Intellectual Property
Law Section Newsletter

A Novel Expression of Confusion

Michael D. Hobbs Jr., Chair | Spring 2005 | Alison Danaceau and Hunter Yancey, editors

Merck v. Integra: Construing the Safe Harbor Provision of the Hatch-Waxman Amendments

By J. Jason Lang and Joshua V. Van Hoven

In the early 1980s, the rigors of the FDA pre-marketing approval process were distorting the patent term of pharmaceutical patents, sparking Congress to enact the Hatch-Waxman Amendments. Specifically, the costly and lengthy FDA approval process was thwarting generic competition, resulting in de facto term extensions on many pharmaceutical patents. The net result of the distortions was inadequate generic competition. In fact, more than 150 brand-name drugs—without patent protection—had no generic equivalent. Accordingly, the aim of the Hatch-Waxman Amendments was to increase generic competition, while still providing adequate incentive to foster pioneering research and development of new drugs.

A provision of the Hatch-Waxman Act, the safe harbor provision, was to facilitate bringing generics to the market in a timely fashion. The provision exempts infringing conduct that reasonably relates to generating information for FDA approval. The scope of the exemption, however, remains subject to fierce debate. Lacking any facial clarity, federal courts have wrestled with the text of the safe harbor exemption for nearly 20 years, with varying results. Most recently, the United States Court of Appeals for the Federal Circuit perceived an injustice whereby the prevailing authority would eviscerate patent protection of many compounds and devices that simply become entangled in the FDA approval process, whether or not they were related to the product being tested.

The Federal Circuit's remedy (which the Supreme Court is now considering) was to draw a rigid line that defines the safe harbor's scope. The Federal Circuit's reasoning is deficient for at least three reasons. First, the Federal Circuit's analysis of the FDA approval process represents a far departure from reality. The Federal Circuit's line (drawn at "clinical trials") is under-inclusive of many activities that are legitimately necessary for FDA approval. Second, altering the timing of the exemption still allows infringement of many patents that are merely used for FDA approval, but have nothing to do with the product being tested. Third, the Federal Circuit's timing logic is unsupported by the plain language of the safe harbor exemption.

The Supreme Court can remedy these errors in a number of ways. If it is necessary to torture the plain language to include an additional test, the Court should import a nexus test that focuses on the relationship between the product being tested for FDA approval and the patent-at-issue. The more distant the relationship, the more likely that the safe harbor does not apply and the involved patent is infringed. A better approach, however, is to simply read the statute as it is written. This is a technically complex matter with far-reaching economic consequences. The judiciary— which lacks the ability to conduct hearings on how the rules imposed would impact medical care or the patent system—is ill equipped to set economic policy here. A clear and simple reading of the rule as it is written will at least provide certainty to industry and the courts, and possibly provide the impetus for a Congressional rewrite of the Hatch-Waxman Amendments.

THE HATCH WAXMAN AMENDMENTS—FROM ENACTMENT TO INTEGRA

Twenty years ago, Congress enacted the Hatch-Waxman Amendments[1], seeking to strike the proper balance between two competing policy interests: (1) fostering pioneering research and development of new drugs; and (2) enabling competitors to efficiently bring low-cost generics thereof to market.[2] The Amendments' primary aim was to address two distortions of the 17-year patent term in the context of inventions subject to the FDA pre-marketing approval[3]. The first distortion was on the front-end of the patent-term, shortening, in effect, the patent term[4]. In the FDA context, a patentee cannot commercially exploit its invention until it receives pre-marketing approval, which averages between 10-15 years[5]. The second distortion was on the back-end of the patent term, lengthening, in effect, the patent term. Patentees of pharmaceuticals would often enjoy monopoly-

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From the Chair

A Few Final Thoughts

by Michael D. Hobbs Jr.

After doing a report in school on Teddy Roosevelt this year, my son Ted has become a big fan of his Presidential namesake. (For many reasons, he should be eternally grateful my wife and I didn't name him Millard). As this Bar year moves to a close and after listening to my son practice for class report, I have been reminded of Teddy Roosevelt's quote on leadership: "The best executive is the one who has sense enough to pick good people to do what he wants done, and self-restraint to keep from meddling with them while they do it." That advice has surely proven sound this year with the IP Law Section.

If you have paid attention this year, you have received more invitations to IP Law Section sponsored events than e-mails offering discount Viagra. These many opportunities for education and socializing have been solely due to the extraordinary work of the section's leadership. Doug Isenberg, Griff Griffin, Todd McClelland and Wab Kadaba have provided sound executive planning, vision and guidance to keep our financial and administrative houses in order, and plan for the future.

Our committee chairs have likewise been remarkable in their energy and organization. A special thanks to Andrew Crain, Art Gardner, Shane Nichols, John Renaud, Jeri Sute and Steve Wigmore. Through their hard work, we have enjoyed social events and excellent speakers from the Federal Circuit, District Court, the Patent and Trademark Office and our own Bar. I would particularly like to highlight the work of the chair of our newest committee, Phillip Burrus, who has stepped in and launched the In-House Counsel Committee with several well-attended events and is actively planning several more in the near future. Lastly and never leastly (a good Dr. Seuss word), the section owes Alison Danaceau and Hunter Yancey its gratitude for creating this publication through their creativity and hard work.

As I prepare to lay down my gavel and march home to the fields of billing 2000 hours a year, a few final thoughts. The past year has convinced me more than ever that the IP Law Section can and should be a vital part of our practices. You will be a better attorney if you attend the section's educational events. You will serve your clients better if you know other attorneys and can resolve disputes with telephone calls instead of angry letters and lawsuits. You will feel part of a profession, and not just part of a business, if you volunteer as part of the section's pro bono partnership with the Georgia Lawyers for the Arts.

