Merck KGaA v. Integra: More Answers Than Questions?

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In *Merck KGaA v. Integra Lifesciences*,[1] the Supreme Court clarified the uncertain scope of the safe harbor under §271(e)(1), following the Federal Circuit's vacillating pronouncements which suggested that the statutory exemption is limited to generic drug applications and to data from human clinical trials.[2] The Supreme Court rejected the Federal Circuit's narrow interpretation, holding that the exemption includes information reasonably related to the development of information submitted for approval of a new drug, as well as a generic equivalent.[3] The statutory immunity from infringement extends to preclinical studies that are reasonably related to approval of an original Investigational New Drug application (IND), including *in vitro* and animal studies demonstrating the safety or efficacy of a new drug candidate compound, which are required by the FDA prior to human trials.[4]

The Court clearly rejected the view that the exemption is restricted to specific phases of research or information developed for particular FDA submissions, and did not attempt to draw a bright line boundary at which experimentation involving a patented compound becomes exempt. Although the decision broadly states that the safe harbor exemption from infringement "extends to all uses of patented inventions that are reasonably related to the development and submission of *any* information under the FDCA,"[5] its holding is considerably narrower. The Court repeatedly emphasized that the limited question which it considered and resolved was the scope of immunity for the use of a patented compound which is a new drug

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1. Merck KGaA v. Integra Lifesciences I, Ltd., 125 S. Ct. 2372 (2005).
2. *Compare* Integra LifeSciences I, Ltd. v. Merck KGaA, 331 F.3d 860 (Fed. Cir. June 6, 2003), *with* the significantly revised decision at 2003 U.S. App. LEXIS 27796 (Fed. Cir. July 10, 2003), *vacated*, 125 S. Ct. 2372 (2005).
3. *Merck*, 125 S. Ct. at 2383.
4. *Id.* at 2380-81.
5. *Id.* at 2380.

candidate, and held that the exemption extends only to uses of the compound "in research that, if successful, would be appropriate to include in a submission to the FDA."[6]

I. The Statutory Safe Harbor Exemption

The safe harbor immunity from infringement is defined by 35 U.S.C. §271(e)(1), which provides in pertinent part as follows (emphases added):

> 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.

II. Divergent Interpretations of the Statutory Exemption

The opinions of the Federal Circuit and the Supreme Court reveal widely divergent concepts of the nature and scope of the statutory exemption, which may be generally characterized as a "temporal" limitation, a "use" limitation, and a "subject matter" limitation.

A. Temporal Limitation: the "Chain of Experimentation"

The Federal Circuit majority clearly considered that the "reasonably related" requirement imposes a definite, temporal limitation on the scope of exempt research and development, and characterized the issue as determining the last protected link in a "chain of experimentation:"

> The Scripps-Merck experiments did not supply information for submission to the United States Food and Drug Administration (FDA), but instead identified the best drug candidate to subject to future clinical testing under the FDA processes. Thus, this court must determine 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.[7]

Under Judge Rader's interpretation, all uses of patented inventions, including biotechnology "research tools," evidently would be exempt from infringement after a threshold event in the chain occurs, such as

6. *Id.* at 2383.
7. *Integra*, 2003 U.S. App. LEXIS 27796, at *12-*13.

the submission of a New Drug Application.[8] Prior to the threshold event, no use of a patented invention, including a drug candidate compound, would qualify for the exemption.

B. Purpose of Use Limitation: "Study" of a Patented Invention

Judge Newman objected that limiting the exemption to a specific, threshold event in the drug approval process would create a "limbo" of infringing activity between initial experimentation protected by a common-law research exemption, and the subsequent filing of a New Drug Application.[9] She maintained that the litmus for exempt research should be the purpose for which a patented invention is used, rather than the stage of drug development. Under this interpretation, a narrower scope of uses, confined to the *study* of patented inventions, would be protected at any stage of the drug development process.[10] The unauthorized *use* of patented inventions, including research tools, would not be exempt at any stage of the drug approval process.[11]

C. Subject Matter Limitation: Use of Patented Compounds

The Supreme Court summarily rejected the "temporal" threshold proposed by the Federal Circuit, commenting as follows:

> There is simply no room in the statute for excluding certain information from the exemption on the basis of the phase of research in which it is developed or the particular submission in which it could be included.[12]

The Court did not address the dilemma of "research tool" patents which preoccupied the Federal Circuit, or the distinction between study and use of patented inventions proposed by Judge Newman.[13] Instead it endorsed a broad exemption, not confined to any specific stage of drug development or use of a patented invention, where the "patented invention" is a chemical compound that is investigated to determine its pharmacological properties or potential therapeutic effects.

