PILLSBURY WINTHROP LLP

Biotechnology and Life Sciences Client Alert

Integra's Win May Give Cause For Re-Evaluation Of Future Exploratory Research Activities

Introduction

The Drug Price Competition and Patent Term Restoration Act, also referred to as the Hatch-Waxman Act, was enacted in 1984, six months after the Court's decision in Roche Prods. Inc. v. Bolar Pharm. Co., 733 F.2d 858, 862 (Fed. Cir. 1984), which held that experimental testing of patented drugs in any commercial context during the entire life of the patent was patent infringement. The purpose of this Act was to overruled the Roche decision by establishing a more efficient procedure for FDA approval. Under Roche, commercial availability of generic drugs would be delayed until long after the expiration of the patent because FDA mandated bioequivalency testing could not begin until after the expiration of the patent. The passage of 35 U.S.C. § 271(e)(1) enabled a generic manufacturer to carry out bioequivalency testing for purposes of obtaining FDA approval of a patented drug prior to patent expiration. The statute is as follows:

> It 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 (other than a new animal drug or veterinary biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Act of March 4, 1913) which is primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other processes involving site specific genetic manipulation techniques) 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.

Generally, the patentee has the right to exclude others from making, using, selling or offering to sell its patented technology. Such actions infringe the patent and are therefore illegal under 35 U.S.C. § 271(a). However, § 271(e)(1) provides an exemption to certain activities from patent infringement, even if the activities fall exactly within the scope of the patent claim language, as long as the use of a patented invention is solely for purposes reasonably related to the development and submission of information for FDA regulatory approval.

What Activities Have Been Found To Be Exempt From Infringement?

Since the enactment of § 271(e)(1), the courts increasingly have expanded the scope of § 271(e)(1) to include the following activities: (1) manufacturing a device or drug in the U.S. (Intermedics, Inc. v. Ventritex, Inc., 775 F.Supp. 1269 (N.D. Cal. 1991), *aff'd*, 991 F.2d 808 (Fed. Cir. 1993), NeoRx Corp. v. Immunomedics, Inc., 877 F.Supp. 202 (Fed. Cir. 1994); (2) selling to institutions/hospitals in the U.S. to obtain premarket approval ("PMA") (Intermedics); (3) selling the device to international distributors for clinical trials; (Intermedics); (4) clinically testing the device or drug in the U.S. and overseas (Intermedics); (5) demonstrating the device at a trade show (Intermedics) and medical conferences (Teletectronics Pacing Systems, Inc. v. Ventritex, Inc., 982 F.2d 1520

(Fed. Cir. 1992)); (6) publishing the features of the device (Intermedics); (7) exporting the reference standards for commercial development overseas (Amgen, Inc. v. Hoechst Marion Roussel, Inc., 3 F.Supp.2d 104 (D. Mass. 1998); (8) conducting purity and safety testing (Amgen); (9) producing scaled up amounts of the drug in the U.S. (Amgen, NeoRx,); (10) characterizing the drug (Amgen); (11) using a patented process (NeoRx); (12) Submitting data for foreign regulatory approval after it was first submitted to the FDA (NeoRx); and (13) conducting product research & development activity "upstream" in product development (Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc., 2001 WL 1512597 (S.D.N.Y. Nov. 28, 2001).

Why Does The Federal Circuit's Ruling In The Integra Lifesciences I, Ltd. v. Merck kGaA Limit The Scope Of Activities Exempt From Infringement?

On June 6, 2003, in a 2-1 decision, the Federal Circuit in Integra Lifesciences I, Ltd. v. Merck kGaA, 331 F.3d 860 (Fed. Cir. 2003) limited the scope of activities exempt under § 271(e)(1). In this case, Integra owned patents that relate to a short polypeptide segment of fibronectin having the sequence Arginine (R), Glycine (G), and Aspartic acid (D) ("the RGD peptide"). The RGD peptide was invented by Integra's predecessor, co-plaintiff Telios. Telios discovered that the RGD peptide promotes cell adhesion by interacting with $\alpha_v\beta_3$ receptors. In theory, the RGD peptide would promote healing and biocompatibility of prosthetic devices. However, Telios was unable to develop a viable commercial product, and sold the patents to Integra.

