No. 03-1237

In the Supreme Court of the United States

MERCK KGAA,

Petitioner,

v.

INTEGRA LIFESCIENCES I, LTD. AND THE BURNHAM INSTITUTE,

Respondents.

On Writ of Certiorari
to the United States Court of Appeals
for the Federal Circuit

Brief of *Amicus Curiae*, Biotechnology Industry Organization, in Support of Neither Petitioner Nor Respondent

Of Counsel:

Scott A.M. Chambers, Ph.D.
Kenneth L. Dorsney
Patton Boggs LLP
8484 Westpark Drive
McLean, VA 22102
(703) 744-8085

Richard J. Oparil
Counsel of Record
PATTON BOGGS LLP
2550 M Street, NW
Washington, DC 20037
(202) 457-6000

Attorneys for Biotechnology Industry Organization

QUESTION PRESENTED

Congress, Federal regulators like those at the Food and Drug Administration ("FDA"), and the public have an interest in bringing new drugs and devices to market in a timely and safe way. To promote that interest, Congress determined that "[i]t shall not be an act of infringement to make, use, offer to sell, or sell . . . 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." 35 U.S.C. § 271(e)(1). The question before this Court is not whether Congress meant to include within the safe harbor of Section 271(e)(1) only generic drugs and/or required regulatory activity but whether, as expressly stated by Congress in Section 271(e)(1), any activity "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" is included in the safe harbor provision.

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BRIEF OF AMICUS CURIAE

Pursuant to Supreme Court Rule 37.3(a), on written consent of all parties filed with the Court concurrently with this submission, the Biotechnology Industry Organization ("BIO") respectfully submits this brief *amicus curiae* in support of neither Petitioner nor Respondent.[1]

INTERESTS OF AMICUS CURIAE

BIO is a trade association consisting of more than one thousand member companies, academic institutions, and biotechnology centers. BIO represents and understands the needs as well as the demanding nature of the biotechnology industry. Segments of this industry provide biotechnology-based products that constitute an important and growing value to the public. To create this value, the biotechnology industry invests heavily in research and development.[2]

Although intellectual property can be protected in a number of ways, patents form the intellectual property cornerstone for protecting research efforts in the biotechnology industry. The possibility of future protection

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[1] Pursuant to Rule 37.6, *amicus curiae* states that no person or entity other than BIO, its members, or its counsel has made any monetary contribution to the preparation or submission of this brief. Further, no counsel for Petitioner or Respondent authored this brief in whole or in part.

[2] The biotechnology industry has been one of the most research-intensive industries in history. Peter Coy, Blue-Sky Research Comes Down to Earth, Business Week, July 3, 1995, 78 (indicating that the top five companies measured by spending per employee on research and development were health care related; according to the report, the average biotechnology company spends $71,000 per employee, and the average pharmaceutical company spends $56,000 per employee while the average company spends only $7,651).

through the patent system permits public disclosure and prompt public dissemination of information about new technology, thereby providing an immediate benefit to the public. This disclosure of information can enable others in the field to build on the technology and further advance the progress of science and the useful arts. Without the potential for meaningful protection through the patent system, some of these advances might remain trade secrets and unavailable to the bulk of the research community. Not only can other researchers build upon the information disclosed in a patent but also the patent system helps to avoid expensive duplication of research efforts by disclosing information that may otherwise be unavailable.

Academic researchers and public institutes also benefit from the broadened interest in and value of biotechnology patents. Many groups have initiated cooperative research and development efforts that assist in maintaining the vitality of American research. The prospect of patent protection is driving these efforts. Royalty revenue from patents also permits research backing at independent public institutes lacking government grants and aid. Once a product is marketed, the exclusive rights conferred by a patent allow the innovator to recoup the investment and continue researching new products.