The broad statutory exemption extends the uses of "inventions" that are reasonably related to regulatory approval, but potentially

8. *Id.* at *18-19.
9. *Id.* at *48 (Newman, J., dissenting).
10. *Id.* at *42 (Newman, J., dissenting).
11. *Id.* at *50 (Newman, J., dissenting).
12. *Merck*, 125 S. Ct. at 2380.
13. *Id.* at 2382 n.7.

limits "a patented invention" to a relatively narrow class of chemical compounds that are expected to have specific pharmacological properties:

> At least where a drugmaker has a reasonable basis for believing that a patented compound may work, through a particular biological process, to produce a particular physiological effect, and uses the compound in research that, if successful, would be appropriate to include in a submission to the FDA, that use is "reasonably related" to the "development and submission of information under... Federal law."[14]

Although this analysis is focused on specific subject matter, the Court envisioned a "penumbra" of protection that extends beyond specific compounds that are the subject of an FDA application:

> [T]he use of a patented compound in experiments that are not themselves included in a "submission of information" to the FDA does not, standing alone, render the use infringing. The relationship of the use of a patented compound in a particular experiment to the "development and submission of information" to the FDA does not become more attenuated (or less reasonable) simply because the data from that experiment are left out of the submission that is ultimately passed along to the FDA.[15]

III. The Dividing Line Between Exempt and Nonexempt Research

The Supreme Court's construction of §271(e)(1) in *Merck* is closely tailored to the specific facts at issue in that case, which are peculiarly narrow. Merck KGaA evidently conducted its extensive initial screening and research in Germany, and this extraterritorial activity was exempt from infringement under §271(a). In a ruling that was not appealed, the district court in an unpublished opinion held that Scripps' activities in the United States prior to the discovery of pharmacological activity of the patented compounds were protected by the common law research exemption.[16] The narrow issue before the Federal Circuit and the Supreme Court was therefore whether specific preclinical research involving a small number of related compounds was protected by §271(e)(1), after the potential therapeutic utility of the compounds had been confirmed by

14. *Id.* at 2383.
15. *Id.*
16. *See* Integra LifeSciences I, Ltd. v. Merck KGaA, No. 96CV1307-B, 2004 U.S. Dist. LEXIS 20725, at *17-*18 (S.D. Cal. Sept. 7, 2004) (decision on remand from the Federal Circuit).

noninfringing experiments.

It is unclear how the Federal Circuit and the lower courts will conceptualize and apply the exemption, given the broad *dicta* and limited holding of the Supreme Court. Except in the unusual circumstances exemplified by Scripps' work, the Court's opinion provides little guidance in determining the dividing line between exempt and nonexempt drug development research. If the exemption extends significantly beyond the use of patented compounds, its scope could be extremely broad in view of the Supreme Court's comments, including the following statement:

> Congress did not limit § 271(e)(1)'s safe harbor to the development of information for inclusion in a submission to the FDA; nor did it create an exemption applicable only to the research relevant to filing an ANDA for approval of a generic drug. Rather, it exempted from infringement all uses of patented compounds "reasonably related" to the process of developing information for submission under any federal law regulating the manufacture, use, or distribution of drugs.[17]

The Court also adopted a broad construction of the requirement that exempt uses of patented inventions be "reasonably related" to the development and submission of information to regulatory agencies, explaining as follows:

> [T]he use of patented compounds in preclinical studies is protected under §271(e)(1) as long as there is a reasonable basis for believing that the experiments will produce "the types of information that are relevant to an IND or NDA."[18]

IV. Subject Matter Scope of the Exemption: "A Patented Invention"

If the subject matter limitation of the exemption for uses of "patented compounds" is expanded to include any "patented invention," at any stage of drug development, the scope of the safe harbor becomes potentially vast. The Supreme Court's endorsement of a broad exemption is clear:

> [W]e think it apparent from the statutory text that §271(e)(1)'s exemption from infringement extends to all uses of patented inventions that are reasonably related to the development and submission of any information under the FDCA.[19]

17. *Merck*, 125 S. Ct. at 2383.
18. *Id.* at 2383-84.
19. *Id.* at 2380.

If this principle is applied to inventions other than specific potential drug candidate compounds such as those at issue in *Merck*, the Court's unrestricted endorsement of a broad exemption could lead to chaotic results in the lower courts.