Dr. David Cheresh, a scientist at The Scripps Research Institute ("Scripps"), had discovered that blocking the $\alpha_v\beta_3$ receptor inhibited angiogenesis (the process of generating new blood vessels), an effect thought to provide an effective means for eliminating tumor growth and for treating a variety of other diseases. Dr. Cheresh's research identified EMD 66203, a cyclic RDG peptide that displayed good inhibition of $\alpha_v\beta_3$ receptors. Merck entered into a research and development agreement with Scripps to bring EMD 66203 or a derivative thereof to clinical trials and through FDA approval. Towards this end, additional Scripps research led to two promising derivatives, cyclic peptides EMD 85189 and EMD 121974, and Scripps scientists conducted several *in vivo* and *in vitro* experiments "to evaluate the specificity, efficacy, and toxicity [of the compounds] for various diseases, to explain the mechanism by which these drug candidates work, and to determine which candidates were effective and safe enough to warrant testing in humans." These experiments included histopathology, toxicology, circulation, diffusion, and half-life of the peptide in the bloodstream and examined the proper mode of administration for optimum therapeutic effect. In 1997, Scripps chose EMD 121974 as the best candidate for clinical development. In 1999, Scripps filed an Investigatory New Drug application ("IND) for EMD 121974 with the Food and Drug Administration (FDA) seeking approval to test the chosen RGD peptide for treatment of solid tumors by starving rapidly dividing tumor cells.

Learning of the Scripps-Merck agreement, Integra contacted Merck and offered a license under its patents, which Merck declined. Integra then sued Merck, Scripps and Dr. Cheresh (collectively "Merck") alleging patent infringement of U.S. Patent No. 4,792,525 (the '525 patent), No. 4,988,621 (the '621 patent), No. 4,789,734 (the '734 patent), No. 4,879,237 (the '237 patent), and No. 5,695,997 (the '997 patent). Integra alleged that Merck used Integra's patented research techniques for identifying and evaluating potential new drug candidates.

The Integra case, thus, relates to the use of research tool patents. Research tool patents relate to reagents and methods for screening chemicals and computer programs that can be used to better design those chemicals. Such tools are infringed when used in developing or validating a new product.

At trial, the jury found Merck liable for infringing the '621, '525, '997, '237, and '734 patents. The district court, however, granted Merck's summary judgment motion for invalidity of Claim 2 of the '621 patent because it was shown to be anticipated by a prior art publication dated almost one year plus two weeks prior to the '621 patents priority filing date. Further, the district court held that the safe harbor provision of § 271(e)(1) did not

immunize Merck against liability for infringement. Merck argued that its drug discovery efforts where exempt from infringement because the use of the patented technology was "reasonably related" to the ultimate goal of obtaining FDA approval. The district court, however, determined that Merck's infringing activities were not exempt under § 271(e)(1) because Merck did not supply information for submission to the FDA, but rather, identified the best drug candidate for future clinical testing for FDA approval. The jury awarded a reasonable royalty of $15,000,000. Merck appealed.

Three issues on appeal were: (1) whether the RGD-containing peptides in Merck's work was exempt from infringement under 35 U.S.C. § 271(e)(1), (2) whether cyclic peptides were within the scope of the claims at issue, and (3) whether the damage award was supported by the evidence.

As to the first issue, the Federal Circuit, affirmed the district court's finding that the safe harbor against patent infringement provided by 35 U.S.C. § 271(e)(1) does not apply to pre-clinical activities to identify and develop new drugs that will eventually be subject to FDA approval. In so holding, the Court contemplated Merck's use of Intergra's research tool patents as suspect.

The Court had not previously opined on whether the § 271(e)(1) safe harbor reaches back down the chain of experimentation to embrace development and identification of new drugs that will, in turn, be subject to FDA approval. Accordingly, the Court referred to the legislative history of the 1984 Hatch-Waxman Act, which implemented the § 271(e)(1) exemption, noting the two-fold legislative goals of: (1) providing additional patent term to compensate patentee's who must endure a protracted regulatory approval period during the term of their patent before they can enjoy market exclusivity, and (2) eliminating the *de facto* patent term extension arising because of the time generic drug companies had to wait for patent expiration before conducting otherwise infringing activities necessary to generate data for regulatory approval, thereby delaying the generic drug's entry into the market.