Patents are vital to the members of BIO in a number of ways. By providing the prospect that any future invention could be protected, BIO members attract money for initial research. Clear evidence of patent protection then attracts further capital for the post-invention research that is needed for the costly development and marketing of an invention. BIO members encompass a heterogeneous group that invent, develop, and/or market valuable products for the world; therefore, BIO members have an interest in maintaining the patent system. Because of this, BIO would be concerned if

this Court's position radically altered the reasonable business backed investment of participants in this industry.

BIO members constitute a broad and diverse group. Some BIO members have therapeutic and diagnostic products that are regulated. These products are subject to long and risky development times at great expense. These BIO members have experience in conducting activities reasonably related to obtaining regulatory approval under Federal laws that regulate drugs, biologicals, and medical devices.

Many biotechnological products are on the market, many biotechnological products are seeking Federal regulatory review, and many biotechnological products are at the early stages of development. While a patent may provide an early proof of concept, a great investment is typically required to develop biotechnological inventions into useable form. Many BIO members take the investment risk to develop the patented inventions that become drug products. Some BIO members invent, develop, and/or sell products that may be useful "tools" in the development of new drugs.

BIO also has members that have licensed their intellectual property ("IP") to other companies and these licensed companies are conducting activities that often relate in some way to the development of new drug products. Many BIO members have obtained capital for their IP, often based on an investor's belief of significant benefits for the incredible risk of capital. Patents and the potential for exclusive rights attract venture capital, collaborative research, and licensing partners.

Accordingly, this Court's interpretation of the breadth of Section 271(e)(1)'s safe harbor will directly impact members of BIO.[3]

SUMMARY OF THE ARGUMENT

Integra Lifesciences I, Ltd. v. Merck KGaA, is not a case about whether Section 271(e)(1) is limited to generic drugs and/or required regulatory activity. 331 F.3d 860 (Fed. Cir. 2003), *reh'g and reh'g en banc denied, cert. granted, Merck KGaA v. Integra Lifesciences I, Ltd.*, 125 S.Ct. 823 (2004). Instead, it is a case about whether the particular animal and *in vitro* studies at issue are "reasonably related to the development and submission of information" for regulatory approval and therefore non-infringing under Section 271(e)(1).

Although the Federal Circuit addressed this factually narrow issue, it did so in a way that appeared to limit Section 271(e)(1) to generic drugs and/or required regulatory activity. BIO is thus concerned that courts will read too much into the language of *Integra* and apply Section 271(e)(1) only to generic drugs and/or required regulatory activity. Of course, this would be in error under this Court's decision in *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 670 (1990). Thus, the Federal Circuit's decision could cause confusion in the law and uncertainty for the members of BIO. What was previously held to be an exempt activity may now be an area of exposure to an infringement claim and this uncertainty creates more hurdles and delays in the drug development pathway. Even the potential for an errant application of *Integra* could have a great and adverse impact

[3] The experimental use exception to patent infringement was not at issue on appeal. BIO limits its brief accordingly.

on many avenues of research and funding critical to BIO members.

Accordingly, BIO respectfully request that this Court confirm that the safe harbor provision of Section 271(e)(1) is not limited to generic drugs and/or required regulatory activity but includes any activity determined to be "reasonably related" after objective analysis of the facts presented.

ARGUMENT

A. Section 271(e)(1) is not limited to generic drugs.

The plain language of Section 271(e)(1) does not limit its safe harbor to research and development required to bring generic equivalents of already approved drugs to market or exclude from its reach New Chemical Entities ("NCEs") or devices. Although Congress enacted Section 271(e)(1) in response to the Federal Circuit's decision in *Roche Products, Inc. v. Bolar Pharmaceutical, Co.*, 733 F.2d 858 (Fed. Cir. 1984), and to eliminate the *de facto* patent term extension that existed at the time, *Eli Lilly*, 496 U.S. at 670, Section 271(e)(1) was not responsive solely to the facts of *Bolar*. As is apparent by its plain language, Congress

drafted Section 271(e)(1) with broader reach.[4] This has been confirmed in this Court, in the Federal Circuit, and in the

