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 FOR THE PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA AS *AMICUS CURIAE* IN SUPPORT OF PETITIONER

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QUESTION PRESENTED

To encourage development and expedite introduction of pharmaceuticals, Congress provided a safe harbor in 35 U.S.C. § 271(e)(1) from claims of patent infringement for drug research "reasonably related to the development and submission of information" to the Food and Drug Administration (FDA or the Agency). Amicus will address the question whether the Federal Circuit erred in concluding that this safe harbor does not protect preclinical studies conducted for the development of new drugs, where the information generated may be used to support applications filed with FDA, and where barring the research until patent expiration could introduce years of additional delay into the development and approval of new drugs?

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The Pharmaceutical Research and Manufacturers of America (PhRMA) submits this brief as *amicus curiae* supporting Petitioner.[1]

INTEREST OF THE AMICUS CURIAE

PhRMA is a voluntary, nonprofit association representing the nation's leading research-based pharmaceutical and biotechnology companies. PhRMA's members invested more than $38 billion in 2004 to discover and develop new medicines. They are responsible for almost all of the innovative medicines that have been approved for use in the United States over the past several decades.

Intellectual property principles, especially those that involve the intersection of patent rights and the process for approval of new drugs by the FDA, are of critical importance to PhRMA's members and to their research and development efforts. PhRMA is interested in ensuring that patent law is applied in a way that promotes the timely development of new

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[1] Pursuant to this Court's Rule 37.3(a), letters of consent from the parties to the filing of this brief have been filed with the Clerk. Pursuant to this Court's Rule 37.6, PhRMA states that no counsel for a party authored this brief in whole or in part, and no person, other than PhRMA or its members, made a monetary contribution to the preparation or submission of this brief. A list of PhRMA's members is available at http://www.phrma.org/whoweare/member/. Although Merck & Co., Inc., is a member of PhRMA, Petitioner Merck KGaA is unrelated to Merck & Co., Inc., and is not a member of PhRMA.

medicines. This goal will be jeopardized if the safe harbor in the patent laws for drug research activity is interpreted not to include preclinical studies that are reasonably related to the development and submission of information to the FDA in connection with the Agency's premarket review of new drugs.

SUMMARY OF ARGUMENT

Section 271(e)(1) of the Patent Code provides an important safe harbor for the development of new drugs, exempting from claims of infringement those 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." The decision of the Court of Appeals in *Integra LifeSciences I, Ltd. v. Merck KGaA*, 331 F.3d 860 (Fed. Cir. 2003), significantly contracts the safe harbor, confining its protections to clinical testing submitted to FDA. To PhRMA's members, who last year spent over $38 billion dollars to discover and develop new drugs and who are responsible for essentially all of the new medicines approved in the United States, the lower court's decision represents a direct and substantial threat to future drug development.

The preclinical work denigrated by the lower court is an essential part of the drug development and review process. Before clinical testing of a potential new drug begins in humans, both law and logic requires that extensive development work, in animals and *in vitro*, be performed first to investigate the drug's pharmacological effects and toxicity and to

ensure that the proposed human testing is reasonably safe to begin. *See* 21 C.F.R. § 312.23(a)(8). Far from being indifferent to such testing, FDA both sets forth by regulation a detailed set of "good practices" for conducting preclinical studies in pursuit of a new drug, *see id.* pt. 58, and reviews the soundness and integrity of the sponsor's conclusion that, based on those studies, clinical testing should begin, *see id.* § 312.42, 312.44. To both the innovator pharmaceutical industry and the FDA, preclinical testing is a necessary and critical step in the regulatory process for approving new drugs for sale in the United States, and that testing is as much a part of the regulatory process for new drugs as is the clinical testing accorded protection by the lower court.

Protection for preclinical studies is equally essential to achieving Congress' goal of expediting drug approvals. As this Court recognized in *Eli Lilly & Co. v. Medtronic, Inc.*, the safe harbor provision is intended to remedy the *de facto* extension of patent term created by FDA's lengthy premarket approval process. *See* 496 U.S. 661, 670 (1990). But it is no remedy at all if, as the Court of Appeals concluded, that provision shields only late stage clinical trials and leaves exposed the preclinical work required before such trials may begin.

