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CLIENT ALERT

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Merck v. Integra: Supreme Court Broadly Interprets Safe Harbor Exemption

In a decision that will have a significant effect on the biotechnology and pharmaceutical industry, the United States Supreme Court unanimously held that the "safe harbor" provision of 35 U.S.C. §271(e)(1) is to be interpreted broadly. It exempts from infringement the use of patented inventions in preclinical research, including experimentation whose results are not ultimately submitted to the Food and Drug Administration (FDA), as long as there is a reasonable basis to believe that the compound tested could be the subject of an FDA submission, and that the experiments will produce the types of information relevant to an application for drug approval. The Supreme Court in *Merck KgaA v. Integra Lifesciences I* determined that the statutory text makes clear that the safe harbor provides a wide berth for the use of patented drugs in legitimate pharmaceutical research activities that are reasonably related to the FDA drug approval process.[1]

Under the Supreme Court's broad reading of §271(e)(1), research and development by a drug maker that may be attributed to the experimentation on patented drugs or the use of patented compounds, the results of which *may* be submitted to the FDA or merely provide underlying support for such a submission, may fall within the exemption of §271(e)(1) if the drug maker reasonably believes that the patented compound may work to produce a particular physiological effect, and if the compound is used in research, which, if successful, would be included in an FDA submission. The interpretation appears to cover a broad range of research and development activities, including basic research, organic chemistry, spectral analysis, as well as developing new chemical entities with patented compounds.

From the perspective of the pharmaceutical industry, the Court's opinion allows drug makers to bring new drug therapies to market quicker, with less cost, and with less risk. By interpreting §271(e)(1) broadly, the Court permits drug makers to conduct pre-clinical research on patented compounds — research that is necessary to ultimately bring new therapies to market. By allowing such research to be conducted without fear of a patent infringement suit, pharmaceutical companies can accelerate the time to develop new drugs and make drug discovery more efficient.

From the nascent biotech industry's perspective, the expansive interpretation of §271(e)(1) may be both beneficial and harmful. A broad exemption from patent infringement could harm many biotech businesses whose research focuses on assay machines, enzymes, genes, proteins, antibodies, kits and methods that manipulate genes and proteins — all of which may have little or no use outside of biomedical research. Such businesses

are likely to view the expansive reach of the exemption as a disincentive to patent their inventions. As a result, such biotech businesses and other research entities may be inclined to protect their inventions as "trade secrets," rather than making them available publicly. A form of trade secret commonly known as a "shrink-wrap contract" is a well-developed concept in software industry. This concept may emerge in the context of biotech or chemical inventions, e.g., for kits and reagents sold such that by opening the product the user "agrees" not to reverse engineer the product: "buy it, use it, but don't study it." While such development may be viewed by some as undermining the dual purposes of the patent system — financial reward for discovering an invention and public dissemination of scientific and technical knowledge — it respects fundamental property rights of scientific discovery through licensure requirements to achieve the former goal. It may also spur creativity by providing an incentive to researchers to engage in independent development aimed at producing competing products.

In its opinion released June 13, 2005, the Supreme Court applied a straightforward reading of the statutory text of §271(e)(1). Under the U.S. patent system, the patent holder is conferred the right to exclude others from using, making, offering for sale, selling in or importing into the United States the patented invention. Section 271(e)(1), however, provides that "it is not an act of patent 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."[2] Based strictly on this language, the Court opined that "[i]t is apparent from the statutory text that §271(e)(1)'s 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. … This 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 in which it could be included."

In discussing the breadth of the exemption, the Court noted that the safe harbor protections were not limited only to the development of information for submission to the FDA or only to filings for approval of a generic drug. Instead, the Court noted that Congress "exempted from infringement *all* 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." The Court found unpalatable categorical exclusions from the safety of §271(e)(1) of experimentation on drugs not ultimately the subject of an FDA submission or the use of patented compounds in experiments that are not ultimately submitted to the FDA. In doing so, the Court noted the limits of §271(e)(1)'s protection, stating 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 'reasonably related to the development and submission of information' to the FDA." Thus, a use could be protected under §271(e)(1) regardless of whether a researching company actually submits to FDA-specific preclinical or clinical data from the scientific research process attendant to that use, as long as the researcher has a reasonable belief that the information would support a regulatory submission in some manner. Hence, "[t]he 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."

