DECEMBER 2003
VOLUME 10
NUMBER 2
ISSN 1462-8732

Journal of Commercial Biotechnology

Abstracted and indexed in ABI/INFORM, BioCommerce Abstracts
CAB Abstracts and CAB Health

Printed by Cambrian Printers, Aberystwyth, Great Britain

This journal is printed on acid-free paper

HENRY
STEWART
PUBLICATIONS

Integra: The research tool patent revival

Charles J. Raubicheck, Barry S. White, Thomas J. Kowalski, Daniel G. Brown, Amy Leahy and Pamela Fekete

Date received (in revised form): 5th September, 2003

Charles J. Raubicheck, Barry S. White, Thomas J. Kowalski and **Daniel G. Brown**
are Partners in Frommer Lawrence & Haug LLP.

Amy Leahy and **Pamela Fekete**
are Law Clerks with Frommer Lawrence & Haug LLP.

Abstract

There was a question as to the value of research tool patents; for instance, whether practising such patents for preclinical research would be within the research exemption of the US Patent Statute. The Federal Circuit in *Integra Lifesciences I, Ltd v Merck kgaA* held that the preclinical research in issue was not within the safe harbour of the research exemption, breathing life into research tool patents; but vacated the damages award because it appeared to have been influenced by hindsight knowledge that a valuable drug candidate had emerged. *Integra* is thus good news and bad news for owners of patents relating to discovery tools.

This paper is not to be considered opinions of Frommer Lawrence & Haug LLP or any of the firm's clients; and nothing in this paper is to be considered as legal advice, a substitute for legal advice, or as positions/strategies, etc taken/employed in, or suitable for, any particular case or set of facts.

Keywords: *research tools, patents, Integra, research exemption, reach-through, royalties*

THE PRE-*INTEGRA* QUESTIONS ON THE VALUE OF RESEARCH TOOLS PATENTS

Research tool patents – patents that cover technology used to discover drugs and drug candidates – after having suffered some diminution of value following the first decision in *Bayer AG v Housey Pharmaceuticals, Inc.*,[1,2] and having their value in question due to uncertainties of the scope of the research exemption under US law,[3] have enjoyed a revival due to the recent Federal Circuit decision in *Integra Lifesciences I, Ltd v Merck KgaA*.[4]

Research tools are at the core of scientific advancement, and the use of biological research tools is usually an initial step in the chain of modern drug discovery. However, certain lower Court cases in the USA had threatened to vitiate the value of research tool patents. For instance, as noted, the first decision in *Housey*[1,2] had called into question the propriety of reach-through licensing – licensing of technology/intellectual property, typically patent rights, with royalties based on a percentage of sales, where the licensed technology/intellectual property, such as basic research, is not incorporated into the end product. The second decision in *Housey*[1,2,5] eased the threat to research tool patents by holding that the patentee did not engage in patent misuse by licences that required the payment of royalties on discovered drugs sales occurring after expiration of patent because the royalties, though payable after expiration of patents, were for pre-expiration use of invention. But, lower court decisions on the research exemption still called into question the value of research tool patents.

THE RESEARCH EXEMPTION

Patent law policy involves two competing interests: the interest of an inventor to have exclusive rights to his or her invention and the interest of the public to benefit from the progress of knowledge and technology. Indeed, a patent may be defined as an agreement between an inventor and the general public, as represented by the government. In exchange for a full public disclosure of the invention, the inventor is granted by the government, for a limited term, the right to exclude others from making, using, selling or offering for sale the invention.[6]

Thomas Kowalski
Frommer Lawrence & Haug LLP,
New York Office,
745 Fifth Avenue,
New York, NY 10151, USA

Tel: +1 212 588 0800
Fax: +1 212 588 0500
E-mail: tkowalski@flhlaw.com

The Hatch-Waxman Act balances competing interests

In the pharmaceutical area, to balance these competing interests, the US Congress enacted the Hatch–Waxman Act of 1984. Principal components of this Act are patent term extension, the research exemption and 'Abbreviated New Drug Application' (ANDA) filing.