Admittedly, the IP Law Section cannot be all things to all people. But, if you can't attend the IP Institute in Puerto Rico this November, attend the many events in the state. If patent law is not part of your practice, attend the events focusing on trademark and copyright. If you have enough CLE hours, attend the social events and get to know each other. You will find wonderful people out there committed to the profession and to the practice of intellectual property law in the state of Georgia. I know I have.

Editors Comments

by Alison Danaceau and Hunter Yancey

Greetings and welcome to the Spring 2005 edition of the Intellectual Property Law Section's Newsletter, *A Novel Expression of Confusion.* This issue contains a great article as well as recaps of and pictures from recent section events. Within this issue, you will find an article by Jason Lang and Josh Van Hoven about the *Merck v. Integra* case and its ramifications on the future of the FDA patent infringement exception for generic drugs. As some of you know, the Supreme Court recently heard arguments in this case, and Jason and Josh's article nicely discusses the case, its history, and the involved issues.

Thank you to each contributor for participation in the Spring 2005 edition of the IP Law Section's newsletter. Thanks also go to Johanna Merrill who did an outstanding job in composing this issue's layout. We also thank the vendors for placing advertisements in the newsletter. Lastly, we welcome any comments or suggestions from our section members.

Have a great summer!

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like protection after the expiration of their patents because the FDA approval process would thwart market entry of generic competition[6].

Enactment of the Hatch-Waxman Amendments

The Hatch-Waxman Amendments provide a compromise for brand name and generic pharmaceutical companies (or makers of other "products" subject to FDA pre-marketing approval). Brand-name pharmaceutical companies have the opportunity to extend the terms of patents covering new drugs (or "products" subject to FDA pre-marketing approval).[7] Generic pharmaceutical companies may infringe brand-name drugs to seek FDA approval (the safe harbor provision or FDA Exemption)[8] and may "piggy-back" the safety and efficacy studies of the new drug by showing "bioequivalency" (ANDA provisions).[9]

The safe harbor provision of the Hatch-Waxman Act was Congress's reaction to the 1984 Federal Circuit decision of *Roche Products, Inc. v. Bolar Pharmaceutical Company*.[10] The safe harbor overturns Roche's holding that the use of a drug product prior to the expiration of a patent covering that drug product constitutes patent infringement, even though the only purpose of that use is to seek FDA approval for the commercial sale of the drug after the patent expires. The safe harbor provision provides:

> 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.[11]

The legislative history strongly suggests that Congress intended that the safe harbor merely overrule *Roche*.[12] While Congress had been considering legislation that included the term-extension and ANDA provisions for years, the FDA exemption became part of the Act only months before its passage, and only months after the *Roche* decision. Also, the congressional record teems with statements that indicate the safe harbor's purpose was to only overturn *Roche*.[13] The statement introducing the safe harbor provision is quite clear: the safe harbor provision will have "the net effect of reversing the holding of the court in *Roche Products, Inc. v. Bolar Pharmaceutical Co., Inc.*"[14]

Evolution and Interpretation of the FDA Exemption

The plain language of the safe harbor provision, however, supports an interpretation that is much broader in scope than overturning *Roche*. The provision's sweeping language is likely the result of sloppy drafting. The Supreme Court, in fact, found the "provision . . . not plainly comprehensible on anyone's view."[15]

The scope of the safe harbor is unclear on at least two

fronts. First, to what "products" does the safe harbor apply, i.e., what patents may one infringe while generating information for FDA approval? Is this a license to infringe any patent so long as an applicant is generating information for FDA approval? Or must the infringer's target-product (product that the infringer is seeking FDA approval therefor) share a nexus with the patent being infringed? Second, how far down the chain of research & development does the safe harbor reach? Does the safe harbor, for example, immunize activities such as screening for candidate compounds?18

The scope of the safe harbor, therefore, has been subject to extensive and sometimes capricious interpretation by the courts.[17] The most significant case that interprets the safe harbor is *Eli Lilly v. Medtronic*.[18] There, the Supreme Court held that the safe harbor applies to medical devices, rejecting that the safe harbor applies to only pharmaceuticals.[19] The Court, in dictum, set forth a "perfect 'product' fit" model. That is, the FDA exemption provision and the term-extension provision are a package, and the safe harbor generally will be applicable to "products" that are (or were) eligible for the term-extension. Accordingly, because the medical device that the defendant was infringing was (or had been) eligible for the term-extension, the Court found the safe harbor exemption applicable.

The exact holding of *Medtronic* was in debate because the only devices at issue were eligible for a term-extension (the devices were subject to FDA pre-marketing approval). One could read *Medtronic*, emphasizing the "perfect 'product' fit" model, as holding that the safe harbor applies to only medical devices that are eligible for the term extension.[20] Or, focusing on sweeping language in the Court's opinion, one could read *Medtronic* as holding that the safe harbor applies to all medical devices. Resolving the dispute, the Federal Circuit held that the FDA exemption applies to all medical devices, regardless of whether the medical device was (or had been) eligible for the term extension.[21] This led to the majority of courts interpreting the safe harbor to apply to any "product."[22]

Medtronic and subsequent opinions from the Federal Circuit, however, left open the nexus debate. All of these cases involve a close nexus between the defendant's target-product, a medical device, and the product-at-issue, a similar medical device. What if, for example, the defendant was generating information for approval of a new pharmaceutical and was using the medical device in clinical trials to obtain this information?