The Court referred to the House Committee's characterization of exempt activities as those which facilitate generic competitors conducting bioequivalency testing required for FDA approval during the lifetime of the patent so that the generic drug could be marketed as soon as the last of the relevant patents expired. The Court also considered important the Committee's characterization of exempt activity as interfering with the patentee's rights in a *de minimis*, rather than a substantial, way. By the plain language of its terms the statute limits the exemption to activities conducted "solely for purposes reasonably related to the development and submission of information under Federal law."

Analyzed in this context, extending the safe harbor provision to embrace new drug development activities would ignore its language and legislative history. Therefore, the Court held that the term "reasonably related" does not embrace all activity in the research and development chain simply because they may lead to an FDA approval process. The Court opined that while infringing activities need not directly produce data that is submitted to the FDA to enjoy the safe harbor of § 271(e)(1), such activities "strain the relationship to the central purpose of the statute." In particular, "[t]he FDA has no interest in the hunt for drugs that may or may not later undergo clinical testing for FDA approval."

Applying this reasoning to the facts of the case, the Court held that Merck's activity, which the Court described as pre-clinical research that did not supply information for submission to the FDA, but rather, identified a **new** drug candidate that would be subject to future clinical testing for FDA approval, was not exempt under § 271(e)(1). Consequently, the § 271(e)(1) safe harbor does not reach back down the chain of experimentation to embrace development of new drugs, that will, in turn, be subject to FDA approval. To view such activities otherwise, would produce an outcome in direct conflict with the legislative intent that the exempt activity have only *de minimis* effect on patent owners' rights.

"After all, patented tools often facilitate general research to identify candidate drugs, as well as downstream safety related experiments on those new drugs. Because downstream clinical testing for FDA approval falls within the safe harbor, these patented tools would only supply some commercial benefit to the inventor when applied

to general research. Thus, exaggerating § 271(e)(1) out of context would swallow the whole benefit of the Patent Act for some category of biotechnology inventions. Needless to say, the 1984 Act was meant to reverse the effects of Roche under limited circumstances, not to deprive entire categories of inventions of patented protection."

Unfortunately, the Court did not provide a bright line test for determining the point at which the otherwise infringing activities become "reasonably related to the development and submission of information" to the FDA. Two things are clear: (1) conducting pre-expiration tests necessary to satisfy FDA requirements after filing an abbreviated new drug application to expedite FDA approval of a generic version of a drug already on the market is within the scope of § 271(e)(1) and (2) pre-clinical activities to identify and develop **new** drugs are **not** within the scope of § 271(e)(1). All other activities, falling between drug discovery and those that directly generate data submitted to the FDA, remain in the gray area.

As to the second issue, the Court affirmed the district court's judgment entering the jury verdict that Merck infringed the patents-in-suit. Merck argued that it did not infringe Integra's patent because Merck used a cyclic RGD peptide. Merck argued that Integra's claims did not cover cyclic configurations, but were limited to linear peptides. However, the district court found that the claims "impose[d] no limitations on the three-dimensional structure of the peptides at issue." Moreover, a person skilled in the art would understand that the term "peptide" represents "two or more amino acids covalently joined by peptide bonds." Moreover, the specification discloses to those skilled in the art both linear and cyclic peptides. Thus, the claims cover cyclic RGD peptides.

Addressing the third issue of damages, the Federal Circuit remanded the jury's $15,000,000 reasonable royalty damages award because it was not supported by substantial evidence and therefore remanded the damages calculation for further consideration. First, the record did not clearly indicate the date of first infringement before which a hypothetical negotiation would have taken place. Second, the record did not show that allegedly comparable Merck negotiations with other licensors occurred under scientific or economic circumstances that would permit comparison to the hypothetical Merck-Integra license. Finally, the awarded royalty did not take into account factors that would have considerably reduced the value of a hypothetical negotiation, such as the point of placement of Integra's technology in Merck's drug development process or the cumulative effect of stacking royalties.

Proposed Steps

In the wake of the Integra Lifesciences I, Ltd. v. Merck kGaA case, companies should consider re-examining their use of patented technology in pre-clinical Research and Development activities. It is therefore critical that companies and their advisors review their Research and Development activities to be certain they are objectively within the scope of permitted investigations under § 271(e)(1).

Contact Pillsbury Winthrop for More Details

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