

# *Nanotechnology Law & Business Journal*

---

*Volume 2, Issue 3*

2005

*Article 4*

---

## Merck V. Integra: The Impact of a Broader “Safe Harbor” Exemption on Nanobiotechnology

Stephen B. Maebius\*

Harold C. Wegner†

\*Foley & Lardner,

†Foley & Lardner,

Copyright ©2005 *Nanotechnology Law & Business Journal*. All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without the prior written permission of the publisher. *Nanotechnology Law & Business Journal* is produced by The Berkeley Electronic Press (bepress).  
<http://pubs.nanolabweb.com/nlb>

# ***Merck V. Integra: The Impact of a Broader “Safe Harbor” Exemption on Nanobiotechnology***

STEPHEN B. MAEBIUS\* and HAROLD C. WEGNER\*\*

## **ABSTRACT**

*The “safe harbor” established under 35 U.S.C. § 271(e)(1) allows one to use a patented invention “solely for uses reasonably related” to FDA approval. Courts have alternately focused on the “solely for” part of the statutory phrase when they wanted to narrow the reach of the safe harbor and the “reasonably related” part of the statutory phrase when they wished to expand the safe harbor. In this article, Stephen B. Maebius and Harold C. Wegner analyze the recent Supreme Court decision in Merck KGaA v. Integra LifeSciences I, Ltd. Maebius and Wegner conclude that there is uncertainty ahead for America’s research use exemption to patent infringement, which might only be clarified through future case law or a legislative solution. However, although some kinds of nanobiotech patents may be weakened by the Merck ruling, there are still plenty of reasons to continue patenting research tools in nanotech and other areas.*

---

## **INTRODUCTION**

The “safe harbor” was established under 35 U.S.C. § 271(e)(1) (2005) in order to permit generic drug applicants to perform testing with a patented drug product prior to expiration of the patent, so that a generic version can be approved by the Food & Drug Administration (“FDA”) and launched immediately following expiration of the patent. However, the language chosen by Congress when it created the safe harbor deliberately went beyond merely permitting preparation of data for an abbreviated new drug application. Instead, the safe harbor allows one to use a patented invention “solely for uses reasonably related” to FDA approval. Courts have alternately focused on the “solely for” part of the statutory phrase when they wanted to narrow the reach of the safe harbor and the “reasonably related” part of the statutory phrase when they wished to expand the safe harbor. Against this backdrop, the case of *Merck v. Integra* arose after Merck utilized certain peptides patented by

---

\* Stephen B. Maebius is Practice Group Leader of the Nanotechnology Industry Team and IP Partner at Foley & Lardner L.L.P. He can be reached at [smaebius@foley.com](mailto:smaebius@foley.com).

\*\* Harold C. Wegner is former Director of the Intellectual Property Law Program and Professor of Law, George Washington University Law School. He is an Partner at Foley & Lardner L.L.P. He can be reached at [hwegner@foley.com](mailto:hwegner@foley.com).

Integra for the purpose of guiding its research in developing a new drug.<sup>1</sup> The case squarely raised the question of whether use of a patented product for drug discovery purposes is infringement *before* a lead compound has been discovered, taken to the clinic and tested in human beings.

The lower court found infringement and ruled in favor of the patent owner, Integra, reasoning that the legislation could not have contemplated encompassing such early stage uses of a patented product. On appeal to the Federal Circuit, the case was affirmed, and the court suggested that the line should be drawn around a clinical/pre-clinical distinction, where research use performed prior to clinical testing in humans would not be covered by the safe harbor because it is at such an early stage.