Courts also grapple with safe harbor's reach, i.e., how far down the chain of research & development the statute exempts infringement. This inquiry hinges on[23] whether the use in question "reasonably relate[s]" to generating information to obtain FDA approval. An influential statement[24] of the standard is:

> Would it have been reasonable, objectively, for a party in defendant's situation to believe that there was a decent prospect that the 'use' in question would contribute (relatively directly) to the generation of kinds of information that was likely to be relevant in the processes by which the FDA would decide whether to approve the product?[25]

In practice, drawing the line of when the safe harbor exempts infringement has proven difficult, and no bright lines were drawn until *Integra*. Long-standing case law has taken a flexible approach. Cases have held that conduct in addition to clinical testing may qualify for the exemption.[26] In *Telectronics Pacing Systems, Inc. v. Ventritex, Inc.*, for example, the Federal Circuit found the exemption applicable to the demonstration of a defibrillator at medical conferences.[27] Other cases held that pre-clinical testing undertaken with an eye towards clinical testing may qualify for the exemption. In *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, for example, the district court held that conducting animal testing to assess a drug's safety for clinical tests qualifies for the exemption because the tests' aim was "to lead to relevant information for submission."[28] The district court found irrelevant that the test results were never part of any submission.[29]

Finally, some courts have held that the statute reaches all the way down the chain to research that involves identifying analogs. In *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*, for example, the court held that the safe harbor immunizes early stage research to develop analogs.[30] The facts of *Rhone* also present the nexus issue. The defendant was infringing the patents-in-suit, covering certain intermediates (taxane derivatives), to research and develop analogs of taxol ("paclitaxel"). This scenario is in contrast to a defendant that uses a brand-name drug to generate information that will support an application to obtain approval of a generic equivalent. The *Rhone* court, however, simply held that the safe harbor applies to the "intermediates." The only remaining issue, then, was whether the infringing conduct reasonably relates to the generating information to submit to the FDA approval. This holding foreshadows the *Integra* court's concern with biomedical tool patents.

Integra v. Merck: The Federal Circuit Reverses Course To Cut Off The FDA Safe Harbor At "Clinical Trials"

Background Technology And The Research That Resulted In Infringement

The technology-at-issue is the RGD-peptide sequence.[31] One possible use of the RGD-peptide sequence is to promote cell adhesion to substrates via its binding action to surface receptors. Promoting cell adhesion, in theory, should promote wound healing and biocompatibility. Additionally, the binding action of RGD-peptides to avB3 receptors

inhibits angiogenesis, the process for generating new blood vessels. Inhibiting angiogenesis, in theory, has applications in cancer treatment by "starving" tumors. Compounds with the RGD-peptide sequence can prevent the growth of new blood vessels that would "feed" the tumors (by forming new capillaries).

Two groups are largely responsible for the research and developments leading to the technology-at-issue in *Integra*. Generally speaking, the first group comprises two scientists, Dr. Erkki Ruoslahti and Dr. Michael Piersbacher, of the Burnham Institute in San Diego (Burnham). And the second group comprises one scientist, Dr. David Cheresh, of the Scripps Research Institute (Scripps), and Merck.

The Burnham scientists were apparently the first to discover the binding action of the RGD-peptide. This discovery led to the filing of the patents-at-issue in 1983 and 1985, which are due to expire between 2003 and 2006. In 1987, the Burnham Institute and investors established Telios Pharmaceuticals to commercially exploit these patents, with a focus was on therapeutic applications to prevent heart attacks, promote wound healing, and inhibit cellular rejection to prosthetic devices. After spending more than $150 million in fruitless efforts to develop a RGD-peptide product of commercial value, Telios declared bankruptcy in January of 1995, at which time the patents-in-suit were sold to Integra for around $20 million.

Dr. Cheresh began his work with integrin proteins in the mid-1980s (with a focus on the avB3 integrin). A notable discovery of Dr. Cheresh was that the avB3 integrin is found on the surfaces of cells in sprouting blood vessels. This was particularly significant to scientists that study cancer because of its potential use in "starving" tumors. Dr. Cheresh began to test this theory using compounds that would "block" the avB3 integrins. In 1990—with antibodies outside the scope of the patents-in-suit—he was successful in demonstrating that a compound could block the avB3 receptor in a manner that prevents it from interacting with other molecules (thereby blocking blood vessel growth). And in 1994, he was able to demonstrate in a living system (a chicken CAM) that his compound could block the receptor and blood vessel growth. Merck was, at least in part, funding this research through an existing 1988 agreement with Scripps.

While Dr. Cheresh was conducting his initial research, Merck had been screening compounds to find a more suitable candidate, including compounds that contain the RGD sequence of the patent. The most promising candidates from these tests were EMD 66203 (EMD 6); EMD 85189 (EMD 8); and EMD 121974 (EMD 12). All three candidates are cyclic peptides that include the RGD-sequence. In early 1994, Merck had Dr. Cheresh test its EMD 6 compound in his chicken CAM model, showing that that EMD 6 was superior to the antibodies that Dr. Cheresh had been testing. Notably, at this point in 1994, EMD-6 was shown via animal studies to retard the growth of blood vessels and "starve" tumors. These results, indeed, led Dr. Cheresh to claim that he had found a potential "treatment of cancer." All of Dr. Cheresh's work up until this point was incorporated into a patent application.

The promising results with EMD 6 led to a new agreement, taking effect in 1995, between Merck and Scripps (and Dr. Cheresh). The agreement's sole purpose — at least facially — was an Investigatory New Drug application (IND) filing of EMD 6 or a derivative thereof in three years.[32] The agreement notes: this was a "project at Scripps . . . that would . . . serve as the basis for potential clinical trials." Merck was to supply compounds, such as EMD 6, EMD 8, and EMD 12, to Scripps to conduct tests to determine their respective angiogenesis-inhibiting activities. Dr. Cheresh also was testing 15-20 of his own antibodies in the same manner. As specific compounds became more promising, Scripps was to conduct experiments with the compounds to demonstrate the efficacy, mechanism of action, pharmacology, pharmacokinetics, and toxicity. Merck took responsibility to assess the compound's toxicity and pharmacokinetics under the standards of the FDA "Good Laboratory Practices."