The patent term extension provision provides a potential five year patent term extension for new drugs approved by the Food and Drug Administration (FDA) to compensate for time lost in the FDA approval process. The ANDA filing provisions allow generic drug manufacturers to submit ANDAs that incorporate the safety and efficacy data from an approved product, saving generic drug manufacturers from the extensive clinical trial period required for new drugs.

The research exemption from infringement protects against an artificial extension of patent monopolies, beyond the expiration of the patent, for activities related to obtaining FDA approval. More specifically, Section 271(e)(1) of Title 35 of the United States Code provides, in part, that it:

> shall not be an act of infringement to make, use, offer to sell, or sell with 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.

Potential competitors to enter market upon patent expiration; FDA approval before expiry

This component of the Hatch–Waxman Act was intended to allow potential competitors to enter the market immediately upon expiration of the patent. All necessary FDA approval procedures could be completed before the patent expires, allowing the product to be launched as soon as possible after the expiration of the patent.[7] The scope of this provision, in particular the extent to which it exempted infringement of research tool patents, was uncertain.

PRE-*INTEGRA* RESEARCH EXEMPTION CASE LAW SEEMED TO UNDERMINE RESEARCH TOOL PATENTS

Prior to the *Integra* case, US District Courts had been generally leaning towards interpreting the research exemption broadly. Thus, most activities directed towards drug discovery would be exempt, vitiating the value of research tool patents.

For example, in *Bristol-Myers Squibb Co. v Rhone-Poulenc Rorer Inc.*,[8] Rhone-Poulenc Rorer owned patents covering processes and intermediates used in the synthesis of the cancer drug taxol. BMS used the patented intermediates for the development of closely related compounds to compete with taxol. The Court held that these uses were exempt from infringement under §271(e)(1). The Court reasoned that even though each use of the patented intermediates may not have directly yielded information that could be submitted to the FDA, the uses related to preliminary activity that could ultimately facilitate or be useful in generating information that could be submitted to the Agency. Thus, the *Rhone-Poulenc* Court adopted a very broad interpretation of the exemption, including activities related to the discovery of drug development candidates.

In *Amgen, Inc. v Hoechst Marion Roussel, Inc.*,[9] Amgen owned patents covering a genetically engineered form of erythropoietin (EPO). Hoechst manufactured and used significant quantities of EPO during the development of a competing product. The various infringing activities included: (1) export of EPO to Japan; (2) purity testing; (3) demonstration of consistency by manufacturing three consecutive batches of EPO; (4) characterisation of the product; (5) viral clearance tests in Europe; and (6) plans/preparation for radiolabelling studies on the product. The Court determined that all of these activities were reasonably

Prior cases broadly interpreted the research exemption

related to the production of information for submission to the FDA for regulatory approval and, thus, were exempt under §271(e)(1). Accordingly, the *Amgen* court also extended the exemption to preclinical drug discovery activities.

Similarly, in *Nexell Therapeutics Inc. v AmCell Corp.*,[10] Nexell owned patents covering specific antibodies and methods for preparing purified suspension of human stem cells. AmCell used the patented antibodies for the development of a magnetic cell separating device and was planning to seek FDA approval for the use of the device in conjunction with the patented antibodies. Nexell sued on the basis of the following activities: (1) sending informational packets and letters to physicians to recruit clinicians to participate in FDA studies to evaluate the safety and effectiveness of the device; (2) maintaining a booth at the American Society of Hematology featuring a display of the device and an accompanying statement that it was now ready to accept IDE clinical protocols; (3) advertising the device in medical journals; (4) soliciting clinicians through its website; and (5) providing the device to FDA-approved clinical investigators for free and providing kits containing the patented antibodies to investigators on a cost–recovery basis. The Court held that the infringing activity was exempt under §271(e)(1) and concluded that activity would only exceed the safe harbour if there was not an objectively reasonable application of the activity towards obtaining FDA approval. The *Nexell* Court likewise extended the exemption to preclinical development activities.