However, the United States Supreme Court disagreed in *Merck KGaA v. Integra LifeSciences I, Ltd.*<sup>2</sup> In *Merck*, the Supreme Court instead painted a broad “safe harbor” under 35 USC § 271(e)(1) (2005) for patent infringement-free use of inventions that are useful in drug discovery; but it elected not to draw any bright line test for determining what constitutes infringement. In a 9-0 reversal of the Federal Circuit, Justice Scalia—author of *Eli Lilly & Co. v. Medtronic, Inc.*,<sup>3</sup> the leading case on this statutory provision—eviscerated the pre-clinical boundary drawn by the Federal Circuit, but failed to offer any substitute test that could be used to separate exempt research activities from non-exempt research activities. In addition, the Court left untouched the scope of the common law experimental use exemption from infringement that will surely now become a hot button issue for future litigation in areas *outside* pharmaceuticals.<sup>4</sup>

The Court was well aware of the several briefs of *amici* supporting the “research tool” industry. While eliminating the pre-clinical boundary of the safe harbor drawn by the lower court, the Court said that it was not dealing with the issue of “research tools” in this case, though it is undeniable that any patented product which has usefulness in the drug discovery process might be impacted by the decision.<sup>5</sup> Professors Duffy and Strandburg and other *amici* who asked the Court to refrain from dealing with the common law experimental use exemption fared altogether much better, as public policy arguments supporting a common law experimental use exemption are certainly consistent with the holding in this case; and the Court expressly refrained from getting into this issue in any way.<sup>6</sup>

## I. MOVING THE BOUNDS OF THE SAFE HARBOR UPSTREAM: HOW IT MAY IMPACT NANOBIO TECHNOLOGY

### 1. *Merck* and the “Safe Harbor” Exemption

On the one end of the spectrum, the Federal Circuit had held that the “safe harbor” exemption from patent infringement covered in essence only the *clinical* testing of a new drug, and not the upstream animal or even more upstream *in vitro* testing. By the time of the oral argument at the Supreme Court, even the respondent was conceding that the upstream bounds of the safe harbor are much further than the Federal Circuit. At the other end of the spectrum, the United States, as *amicus curiae* in its brief on

---

<sup>1</sup> Specifically, Merck utilized the peptides which contained the tripeptide RGD as a benchmark for measuring activity in an assay to compare the level of activity of its own compounds, allowing it to eventually discover a compound with a strong enough profile to seek FDA approval. Thus, the patentee’s RGD peptides were used to benchmark or guide research that eventually led to the development of a candidate strong enough to test in clinical trials on humans following the filing of an IND by Merck.

<sup>2</sup> 125 S. Ct. 2372, 162 L. Ed. 2d 160 (June 13, 2005).

<sup>3</sup> 496 U.S. 661 (1990).

<sup>4</sup> See Part I, *Moving the Bounds of the Safe Harbor Upstream: How It Could Impact Nanobiotech*, *infra*.

<sup>5</sup> See Part II, *Lip Service to the Research Tool Industries*, *infra*.

<sup>6</sup> See Part III, *Experimental Use under the Common Law*, *infra*.

behalf of the FDA, had taken the view that screening to *identify* the ultimate drug target is exempt from infringement even where

“hundreds or even thousands [of compounds] must be tested.” As long as a scientist is working on developing a particular drug. . . , the number of compounds screened has nothing to do with whether the screening was reasonably related to the development and submission of information to FDA. Instead, it reflects the luck (or intuition) of the scientist, or the difficulty of the task.”<sup>7</sup>

The Court clearly came down on the side of the government. It first determined that there *are* upstream limits that remain:

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.<sup>8</sup>

Immediately thereafter, however, the Court concluded that

[i]t does not follow from this, however, that § 271(e)(1)’s exemption from infringement categorically excludes either (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. Under certain conditions, we think the exemption is sufficiently broad to protect the use of patented compounds in both situations.<sup>9</sup>

Yet, in a statement that is difficult to balance against other statements in the opinion, the Court stated: “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.”<sup>10</sup>

In sweeping statements the Court eviscerated the upstream boundaries of the safe harbor:

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. See *Eli Lilly*, 496 U.S., at 674. We decline to read the “reasonable relation” requirement so narrowly as to render § 271(e)(1)’s stated protection of activities leading to FDA approval for all drugs illusory. Properly construed, § 271(e)(1) *leaves adequate space for experimentation and failure on the road to regulatory approval: 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.”* § 271(e)(1).<sup>11</sup>

<sup>7</sup> Brief of Amicus Curiae United States of America at 18-19, *Merck KGaA v. Integra LifeSciences I, Ltd.*, 125 S. Ct. 2372, 162 L. Ed. 2d 160 (June 13, 2005) (internal citations omitted).

