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Research exemptions: do patents inhibit biomedical innovation?

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Research exemptions: do patents inhibit biomedical innovation?

By **Cathryn Campbell**, Needle & Rosenberg, San Marcos

The case of *Integra LifeSciences v Merck KGaA* has revitalised debate over whether basic research should be subject to claims of patent infringement. While it is often believed that patents do not apply to those performing basic research – particularly in an academic setting – this assumption is contrary to the explicit wording of the patent statutes. Infringement is defined as making, using, selling, offering for sale or importing into the US a patented product or method; there is no requirement that infringement be limited to work undertaken for commercial purposes. The *Integra* case, which was filed well over a decade ago, wended its way from trial through appeal and up for review by the United States Supreme Court. Almost two years have passed since the Supreme Court handed down its opinion, remanding the case once again to the Court of Appeals for the Federal Circuit. Oral arguments before the CAFC were heard last June, but as yet no opinion has been issued.

No judicial guidance

Thus, while no further judicial guidance on the issue of the scope of the FDA Exemption to patent infringement has emerged since my previous article on the topic appeared in this publication's predecessor last year (*From IP to IPO 2006*, page 42), public comment and commentary have continued unabated. In fact, it is unlikely that ensuing opinions in the *Integra* case will provide my further answers to the many questions which have been raised relating to the issue of whether basic research is immune from claims of patent infringement. While it is instructive to review the decisions the courts have provided to date in this case, it is cogent at this point to consider whether a research exemption is beneficial to the

progress of biomedical technology, and, if so, how it could and should be implemented.

In fact, there are only two potential exemptions to patent infringement: the so-called “common law exception” and the “FDA Exemption”, which is also referred to as the 271(e) Exemption, reflecting its codification in volume 35 of the federal statutes.

Although a limited common law exception was first enunciated by courts in the nineteenth century, the recent appellate decision in *Duke v Madey* removed any doubt that this exception could extend beyond work done for “merely philosophical” purposes. In that case, use of patented machinery for research and teaching at Duke University was held to constitute infringement as it was undertaken as part of the University's business of obtaining grants and educating students.

The FDA Exemption specifies that it shall not be an act of infringement to make, use, sell, offer to sell or import a patented invention “solely for uses reasonably related to the development and submission of information” to the Food and Drug Administration or other Federal agency regulating drugs. The FDA Exemption was enacted as part of the Hatch Waxman Act; the legislative history indicates that its purpose was to allow generic drugs to receive FDA approval in time that they could reach market as soon as the branded drug went off patent. As drafted, however, the statute is not limited to generics and the courts have generally interpreted its scope broadly. It is this statute which has become the issue in the *Integra* case.

Origins of the case

In the early 1980s, scientists at the Burnham Institute for Medical Research (then called La Jolla Cancer Research Foundation) discovered that the amino acid sequence RGD provides the site of attachment for cells to the extracellular

matrix. This discovery has important ramifications for pathologies as diverse as cancer metastasis, heart disease and wound healing in which cells inappropriately adhere, or fail to adhere, to the matrices which anchor them in their proper place. United States patent applications claiming RGD containing peptides, methods of their use and certain receptors to which they bind were filed by Burnham in the 1980s. These patents were eventually exclusively licensed to Integra LifeSciences.

The discovery that this small three amino acid sequence is the cell adhesion site was truly a pioneering invention. Labs across the world began investigating RGD peptides and their uses to affect various disease states. Investigators at Scripps Research Institute suggested that RGD peptides could inhibit the development of solid tumours by interfering with the formation of blood vessels necessary to support the tumour. Upon learning of this work, Germany-based Merck KGaA entered into a collaborative research agreement with Scripps and the scientist studying this particular effect. The goal of the project was to identify particular RGD containing peptides which would be appropriate drug candidates to treat solid tumours.

