Integra Lifesciences I, Ltd. v. Merck KG aA (Merck II), Nos. 02-1052, -1065 (Fed. Cir. July 27, 2007)

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Summary

The Federal Circuit ruled on the Supreme Court's broad interpretation of the regulatory review exemption to patent infringement, also known as the Bolar exemption. The Federal Circuit reversed its previous decision of infringement, holding that Merck's preclinical development activities that were ultimately not the subject of a submission to United States Food and Drug Administration (FDA) were still exempt from infringement under the regulatory review exemption.

The Facts

The dispute dates to 1996, when Integra sued Merck for infringement of its patents on 'RGD peptides'[1] known to promote cell adhesion. Integra alleged that Merck infringed its patents during experiments to identify and develop potential drug candidates to inhibit angiogenesis and sought damages. Merck denied infringement by arguing that the use of Integra's patented peptides to conduct angiogenesis research fell within the 'safe harbour' provision of 35 U.S.C. §271(e)(1). The provision permits activities conducted to obtain regulatory approval of a product that would normally be considered patent infringement. It provides that:

> "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 (…) 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."[2]

The jury found infringement, a decision that was sustained by the district court which described Merck's experimental activities as "insufficiently direct to qualify" for the regulatory review exemption.

Merck appealed to the U.S. Court of Appeals for the Federal Circuit (hereinafter 'the Federal Circuit'), which ruled in favour of Integra in 2003[3]. It adopted a narrow reading of the safe harbour provision, holding that the regulatory review exemption should only have a *de minimis* impact on the patentee's rights. The court emphasized that the safe harbour provision does not embrace all new drug development activities that could potentially lead to an FDA approval process.

It concluded that Merck's research was not "clinical testing to supply information to the FDA, but only general biomedical research to identify new pharmaceutical compounds". In the view of the Federal Circuit, Merck's preclinical testing of drugs was not "solely for uses reasonably

[1] 'RGD peptides' consist of Arginine (R), Glycine (G), and Aspartate (D).
[2] 35 U.S.C. §271(e)(1).
[3] Integra Lifesciences I, Ltd. v. Merck KGaA, 331 F.3d 860 (Fed. Cir. June, 2003).

related" to clinical testing for FDA as set forth in the safe harbour provision and therefore infringed Integra's patents.

In 2005, however, the U.S. Supreme Court (hereinafter 'the Supreme Court') granted certiorari to review the Federal Circuit's interpretation of the safe harbour provision.[4] It limited its review to the question whether uses of patented inventions in preclinical research, the results of which are not ultimately included in a submission to the FDA, are exempted from infringement by the safe harbour provision

The Supreme Court interpreted the safe harbour provision as providing "a wide berth for the use of patented drugs in activities related to the federal regulatory process". In the Supreme Court's view, the safe harbour provision does not necessarily exclude (1) experimentation on drugs that are not ultimately the subject of an FDA submission or (2) use of patented compounds in experiments that are not ultimately submitted to the FDA.

The Supreme Court held that the exemption from infringement extends to all uses of patented inventions that are reasonably related to the development and submission of any information under the FDA. Given the uncertainties of scientific investigation, the Court construed the term "reasonably related" of the safe harbour provision broadly, in a way that "leaves adequate space for experimentation and failure on the road to regulatory approval". Accordingly, the use of patented compounds in preclinical testing can be protected under the safe harbour provision if there is a reasonable basis for believing that the experiments will produce relevant information to the FDA. The Supreme Court therefore vacated the judgment of the Federal Circuit and remanded the case for proceedings consistent with this opinion.

On remand, the Federal Circuit reversed the district court's judgement of infringement in 2007, holding that all the experiments conducted by Merck fell within the regulatory review exemption.

The Legal issues

The Federal Circuit was asked on remand to review Merck's challenged experiments on the broad construction of the safe harbour provision adopted by the Supreme Court in *Merck KG aA v. Integra Lifesciences (2005)*. The Federal Circuit's main task was to assess whether the experiments conducted by Merck were reasonably related to research that, if successful, would be appropriate for FDA submission, even though not all of the experiments ultimately resulted in an FDA submission.

According to the Federal Circuit, since all of the challenged experiments were conducted after the discovery of a cyclic RGD peptide that inhibited angiogenesis, they were not "basic scientific research" unrelated to the development of a particular drug. On the contrary, the Court found that the series of experiments aimed at determining the best angiogenesis inhibitor candidate.

[4] Merck KG aA v. Integra Lifesciences I, Ltd., et al., 545 U.S. 193 (June 2005). See the summary in this database.

The Federal Circuit further explained that the criterion of being reasonably related to research is established at the time of the experiments, and thus, "does not depend on the success or failure of the experimentation or actual submission of the experimental results".

Based on these findings, the Federal Circuit concluded that the challenged experiments using Integra's patents were reasonably related to research that, if successful, would be appropriate to include in a submission to the FDA. Accordingly, Merck's experiments, including those that were not ultimately taken to clinical trials and submitted to the FDA, qualified under the regulatory review exemption, and did not infringe Integra's patents on RGD peptides. The Federal Circuit thus reversed the district court's judgement of infringement.

In a dissenting-in-part and concurring-in-part opinion, Judge Rader, one of the three-judge panel, criticized the potential impact of the Federal Circuit's decision on research tools. Judge Rader argued that the Federal Circuit expanded the regulatory review exemption beyond the Supreme Court's already broad construction, eliminating thereby patent protection for research tool inventions. Judge Rader pointed out that the Supreme Court interpreted the regulatory review exemption as covering the use of "patented compounds" (i.e. product patents) in experiments, without addressing research tools (i.e. process patents). However, in its decision, the Federal Circuit did not examine the patents at issue, ignoring the distinction between product and process patents. According to Judge Rader, two of Integra's patents were research tools, applying only to "laboratory methods without any possibility of submission to the FDA". Consequently, since Merck's use of these two patents could not be "reasonably related" to the submission of FDA information as required by the safe harbour provision, these two patents deserved protection.

Points of Significance

- The interpretation of the regulatory review exemption by the Supreme Court and its application in *Integra Lifesciences v. Merck KG aA (2007)* by the Federal Circuit can limit the chance of challenging preclinical development activities that were ultimately not the subject of a submission to the FDA in as far as the research and any other use are reasonably related to the development and submission of any information to the FDA.
- It is still unclear after *Integra Lifesciences v. Merck (2007)* whether or not the use of research tools falls within the regulatory review exemption. According to Judge Rader's dissent, an overly expansive interpretation of the regulatory review exemption would weaken patent protection for research tools and threaten the entire research tool industry.

Key words

Bolar exemption, regulatory review exemption, regulatory review exception, safe harbour provision, preclinical testing, research tool.

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