Nor does the statutory text provide any warrant for the lower court's constricted reading. By its plain terms, section 271(e)(1) extends its protections to any use reasonably related to the development and submission of information in connection with FDA's

premarket review of a new drug. Preclinical work meets this test, both on account of FDA's oversight and review of preclinical studies and independently through its relationship to the subsequent clinical testing that even the lower court acknowledged falls within the statute's protections. The decision below should be reversed.

ARGUMENT

THE DECISION BELOW IMPAIRS NEW DRUG DEVELOPMENT, IMPEDES THE STATUTORY PURPOSE, AND SHOULD BE REVERSED.

In *Eli Lilly*, this Court interpreted section 271(e)(1) to encompass the entire range of FDA premarket review. *See* 496 U.S. at 666-67. Under that decision, the full scope of FDA's review process constitutes a "Federal law which regulates the manufacture, use, or sale of drugs ..." giving rise to the safe harbor provisions. Consequently, all activities "reasonably related" to acquiring FDA approval, including preclinical studies, should fall within the statutory safe harbor.

The Court of Appeals avoided this simple logic by denigrating the significance of preclinical work. The linchpin of the lower court's reasoning was its assertion that

> [t]he FDA has no interest in the hunt for drugs that may or may not later undergo clinical testing for FDA approval. For instance, the FDA does not require information about drugs other than the

compound featured in an Investigational New Drug application.

P.A. 12a.[2] This assertion is misguided. The preclinical work denigrated by the lower court is in fact an essential part of the regulatory review process for new drugs and of great interest to both the innovator pharmaceutical industry and FDA. Protection from claims of patent infringement is a critical element to achievement of the statutory purpose.

A. Preclinical Studies Are An Essential Part Of The New Drug Regulatory Review Process

Throughout the approval process, pharmaceutical research and development is a highly focused activity. Over the years, a new drug candidate undergoes extensive testing and analysis designed to further the ultimate goal of obtaining regulatory approval of new drugs that address the public's medical needs. Because the risks and costs of pharmaceutical research and development are so high, every experiment has a purpose, and every step has a rationale. At the preclinical stage, the testing is designed to eliminate unpromising candidates and to generate information concerning promising candidates that will support the move to clinical testing and help FDA make the

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[2] The Appendix to the Petition for Writ of Certiorari is cited as "P.A."

ultimate determination whether the drug is safe and effective enough for human use.

As discussed below, the FDA clearly views preclinical activity as an important part of the process to obtain marketing approval, *see infra* at 9-12, and for good reason: Preclinical studies can provide substantial information about a drug candidate's safety and effectiveness. An FDA report on new drug development noted that preclinical animal tests point the way to subsequent human testing by "show[ing] whether a potential drug has toxic side effects and what its safety is at different doses." Jeffrey P. Cohn, *The Beginnings: Laboratory and Animal Studies*, FDA CONSUMER SPECIAL REPORT FROM TEST TUBE TO PATIENT: NEW DRUG DEVELOPMENT IN THE UNITED STATES (Jan. 1995), *available at* http://www.fda.gov/fdac/ special/newdrug/begin.html. Preclinical tests also provide important insight into the pharmacology of the candidate drug: "[I]n animal testing, scientists measure how much of a drug is absorbed into the blood, how it is broken down chemically in the body, the toxicity of its breakdown products (metabolites), and how quickly the drug and its metabolites are excreted from the body." *See id.* The results allow evaluation of the possible effectiveness of the drug and help establish the proper dosage range for further testing in humans. *See id.*

As technology has allowed testing regimes to become more sensitive, preclinical testing has become increasingly important to the drug approval process.

> The science of non-clinical drug development has been dramatically affected by the emergence of sensitive analytical instrumentation and by the application of molecular genetics to enable the detection of changes in the expression of human proteins that could affect, or be affected by, new drug candidates. . . . Increasingly, more knowledge about the characteristics of a drug is expected by decision makers at each phase of drug development in order to reduce risk to human subjects and to increase the chance of picking a winning therapeutic molecule.

J. Fred Pritchard et al., *Making Better Drugs: Decision Gates in Non-Clinical Drug Development*, NATURE 542, 543 (July 2003). For example, the level of information that can be learned about a drug candidate's toxicology through preclinical studies has grown dramatically in recent years.

> Not so long ago, the toxicologist would only become involved in drug development when the discovery research scientist handed over one precious candidate drug and got busy discovering the next. Nowadays, toxicology and safety pharmacology are involved much earlier and play an increasingly important role in the decision of whether to move a lead

> candidate into regulated in vivo toxicology studies.