The *Integra* court clarified that all experimental activity is not within the safe harbour

Thus, while none of the *Rhone-Poulenc, Hoechst Marion Roussel* and *Nexell* cases directly addressed the research tool situation, there was concern that a continuing broad interpretation of the research exemption would greatly reduce the value of patents whose sole function was the discovery of new drugs.

INTEGRA

In *Integra*, Integra sued Merck for infringement of patents covering peptides that promote cell adhesion, known as 'RGD peptides'. Under an agreement with Merck, researchers at Scripps conducted preclinical tests for the identification and development of potential drug candidates to inhibit angiogenesis. The patented peptides were used to test several potential drug candidates, one of which was eventually selected for clinical development.

The specific issue in this case was whether the preclinical research was exempt from liability for infringement under §271(e)(1).[11] The Court held that the safe harbour provision of §271(e)(1) did not encompass the preclinical identification and development of a potential drug candidate and, therefore, the research conducted pursuant to the Scripps–Merck agreement was not exempt from liability for patent infringement.[12]

The Court affirmed the district court's interpretation of §271(e)(1)'s exemption of 'reasonably related' activity as activity that 'would contribute relatively directly' to information the FDA would consider in approving a drug.[13]

The Court clarified its conclusion by stating '§ 271(e)(1) simply does not globally embrace all experimental activity that at some point, however attenuated, may lead to an FDA approval process', ie the 'safe harbor does not reach any exploratory research that may rationally form a predicate for future FDA clinical tests.'[14]

While the Court did not enunciate specifics as to the types of experimentation that 'would contribute relatively directly' to information that the FDA would consider in approving a drug, it did refer to the fact that the Scripps–Merck activities involved the preclinical testing of drugs other than the candidate ultimately chosen for FDA approval. The Court described this additional activity as something in which the FDA had no interest.[14]

When the exemption applies was not expressly determined by *Integra*

Additionally, the Court looked to the role of the Hatch–Waxman Act in facilitating expedited approval of generic drugs, and stated that the purpose of §271(e)(1) was to create a safe harbour for the pre-patent expiration tests necessary to facilitate the immediate entry of generic drugs into the market upon drug patent expiration.[15]

The Court did not, however, expressly limit the scope of the exemption to tests necessary for approval of a generic drug. In particular, the Court stated that an 'expansion of §271(e)(1) to include the Scripps–Merck activities would effectively vitiate the exclusive rights of patentees owning biotechnology tool patents', and contrasted such activity to the downstream clinical testing for FDA approval, which the Court described as falling within the safe harbour.[13]

Thus, while the Court did not expressly limit the exemption of downstream clinical testing for FDA approval to that required for generic drug approval, it also did not expressly determine at what point the safe harbour begins to apply beyond the preclinical identification of a potential drug candidate.

Research tool patents may be valued at time of alleged infringement; knowledge of valuable candidate discounted

The *Integra* Court also vacated and remanded a US$15m damage award by the jury in the district court action.[16] More specifically, in the proceedings in the District Court, the jury had awarded Integra US$15m in damages.[17] This award was vacated and remanded because the jury had failed to consider the fact that at the time of the infringement, it was uncertain whether a useful drug would ever be developed using the technology. That is, the Federal Circuit reasoned that the damages analysis was flawed because the jury failed to employ a reasonable royalty analysis using a hypothetical negotiation that occurred at the time of the infringement.[18] The damages calculation, it was reasoned, appeared to have been influenced by hindsight knowledge that a valuable drug candidate had emerged later in the process, after the infringement had occurred.

RAMIFICATIONS OF *INTEGRA* – THE GOOD NEWS AND BAD NEWS

Integra is clearly good news for owners of patents relating to discovery tools, especially screening methods. Beyond that specific situation, it is too early to predict the full impact of the case.

For example, the Court relied on the fact that Merck used the patented technology at a preclinical stage to discover new drug candidates, not at the clinical stage to develop information to submit to FDA. It is not clear after *Integra* how research or diagnostic patents will be treated during the clinical stage. Nor is it clear where exactly the line between exempted and non-exempted activity falls.

