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'Integra': A Fatal Blow to Biotechnology?

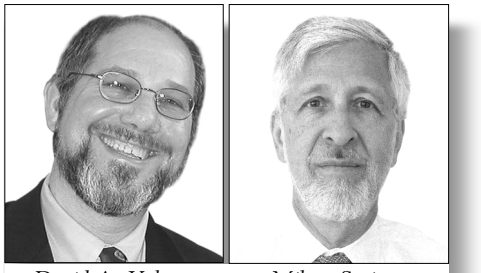
Many in the biotechnology industry feel that the U.S. Supreme Court, in *Merck KGaA v. Integra Lifesciences I, Ltd.*, 125 SCt 2372 (June 13, 2005), has dealt a heavy, maybe fatal, blow to patented research tools (e.g., cell lines, peptides, antibodies; chemical compounds, labs-on-a-chip and high throughput screening techniques) used in new drug development, rendering them potentially valueless.

In a nutshell, the Court's decision expanded the scope of the safe harbor provision of 35 USC §271(e)(1)[1] to allow pharmaceutical companies to infringe a biotechnology company's patent without liability as long as the infringing acts (e.g., pre-clinical experiments using a rival's patented technology) are "reasonably related" to the development and submission of drug information to the Food and Drug Administration (FDA). According to the Court, the safe harbor provision applies even when the pre-clinical experiments are not ultimately submitted to the FDA.

Warnings Ignored

By its decision, the Supreme Court appears to have ignored the warnings of the Court of Appeals for the Federal Circuit and of some amicus filings that expanding the scope of the safe harbor to exempt from patent infringement pre-clinical experiments conducted early on in drug development would ultimately destroy the value of research tool patents that the biotechnology industry relies so heavily on for licensing revenues.[2]

Such a "pro-pharma" result is particularly ironic because the Hatch-Waxman Act, §271(e)(1) was originally enacted in part to protect the smaller generic drug companies from patent infringement suits initiated by big pharmaceutical companies. For instance, §271(e)(1) allows the generic drugmaker to conduct infringing experiments, before the big pharmaceutical company's drug patent expires.



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This is to show the FDA that the generic drug is a bioequivalent, so that the generic drugmaker can be ready to start selling the drug the day after the patent expires. In this way, a less expensive generic drug can be introduced into the market place without delays from the generic drugmaker's bio-equivalency testing being attacked as patent infringement before the patent expires. Now, the Court appears to have inverted this intent, to the detriment of biotechnology companies, and expanded the scope of §271(e)(1) to protect big pharmaceutical companies from patent infringement suits by the smaller biotechnology companies.

'Integra'

The history of the *Integra* case is illustrative of what expanding the scope of the safe harbor provision can do to the detriment of a biotechnology company. Integra, a biotechnology company, owned five patents related to certain amino acid sequences called RGD peptides. Scripps Research Institute, funded by Merck KGaA, discovered that these RGD peptides bind to receptors called integrins and inhibit new growth of blood vessels in a process known as angiogenesis.[3] Merck KGaA entered into a collaboration agreement and paid $6 million over three years to Scripps to further test certain RGD peptides to determine which peptides were the best drug candidates that inhibit angiogenesis and could potentially be used to treat cancer, diabetes and other diseases. Merck conducted several preclinical experiments to evaluate each RGD peptides' mechanism of action, efficacy, and toxicity and determine which peptide would be ideal for human testing. After the preclinical testing, Merck determined that a cyclic RGD peptide 121974 was the best drug candidate and shared its results with the National Cancer Institute (NCI). An investigational new drug application (IND) was submitted to the FDA and the NCI agreed to sponsor clinical trials.

After extensive licensing negotiations between Integra and Merck fell through, Integra filed a patent infringement suit claiming that Merck's use of Integra's patented RGD peptides constituted patent infringement. Merck defended by claiming that its use of the RGD peptide did not infringe any patent and, in any event, should be protected by the safe harbor under §271(e)(1) because Merck used the peptides in research reasonably related to the development and submission of information to the FDA. At trial, a jury awarded Integra $15,000,000, later reduced to $6,375,000, for infringement of its RGD patents and found that Merck failed to show that Scripps' experiments with RGD peptides were protected by §271(e)(1). The court of appeals affirmed on the grounds that the §271(e)(1) safe harbor did not apply because Merck's work was not clinical testing, but only general biomedical research performed in the preclinical stage to identify the best drug candidate for future clinical testing and thus

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not reasonably related to the development and submission of information to the FDA. According to the court of appeals, §271(e)(1) applies to experiments conducted in the clinical stage of drug development and did not embrace all experimental activity that at some point, however attenuated, might lead to an FDA submission. Expanding §271(e)(1) to include Merck's activity, the court warned, would effectively vitiate research tool patents and swallow the whole benefit of these patents to the biotechnology industry.