[4] Justices Kennedy and White dissented in *Eli Lilly*, reasoning that Section 271(e)(1) "addresses the legal regulation of drugs as opposed to other products." 496 U.S. at 680 (Kennedy and White, JJ., dissenting). Although Section 271(e)(1)'s safe harbor is indeed tied to "a Federal law which regulates the manufacture, use, or sale of drugs[,]" the plain language of Section 271(e)(1) does not limit its safe harbor to drugs but broadly states that "[i]t shall not be an act of infringement to make, use, or sell . . . 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." *Id.* Section 271(e)(1)'s safe harbor is thus tied also to "veterinary biological products" and, more critically, it exempts infringement of "a patented invention" when that infringement was done "solely for uses reasonably related to the development and submission of information" under a Section 271(e)(1) Federal law. *Id.* Similarly, "solely" in Section 271(e)(1) was not intended by Congress to modify "a patented invention." If that were the case, the only patented inventions falling within Section 271(e)(1)'s safe harbor are patented inventions that have few other uses except those "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." *Id.* Even pioneering drugs would not fall within the ambit of such a limited description.

District Courts.[5] As this Court recognized in *Eli Lilly*, the safe harbor of Section 271(e)(1) is not limited to a subset of the Food, Drug, and Cosmetic Act, Pub. L. No. 100-670, 102 Stat. 3971 (1988) (codified as amended 21 U.S.C. §§ 301-93), or some other Section 271(e)(1) Federal law. 496 U.S. at 665-79. The suggestion, therefore, that the Federal Circuit in *Integra* ignored the plain language of Section 271(e)(1) and might only apply Section 271(e)(1)'s safe harbor to generic drugs and/or required regulatory activity is of concern to BIO.

Although the Federal Circuit issued an errata sheet in an attempt to quell concern and included in *Integra* indications that Section 271(e)(1)'s safe harbor was not limited to generic drugs and/or required regulatory activity, the Federal Circuit did not make it abundantly clear in *Integra* that Section 271(e)(1) applies broadly. In fact, the Federal Circuit's language appears to place all activity not

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[5] *Eli Lilly*, 496 U.S. 661 (implantable cardiac defibrillator); *Abtox, Inc. v. Exitron Corp.*, 122 F.3d 1019, 1027-30 (Fed. Cir. 1997), *amended on other grounds*, 131 F.3d 1009 (Fed. Cir. 1997) (FDA class II medical device) (applying *Eli Lilly*); *Chartex Int'l PLE v. M.D. Pers. Prod. Corp.*, 5 F.3d 1505 (Fed. Cir. 1993) (FDA class I or II medical device); *Telectronics Pacing Sys., Inc. v. Ventritex, Inc.*, 982 F.2d 1520 (Fed. Cir. 1992) (demonstration of defibrillator at medical conference); *Wesley Jessen Corp. v. Bausch & Lomb Inc.*, 235 F. Supp. 2d 370 (D. Del. 2002) (amending injunction to permit post-approval FDA study of contact lenses); *Nexell Therapeutics, Inc. v. Amcell Corp.*, 199 F. Supp. 2d 197 (D. Del. 2002) (system for isolation of stem cells in blood sample); *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 3 F. Supp. 2d 104 (D. Mass. 1998) (the hormone erythropoietin); *Key Pharm., Inc. v. Hercon Labs. Corp.*, 981 F. Supp. 299, 305 (D. Del. 1997), *aff'd*, 161 F.3d 709 (Fed. Cir. 1998) (transdermal nitroglycerin patches) (dicta); *Baxter Diagnostics, Inc. v. AVL Scientific Corp.*, 954 F. Supp. 199 (C.D. Cal. 1996) (development and testing of single layer sensor); *Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269 (N. D. Cal. 1991) (implantable defibrillator), *aff'd by Intermedics, Inc. v. Ventritex Co., Inc.*, 991 F.2d 808 (Fed. Cir. 1993) (unpublished).

specifically required for regulatory approval in question and suggests that Section 271(e)(1) may only be invoked for generic drugs.