While licence negotiations were conducted between Scripps and Merck, no agreement was reached. Integra eventually sued Merck in the Federal district court in San Diego for patent infringement based on its importation of RGD peptides into the US and for inducing infringement by Scripps. Merck defended on various grounds and sought to invoke the safe harbour of the FDA Exemption, claiming that any infringing work was reasonably related to obtaining FDA approval. The evidence at trial established that the majority of the work performed at Scripps involved the study of blood vessel formation in fertilised chicken embryos, which is not a recognised model for safety in humans. Moreover, the principal work to support an Investigation New Drug Application was to be performed by Merck in Germany and thus would not infringe US patents. After a 25-day trial, the jury held that Merck had directly infringed the patents by supplying RGD-containing peptides to Scripps and had induced Scripps to infringe by virtue of the collaborative research agreement. The jury further found that the infringement was not protected under the FDA Exemption.

Supreme Court overrules CAFC

The verdict was appealed to the US Court of Appeals for the Federal Circuit which is charged with hearing appeals in all patent

cases. Merck argued before a three-judge panel of the court that under a rational predicate theory all activities in the causal chain of research towards FDA approval should be exempt from a claim of infringement. This proffered standard would have effectively converted the FDA Exemption into a general exemption for all biomedical research. The Federal Circuit, in an opinion issued by Judge Rader, declined to adopt this expansive view, holding that the FDA Exemption: “Does not globally embrace all experimental activity that at some point, however attenuated, may lead to an FDA approval process.”

Merck sought review by the Supreme Court, asserting that the Federal Circuit’s opinion inappropriately narrowed the FDA Exemption; if adopted, this interpretation would slow the drug discovery process itself, potentially depriving millions of patients of new drug treatments. Over 20 friend-of-the-court briefs were filed by groups as disparate as pharmaceutical companies, non-profit agencies and lawyers bar associations, each supporting one or the other party. After oral argument, the Supreme Court issued its opinion, which may be notable more for what it did not say than for what it did. The Court declined to draw any bright-line rule as to what research does or does not fall within the scope of the FDA Exemption, promoting instead a case-by-case determination based on the particular facts of each case. The Court emphasised that the statute applies only to activities which are “reasonably related” to FDA approval, a determination which must take into the consideration the totality of the circumstances. Importantly, the Court declined to consider whether the FDA Exemption applies to infringement of tool patents, those which cover a method of discovering or identifying a drug, for example, but do not claim the drug itself. The Court vacated the Federal Circuit’s decision, sending it back to them for further consideration of whether there was sufficient evidence to support the jury’s determination that the FDA Exemption did not shield the infringing activities in this case.

In a rehearing last June before the same panel of the Federal Circuit that had originally issued the opinion, Judge Rader raised the issue of how research tools would be impacted by the Supreme Court’s interpretation of the FDA Exemption. Both Integra and Merck took the position that the case did not involve research tools. Integra, in particular, objected to Judge Rader’s

suggestion that a new trial focusing on the research tool issue might be in order. Both parties told the panel that the decision in this case should be decided based on a traditional analysis of whether the jury's verdict is supported by sufficient evidence. Failure of the court to issue a decision more than seven months after the oral argument suggests that the panel has as yet been unable to resolve the research tool question.

Patents on tool technology

An issue of prime importance to the biotechnology industry is whether the FDA Exemption applies to so-called tool technology. Biotechnology is unique in that the discoveries which underlie the remarkable growth of the industry over the last 30 years relate largely to platform technology, new methods to identify useful new drugs. For example, the ability to insert human genes into bacteria through methods of recombinant DNA has led to commercial drugs such as human growth hormone and human insulin, both of which are improvements over the previous forms of the proteins isolated from animals. Similarly, the development of techniques to make highly specific antibody preparations has led to the development of over-the-counter pregnancy tests. The basic recombinant DNA technology, patented jointly by Stanford University and the University of California, was highly profitable to both institutions.

Tool technology has not traditionally been the subject of patents in industries other than biotechnology. In most other industries, such new technology platforms are often held as trade secrets. Patents are reserved for the commercial products developed using the platform technology. Thus, for example, a new method of designing a better bicycle would be unlikely to be patented; the developer of such technology would be far more likely to maintain it as a trade secret and seek patents on the improved bicycle itself. Not so in biotechnology. Much of the basic technology in the field has been developed by academics who are under publish or perish pressure to disclose their inventions. Further, the platform technology may have such wide applicability that no one company can fully exploit it. Thus biotechnology has engendered a multitude of patents claiming technology tools.