Around this point, testing began that was found to infringe the patents-in-suit, spanning between August 1994 through 1998. The experiments, in general, include: (1) test-tube studies to determine how well each candidate would bind to the cell surface receptor and how well each blocks other agents from binding to that receptor (minority of testing relative to animal testing); (2) animal studies with chicken embryos to observe the effect on blood vessel formation; and (3) animal studies with mice to observe the effect on blood vessel development and tumors.

Merck's goal to obtain FDA approval for EMD 6, EMD 8, or EMD 12 became palpable by at least 1996. In November of 1996, for example, Merck appointed a formal inter-disciplinary team to oversee the research, regulatory approval, marketing, and manufacturing. That team began to convert Dr. Cheresh's prior work and ongoing results to a specialized computer system, MEDIS, which reports data in a FDA-required format. By at least 1996, Merck had Dr. Cheresh focus on EMD 8, and by at least early 1997, chose EMD 12 as the best candidate for clinical development. Also, around early 1997, Merck hired independent consultants to assist in preparing an IND application (described in more detail *infra*). At this time, preliminary reports included all of Dr. Cheresh's CAM experiments on mice and chicken, as well as a summary of the test-tube testing.

In 1997, Merck had enough scientific support to file a request to commence clinical testing in Europe. That scientific support was sufficient for European approval; those tests are under way. And, in 1998, Merck had enough scien-

tific support to file an IND application. The record fails to reflect, due to the discovery cut-off, that the FDA did approve that IND application, permitting clinical trials to proceed.[33]

Integra Files Suit And The Federal Court Limits The FDA Exemption

In December 1997, Integra offered Merck a license at a long-term cost of several million dollars.[34] Extensive negotiations broke down, and Integra brought suit for patent infringement against Merck and Scripps.[35] At trial, the jury found Merck liable for infringing several of Integra's patents and awarded Integra a reasonable royalty of $15 million. The district court determined that the safe harbor exemption does not embrace the experiments at Scripps between August 1994 through 1998. The court thus let the jury's award stand.[36]

The case eventually found its way to the Court of Appeals for the Federal Circuit, where Merck's principal infringement defense was the statutory safe harbor of 35 U.S.C. § 271(e)(1). The Federal Circuit addressed the question of what activities (discovery, evaluation, clinical testing, etc.) are protected by the safe harbor. Simply put, the issue became how far the safe harbor provision reaches down the chain of research & development. In a departure from previous cases, the Federal Circuit resolved this dispute by drawing a bright line at "clinical testing."[37] Activities "reasonably related" to clinical testing are protected by the safe harbor; "all experimental activity that at some point, however attenuated, may lead to an FDA approval process" is not.[38] Under this reading of the statute, the testing from 1994-1998, which was the "Scripps-Merck general biomedical experimentation" according to the Federal Circuit, was not protected by the safe harbor.[39]

THE FEDERAL CIRCUIT'S INTEGRA ANALYSIS IGNORES THE REALITIES OF PHARMACEUTICAL DEVELOPMENT AND FDA APPROVAL PROCESSES

The Federal Circuit's Decision Ignores That Pre-Clinical Testing Directly Relates To FDA Approval for New Drugs

The legal and policy issues of *Integra* unfold in the context of the FDA regulatory framework. Generally speaking, the FDA regulatory scheme has two regimes:[40] one for new drug approval and one for generic drug approval. The following summarizes each in turn.

Typically, scientists first identify a medical problem that they wish to solve, and they then seek to identify candidate compounds that might solve that medical problem ("drug discovery"). This drug discovery phase can be very broad. New technology, such as high-throughput screening technology (a biomedical or research tool), facilitates fast, efficient testing to identify candidate compounds, which may number in the hundreds. After identification of a lead compound ("post-identification"), scientists typically select certain candidate compositions for pre-clinical testing. Testing on multiple candidates represents the norm because any particular candidate may be unsuitable for human therapy or may be unsuitable for non-clinical reasons.

By at least the post-identification phase, FDA regulations significantly affect the manner in which scientists proceed. In most cases, obtaining FDA approval to market a new pharmaceutical requires two stages of FDA approval, which the applicant obtains by filing two applications: (1) an Investigatory New Drug application (IND);[41] and (2) a New Drug Application (NDA).[42] The stages are sequential. The first stage involves demonstrating through data and evidence from pre-clinical testing (animal and *in vitro* testing) that the candidate compounds are sufficiently safe for human testing.[43] The second stage involves, *inter alia*, demonstrating through clinical tests that the pharmaceutical is both safe and effective in human therapy; this stage also entails submitting non-clinical information that may duplicate portions of the IND submission.

In working towards an IND application, the applicant must obtain specific information that FDA regulations require the applicant to include.[44] The application, for example, must include pharmacology and toxicology studies that demonstrate the drug is reasonably safe for human testing.[45] The application must also include: (1) a description of the pharmacological mechanism(s) of action of the drug in animals; (2) information on the absorption, distribution, metabolism, and excretion of the drug; and (3) a summary of the toxicological effects on the drug in animals and *in vitro*.[46] FDA regulations also impose standards that govern the methods and environment to which the applicant must adhere when satisfying the requirements ("Good Laboratory Practices").

