Industries Await Exemption Verdict

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Imagine that the cost of bringing a new drug to market skyrockets beyond the $802 million currently estimated. Further imagine that it takes decades to bring a drug to market — far longer than the current 10-15 year cycle. Frustrated with the unfavorable environment in the U.S., pharmaceutical companies transfer all of their research and development (R&D) activity to foreign countries. Despite this, far fewer new drugs are introduced and their price is so high that patients can barely afford them. This imagination underlies policy arguments advanced by the pharmaceutical industry, which has a keen interest in the U.S. Supreme Court's forthcoming decision in *Merck KGaA v. Integra Lifesciences I*. At issue in this case is the breadth of the statutory "safe harbor" exemption to patent infringement, which 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." The last time the Supreme Court interpreted this exemption, it stated that the exemption applies broadly to medical devices, food additives, color additives, new drugs, antibiotic drugs, and human biological products — all of which are regulated under the Federal Food, Drug, and Cosmetic Act.

The Dispute

Integra Lifesciences ("Integra") owns five patents relating to the discovery of a key protein fragment (containing an "RGD" amino acid sequence) that encourages attachment of different cell types, a process called cell adhesion. Cell adhesion is responsible for the growth of new blood vessels that feed tumors. Merck KGaA ("Merck") paid the Scripps Research Institute ("Scripps") to perform research to identify chemical compounds that might inhibit cell adhesion. That research initially included testing different chemical compounds, including an RGD-containing fragment, to determine whether one of the tested compounds could inhibit the growth of new blood vessels. Merck supplied Scripps with the original RGD-containing fragment and Scripps identified two other RGD-containing derivative compounds with inhibitory activity.

Merck paid Scripps to conduct additional experiments to evaluate the biological bases of activity and satisfy regulatory requirements imposed by the FDA so that Merck could move forward with clinical trials utilizing the compound or derivatives thereof. Scripps conducted several experiments in test tubes and in animals to evaluate the specificity, efficacy, and toxicity of the three inhibitory compounds for various diseases, to explain the mechanism by which these compounds work, and to determine which of the three were sufficiently safe and effective to warrant testing in humans. Ultimately, the Scripps

research team chose one of the derivative compounds as the best candidate for clinical development.

When it learned what Merck and Scripps were doing, Integra offered to license its patents to Merck; however, no license agreement was ever reached. Accordingly, Integra sued Merck for inducing patent infringement by supplying Scripps with the RGD-peptide compounds and by hiring Scripps to perform experiments that infringed Integra's patents on methods that used the compounds. Merck answered that all of the Integra patents are invalid and that Merck's activities nevertheless fell within the statutory exemption from patent infringement. At trial, the district court found that Merck's activities infringed four of the five patents and that those activities were not exempt from patent infringement.

On appeal, a divided three-judge panel of the Court of Appeals for the Federal Circuit interpreted the exemption and held that it did not apply to Merck's activities. The court characterized the Merck-sponsored work by Scripps as general biomedical research to identify new pharmaceutical compounds, "not *clinical testing* to supply information to the FDA." The court reviewed the legislative history of the statutory exemption and concluded that its objective "was to facilitate immediate entry of safe, effective generic drugs into the marketplace upon expiration of a pioneer drug patent." Accordingly, the court stated that the exemption "does not [] encompass drug development activities far beyond those necessary to acquire approval of a patented pioneer drug already on the market." Because, according to the court, the "FDA has no interest in the hunt for drugs that may or may not later undergo *clinical testing* for FDA approval," the court held that the statutory exemption from patent infringement does not stretch back down the chain of experimentation to "reach any exploratory research that may rationally form a predicate for future FDA *clinical tests*."

Moreover, the court suggested that expanding the exemption out of the context in which it was enacted would devalue an entire category of biotechnology patents relating to research tools (i.e., patents that cover products or processes used for discovering drugs, but do not cover the drugs that are discovered). By way of a simplistic analogy, research tools are like a metal detector that someone can use to locate a metal-containing treasure (a drug candidate). While the treasure might have been found by random digging without the use of the metal detector, the certainty of finding any treasure without the metal detector would be far less and the cost far more.