<sup>8</sup> *Merck*, 125 S. Ct. at 2382 (emphasis added in part).

<sup>9</sup> *Id.*

<sup>10</sup> *Id.* at 2380.

<sup>11</sup> *Id.* at 2383 (emphasis added in part).

The Court continued with the following:

. . .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. Moreover, many of the uncertainties that exist with respect to the selection of a specific drug exist as well with respect to the decision of what research to include in an IND or NDA. As a District Court has observed, “It will not always be clear to parties setting out to seek FDA approval for their new product exactly which kinds of information, and in what quantities, it will take to win that agency’s approval.” *Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269, 1280 (N.D. Cal. 1991), *aff’d*, 991 F.2d 808 (C.A. Fed. 1993). This is especially true at the preclinical stage of drug approval. FDA regulations provide only that “the amount of information on a particular drug that must be submitted in an IND . . . depends upon such factors as the novelty of the drug, the extent to which it has been studied previously, the known or suspected risks, and the developmental phase of the drug.” 21 C.F.R. § 312.22(b). We thus agree with the Government that the 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.” Brief of United States as *Amicus Curiae* 23.<sup>12</sup>

The above passages make clear that the safe harbor may extend quite far upstream in the drug discovery process, encompassing research in animals and *in vitro* testing provided there is a “reasonable basis” for believing that such research will yield results relevant to the FDA approval process.

## 2. Applying *Merck* to Nanotechnology

This wider berth for the safe harbor may impact nanobiotech inventions that are useful in the drug discovery process; however, it is also true that many nanotech research tools may not be impacted, as explained below. The remand of the *Merck* case (which is now in the hands of the Federal Circuit again) and future cases may force the lower courts to further flesh out the scope of the safe harbor, providing clearer boundaries.

It is important to distinguish two types of situations involving “research tool” patents. In one type of situation, a patented research tool product is used to discover a drug that is not covered by the research tool patent. However, in another situation, the drug that is discovered may be encompassed by the claims of the “research tool” patent. As to this latter type of situation, one must remember that the safe harbor only applies until such time as approval is obtained. In other words, consider the following example. Suppose the patent covered a dendrimer conjugated to a therapeutic agent. One might be able to use the safe harbor as a defense to permit testing of such a product to generate information useful for the FDA approval process. However, if approval is obtained and the product is covered by the research tool patent, then, at that point, the safe harbor would end; and infringement would begin.

Several other scenarios may be envisioned where a nanotech research tool patent used in drug discovery is not impacted by the *Merck* case. For example, someone who has patented a lab-on-a-chip or a nanoarray which cannot easily be duplicated in-house at a pharmaceutical company will likely enjoy continued sales of their product. The customers in this scenario need to buy the product from them because such a product may be too difficult to replicate, even if that customer believed they could avoid infringement if they made it themselves in-house.

---

<sup>12</sup> *Id.* at 2383-84 (emphasis added in part).

In other situations, a pharmaceutical company may utilize a nanobiotech research tool at a point in research that is too remote from yielding results relevant to FDA approval, thereby creating a question of whether there is a “reasonable basis” in the words of the *Merck* opinion on which to anticipate submission of such results to the FDA in a drug approval application. For example, a pharmaceutical company using a patented quantum dot targeted conjugate to learn more about how cancer cells metastasize, without seeking to develop data or results related to approval of any particular drug, might be unsure whether it is within the safe harbor and therefore elect to obtain a license for insurance (i.e., to avoid even a question of infringement).

These scenarios are offered merely for illustration. There are many other scenarios possible, and many factual nuances not described that could tilt the argument to one side or the other as to whether such research activity is protected or not. Such factual nuances will need to be carefully considered in determining whether to litigate or license.