Id. at 546 (citing FDA, *Guidance for Industry: Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies* In Vitro (1997), *available at* http://www.fda.gov/cder/guidance/clin3.pdf (encouraging routine, thorough evaluation of drug metabolism and interactions *in vitro* whenever feasible and appropriate)). Preclinical toxicology studies help narrow down potential drug candidates before clinical testing, furthering the regulatory objective of "reasonably safe" clinical trials and the ultimate evaluation of drug safety and effectiveness.

The importance of preclinical testing to the regulatory process is not altered by the fact that more than one possible candidate may be studied. Indeed, the FDA has embraced the study of more than one candidate in the clinical context. The FDA permits a drug company to present multiple variants of a drug in a single IND, through a procedure called a "screening IND," in order to allow studies on "a number of closely related drugs to choose the preferred compound or formulation." FDA, *Manual of Policies and Procedures, Center for Drug Evaluation and Research, INDs: Screening INDs* 1 (May 9, 2001), *available at* http://www.fda.gov/cder/mapp/6030-4.pdf. The reasons supporting the testing of more than one candidate in the clinical context applies equally as strongly to the preclinical context. In both cases, testing of close analogs potentially provides useful

information to allow the FDA to evaluate the safety and efficacy of a proposed new drug.

Furthermore, a use may be reasonably related to the development and submission of information even if the preclinical studies fail and an IND not submitted. Preclinical testing of drug candidates is undertaken with the goal of submitting the candidate to FDA for approval, and to be effective as a safe harbor the statutory provision must protect failures as well as successes. Indeed, the legislative history of section 271(e)(1) clearly provides that a party that develops the type of information submitted to the FDA for regulatory approval, "but decides not to submit an application for approval, is protected as long as the development was done to determine whether or not an application for approval would be sought." H.R. Rep. No. 98-857 (Pt. 1), at 45 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647, 2678. Courts have recognized that the test for applying the safe harbor is prospective, and it evaluates the potential infringer's activities at the time they were undertaken, without regard to the actual outcome of the development effort. *See Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 3 F. Supp. 2d 104, 108 (D. Mass. 1998).

B. The Information Produced During Preclinical Testing Is Of Interest To FDA And Reasonably Related To Obtaining FDA Approval Of A New Drug

FDA too has a pronounced interest in preclinical studies. The statutory scheme itself calls for

preclinical research to be submitted to the FDA as part of the new drug approval process. Congress has exempted from the pre-market approval requirements "drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs," 21 U.S.C. § 355(i)(1), and it has authorized the Secretary to promulgate regulations "conditioning such exemption upon . . . the submission to the Secretary . . . of *preclinical tests (including tests on animals)* of such drug adequate to justify the proposed clinical testing." 21 U.S.C. § 355(i)(1)(A) (emphasis added). The Secretary has designated FDA to review these submissions through an investigational new drug (IND) application process.

In order to coordinate the investigational phase of the new drug approval process, the Secretary promulgated regulations setting forth the requirements for IND applications. *See* 21 C.F.R. § 312.20 et seq. New drug developers cannot perform clinical studies on a research drug in humans until they submit an IND application to FDA and the IND becomes effective. The FDA will not allow an IND to become effective or remain in effect unless it is convinced that the drug does not pose a significant health risk to humans. *See* 21 C.F.R. § 312.42, 312.44. While the information that must be submitted in support of a particular drug depends on factors such as the novelty of the drug and the extent to which it has been studied previously, *see* 21 C.F.R. § 312.22(b), the FDA regulations expressly contemplate the submission of preclinical studies as part of the IND.

FDA then looks to the information again in connection with the New Drug Application, filed following clinical trials, to determine the safety and efficacy of the proposed drug. *See* 21 C.F.R. § 314.50(d)(2) (requiring the NDA to describe the animal and *in vitro* studies performed with the proposed drug as part of the "nonclinical pharmacology and toxicology" section of application). Thus, preclinical studies remain relevant to drug approval throughout the regulatory review process for a new drug.

