exemption to the drug development process and expressly declined to consider whether any exception to the Hatch-Waxman Safe Harbor exists for patented research tools. See *id.* at *22, n.7. Thus, while the Supreme Court's ruling improves the outlook for innovator drug companies, it stops short of creating the seamless protection for the entire drug development process envisioned by Judge Newman and leaves open the question of the safe harbor's application to patented research tools.

The Federal Circuit's decision on remand should be watched closely, since it may expand on the legal standards articulated by the Supreme Court and shed light on how those standards are to be applied to the facts in a particular case.



1. Merck KGaA and Merck & Co. share a common ancestry but have been separate entities since 1917. Merck KGaA is a German firm and a party before the Court. The U.S.-based Merck & Co. has no involvement in this case.

2. Codified at 35 USC §271(e)(1).

3. The Federal Food, Drug, and Cosmetic Act (FDCA) is the federal statute that regulates the manufacture, use, or sale of drugs in the United States.

4. The common-law research exemption is a judicially created doctrine that exempts from infringement research activities undertaken for philosophical inquiry and without commercial purpose. See, e.g., *Chesterfield v. United States*, 159 F.Supp 371 (Ct. Cl. 1958); *Ruth v. Stearns-Roger Mfg. Co.*, 13 F.Supp 697 (D. Colo. 1935).

5. The district court found that certain earlier Merck experiments were covered by the common-law research exemption, but *Integra* did not challenge that finding. As to the experiments at issue on appeal, Merck relied solely on the statutory safe harbor. See *Integra*, 2003 U.S. App. LEXIS 27796.