### **3. Implications for Nanotechnology Patent Strategy**

Nanobiotech companies with easily duplicated patented research tools that may be used by the pharmaceutical industry in the drug discovery process will need to think carefully about the claim strategies they employ in their patent applications as a result of this decision.

Claiming the end products that result from use of the research tool is one option, though pure “reach-through” claims in a research tool patent may be vulnerable to attack based upon lack of enablement or lack of written description, depending on the scope of the claim in relation to the number and quality of supporting examples in the application. Such applications might seek to include “hybrid” claims that offer at least some structural core or motif to identify the end product with optional additional functional limitations and supporting examples in the specification. For example, if the invention is a screening assay employing a nanoarray that identifies compounds with activity against diabetes, then it may be valuable before filing the patent application to first employ the nanoarray in order to identify some of the end products with activity, which could be included in the application to support end product claims.

Another alternative is to keep the research tool as a trade secret rather than patenting it, so that research may be performed in secrecy allowing the innovator to find the pharmaceutical end product, itself, which could then be the subject of patent filing.

Another potential impact is on current and future license agreements where a nanotech research tool patent is licensed to permit research for drug discovery purposes. Pharmaceutical companies may be emboldened by the *Merck* decision to reevaluate current licenses under which they are paying royalties to the owner of a nanotech research tool patent owner. In the case of an existing license, depending on the exact language (e.g., where fees or running royalties were not designated as non-refundable), the licensee might claim that their activities are now protected under the safe harbor and therefore do not require a license. Future licenses might be harder to negotiate in some cases if the pharmaceutical company believes a license is not needed for an activity that might fall within the scope of the safe harbor.

## **II. LIP SERVICE TO THE RESEARCH TOOL INDUSTRIES**

In its penultimate footnote, the Court acknowledged the research tool issue and that “[t]he Court of Appeals . . . suggested that a limited construction of § 271(e)(1) is necessary to avoid depriving so-called ‘research tools’ of the complete value of their patents.”<sup>13</sup> But, after quoting Judge Newman’s dissent with approval (“Use of an existing tool in one’s research is quite different from study of the tool itself”), the

---

<sup>13</sup> *Id.* at 2382, n.7.

Court said that “[w]e . . . need not—and do not—express a view about whether, or to what extent, § 271(e)(1) exempts from infringement the use of research tools; in the development of information.”<sup>14</sup>

In the end, we are left with uncertainty. Although the Supreme Court’s footnote says the case does not address research tool patents, the heart of the opinion is directed to the question of whether research involving a patented product to guide drug discovery is exempt from infringement under the safe harbor. The statutory provision construed by the Supreme Court does not contain any distinction for claims directed to research tools—it only refers to a “patented invention.” Notwithstanding the Supreme Court’s footnote, it seems hard to deny that this holding would apply to any patented invention, whether it is a patented nanoarray or a patented peptide. Yet, the absence of a clear test for differentiating exempt and non-exempt activities ensures continued uncertainty about the scope of the safe harbor in the context of research tools.

### III. EXPERIMENTAL USE UNDER THE COMMON LAW

The Court *sub silentio* heeded the advice of Professors Duffy and Strandburg, the Bar Association of the District of Columbia and others in their *amici* filings that the Court refrain from entering the controversy over what is a common law experimental use.

There will still remain limited areas where this issue is important for the pharmaceutical field; but, in other areas, particularly agricultural research, the issue will remain a hot button topic for consideration by the lower courts and a possible trip back to the Supreme Court.

### IV. CONCLUSIONS

Ultimately, there is uncertainty ahead for America’s research use exemption to patent infringement, which might only be clarified through future case law or a legislative solution. Although some kinds of nanobiotech patents may be viewed as less valuable by the pharmaceutical industry in the wake of the *Merck* ruling, there are still plenty of reasons to continue patenting research tools in nanotech and other areas. With adjustments in claim strategy, owners of nanobiotech patents may realize greater returns despite this ruling. However, they may face increased resistance to attempt to license such patents on the part of emboldened pharmaceutical companies in situations where the tool in question may be easily replicated.

---

<sup>14</sup> *Id.*