The safe harbor of Section 271(e)(1), however, is not so easily pigeonholed, nor should it be. Section 271(e)(1)'s safe harbor serves as a balance between two very important and competing public interests. The need to provide incentive through the patent system to innovators to expend resources and develop new technologies and the need to recognize places where that system has stopped working to the benefit of the public and has instead begun to work to its detriment. Section 271(e)(1)'s safe harbor does not strike this balance if limited only to generic drugs and/or required regulatory activity.

Contrary to the statement in *Integra* that the FDA is not interested in "the hunt for drugs" because the FDA only requires information about the drug compound featured in an Investigational New Drug application, *Integra*, 331 F.3d at 866, the FDA, Congress, and the public have an interest in finding new drugs and devices and in bringing them to market to benefit patients. Health care costs are skyrocketing in this country, in no small measure due to the lack of alternative cures for patients. NCEs and other regulated devices promise hope -- hope for today, not tomorrow, if Section 271(e)(1) applies as written and clearly intended by Congress.

B. Section 271(e)(1) is not limited to required regulatory activity.

Normally envisioned testing, not just clinical testing, must fall within the safe harbor of Section 271(e)(1) if that section is to have the flexibility needed to endure and meet its intended purpose. The test for reasonably related

therefore must be fact-specific. Times change, new technologies are created, new risks are discovered, and testing techniques evolve. Federal regulators recognize this and consider relevant data not expressly required when making decisions.

Federal regulators must presume that companies who want to test pharmaceuticals on humans are going to act reasonably in deciding whether the potential benefits are great enough to assume the risks involved. Activities having to do with safety, efficacy, dosing and pharmacology are envisioned as reasonably related to a decision to test a drug in humans. The purpose of the safe harbor provision of the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act), Pub. L. No. 98-417, § 202, 98 Stat. 1585, was for development and submission of information to Federal regulators. There is nothing in the language of Section 271(e)(1) to preclude particular testing like that occurring in the pre-clinical stage. The only requirement in Section 271(e)(1) is that the activity be "solely for uses reasonably related to the *development* and *submission* of information." (Emphasis added).

Section 271(e)(1)'s safe harbor must also be understood to include reasonably related activities, even if those activities do not produce information that is ultimately submitted to Federal regulators. There is not a finite number of activities or paths to regulatory approval. Much of the process depends not on what Federal regulators have done in the past but on what applicants must do now and in the future to obtain regulatory approval. A restrictive approach to interpreting the phrase "reasonably related" will not permit healthy communication between the scientific community and Federal regulators. If it were as simple as saying this is needed and that is not, Congress would have done so. Instead, Congress provided a guiding principle --

reasonably related -- and left it to the fact-finder to determine what should and should not be accepted as falling within the contour of that principle.

C. Section 271(e)(1) protects "reasonably related" testing activities.

Testing is necessary in research to generate information as to safety, efficacy, pharmacokinetics, pharmacology, carcinogenicity, dosing, route of administration, mutagenicity, or any of a host of other factors that may go into the decision to administer a particular compound to humans safely. Whether testing is needed and in what amount, however, is fact-sensitive. Not all compounds are the same, not all uses are the same.

Section 271(e)(1) provides the flexibility researchers need to make those decisions without fear of infringement liability through the use of the phrase "reasonably related." Other than finding that non-required activity may be within Section 271(e)(1)'s safe harbor, this Court need not define any further standard other than that contained in Section 271(e)(1) for judging what tests in a drug's lifecycle are exempt from infringement.