In accordance with FDA regulations, applicants submit the results of preclinical animal studies as well as *in vitro* studies to the Agency. Indeed, the regulations require the submission of an investigator's brochure containing, among other things, a description of the drug substance and formulation, a "summary of the pharmacological and toxicological effects of the drug in animals," and a "summary of the pharmacokinetics and biological disposition of the drug in animals." 21 C.F.R. § 312.23(a)(5)(i)-(iii). The regulations also specify that an IND application should contain "[a]dequate information about *pharmacological and toxicological studies of the drug involving laboratory animals or in vitro,* on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations." 21 C.F.R. § 312.23(a)(8) (emphasis added). This includes "[a] section describing the *pharmacological effects and mechanism(s) of action of the drug in animals*, . . . information on the absorption, distribution, metabolism, and excretion of the drug, if

known, ... [and a]n integrated summary of the toxicological effects of the drug *in animals and in vitro*." 21 C.F.R. § 312.23(a)(8)(i) and (ii) (emphases added). In sum, as the Government noted in its brief in support of certiorari, preclinical research is "as relevant to an IND as clinical trials are to [a new drug application]." Gov't Cert. Brief at 13.

Moreover, while the precise tests that may be done to support clinical testing may vary depending on the nature of the drug, the manner in which many of those tests are conducted is regulated by FDA. By regulation, the Agency sets forth a set of "good practices" to be followed for certain nonclinical studies used "to support applications for research or marketing permits for products regulated by [FDA]." 21 C.F.R. § 58.1(a). These regulations establish minimum requirements for various aspects of the testing procedures and provide FDA with authority to inspect and impose penalties for non-compliance. *See id.* pt. 58. These regulations manifest FDA's enduring interest in both the conduct and outcome of preclinical testing in connection with its statutory charge to evaluate the safety and efficacy of proposed new drugs.

C. Restricting The Section 271(e)(1) Safe Harbor To Protect Only Clinical Testing Thwarts Congress' Intent In Enacting The Provision And Threatens The Development And Submission Of Information To FDA On Promising New Drugs.

As recognized by this Court in *Eli Lilly*, the safe harbor provision addresses the *de facto* extension of the patent term that is created by the lengthy FDA approval process for drugs. *See* 496 U.S. at 670. It does so by allowing the drug development process to proceed during the patent term. It cannot succeed, however, if the preclinical studies necessary to commence clinical tests are not themselves protected under the safe harbor.

The necessity of protecting preclinical studies is apparent when one considers the length of time it takes for a new drug to proceed through the regulatory approval process. It is estimated that an average drug development program – from research idea to approved product – takes between 10 to 15 years and over 800 million dollars. *See* Tufts Center for the Study of Drug Development, *Outlook 2002*, at 1, *available at* http://csdd.tufts.edu/InfoServices/OutlookPDFs/Outlook2002.pdf. More than a quarter of this time (about 52 months) is spent on preclinical studies intended to advance from first synthesis of a drug compound to initial human testing. *See* Joseph A. DiMasi, Ronald W. Hansen & Henry G. Grabowski, *The Price of Innovation: New Estimates of Drug Development Costs*,

22 J. HEALTH ECON. 151, 166 (2003). The average time from the start of clinical testing in humans to marketing approval was 90.3 months. *See id.* at 164. Thus, on average, the drug development process takes almost a dozen years. In the absence of a safe harbor that encompasses preclinical studies, the availability of life-saving drugs could be delayed by a decade or more. If the FDA approval process is allowed to run in parallel with the term of an existing patent, however, the likelihood will be reduced, as Congress intended, that final marketing approval of the new drug may be delayed beyond expiration of the patent.

The safe harbor provision also affects the cost of new drug development. The average capitalized cost of bringing a new drug to market in the 1990s was $802 million. *See id.* at 161. Approximately half of that total was attributable to the opportunity cost of expending the capital over a number of years. *See id.* As the development process becomes more protracted, therefore, the overall cost of drug development is increased.

These costs would be compounded by the narrow interpretation of the safe harbor put forward by the Court of Appeals. Of the 284 drugs approved in the United States in the 1990s, more than 90% originated from industrial sources, rather than government, academic, or other non-profit sources. *See* DiMasi, Hansen & Grabowski at 157. The costs and uncertainties surrounding patent licensing in the preclinical context, where the results of initial testing may lead researchers to change course and study

compounds or processes that were not previously contemplated, would make licensing a poor substitute for statutory protection under section 271(e)(1), which Congress specifically created to obviate the need to obtain licenses in order to engage in activities within its scope.[3] Recognizing the proper scope of the statutory safe harbor therefore would facilitate the testing and ultimate approval and availability of new medicines.