A. Inventions Other Than Chemical Compounds

A principal question raised by this expansive construction is whether §271(e)(1) exempts uses of patented inventions, other than chemical compounds, where the sole or principal utility of the invention is the development of information for submission to the FDA. Judge Rader's concern was principally with this issue:

> [E]xpansion of § 271(e)(1) to include the Scripps-Merck activities would effectively vitiate the exclusive rights of patentees owning biotechnology tool patents. After all, patented tools often facilitate general research to identify candidate drugs, as well as downstream safety-related experiments on those new drugs. Because the 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.[20]

Judge Newman sharply disagreed with this suggestion, reasoning as follows:

> The panel majority states that acceptance of a common law research exemption would eliminate patents on "research tools." That is a misperception. There is a fundamental distinction between research into the science and technology disclosed in patents, and the use in research of patented products or methods, the so-called "research tools."
>
> A research tool is a product or method whose purpose is use in the conduct of research, whether the tool is an analytical balance, an assay kit, a laser device... or a biochemical method such as the PCR (polymerase chain reaction).[21]

The Supreme Court avoided the issue entirely, concluding that Integra "never argued the RGD peptides were used at Scripps as research tools, and it is apparent from the record that they were not."[22]

The questions raised by the Federal Circuit with respect to the

20. *Integra,* 2003 U.S. App. LEXIS 27796, at *18-*19.
21. *Id.* at *50 (Newman, J., dissenting).
22. *Merck*, 125 S. Ct. at 2382 n.7, citing Judge Newman's opinion.

kinds of patented inventions that may be employed *solely* for uses *directly* related to the development and submission of information to the FDA remain unanswered. For example:

- Does the exemption apply to an animal model whose only use is in determining the toxicity of a drug candidate compound?
- Does the exemption apply to an assay that must be used to develop information required by the FDA?

In the absence of an implied subject matter limitation, restricting the scope of "a patented invention" in §271(e)(1), it seems apparent that any uses of these patented inventions are solely and "reasonably related to the development and submission of information" under the FDCA. They have no other utility.

B. Chemical Intermediates and Methods Used to Make Candidate Compounds

The statutory exemption under §271(e)(1) is not limited to uses of a patented invention, and instead encompasses other acts of infringement, including the act of making a patented drug candidate compound.

A further question is whether the subject matter "penumbra" of the Supreme Court's chemical compound safe harbor exempts use of compounds that are essential intermediates for producing drug candidate compounds, or methods that are used for synthesizing drug candidate compounds.[23]

C. Uses of Non-Candidate Compounds

A significant question is whether the safe harbor encompass uses of patented compounds that are not themselves drug candidates, in order to evaluate other drug candidate compounds. For example, if patented compounds are used as controls in research to evaluate drug candidate mimetics or homologs (designed to have the same mechanism of action as the claimed compounds), in order to determine the relative efficacy of the mimetics or homologs, is this use exempt?

This question may be addressed on remand in *Merck*, in view of the Supreme Court's following statement:

23. *See, e.g.*, Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc., No. 95 Civ. 8833, 2001 U.S. Dist. LEXIS 19361 (S.D.N.Y. November 28, 2001) (intermediates for making taxol analogs).

> [Scripps'] tests measured the efficacy, specificity, and toxicity of the particular peptides as angiogenesis inhibitors, and evaluated their mechanism of action and pharmacokinetics in animals.... Based on the test results, Scripps decided in 1997 that EMD 121974 was the most promising candidate for testing in humans.... Over the same period, Scripps performed similar tests on LM609, a monoclonal antibody developed by Dr. Cheresh.... Scripps also conducted more basic research on organic mimetics designed to block αvβ3 integrins in a manner similar to the RGD peptides... it appears that Scripps used the RGD peptides in these tests as "positive controls" against which to measure the efficacy of the mimetics[.][24]

V. Temporal Scope of the Exemption: "Uses Reasonably Related" to Development and Submission of Information

The Supreme Court effectively obliterated any definite threshold event in the drug development or FDA approval process at which the statutory exemption arises. In view of the Federal Circuit's sharp division on the question of whether a temporal limit should be applied to the exemption, a major question that remains unanswered by *Merck* is how far back down the "chain of drug development" the safe harbor exemption should extend.

This issue is complicated by the Court's instruction that no bright-line boundary may be drawn, based simply on the stage of regulatory approval. It will be necessary for the lower courts to develop a new calculus for determining whether drug development activity involving patented compounds is "reasonably related" to the development and submission of information to the FDA.

It is clear that the Supreme Court contemplated that at least some uses of patented compounds which later become the subject of new drug applications are not protected by the safe harbor.