Drug development takes a long time. The molecule that will later form the active pharmaceutical ingredient of a drug must be identified and characterized with respect to its fundamental biological activity, *e.g.*, its ability to interact with specific biological receptor proteins or to exert activity in animal models of human disease. Although scientists develop information about the molecule and its activity in test-tube systems and animal models, it is exceedingly difficult to predict at these early stages how the drug candidate may best be developed and used in human therapy.

Typical activities after identification of lead compounds include formulating the molecule in a pharmaceutical composition and putting it through animal and *in vitro* studies on absorption, distribution, retention, breakdown, excretion, and toxicity of the candidate compound. These pre-clinical studies are necessary and required prior to beginning clinical trials. Since these activities are undertaken in preparation for possible initial human testing, however they are conducted under strictly controlled conditions to meet the FDA's very high quality standards and require a significant commitment of time, effort, and money.

Subsequent initial human testing -- phase I clinical trials -- must be cleared by the FDA. This is typically done in healthy volunteers to determine, preliminarily, the investigational new drug's safety and metabolic profile. If satisfactory, the drug candidate will advance to phase II clinical trials in a larger number of subjects, often several hundred, who actually suffer from the medical condition the drug is intended to treat. Phase III clinical trials often involve long-term testing in thousands, sometimes tens of thousands of patients with the investigational drug, which should at this time be as close as possible to the final commercial product for which approval is sought.

The vast majority of newly discovered molecules, however, never progress to market. To file for marketing, an applicant must submit "investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use." 21 U.S.C. § 355(b)(1). Only about 1 in 1000 is proposed to the FDA for initial human testing. *See* C.P. Adams and V.V. Brantner, FTC 2003 White Paper: *New Drug Development: Estimating Entry from Human Clinical Trials* at 8. Of those drugs that begin phase I human testing, a further 78.5% are eliminated during

rigorous clinical trials or are rejected by the FDA as unsuitable for human therapy. *See* J.A. DiMasi *et al.*, *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. Health Econ. 151 at 165 (2003). FDA-mandated clinical trials alone account for an average of over eight years out of a total development time of 10-15 years. *See* J.A. DiMasi, *New Drug Development in the United States from 1963 to 1999*, 69 Clin. Pharmacol. Ther. 286 at 292 (2001). The cost of bringing a pioneering drug to market is estimated at $403 million; accounting for the time between investment and marketing raises this figure to $802 million. *See* DiMasi, 22 J. Health Econ. at 166.

As a matter of regulatory practice, developers of new drugs deliberate internally, and negotiate with the FDA, the number, type, timing, size and quality criteria of the scientific studies needed to prove that a drug is safe and effective for its intended use. If a determination of what is reasonably required for approval is open to dispute, then the determination of what is "reasonably related to the development and submission" of that information is even more poorly defined and thus is especially suitable for examination on a case-by-case basis.

BIO recognizes that patent rights are vitally important to its members. BIO also recognizes that Section 271(e)(1) was designed to provide greater freedom to operate. Measuring that freedom is performed under Section 271(e)(1)'s reasonably related test and must be done on a case-by-case basis. BIO does not believe Section 271(e)(1) abrogated all patent rights for research testing. Congress did not provide unfettered discretion to infringe. Innovators need the incentive to invent that the patent system provides.

For example, many patented biotechnology based inventions are used in the research of new drug candidates.

Although these patents may also be susceptible to Section 271(e)(1)'s safe harbor, much of their real value would be obviated by a wholesale right to infringe. There are times where it may be necessary to analyze a number of compounds to provide adequate data to justify and support a determination of safety and efficacy in humans. For the same reasons "required" cannot be the standard, however, "necessity" cannot be the standard either. "Reasonably related" must mean "reasonably related." "Reasonably related" testing must be within Section 271(e)(1)'s safe harbor, indiscriminate infringement must be out for Section 271(e)(1) to have the balance Congress intended.