In addition to above explicit requirements, however, much more information is relevant and often necessary. The overriding consideration in the IND approval process is whether the potential benefit of the new drug justifies the attendant risk to clinical testing.[47] All information, therefore, that evidences either the drugs potential benefit or the drugs attendant risk is relevant to the FDA. To name a few, safety profiling (such as assays), dosing, and comparative studies are relevant.

Only once this IND pre-clinical testing is complete — and receives FDA approval — may the applicant proceed to the NDA or clinical-testing stage. Yet, despite the pervasive FDA regulations that effect pre-clinical testing, the *Integra* court apparently[48] held that all of the IND testing (and pre-clinical testing) is not "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."

Clearly, from the above, pre-clinical testing involves generating information that directly relates to "development and submission of information" for FDA pre-marketing approval. Common-sense indicators bolster this claim. For example, when generating information for submission to the FDA, firms generally bring in expert personal (such as FDA consultants or an advisory team).[49] Also, pharmaceutical or research entities often communicate with the FDA during this period, inquiring as to what information that the FDA may find helpful to its determination.[50]

The facts of *Integra* illustrate that the Federal Circuit clearly ignored the realities of the FDA process. The opinion fails to explain why this information — clearly relevant (or a mandate) in IND applications — is not "reasonably related" to FDA pre-marketing approval. The aim of the 1994-98 experiments appears to have been generating the necessary information to file an IND application (and ultimately to obtain FDA pre-marketing approval). Delving into the specific facts, each test was to demonstrate one or more of the following: efficacy, mechanism of action, pharmacology, pharmacokinetics, and toxicity. As set forth above, an applicant must provide this information. In regards to the testing of compounds other than EMD 12, the FDA deems relevant information on derivatives of, and drugs that relate to, the candidate compound.[51]

A change in the agreement between Merck and Scripps and other anecdotal evidence also suggest that the 1994-98 experiments were to generate the requisite information to obtain an IND. The new agreement, taking effect in early 1995, on its face notes: this was a "project at Scripps . . . that would . . . serve as the basis for potential clinical trials."[52] In fact, under the new agreement, Merck took responsibility to assess the compound's toxicity and pharmacokinetics under the standards of the FDA "Good Laboratory Practices." The 1995 Agreement also set a three-year deadline for completion of the pre-clinical studies at which point "an IND will be filed."[53]

Other anecdotal evidence suggesting that FDA approval was the salient focus of this testing includes changing personal and correspondence with the FDA. In November of 1996, Merck appointed a formal inter-disciplinary team to oversee research, regulatory approval, marketing, and manufacturing.[54] This team began to convert Dr. Cheresh's prior work and the results of the 1995 experiments to a specialized computer systems, MEDIS, which reports data in format the FDA requires. Then, in 1997, Merck hired an independent consultants to assist in preparing an IND application. At this time, preliminary reports included all of Dr. Cheresh's CAM experiments on mice and chicken, as well as a summary of the test-tube testing.[55]

Another piece of evidence, not part of the Federal Circuit's analysis, strongly suggests that these tests were to generate the necessary evidence for FDA approval. Namely, Dr. Cheresh and Merck knew what information the FDA would require in an IND application because Dr. Cheresh

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Chair-elect Doug Isenberg and Alison Danaceau.

Section Hosts Dual CLE events and St. Patrick's Day Social

On March 17 the section's licensing and trademark committees offered two simultaneous one-hour CLE seminars, followed by a St. Patrick's Day social at the Bar Center in Atlanta.

The Licensing Committee program, "Patent Claim Drafting with an Eye Towards Licensing," was a panel discussion with panalists Bill Hartselle, of Bell South Intellectual Property Marketing Corp.; Cheryl Tubach of The Coca-Cola Company; Brenda Holmes of Kilpatrick Stockton LLP; and Griff Griffin of Sutherland Asbill & Brennan LLP. The Trademark Committee program, "The Trademark Dirty Dozen—Practice Pitfalls and Popular Palliatives," featured speakers Joan Dillon of Joan Dillon Law, LLC; Jim Johnson of Sutherland Asbill & Brennan LLP; and Charlie Henn of Kilpatrick Stockton LLP.

Below: Scott Griffith and Jeri Sute

Left: Jim Meadows and Todd McClelland

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was overseeing the experimentation to obtain FDA approval of an analogous compound, which was progressing ahead of the EMD experimentation. The analogous compound was the non-infringing antibody of Dr. Cheresh's early testing. This antibody was licensed to Ixsys for development in return for a commitment to fund Scripps and Dr. Cheresh to conduct the pre-clinical research to file an IND application. As early as 1996, Scripps researchers met with FDA officials to discuss what information would be helpful for the FDA review. The pre-clinical research for this antibody mirrors the activities found to infringe in *Integra*, including testing in test-tubes, with chicken CAM's, and with mice. All the results from the Scripps-Ixsys testing became part of Ixsys's IND application. And, in 1997, the FDA approved this application. Dr. Cheresh obviously knew that the information necessary to support the EMD 12 filing would be nearly identical to the information for the Ixsys application.

Finally, the Federal Circuit's opinion seems to obfuscate the true state of development of EMD 6, 8, and 12 by using such references as "fishing expedition." The only experiments-at-issue are those between 1994-1998. By 1994, EMD-6 was shown via animal studies to retard the growth of blood vessels and "starve" tumors, prompting Dr. Cheresh to claim that he had found a potential "treatment of cancer." In fact, in 1997, Merck had enough scientific support to file a request to commence clinical testing in Europe. That scientific support was sufficient for European approval. And in 1998, Merck had enough scientific support to file an IND application. That support, likewise, was sufficient for clinical trials to proceed.[56]

In sum, the *Integra* court focused on the timing of FDA approval but drew the line (clinical/pre-clinical) in a manner that draws no support from the statutory language or the real world, since the pre-clinical stage is tightly entwined in activities reasonably related to FDA approval.