However, at least some of the testing undertaken by Scripps did provide the kinds of information that would be submitted to the FDA as part of the drug-approval process. The Federal Circuit's majority characterized the experiments as including studies "to evaluate the specificity, efficacy, and toxicity of [the three compounds] for various diseases." These are types of studies that could be included in an FDA application for approval to administer a drug to humans.

Dissatisfied with the Federal Circuit's decision and reasoning, Merck asked the Supreme Court to review the decision. Merck took issue with the decision's implication that only clinical testing (i.e., testing in humans) is covered by the safe harbor exemption, and that the safe harbor excludes pre-clinical testing (i.e., test tube and animal experiments) of the type that must be submitted to the FDA before beginning any clinical study. Merck specifically asked the Court to consider whether the exemption applies to research activities "of the sort that are essential to the development of new drugs, where the research will be presented to the FDA, and where barring the research until the expiration of the patent could mean years of delay in the availability of life-saving new drugs." In opposing Merck's request, Integra rephrased Merck's question in terms of whether the ex-

emption "globally embrace[s] all experimental activity that at some point, however attenuated, may lead to an FDA approval process." Integra suggested that at stake in the case was not the future of drug research or patient health care, but rather Merck's desire to protect the size of its purse in refusing to pay Integra for a license to its patents.

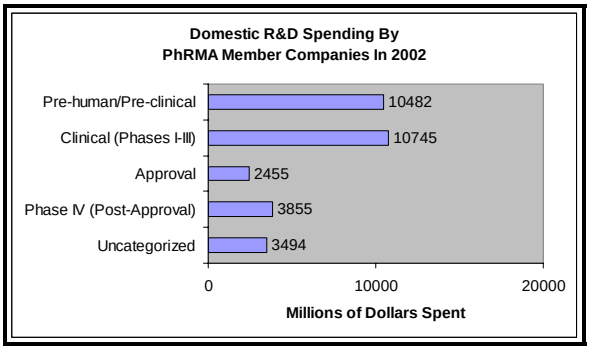
Through the Solicitor General, the U.S. government urged the Court to consider and vacate the Federal Circuit's decision because the Federal Circuit's legal reasoning and conclusion were incorrect and pose a direct and substantial threat to new drug research. The government commented that the Federal Circuit's delineation — between *clinical testing* as exempt and *pre-clinical testing* as non-exempt — is inconsistent with the language of the statute and reflects a mistaken view of the types of information relevant to FDA approval. In fact, pre-clinical test results are submitted to the FDA as part of the drug approval process.

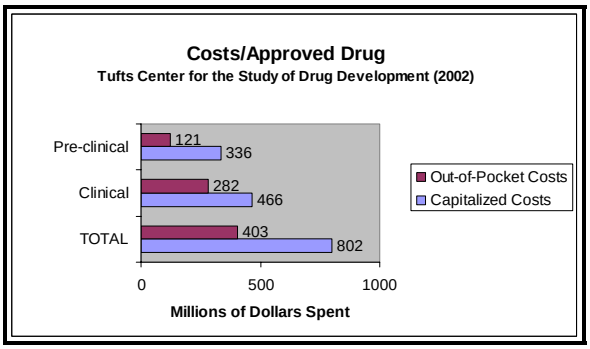
The Supreme Court agreed to review the Federal Circuit's decision and is expected to issue its decision by July.

What Really is at Stake in this Dispute?

At stake in this dispute are competing interests within the pharmaceutical and biotech industries. If the Supreme Court construes the statutory exemption to encompass exploratory drug discovery research, then companies that conduct drug research would benefit, but an entire category of research tool patents would be devalued. Many companies even do both — they conduct drug research and obtain patents on research tools.

Pharmaceutical companies devote about the same amount of money to pre-clinical R&D activities as to clinical testing. The Pharmaceutical Research and Manufacturers of America (PhRMA) issued a report in 2004 indicating that PhRMA members spend 33.8% of their domestic R&D budget on pre-clinical work — a figure that totaled $10.5 billion in 2002 — and 34.6% on clinical testing before approval. In contrast, their annual sales in 2002 were $192.8 billion.