D. The Court Of Appeals' Narrow Construction Of Section 271(e)(1) Is Unwarranted By The Language Of The Statute.

The narrow construction of section 271(e)(1) by the Court of Appeals finds no support in the statutory text. The safe harbor exempts from liability otherwise infringing activities that are "solely for uses

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[3] Further, the law provides no other adequate protection for preclinical research conducted as part of the FDA drug approval process. In creating the statutory safe harbor in 1984, Congress recognized that the common law research exemption was not adequate to protect new drug development. Since then, the common law exemption has not expanded to provide any more protection to research. *Compare Madey v. Duke University*, 307 F.3d 1351, 1362 (Fed. Cir. 2002) (limiting the exemption to activities pursued "solely for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry"), *cert. denied* 539 U.S. 958 (2003) *with* 21 C.F.R. § 312.160(b)(2) (providing FDA with authority to suspend a sponsor's authority to ship a drug for purposes of animal or *in vitro* testing where the purpose is "other than bona fide scientific investigation").

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). Because the federal laws governing new drug approval expressly contemplate that the results of preclinical testing in animals and *in vitro* will be submitted to the FDA, such testing necessarily warrants the protection of the safe harbor provision of section 271(e)(1).

Before Congress passed the 1984 Act, it was considered an act of infringement to use a patented drug in conducting tests for the purpose of developing information for submission to the FDA. *See Roche Products, Inc. v. Bolar Pharmaceuticals Co.*, 733 F.2d 858, 860-65 (Fed. Cir.) (addressing tests to obtain stability data and dissolution rates, bioequivalency studies, and blood serum studies performed by a generic drug company before the expiration of the pioneer drug patent), *cert. denied* 469 U.S. 856 (1984). However, section 202 of the 1984 Act, subsequently codified at 35 U.S.C. § 271(e)(1), created a safe harbor against patent infringement liability for drug development activity that is "reasonably related" to the development and submission of information for obtaining regulatory approval. In creating this safe harbor, Congress cut back on the *de facto* extension of a patentee's monopoly at the end of the patent term that was created by "the combined effect of the patent law and the premarket regulatory approval requirement" for pharmaceuticals and other products. *Eli Lilly*, 496 U.S. at 670-71. Without the safe harbor, drug developers – both generic and innovators

– would be precluded from even *beginning* the FDA approval process until completion of the patent term.

The analysis of the Court of Appeals was colored by its conclusion that Congress created the safe harbor merely as a response to the decision in *Roche* and was exclusively focused on the limited clinical testing required for approval of generic versions of drugs already on the market. As this Court noted in *Eli Lilly*, however: "Undoubtedly the decision in *Roche* prompted the *proposal* of § 202; but whether that alone accounted for its *enactment* is quite a different question." 496 U.S. at 670 n.3. Indeed, the safe harbor provision by its terms is not limited to clinical testing or to generic drugs, but instead speaks in general language. This Court's decision in *Eli Lilly* accordingly interpreted section 271(e)(1) to apply to the entire FDA statutory scheme of regulation, not merely a specific narrow subsection of federal law. *See* 496 U.S. at 666-70 (concluding that the testing of medical devices is covered by the safe harbor). The decision by the Court of Appeals is in conflict with the statute's plain language and this Court's holding in *Eli Lilly* because it excludes preclinical testing, a vital part of the FDA drug approval process, from protection.[4] Rather than focus on the language in the statute, the Court of Appeals instead expressed

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[4] PhRMA agrees with and refers the Court to the more extensive analysis of the plain language of the statue contained in the Petitioner's Brief. *See* Pet. Brief at 32-36.

concern with what was not in the statute – namely, a clear line that would prevent the safe harbor from extending to the stage of basic research and discovery. *See* P.A. 10a. But the lower court's concern with line drawing does not justify its disregard for the statute's plain text, or with the protections necessary to serve Congress' concern with expediting drug development. The line drawn by the Court of Appeals – that between clinical and preclinical research – disserves Congress' intent and appears wholly arbitrary in light of the statutory touchstone of FDA regulation. Instead, the statutory "line" set forth by Congress is one of reasonable relationship to the development and submission of information to FDA. As discussed above, it is only by according the safe harbor its natural scope that adequate protection for the development of new drugs can be accomplished and undue delay in new drug approvals avoided.

CONCLUSION

The judgment of the Court of Appeals should be reversed.

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