Generic Drugs Employ A Wholly Separate Testing Regime

Development and FDA approval for a generic drug, naturally, pales in comparison to the rigors that a new drug applicant faces.[57] An applicant needs to only show that the generic version is bioequivalent to the new drug (absent "grandfather" provisions).[58] Rather than an IND and NDA, the applicant files only an abbreviated new drug application (ANDA), which addresses only bioequivalency.[59] Bioequivalency may be shown in different manners. The manner is often dependent on the class of the new drug.

The *Integra* court was quite clear that the safe harbor embraces development of generic drugs. The line that the court drew, however, casts doubt on whether even generic pharmaceutical companies may conduct the full gamut of activities in developing pharmaceuticals. For example, a generic company can formulate a bioequivalent drug that switches out an excipient, which may involve the same experiments found to fall outside the safe harbor in *Integra*.[60]

The Biomedical (Research) Tool Problem Demonstrates That Courts Should Focus On The Nexus Between The Patent And The Pharmaceutical Being Developed

Bubbling beneath the surface of the timing debate, the judges also sparred over what types of patents are even entitled to protection. On the one hand, the majority characterized Merck's use of the peptide sequence as part of a larger effort to develop different and unique products. The dissent took a different approach, and instead described Merck's activities as experimentation on the patented product that is allowed by the "experimental use" exception. This disagreement turned, in part, on the proper definition of a "research tool"; the majority believed that use of the peptide sequence as a biomedical research tool to develop different drugs did not fall within § 271(e)(1) (at least until clinical trials), while the dissent simply stated that they were not used as biomedical research tools.

The *Integra* dissent would draw a line between "investigation into patented things, as has always been permitted, and investigation using patented things, as has never been permitted." Unfortunately, the real world does not accommodate this tidy dichotomy. An entire branch of the pharmaceutical and biotechnology industries develops (and patents) compounds and compositions that have little or no likelihood of resulting in a saleable product. Rather, they are a step toward an ultimate breakthrough. Is a company's use of such a patent to develop a profitable pharmaceutical "investigation into a patented thing" or is it "investigation using a patented thing?"

At least one commentator has coined the term "partial research tools" for patents that might be used for research but also might be used in a non-research capacity.[61] "Pure research tools"—which cannot be used for any purpose other than research—occupy one end of the spectrum and "pure research" of a patented device occupies the other end; partial research tools occupy the significant grey area between the two. The RGD peptide sequence is best described as a partial research tool. Millions of dollars in investment failed to produce a potentially profitable product for the patent owner. Nevertheless, Merck's use of the RGD peptides in research ultimately resulted in the development of anti-angiogenesis drugs.

This debate over biomedical research tools further demonstrates that the Federal Circuit's "clinical testing" line cannot withstand scrutiny. Application to pure research tools

illuminates the absurdities of that approach. Pure research tools might include items such as screening methods, a computer program, beaker, immunoassay, or other laboratory devices. Under Integra (the timing approach), the safe harbor does not distinguish among the patents that can be infringed for purposes of FDA testing, as long as they are infringed during clinical testing. Congress surely did not intend to exempt infringement of all patents during periods of FDA testing, but that is the result that rigid adherence to the timing approach reaches.

The real line-drawing is not at the timing of testing, but rather the type of product being infringed during testing. This is best illustrated with partial research tools such as the peptide sequence in *Integra*. Although we do not attempt to draw the line here, courts must compare the patent that is infringed and the product the infringer is testing for FDA purposes, and assess whether there is a sufficient nexus between the two. A close nexus (e.g., approaching pure research – the patent is highly similar to the product being tested) indicates that the safe harbor should apply to shield the activity from infringement. A strained nexus (e.g., approaching a pure research tool – the patent is unrelated to the product being tested) indicates that the safe harbor should not shield the infringer's activities from infringement.

How Does The Supreme Court Solve This Problem?

First of all, the Federal Circuit's "clinical testing" line must be discarded. As was clearly indicated by the above discussion of the FDA testing regimes, and more clearly on the facts of *Integra*, much of the pre-clinical testing is not merely reasonably related, but necessary for FDA approval.

Second, if the Court is to draw any lines to strengthen patent protection, it must be along those illustrated by the biomedical research tool problem. Infringers of biomedical research tools that are useful not as drugs, but in developing new drugs, should not be able to claim benefit of the safe harbor since there is no nexus between the patent being infringed and the product being tested for FDA approval. On the other hand, pure research into a product for FDA purposes is at the core of the safe harbor and the nexus between the patent and the product is clear. Where to draw the difficult lines, as in *Integra*, for partial research tools that result in related but not identical products, is a difficult question the Court may have to grapple with, should it decide to tackle this issue.

This second point illustrates the central problem the Court faces. Just as the Federal Circuit tortured the language of the exemption to create an irrational line at clinical testing, the Court would have to torture the language to draw a rational line for a nexus test. Although the result might be justified, or at least logical, the statutory basis for doing so is sketchy at best. Surely, a creative linguist could parse some legislative history together with the words "solely" and "reasonably related" to reach a temporarily pleasing result, but what happens 10 years down the line when cases are sifting throughout the lower courts?

Thus, the best result might be to place the onus on Congress and industry by reading the statute according to its plain language. The statute exempts infringements of all patents for all activities reasonably related to FDA approval. This is a bright line that industry can rely on, and if necessary, work to change through the Congress.