Do patents on tool technology inhibit research? Opinions vary. A more critical factor than the issuance of such patents appears to be the availability of licences on reasonable terms. A comparison of licensing strategies between two important

biotechnology inventions is illustrative of this point. Stanford University and the University of California, owners of the fundamental patents on recombinant DNA technology, deserve enormous credit for crafting a licensing strategy specifically designed to promote the use of the technology to develop commercial products while at the same time obtaining just financial reward. Non-exclusive licences were available for the nominal annual cost of US\$10,000, with royalties on products ranging between 0.5% and 4%. Importantly, non-profit research institutions were given a free licence to use the patented technology. The strategy paid off handsomely; the Universities received in excess of US\$300 million before the patents expired. And the technology provided enormous benefits to the public; it is estimated that revenues from drugs developed with the technology exceeded US\$30 billion. The patents were widely licensed, with over 350 companies holding licences at the time the patents expired. Clearly, this case provides an example where patents did not hinder the advancement of science.

The WARF patents

In contrast, patents relating to human embryonic stem cells are frequently cited as thwarting potentially life-saving research. The Wisconsin Alumni Research Foundation (WARF) owns patents which cover not only certain methods of making human embryonic stem cells but the cells themselves.

The potential of stem cell research to eventually provide cures for numerous debilitating diseases from diabetes to Parkinson's Disease has been widely touted and has garnered much public support, as demonstrated, for example, by California's US\$3 billion bond measure to support such research. However, WARF's licensing policy would not seem to promote wide spread use of the technology as did that of Stanford and the University of California. First, WARF has given an exclusive licence to the biotechnology company Geron Inc for commercial use in the neural, pancreatic and cardiac fields. Thus, companies wishing to commercialise stem cells covered by the WARF patents in these areas must negotiate a licence with Geron, which may in fact be one of their competitors.

Second, WARF (through its licensing arm WiCell) has set a high price for its licences. While WiCell no longer provides information on licensing provisions on its website, recent publications indicate that licensing fees for

criminal companies can range from a low of US\$75,000 upwards to US\$250,000 per year. For a small biotechnology company, such a fee can be an obstacle, if not a preclusion, to undertaking stem cell research. WARF's ability to stymie such work is cause for concern.

Regulating licensing

Would a broad interpretation of the FDA Exemption be the best vehicle to assure that patents do not impede research? Probably not. The Supreme Court has emphasised that its protection extends only to activities reasonably related to FDA approval. Clearly much early stage research, such as that necessary to develop cures using stem cells, will not fall within the ambit of FDA related work.

An alternative strategy for ensuring the wide availability of patented technology may lie in the regulation of licensing activities. Many countries have systems for the compulsory licensing of patents; in fact, the United States is probably in the minority by allowing patented technology to be held exclusively, whether it is developed or not. Particularly in the case of tool technology, it may serve the needs of research for patent holders to be obligated to license their rights for research purposes in exchange for a reasonable royalty.

Such a change to the system would require legislation, of course. But the stakes are high. Since the beginnings of the biotechnology industry only some 30 years ago, it has proven to be a robust field, capable of developing diagnostic and therapeutic products which have increased the quality and extended the length of innumerable lives. We must remember that the original goal of the patent system was to promote scientific innovation. While the incentives provided by the exclusivity conferred by a patent may still promote innovation, it is important to assure that they do not inhibit further research. Making tool technology widely available while still rewarding inventors may forge a beneficial balance.



Needle & Rosenberg PC

950 Boardwalk Suite 201,
San Marcos, CA 92078, USA

Tel: +1 619 994 2056

Fax: +1 678 420 9301

www.needlerosenberg.com

Cathryn Campbell

Counsel

CCampbell@needlerosenberg.com

Cathryn Campbell, PhD, is Counsel to the law firm of Needle & Rosenberg, PC. For over 20 years she has focused her legal practice on issues relating to intellectual property in the life sciences industries. She has lectured and written extensively on both scientific and legal issues.

She wrote and prosecuted the patents at issue in Merck v Integra LifeSciences and has been part of the team which has handled the case from the trial court up through the Supreme Court.

Needle & Rosenberg PC

950 Boardwalk Suite 201,
San Marcos, CA 92078, USA

Tel: +1 619 994 2056

Fax: +1 678 420 9301

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