The value of research tool patents is difficult to estimate. One report indicates that US chemical and pharmaceutical corporations earned $8.6 billion in royalty income through technology licensing to unaffiliated entities in 1996. The mapping of the human genome and advances in biotechnology and combinatorial chemistry have led to an abundance of new biological targets (which are an important research tool) and have the potential to make it easier and cheaper to discover new drugs. Companies have been willing to pay millions of dollars for access to such targets and technology. For example, in 1998 Millennium Pharmaceuticals entered into a drug discovery alliance with Bayer AG under which Bayer committed to payments of $465 million to gain access to Millennium's technology and drug targets. Millennium announced that with the Bayer alliance, Millennium had reached over $1 billion in potential pharmaceutical partnership funding.

Merck is expected to argue that the Federal Circuit's decision upends twenty years' worth of settled expectations shared by an entire industry. Those expectations are based on prior federal court decisions exempting a wide variety of activities from patent infringement, such as activities soliciting clinicians to enter into FDA-approved clinical trials, use of patented chemical intermediates to investigate potential new drug candidates, animal testing to determine a drug's safety for clinical tests, and trade-show displays of medical devices to solicit clinical investigators for clinical trials. Merck's brief and many of the amicus briefs filed in support of Merck predict dire consequences if the Federal Circuit's reasoning is upheld. Merck and these amici fear that narrowing the exemption will substantially delay development of new and better drugs and significantly increase the costs of developing drugs, or, even worse, that promising drugs and medical technology will never be developed. The free exchange of scientific knowledge and progress in medical research will be impeded by making it impossible or more costly for researchers to obtain needed tools and materials. Even if licenses are available for research tool patents they will add to the costs of discovering and developing drugs. Drug R&D, intellectual capital, and valuable jobs in the United States will move to countries having more favorable legal environments.

This dire scenario may exaggerate the likely effects of a narrow exemption. The Committee on Intellectual Property Rights of the National Research Council (a private, nonprofit institution that provides science and technology policy advice under a congressional charter) issued a report in 2004 indicating that the majority of respondents in the pharmaceutical and biotech industries did evaluate the patent landscape for R&D projects, contradicting Merck's suggestion of a settled expectation that one may freely infringe patents during drug discovery research. The report also found that projects rarely stop solely because of patent concerns, and identified a number of commonly used alternatives to ceasing research, including licensing patents, designing around patents, carrying out research activities in a foreign venue, and challenging the patents in court.

Another recurring theme from Merck and its amici is that the patent owner will enjoy a de facto patent term extension while potential treatments are denied to patients for years after all relevant patents expire. This highly undesirable extension reflects a reality where the process to develop new drugs does not even begin until the patents expire, and then takes 10-15 years to complete. An owner of patents covering ways to develop competing products can block development of such competing products until its patents expire. Because the time required to develop an innovative new drug is so long, the patent owner will enjoy extended market exclusivity for its products. While this argument is convincing with respect to patents covering the ultimate drug product, it is not convincing with respect to patents covering research tools, because the public can freely use those tools on the day those patents expire and, thus, the patent owner enjoys no extended market exclusivity.

Integra can be expected to argue that this case is really about whether the pharmaceutical industry can use research tools patented by others to discover new drugs, yet avoid sharing the profits it earns from the drug. Moreover, Integra can be expected to argue that if the Federal Circuit's decision is overturned and the exemption is broadly interpreted to cover drug discovery research, then, for research tool patents, the Court will have effectively eviscerated the very rights the U.S. patent system bestows on inventors. The Federal Circuit was concerned that a broad application of the statutory exemption could devalue research tool patents. Without exclusive rights, there would be no economic incentive to discover those tools in the first place. The

reduction in number or quality of research tools could actually reduce the number of pioneering drugs from which the public can benefit. Even if companies did discover new research tools, they would have no incentive to disclose them through the patent system.