The Court acknowledged the many unknowns along the drug discovery path and the role of the scientific research method in the decision to pursue a product approval, while asserting that §271(e)(1)'s protections potentially extend to provide coverage for activities reasonably believed to produce information for submission to the FDA. "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' to the 'development and submission of information under … Federal law.'"

As for the factual case context, Merck provided Dr. David Cheresh of Scripps Research Institute with RGD peptides covered by patents held by Integra Lifesciences I, Ltd. and the Burnham Institute (collectively "Integra"). Dr. Cheresh's research focused on the use of the RGD peptides to inhibit angiogenesis — the process for generating new blood vessels — in solid tumor cancers.

Inhibiting angiogenesis could be used as a means to stop tumor growth by starving the tumor cells of required nutrients. In addition, anti-angiogenesis therapies could include treatments for other diseases such as diabetic retinopathy, rheumatoid arthritis, psoriasis and inflammatory bowel disease. Dr. Cheresh's intention was to use results of his research, if successful, for an FDA approval to proceed to clinical trials.

Integra sued Merck for willfully infringing and inducing others to infringe Integra's patents by supplying the RGD peptides to Scripps, and Dr. Cheresh and Scripps for infringing the same patents by using the RGD peptides in experiments related to angiogenesis. Merck responded in part that their actions did not infringe and were protected by §271(e)(1). The District Court held that whether Merck's use of the RGD peptides fell within the §271(e)(1) safe harbor was a question of fact. The District Court went on to interpret §271(e)(1) in a jury instruction, stating that to prevail Merck "must prove by a preponderance of the evidence that it would be objectively reasonable for a party in [their]… 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." Further, the District Court ruled that "[e]ach of the accused activities must be evaluated separately to determine whether the exemption applies" but that Merck "does not need to show that the information gathered from a particular activity was actually submitted to the FDA." The District Court, in confirming a jury's $15 million award to Integra, held that the evidence was insufficient to show any connection between the infringing experiments and FDA review to qualify for the §271(e)(1) exemption.

On appeal, the Court of Appeals for the Federal Circuit more narrowly interpreted §271(e)(1)'s exemption as being limited to those activities more directly applicable to an FDA submission and excluding activities that "however attenuated, may lead to an FDA approval process," and held that the safe harbor did not apply because the Scripps work sponsored by Merck was not clinical testing to supply information to the FDA but was general biomedical research to discover new pharmaceutical compounds.

The Supreme Court vacated the CAFC decision and remanded the case for consideration of whether the evidence was sufficient to establish that the accused activities were covered by the exemption from patent infringement of Section 271(e)(1), under the standards of the jury instruction.

Like many Supreme Court decisions, the issues raised in this case are far from settled after issuance of the Court's opinion. First, the facts in the case will now have to be applied to the Court's new legal standard. This may or may not result in a new trial and a new outcome.

Second, it will be left for future courts to determine what proof is required to meet the Court's "reasonable belief" standard. For instance, is the standard an objective standard that should be determined irrespective of the drug maker's actual belief or intent, or is it a subjective standard? How will this standard be met by a drug maker? Researchers working in this area would be well-advised to create and maintain records evidencing the purpose of their research and to document that such research falls within the safe harbor in the event of litigation.

Third, while the opinion commented extensively on the use of patented compounds in research endeavors, the Court expressed no view about whether, or to what extent, §271(e)(1) exempts the use of "research tools" in the development of information for the regulatory process from infringement.[3] The issue of whether the use of patented "research tools," as compared to patented compounds, falls under the safe harbor's protection has been left open and will likely be a debated topic for industry, regulators, and the courts in future years.

Endnotes

[1] *Merck KGaA v. Integra Lifesciences I. Ltd.*, et al. 545 U.S. ___ (2005), No. 03-1237.

[2] 35 U.S.C. §271(e)(1).

[3] *Merck KGaA v. Integra Lifesciences I. Ltd.*, et al. 545 U.S. ___, fn. 7 (2005).