The bad news for research tools patent holders is how the Federal Circuit addressed damages. By discounting the knowledge of a later-emerged valuable drug candidate in the damages calculation, the Court has diminished the 'but for' value of the research tool patent. Namely, damages are not calculated with knowledge that, but for infringement of the research tool patent, the research would not have continued to the point of the later-emerged valuable drug candidate.[2,19] The contours of these issues will likely be further clarified in later decisions.

Nonetheless, the case is an important step forward for owners of research tool patents.

References and notes

1. 169 F. Supp. 2d 328 (D. Del. 2001) (allegations of patent misuse from screening method patent reach-through licensing not dismissed as failing to state claim of patent misuse); *but see Bayer AG v Housey Pharmaceuticals, Inc.*, 228 F. Supp. 2d 467 (D. Del. 2002) (patentee for method of identifying and generating data used to develop new pharmaceutical drugs did not engage in patent misuse by granting licences that required payment of royalties on discovered drugs sales occurring after expiration of patent; royalties, though payable after expiration of patents, were for pre-expiration use of invention). *See also Bayer AG v Housey Pharmaceuticals, Inc.* No.

02-1598, 2003 WL 21991600 (Fed. Cir. 22nd August, 2003).

2. For a discussion of reach-through royalties see Kowalski, T. J. and Smolizza, C. M. (2000), 'Reach-through licensing: A US perspective', *J. Comm. Biotechnol.*, Vol. 6(4), pp. 349–357.
3. 35 USC §271(e)(1).
4. *Integra Lifesciences I, Ltd v Merck KgaA*, 331 F.3d 860 (Fed. Cir. 2003).
5. 228 F. Supp. 2d 467 (D. Del. 2002).
6. *See* Kinter, E. and Lahr, J. (1982), 'An Intellectual Property Law Primer 7'; 35 USC §§111, 112, 154. *See also* US Const. Art. I §8 cl. 8: 'The Congress shall have Power . . . To Promote the Progress of Science and Useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries.'
7. Without such a provision as Section 271(e)(1) in the statute, a potential competitor, to avoid infringement liability, would have to wait until expiration of the patent to deal with FDA-approval procedures, *see Roche Products, Inc. v Bolar Pharmaceutical Co.*, 733 F. 2d 858, 221 USPQ 937 (Fed. Cir. 1984). Specifically, the Act sought to ensure that a patentee's rights did not *de facto* extend past the expiration of the patent term because a generic competitor also could not enter the market without regulatory approval. *See Eli Lilly & Co. v Medtronic, Inc.*, 496 US 661, 669-70, 110 S. Ct. 2683, 110 L. Ed. 2d 605, 58 USLW 4838, 15 USPQ2d 1121 (1990). Thus, the Act permitted those competitors to conduct experiments in advance of the patent expiration as long as those activities were reasonably related to securing regulatory approval. As noted by the Federal Circuit, 'Section 271(e) permits premarket approval activity conducted for the sole purposes of sales after patent expiration.' *Hoechst Roussel Pharms., Inc. v Lehman*, 109 F.3d 756, 763, 65 USLW 4838, 42 USPQ2d 1220, 1226 (Fed. Cir. 1997).
8. 2001 US Dist. LEXIS 19361 (SDNY 27th November, 2001).
9. 3 F. Supp. 2d 104, 46 USPQ2d 1906 (D. Mass. 15th April, 1998).
10. 199 F. Supp. 2d 197 (D. Del. 19th April, 2002).
11. 331 F.3d 860, 865 (Fed. Cir. 2003)
12. *Id.* at 866.
13. *Id.* at 867.
14. *Id.* at 866.
15. *Id.* at 866-867.
16. *Id.* at 872.
17. *Id.* at 869.
18. *Id.* at 871.
19. Raubicheck, C. *et al.* (2003), '*Integra v Merck*: A mixed bag for research tool patents', *Nature Biotechnol.*, Vol. 21(9), pp. 1099–1101.