Perhaps most importantly, the nexus line is difficult to draw, just as the timing line was. The Federal Circuit, which specializes in patent cases, could not draw the timing line properly. Holding Congress to its words will likely bring pressure from industry (generic and brand name companies), which will hopefully result in a change after extensive consideration and investigation of the economic and social costs of expanding or limiting the safe harbor.

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Endnotes

1. Drug Price Competition and Patent Term Restoration Actor of 1984, Publ. L. No. 98-417, 98 Stat. 1585 (codified as 21 U.S.C. 355, 360, and 35 U.S.C. 156, 271, 282 (2000).
2. See Andrx Pharms., Inc. v. Biovail Corp., 276 F.3d 1368, 1371 (Fed. Cir 2002); see also Richard J. Smith, Hatch-Waxman 2003—Patented v. Generic Drugs: Regulatory, Legislative and Judicial Developments, 20 Santa Clara Computer & High Tech. L.J. 695, 698 (2004).
3. See Eli Lilly v. Medtronic, Inc., 496 U.S. 661, 669-70 (1990).
4. *See id.*
5. In the FDA context, a patentee cannot commercially exploit its invention until it receives pre-marketing approval, which averages between 10-15 years. See J.A. DiMasi et al., The Price of Innovation: New Estimates of Drug Development Costs, 22 J. HEATH ECON. 151, 165 (2003).
6. See Medtronic, Inc., 496 U.S. at 669-70.
7. See 35 U.S.C. 156.
8. See 35 U.S.C. 35 U.S.C. 271(e)(1).
9. See 21 U.S.C. 355(j)(2)(A)(iv).
10. 733 F.2d 858 (Fed. Cir. 1984), cert. denied, 469 U.S. 856 (1984); see Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661,

670 (1990) (noting that the primary purpose of the safe harbor provision was to overturn Roche).

11. 35 U.S.C. § 271 (e)(1).
12. See generally George Fox, Intellectual Property: Patent: Note: Integra v. Merck: Limiting the Scope of the 271(e)(1) Exception to Patent Infringement, 19 Berkeley Tech. L.J. 193 (2004).
13. *See id.*
14. H.R. REP. 98-857, pt. 2, at 27 (1984), reprinted in 1984 U.S.C.C.A.N. 2647, 2711.
15. See Medtronic, Inc., 496 U.S. at 669.
16. These stages of drug development are discussed in detail infra § III(A).
17. See generally David Bloch, If It's Regulated Like a Duck ... Uncertainties in Implementing the Patent Exceptions of the Drug Price Competition and Patent Term Restoration Act, 54 Food & Drug L.J. 111, 120-26 (1999); Courtenay Brinckerhoff, Can the Safe Harbor of 35 U.S.C. 271(e)(1) Shelter Pioneer Drug Manufacturers?, 53 Food & Drug L.J. 643, 648-54 (1998).
18. 496 U.S. 661, 669-70 (1990).
19. Medtronic, Inc., 496 U.S. at 669.
20. Medical devices fall into three FDA classifications. Class III devices, as was the device in Medtronic, are eligible for a term-extension because these devices are subject to FDA pre-marketing approval. Class I and II devices, in contrast, are ineligible for a term-extension because these devices are not subject to FDA pre-marketing approval.
21. See Chartex Int'l PLC v. M.D. Personal Prods. Corp., 1993 U.S. App. LEXIS 20560, at *6 (Fed. Cir. Aug. 12, 1993) (holding that the FDA exemption applies to medical devices that are ineligible for the term-extension); see also Abtox, Inc. v. Exitron Corp., 122 F.3d 1019, 1028-29 (Fed. Cir. 1997) (holding that the FDA exemption applies to all classes of devices and reasoning that because the Medtronic Court made no explicit delineation between classes of medical devices, Medtronic mandates application of the exemption, despite its reference to the "perfect 'product' fit" model).
22. Compare Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc., 2001 U.S. Dist. LEXIS 19361.), at **23-26 (November 27, 2001 S.D.N.Y) (interpreting the statute to apply to any activities in connection to seeking FDA approval), with Infigen, Inc. v. Advanced Cell Technology, Inc., 65 F. Supp. 2d 967, 980 (W.D. Wis. 1999) (interpreting the safe harbor to exempt infringement of products that are eligible for the term-extension).
23. The focus of many early court opinions was the "solely" phrase of the statute. See, e.g., American Standard Inc. v. Pfizer Inc., 722 F. Supp. 86, (D. Del. 1989). Courts subsequently held that "solely" modifies "uses." See Elan Transdermal Ltd. v. Cygnus Therapeutic Sys., 24 U.S.P.Q.2d (BNA) 1926, 1932-33 (N.D. Cal. 1992). Conduct that "reasonably relate[s]" to FDA approval, therefore, qualifies for the exemption regardless of if that conduct has other non-FDA purposes and regardless of the infringer's intent. See Telectronics Pacing Systems, Inc. v. Ventritex, Inc., 982 F.2d 1520, 1524 (Fed. Cir. 1992). The "solely" term is thus rarely an issue.
24. See 5 Donald S. Chisum, Chisum on Patents, § 16.03[1][d][iii] (1997 & 2004 Supp.); see, e.g., Telectronics Pacing Sys., Inc. v. Ventritex, Inc., 982 F.2d 1520, 1528 (Fed. Cir. 1992); Nexell Therapeutics, Inc. v. Amcell Corp., 199 F. Supp. 2d 197, 2002 U.S. Dist. LEXIS 7308 (D. Del. 2002).
25. Intermedics, Inc. v. Ventritex, Inc., 775 F. Supp. 1269, 1280 (N.D. Cal. 1991), aff'd. 991 F.2d 808 (Fed. Cir. 1993).
26. See, e.g., Intermedics, 775 F. Supp. at 1280; Telectronics, 982 F.2d at 1528.
27. 982 F.2d 1520 (Fed. Cir. 1992).
28. 3 F. Supp. 2d 104, 110 (D. Mass. 1998).
29. *See id.*
30. See 2001 U.S. Dist. LEXIS 19361, at **23-26 (November 27, 2001 S.D.N.Y.). The research group, "The Drug Discovery Group," was conducting basic research to create new analogs of existing drugs. *See id.*, at *16. One could deem this a "fishing expedition"; over a five year period, the research group was identifying 2-3 analogs per week, conducting primary screening testing, conducting secondary screening testing, and then "narrow[ing] down the leads until [they found] the ultimate lead." *See id.* at *16-17.
31. See Integra Lifesciences I, Ltd. V. Merck KGaA, 331 F.3d 860, 862 (Fed. Cir. 2003). "RGD" denotes a three amino acid peptide having the sequence argine-glycine-aspartic acid.
32. *See id.* at 863. Funding was for the "necessary experiments to satisfy the biological bases and regulatory (FDA) requirements for implementation of clinical trial" with EMD 6 or a derivative thereof. *See id.*
33. *See id.* at 863, 874.
34. *See id.* at 863, 874.
35. *See id.* at 863, 874.
36. *See id.*
37. *See id.*
38. *See id.*
39. *See id.*
40. Generic drugs, under the statute, constitute a subset of new drugs. See 21 U.S.C. § 355(j). Treating generics and new drugs as distinct categories, however, is common parlance.
41. 21 C.F.R. §§ 312.20(a), (b).
42. 21 C.F.R. § 314.50.
43. See 21 C.F.R. 312.22(a), (c).
44. See 21 C.F.R. 312.23.
45. See 21 C.F.R. 312.23(a)(5).
46. See 21 C.F.R. 312.23(a)(8)(i), (ii).
47. The overriding consideration in the IND approval process is whether the potential benefit of the new drug justifies the attendant risk to clinical testing. See 21 C.F.R. § 312.23(a)(i); FDA, IND Review Process 4, available at http://www.fda.gov/cder/handbook/ind.htm.

