Pre-Clinical Research Bombshell

Court narrows exemption from patent-infringement claims.

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A June 2003 court decision boosting the importance of "biotechnology (research) tool patents" will affect everyone engaged in biomedical research. In the case of *Integra Lifesciences I, Ltd. v. Merck KGaA*, the US Court of Appeals for the Federal Circuit limited the scope of the statutory exemption from patent infringement for both generic and research-based pharma companies engaged in pre-clinical research. Despite the opinion's far-reaching potential, however, the court left open several questions.

The lawsuit arose out of research done at Merck and the Scripps Research Institute based on Scripps scientist David Cheresh's discovery that blocking certain receptors inhibits angiogenesis. The research ultimately led to the discovery of three cyclic RGD peptide drug candidates. But Integra and two other entities already owned several patents relating to RGD peptides. After learning about the Scripps–Merck research agreement, Integra offered Merck licenses to those patents. Following lengthy negotiations, Merck rejected the offer. Integra and the other patent owners then sued Merck, Scripps, and Cheresh for infringement. A jury found Merck liable and returned a $15 million verdict.

The decision marked a departure from a lower court's ruling in a separate case that allowed pre-clinical research—prior to the filing of an investigational new drug (IND) application with the FDA—for new drug candidates to be exempted from patent infringement. The *Integra v. Merck* decision takes precedence over the lower court's decision.

In its appeal, Merck argued it was exempt from infringement for its pre-clinical research under a provision of the 1984 statute commonly known as Hatch-Waxman. That provision generally exempts from infringement use of a patented invention "solely for uses reasonably related" to developing and submitting information to the FDA. The court observed that the "Scripps–Merck experiments did not supply information" to the FDA "but instead identified the best drug candidate to subject to future clinical testing under the FDA processes." Permitting the statutory exemption to cover the Scripps–Merck research, the court stated, would "vitiate" the rights of patent holders "owning biotechnology tool patents." The court ruled, therefore, that the "FDA has no interest in the hunt for drugs that may or may not later undergo clinical testing for the FDA approval." In rejecting Merck's argument, the court reasoned that the "FDA does not require information about drugs other than the compound featured in an [IND]."

In light of the new decision, both generic and research-based pharma companies will need to take greater stock of their preclinical investigations.

Open Questions

Meanwhile, the court failed to decide whether there could be some pre-clinical activities that are close enough to filing an IND to qualify for exemption from infringement. The court noted that "some activities that are not themselves the experiments that produce the FDA information" can qualify for the statutory exemption as "reasonably related" to clinical tests for the FDA.

Second, it left open the question of how to compute the value of research tool patents. The appeals court nullified Integra's earlier $15 million jury award because it did "not appear to take into account numerous factors that would

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considerably reduce the value of a [license]." The value to a licensee of research tools," the court stated, can depend on "the point at which those tools are employed in the drug development continuum."

The Integra patents' value could have been less at an earlier point in time "due to the more nascent state of RGD peptide research in 1994." The effect of "stacking royalties" from the need to obtain a variety of licenses to develop a single drug, and the possibility of a "reach-through royalty" based on the profitability of any successful drug discovered using the research tool might also need to be taken into account in computing the value of Integra's patents.

The owners of research tool patents will likely be emboldened by the ruling to identify potentially infringing research programs.

The Impact

The court's decision substantially eliminates the possibility that pre-clinical research will be exempt from infringement claims based on research tool patents. In light of the new decision, both generic and research-based pharma companies will need to take greater stock of their pre-clinical investigations. The owners of research tool patents will likely be emboldened by the ruling to identify potentially infringing research programs. Integra, for example, brought suit only after learning about the Merck–Scripps program by reviewing the Merck-Scripps joint research agreement.

To avoid charges of infringement, companies that need to use patented research tools should obtain licenses to those patents at an earlier stage. That approach will not only reduce litigation, it may also help companies negotiate lower royalty rates based on the more uncertain prospects of success at an earlier discovery stage. Furthermore, licensing research tools during early-stage discovery gives developers greater certainty in the amount of revenue they might obtain in the event of successful drug development. ▮

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