Rejecting the court's distinction between early stage preclinical research and later stage clinical research, the Supreme Court ruled that the safe harbor extends "to all uses of patented inventions that are reasonably related to the development and submission of any information" to the FDA. This necessarily includes preclinical experiments using patented compounds that are appropriate for FDA submission. There is "simply no room" under §271(e)(1) to exclude early acts of infringement from exemption on the basis of the stage of research. The key to the §271(e)(1) safe harbor, according to the Supreme Court, is that the experiments conducted are "reasonably related" to an FDA submission. Safe harbor can apply even when the experiments are not ultimately submitted to the FDA.

Although the interpretation that the Supreme Court gave to the safe harbor provision potentially has a tremendous impact on research tool patents, Justice Scalia's only mention of the court's warning about extending the scope of the §271(e)(1) safe harbor to devalue research-tool patent is in a single footnote. The Supreme Court did make clear, however, that safe harbor does not apply to basic scientific experiments performed where there is no intent by the scientist to develop a drug. The Court remanded the case for further proceedings to determine if Merck's preclinical experiments fell within its broadened interpretation of the §271(e)(1) safe harbor and were "reasonably related" to an FDA submission.

Implications

Only time will tell how the court of appeals will interpret the new reasonable relationship standard dictated in *Integra* and provide guidelines as to how early in the drug development chain can pharmaceutical companies ignore research tool patents and claim safe harbor.

In the meantime, pharmaceutical companies are well advised to continue to steer their experiments and use of patented research tools with an eye toward an FDA submission. Alternatively, with the expanding global economy, some drug development can be outsourced overseas to countries where patent protection has not been obtained for the candidate or research tool (e.g., India, China, Mexico). The pharmaceutical company, however, should be wary of the U.S. secrecy, import and export laws when conducting research overseas.

Although the biotechnology industry appears to have been mortally wounded by this Court ruling— expanding the scope of safe harbor to include any research that is reasonably related to the development and submission of information to the FDA—there are several options available for biotechnology companies to transform this fatal blow into merely a flesh wound. Biotechnology companies may:

- consider aggressively revising their license agreements to include, if at all possible, field-of-use restrictions limiting the pharmaceutical companies use of patented research tools for basic scientific research only, while at the same time, excluding use of the research tools to generate information for the development and submission to the FDA.
- offering the patented research tool to pharmaceutical companies at a relatively low price and revising license agreements to include reach-through royalties (e.g., where the research tool company can obtain royalties from the pharmaceutical company on future sales of marketed drugs developed using the patented research tool).
- consider offering pharmaceutical companies a research tool package, where the patented research tool is combined with a patented computerized device that can read the results generated by the research tool. For example, there are computerized plate readers that can read certain biological and chemical reactions that occur in a microtiter plate. These computerized devices should be difficult to copy or too expensive for the pharmaceutical company to manufacture or design around, thus the cost of a license, rather than the design around, is much easier for the pharmaceutical company to justify.
- consider changing their patent filing strategy and file in countries that do not grant a research safe harbor where the pharmaceutical companies are likely to conduct basic preclinical and clinical research (e.g., India, China). However, patent enforcement in these countries, while slowly improving, still remains problematic.
- consider changing their intellectual property strategy and maintain research tool technology as a trade secret instead of patenting them. Research tools could be offered as a service to the pharmaceutical company, where the biotechnology company's own scientists perform the actual drug development experiments using their own research tool.
- rally the industry in some cases and partner with other biotechnology companies to create a research tool consortium and offer the research tool, without raising anti-trust concerns, at a price favorable to the consortium.
- consider seeking congressional amendments to clarify or change 35 USC §271(e)(1).

Conclusion

It appears, in light of *Integra*, that the pharmaceutical companies have won this latest round. However, in the long run, pharmaceutical companies could lose the goose that lays the golden egg, because research tool patents grease the wheels for pharmaceutical companies, not only to identify new drug candidates, but also to significantly reduce research and development timelines and speed the drug through the FDA approval process.

Even with the aid of patented research tools, drug making is no easy business. On average, according to Tufts Center for the Study of Drug Development, it takes about 12 years from discovery in the scientist's lab to bring a new drug to market, costing the drugmaker close to one billion dollars.[4] Pharmaceutical companies' new drug pipelines are already starting to run dry with very few new drug candidates making it to clinical trials in humans.

Without patent protection and financial incentive to push new research tools into the drug discovery market and make them available for pharmaceutical companies, advances in finding, hopefully, safe and effective new drugs well be thwarted, causing fewer drugs to be available in the pharmaceutical companies already struggling new drug pipeline. Without meaningful protection, these new research tools will not be nurtured to practical availability. The net result could be a mortal blow for both the biotechnology and pharmaceutical companies as well as to the public, because new drugs will not be available to prevent or treat disease. Clearly, the pharmaceutical companies should not desire such a fate.

1. 35 USC §271(e)(1) provides:

> It shall not be an act of infringement to…use…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.

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

3. *Scripps* and *Merck* are sometimes collectively referred to as Merck in the remainder of the article.

4. Tufts Center for the Study of Drug Development: How New Drugs Move Through the Development and Approval Process (Nov. 1, 2001)