Devaluing research tool patents disproportionately affects smaller biotechnology companies, which frequently lack resources needed to develop a drug and, therefore, depend on licensing others to use their technology to develop new drugs. The devaluation also will affect large pharmaceutical companies. Part of the value of a pharmaceutical company's patents relating to a blockbuster drug is the right to enjoin competitors from experimenting with that drug and related derivatives. With a narrow exemption, only the patent owner would conduct such experiments and, thus, only the patent owner would be in a position to introduce a second generation "improved" version of the drug when the drug patents expire. In contrast, a broad exemption permitting exploratory drug research will encourage competitors to freely infringe the drug patent by attempting to design their own improved versions for introduction into the market as soon as the patents expire. In theory, then, the second generation drug introduced by the patent owner will face immediate competition from numerous other improved versions.

Which View Will Prevail?

Whatever decision the Supreme Court reaches, it is sure to have an enormous impact on the way the pharmaceutical and biotech industries behave. Drawing a bright line between clinical and pre-clinical testing has provided clarity, but may not have been correct. To suggest that pre-clinical tests that are included in FDA applications are not "reasonably related" to FDA approval is inconsistent with the plain language of the statute. Moreover, drawing the line between pre-clinical and clinical testing could have the bizarre effect of creating an incentive to sue companies during the preclinical phase, in order to stop their FDA-related activities or force them to pay license fees before their research advanced to the human clinical phase.

However, the other extreme of broadening the exemption to include exploratory research could dangerously devalue research tool patents. However much pharmaceutical companies would welcome freedom in undertaking their own research, such freedom is dearly bought if it significantly diminishes their own or others' patent estates. Even though they disagree with the Federal Circuit's reasoning regarding pre-clinical testing, both the government and the American Intellectual Property Law Association state that the exemption should exclude exploratory drug discovery activity that aims merely to identify what compounds might warrant further study.

There is a reasonable middle ground between the two extremes, i.e., that only human clinical testing is exempt, or all drug discovery activities are exempt. An oft-cited, early decision by a federal district court that interpreted the statutory exemption, *Intermedics v. Ventritex*, posits: would it have been objectively reasonable for a party to believe that there was a decent prospect that the use in question would contribute (relatively directly) to the generation of the kinds of information likely to be relevant in the processes by which the FDA would decide whether to approve the product? Other federal courts, including the Federal Circuit, have applied this test to determine the exemption's applicability. Indeed, the Federal Circuit *cited* the test in this case, although Merck and the government argue that the Federal Circuit actually *applied* a different test.

The government proposes a slightly different test setting forth two criteria: the exemption protects experiments that are undertaken in the course of an attempt to develop a particular drug, and that are reasonably re-

lated to the development of the types of information that would be relevant to an application submitted to the FDA. Such experiments are "reasonably related" to FDA approval because it is "reasonably foreseeable" that an FDA application will be submitted if the experiments succeed. The government advocates such a prospective standard because it would be illogical for the exemption's applicability to hinge on the favorable outcome of experiments, where an unfavorable outcome would deprive the researcher of the exemption retroactively.

The government also suggests that the statute could be interpreted to exclude research tool patents from the types of patents the exemption covers. However, when the Supreme Court first interpreted this statute in 1991, it stated that "the phrase 'patented invention' is defined to include all inventions, not drug-related inventions alone." Thus, the exemption might apply to *any* patented invention used in drug research, including sequencing and spectroscopy machines, or even computers.

While each party will present laudable policy arguments to sway the Court's decision in its favor, the Court will be constrained by the language of the statutory exemption it is being asked to review. The Court's prior decision construing this statute cautioned against the use of legislative history to rewrite the legislation. The text of the statute does not distinguish the type of patented invention, timing, infringing activities, type of FDA application, or product being approved. As Merck has suggested, even if some patents can be infringed freely by the pharmaceutical industry in its quest to find the next blockbuster drug, it is because the plain language of the statute exempts that infringement. It is now up to the Supreme Court to provide guidance on the boundaries of the exemption so that the pharmaceutical and biotech industries can make informed decisions about how, where, and whether to invest in research and development of the next potential blockbuster drug.

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