> Basic scientific research on a particular compound, performed without the intent to develop a particular drug or a reasonable belief that the compound will cause the sort of physiological effect the researcher intends to induce, is surely not "reasonably related to the development and submission of information" to the FDA.[25]

It is equally clear that the exemption extends to preclinical studies using patented compounds:

24. *Merck*, 125 S. Ct. at 2378-79.
25. *Id.* at 2382.

> [T]he use of patented compounds in preclinical studies is protected under §271(e)(1) as long as there is a reasonable basis for believing that the experiments will produce 'the types of information that are relevant to an IND or NDA.[26]

In view of the purposeful indefiniteness of these benchmarks, the lower courts will be required to fashion an exemption that avoids the limbo of infringement identified by Judge Newman:

> It would be strange to create an intervening kind of limbo, between exploratory research subject to exemption, and the FDA statutory immunity, where the patent is infringed and the activity can be prohibited. That would defeat the purposes of both exemptions; the law does not favor such an illogical outcome.[27]

A. Experimentation To Discover or Confirm Expected Activity

It is manifestly unclear whether the exemption extends significantly down the chain of experimentation, behind "preclinical" experiments conducted to justify the proposed clinical testing necessary for an IND, such as toxicology, efficacy, specificity, mechanism of action, pharmacology or pharmacokinetics tests at issue in *Merck*.

If so, does the exemption apply to initial experimentation conducted to discover the physiological or pharmacological activity of a patented compound, prior to the confirmation of any specific pharmacological or therapeutic utility? Although Merck KGaA's initial screening was performed in Germany, and was thus noninfringing under §271(a), its early work with Scripps in the United States may nonetheless clarify this issue.

Prior to 1994, Merck KGaA "had developed and screened hundreds of chemicals in test tubes... in an effort to find a handful that could also jam a blood vessel's surface protein" and confirmed that EMD 66203 effectively "jammed the $\alpha_v\beta_3$ receptor on the surface of blood vessel cells."[28] In the district court on remand from the Federal Circuit's decision, a principal issue with respect to damages was whether Dr. Cheresh's chick embryo pharmacokinetics experiments, which proved that EMD 66203 retarded the growth of blood vessels, was the first act of infringement which determined the

26. *Id.* at 2383-84.
27. *Integra,* 2003 U.S. App. LEXIS 27796 at *48 (Newman, J., dissenting).
28. Integra's Supreme Court Brief at 10-11.

hypothetical negotiation date for determining a reasonable royalty.[29] When the district court revisits this issue applying the *Merck* standard, it is likely to be presented with the question of whether the statutory exemption commenced with this discovery.

B. "Intent To Develop a Particular Drug"

A far more difficult issue is presented by the Supreme Court's suggestion that the exemption may commence with "the intent to develop a particular drug or a reasonable belief that the compound will cause the sort of physiological effect the researcher intends to induce."[30] This standard, phrased in the alternative, embraces two widely divergent possibilities.

A first question which is certain to arise is whether specific "intent to develop a particular drug" is sufficient to exempt random experimentation with patented compounds, to determine if any of them has any activity that might be useful as a drug. For example, does the exemption apply to the use of each of thousands of patented compounds screened in an assay to discover pharmacological activity, without any reason for believing that any one of the compounds is likely to have therapeutic utility? As a practical matter, how will new drug candidates be identified without extensive screening of potential candidates?[31]

Would it make a difference if the screened compounds are "structurally obvious" homologs or analogs of compounds having known pharmacological activity? If so, the exemption would protect research directed to intelligent design of new drug candidates, based on a reasonable expectation of similar or enhanced activity possessed by existing compounds.

C. "Reasonable Belief that the Compound Will Cause the Sort of Physiological Effect" Intended by the Researcher

An equally difficult question is presented by the Supreme Court's suggestion that research may be exempt under §271(e)(1) if the researcher has "a reasonable belief that the compound will cause the

29. *See* Integra LifeSciences I, Ltd. v. Merck KGaA, No. 96CV1307-B, 2004 U.S. Dist. LEXIS 20725, at *14-*15 (S.D. Cal. Sept. 7, 2004).

30. *Merck*, 125 S. Ct. at 2382.