48. Courts could interpret the "clinical testing" line in the Integra opinion loosely to lessen its impact.
49. *See*, e.g., Brief for Petitioner, Merck KGaA v. Integra LifeSciences I, Ltd. and The Burnham Institute, No. 03-1237, February 15, 2005, at 40.
50. *See* generally Michelle Meadows, The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective, FDA Consumer Mag., Jul.-Aug. 2002, available at http://www.fda.gov/fdac/features/2002/402_drug.html.
51. *See* 21 C.F.R. § 312.23(a)(5)(v).
52. *See* Brief for Petitioner, Merck KGaA v. Integra LifeSciences I, Ltd. and The Burnham Institute, No. 03-1237, February 15, 2005, at 14.
53. *See id.* at 15.
54. *See id.* at 16.
55. *See id.* at 17-18.
56. *See* Integra Lifesciences I, 331 F.3d at 863, 874.
57. *See* 21 U.S.C. § 355(j).
58. 21 U.S.C. § 355(j)(2)(A)(iv).
59. *See id.*
60. Brief of Eon Labs, Inc. as Amicus Curiae in Support of Petitioner, Merck KGaA v. Integra Life Sciences, Inc., No. 03-1237, at 12.
61. Natalie M. Derzko, In Search of a Compromised Solution to the Problem Arising from Patenting Biomedical Research Tools

Fiesta

Section members and their guests, (l-r) Doug Salyers, Section Chair Mike Hobbs, Art Gardner and Ginny Hobbs enjoy dinner together during the 2004 Intellectual Property Law Institute in Cabo San Lucas, Mexico.

In-House IP Attorneys: a Committee for You

The In-House IP Committee, which is comprised solely of in-house attorneys, was created to serve the special needs of in-house legal counsel that sometimes are not addressed by other sections of the Bar. In addition to providing a network of in-house attorneys throughout Georgia, the In-House IP Committee offers CLE and other educational opportunities, social events and opportunities for pro bono work.

Why should you join? Consider this: Unlike the firm environment, where a hundred or more lawyers may reside, many in-house legal departments are small. Often the legal department is one attorney, or maybe two. How often have you thought, "This is a weird issue – it surely would be nice to be able to walk down the hall and have a second set of eyes look at this…" If you are the only person in the shop, however, that can be difficult or even impossible to do. If that has ever happened to you, you should join us.

One event coming in June, designed just to address this problem, is our second "Bring Your File" luncheon. We had a similar event in March and it was very successful. At these lunches, we get together – no speakers or presentations – and simply bring in issues for discussion. It's a fantastic opportunity to bounce that one troubling issue off peers who may face similar situations. Additionally, we also have roundtable luncheons, where speakers address problems and issues that we all face working in-house.

This new committee is open to all IP Law Section members who work in-house for corporations, businesses, non-profits, governmental agencies, and the like. The committee is planning events and activities throughout the remainder of the year. It will be a great chance to meet other in-house practitioners. If you are interested in joining our committee, please contact me, Philip Burrus, at Philip.Burrus@motorola.com.

Philip Burrus is a Sr. Patent Attorney for Motorola, Inc. He supports both the Energy Systems Group and the Mobile Devices Business, focusing primarily on patents, with additional expertise in licensing, copyright, portfolio management and general transactional business matters. Prior to working in intellectual property, he worked as an electrical engineer at both Motorola and Schlumberger. Philip has a MBA and JD from Emory University, and master's and bachelor's degree in electrical engineering from Georgia Tech. He is licensed to practice in Georgia, North Carolina, Washington D.C., and before the the US Patent and Trademark Office.

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