D. Section 271(e)(1)'s "reasonably related" inquiry must be fact-based.

Ultimately, it is the fact-finder that must determine whether the activities in question were "reasonably related to the development and submission of information" under a Federal law that regulates drugs. Human physiology is not fully understood. What may seem appropriate in one case may be highly inappropriate in another. Researchers make difficult decisions every day to mitigate the dangers inherent in placing new chemical entities and devices within a living person based on discretion developed through training and experience. Sometimes they differ as to what should be done. If more than what Federal regulators require is thought needed to show safety, a researcher should not be punished for being careful. Even trained regulators differ as to what is required to show safety. Often it is only with hindsight that a researcher painfully learns what is "required" and what is not.

For example, in the early 1960s, European regulators determined that the testing of the development and submission of information on 2-(2,6-Dioxo-3-piperidinyl)-

1*H*-isoindole-1,3(2*H*)-dione was sufficient to permit its use by humans. At that time, the FDA stated that there was insufficient proof of the drugs safety in humans and required additional safety testing.[6] Before the necessary testing on safety was completed, the compound, known as thalidomide, was found to promote birth defects and was removed from the market. The European and FDA regulators were both trying to protect the public but even these trained regulators differed as to what testing was required to show safety. Congress, Federal regulators, and the public surely do not want disputes resolved by accepting the lowest common denominator of testing.

The scientific community in conjunction with the appropriate Federal regulators will take steps to protect the public in the future. A number of steps have become "required" already because Federal regulators, the scientific community, and history dictated that they are. What is "required" today based on what happened yesterday, however, will not prevent unfortunate events like thalidomide from happening tomorrow. Human discretion and rigorous science may so, however. "Reasonably related" therefore cannot be interpreted to mean what is "required" by Federal regulators. Only objective analysis of the facts presented in each case can ensure that Section 271(e)(1)'s safe harbor will meet the demands of today and tomorrow.

Although BIO members generally, though not uniformly, agree that screening large numbers of compounds not known or reasonably expected to have a particular effect simply for the purpose of attempting to identify candidates with a desired or unique effect is rarely if ever within the ambit of the Section 271(e)(1) safe harbor, BIO does not

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[6] http://cerhr.niehs.nih.gov/genpub/topics/thalidomide2-ccae.html (visited February 20, 2005).

believe the safe harbor is susceptible to a bright-line rule dividing exempt and non-exempt activities. The statute provides flexibility by use of the words "reasonably related." The fact-finder must ultimately determine whether the activities in question were "reasonably related to the development and submission of information" under a Federal law that regulates drugs.

If, after consideration of all the relevant facts, an activity is not reasonably related to the development and submission of information under a Section 271(e)(1) Federal law, Section 271(e)(1)'s safe harbor should tip toward the patentee. If it is reasonably related after consideration of the facts, it should tip the other way. BIO believes that this is what Congress intended in enacting Section 271(e)(1). While this may be what the Federal Circuit was saying in its *Integra* decision, the equivocal nature of its decision in *Integra* creates uncertainty. Section 271(e)(1)'s safe harbor should not be limited to generic drugs or to required regulatory activity but must include any activity determined "reasonable" after objective analysis of the facts presented.

CONCLUSION

This Court must confirm that the safe harbor of Section 271(e)(1) is not limited to generic drugs and/or required regulatory activity but includes any activity determined to be "reasonably related" after objective analysis of the facts presented. A determination of that reasonable activity is fact intensive and must be decided on a case-by-case basis.

Dated: February 22, 2005 Respectfully submitted,

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Richard J. Oparil
Counsel of Record
PATTON BOGGS LLP
2550 M Street, NW
Washington, DC 20037
(202) 457-6000

Attorneys for *Amicus Curiae*
Biotechnology Industry
Organization

Of Counsel:

Scott A.M. Chambers, Ph.D.
Kenneth L. Dorsney
8484 Westpark Drive
McLean, VA 22102
(703) 744-8085