31. *See, e.g.*, Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc., No. 95 Civ. 8833, 2001 U.S. Dist. LEXIS 19361 (S.D.N.Y. November 28, 2001) (substantial information (*in vitro* and *in vivo* data) on more than 1,000 compounds synthesized in Drug Discovery).

sort of physiological effect the researcher intends to induce."[32] The Court elaborated on this threshold event as follows:

> At least where a drugmaker has a reasonable basis for believing that a patented compound may work, through a particular biological process, to produce a particular physiological effect, and uses the compound in research that, if successful, would be appropriate to include in a submission to the FDA, that use is "reasonably related" to the "development and submission of information under... Federal law."[33]

In the hands of the lower courts, the inquiry into whether a researcher has a "reasonable basis" for believing that a patented compound may work "through a particular biological process, to produce a particular physiological effect" may lead to elaborate analysis invoking interference law concepts such as conception of a specific "practical utility," as a prerequisite for the safe harbor exemption. In general, the Federal Circuit has required laboratory data confirming an expected and plausible but disputed utility, in the interference context.[34] Does this requirement limit the availability of the safe harbor exemption, and if so, how will Judge Newman's limbo be avoided?

If conception of a specific therapeutic utility is required to exempt further experimentation under §271(e)(1), does the conception require appreciation of the specific mechanism of action that leads to a particular physiological effect? In the interference context, an effective conception requires the formation in the mind of the inventor of a definite and permanent idea of the complete and operative invention, as it is thereafter to be applied in practice. A complete conception must include every feature or limitation of the later-claimed invention, and may be negated by subsequent experimentation that disproves an initial thesis. These fairly rigorous requirements for establishing conception may well be adopted in view of the Supreme Court's emphasis on appreciation of a potential drug candidate's utility to produce a particular physiological effect "through a particular biological process."

VI. Experimental Use and Research Tools

The Supreme Court in *Merck* did not consider whether an

32. *Merck*, 125 S. Ct. at 2382.
33. *Id.* at 2383.
34. *See, e.g.*, Fujikawa v. Wattanasin, 93 F.3d 1559 (Fed. Cir. 1996); Rasmusson v. SmithKline Beecham Corp., 413 F.3d 1318 (Fed. Cir. 2005).

experimental use or common law research exception applies to screening and testing of drug candidate compounds, prior to commencement of activities reasonably related to development and submission of information to the FDA.[35] This question deeply divided the Federal Circuit in *Embrex*[36] and *Madey*,[37] and fueled Judge Newman's spirited dissent in *Merck*.

The issue is not merely of theoretical interest. In the absence of a well-defined and judicially accepted experimental use or common law research exemption, which applies at least to drug candidate chemical compounds, early drug discovery research will be exported to avoid infringement. Merck KGaA avoided this problem by conducting its preliminary screening in Germany, but innovative U.S. drug research companies now have no indication from the courts with respect to the limits of the safe harbor exemption.

The debate over infringement by "research tools," which consumed the Federal Circuit in *Merck*, provides little hope of clarification. It is unclear how a court concerned with early drug development could draw the line proposed by Judge Newman, between a chemical compound that is a "research tool" and the same compound that is evaluated as potential new drug candidate. Judge Newman maintained that "[u]se of any existing tool in one's research is quite different from study of the tool itself."[38] Unlike a microscope, a chemical compound does not have a single, easily-defined utility as a "research tool." A microscope can be used to study diseases, but not to treat them. A chemical compound, such as a phenolphthalein dye, may be useful both as a pH indicator in laboratory research, and as a therapeutic agent for treatment of constipation. Multiple utilities of chemical compounds are inherent properties, and the debate in the Federal Circuit has failed to address the complexity of the "research tool" question in the context of drug development.

Moreover, adoption of a "research tool" exception from the §271(e)(1) safe harbor could permit a patent owner to prevent others from using the chemical "tool" to conduct basic research in order to discover improvements that would affect its commercial interests, and to block approval for new therapeutic uses of such chemical "tools."[39] One disclosed utility of the RGD compounds at issue in

35. *Merck*, 125 S. Ct. at 2382 n.7.
36. Embrex, Inc. v. Service Eng'g Corp., 216 F.3d 1343 (Fed. Cir. 2000).
37. Madey v. Duke Univ., 307 F.3d 1351 (Fed. Cir. 2002).
38. *Integra*, 2003 U.S. App. LEXIS 27796, at *50 (Newman, J., dissenting).
39. *Cf., e.g.*, *In re* Fisher, 421 F.3d 1365 (Fed. Cir. 2005) (discussing the utility required for patentability of ESTs).

Merck was as a laboratory "tool" for gluing cells to a substrate; the patents at issue did not mention angiogenesis or the compounds' ability to block $\alpha_v\beta_3$ integrins. This therapeutic utility was Scripps' discovery. If a specific, substantial and credible utility such as cellular glue is disclosed for a compound such as an RGD peptide, can the RGD patent owner block subsequent researchers from initial experiments using this "research tool" compound to discover unforeseen therapeutic applications?