NO. 11-1078

IN THE

Supreme Court of the United States

GLAXOSMITHKLINE,

Petitioner,

V.

CLASSEN IMMUNOTHERAPIES, INC.,

Respondent.

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

BRIEF OF AMICUS PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA IN SUPPORT OF PETITIONER

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INTEREST OF AMICUS CURIAE

The Pharmaceutical Research and Manufacturers of America (PhRMA) is an association of leading research-based pharmaceutical innovators devoted to developing medicines that allow patients to live longer, healthier, and more productive lives.[1] In the past decade, PhRMA's members have invested more than $406 billion to discover and develop new medicines and new uses for existing medicines. *See* PhRMA, PHARMACEUTICAL INDUSTRY PROFILE 2011 at 42 (2011). In 2010 alone, the pharmaceutical industry invested a record $67.4 billion in such research and development. The results of this research save and improve lives. *See generally* Frank R. Lichtenberg, *The Impact of New Drug Launches on Longevity: Evidence from Longitudinal, Disease-Level Data from 52 Countries, 1982-2001*, 5 Int'l J. of Health Care Fin. & Econ. 47, 71 (2005).

In the course of their work in this area, PhRMA members develop and submit an enormous amount of information to the FDA to ensure their products' safety and efficacy. The decision below is of great concern to PhRMA's members because it exposes them to suits for patent infringement arising out of

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[1] A list of PhRMA's members is available at http://www.phrma.org/about/member-companies (last viewed Mar. 19, 2012). Petitioner GlaxoSmithKline is a member of PhRMA. No counsel for any party has authored this brief in whole or in part, and no person other than amicus and its counsel have made any monetary contribution intended to fund the preparation or submission of this brief. All counsel of record for all parties received timely notice of amicus's intent to file this brief and all parties have consented to its filing.

the development and submission of that information – contrary to the plain language of federal statutory law and this Court's precedents.

Specifically, 35 U.S.C. § 271(e)(1), commonly known as the "safe harbor" provision, bars infringement claims based on actions taken "solely for uses reasonably related to the development and submission of information" under federal drug law. The ruling below appears to limit that safe harbor by stating that it extends only to actions related to information concerning the "*premarketing* approval of *generic* drugs." Pet. App. 27a (emphasis added). To the extent that such limits apply, there is no assurance of protection for actions taken in connection with post-approval activities, or indeed in connection with securing approval for *new* medicines rather than generic products. Because the ruling below creates improper limits and will hinder the discovery, development, and refinement of new medications, PhRMA urges this Court to grant review.

INTRODUCTION AND SUMMARY OF ARGUMENT

The safe harbor provision states that "[i]t shall not be an act of infringement to make, use, offer to sell, or sell within the United States … a patented invention … solely for uses reasonably related to the development and submission of information under Federal law which regulates the manufacture, use, or sale of drugs." 35 U.S.C. § 271(e)(1). This Court has twice held that this provision means what it says: "[Congress] exempted from infringement *all* uses of patented compounds 'reasonably related' to the

process of developing information for submission under *any* federal law regulating the manufacture, use, or distribution of drugs." *Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193, 206 (2005) (emphasis in original); *see also Eli Lilly v. Medtronic, Inc.*, 496 U.S. 661 (1990) (rejecting argument that statute's scope is limited by legislative history).

PhRMA urges review of the decision below because it describes the scope of the § 271(e)(1) safe harbor in limiting ways that may have profound implications for PhRMA's members. Under the Federal Circuit's reading, the safe harbor does not apply except in cases where the information is submitted in regard to the "*premarketing* approval of *generic* drugs." Pet App. 27a (emphasis added). These limitations are found nowhere in the statute, which by its plain terms does not distinguish between "pre-marketing approval" and subsequent undertakings, or between "generic" and innovative drugs. The safe harbor simply applies to all allegedly infringing activities so long as they are undertaken solely for uses reasonably related to the development and submission of information under drug-related federal law.

The Federal Circuit divined its interpretation not by reading the language of the safe-harbor provision, but by plumbing the statute's legislative history. Privileging legislative history over statutory text would be inappropriate under any circumstances, but it is particularly unwarranted here given that this Court has expressly held with respect to this very statute that its scope is not limited to purposes "explicitly mentioned in its legislative history." *Eli*

Lilly, 496 U.S. at 669 n.2 (internal quotation marks omitted).

In charting a legally erroneous course, the ruling below threatens to materially hinder the development of new medicines. To be sure, not every action taken by a drug manufacturer is "solely" undertaken for "uses reasonably related to the development and submission of information under Federal law," but many actions are. Innovators are required by federal law to submit a host of information to the FDA post-approval to ensure the efficacy and safety of drugs. They also routinely submit such information in the process of understanding and developing new uses for existing drugs. All of these undertakings will be far more difficult and expensive if innovators are denied the protection of the safe harbor and made subject to potential infringement liability. These post-approval efforts to make drugs safer, more effective, and more useful are just as important as, and often indistinguishable from, their pre-approval counterparts. There is simply no reason – and certainly none discernible from the statute – to protect one but not the other.

Moreover, it is not just post-approval endeavors that are at risk; the decision below also threatens to hamper actions undertaken to secure approval of new drugs in the first instance. Innovator manufacturers develop and submit information to obtain marketing approval from the FDA just as generic manufacturers do, and yet the Federal Circuit's ruling suggests that only the latter group should receive protection. But federal law provides a level playing field for innovators in this area, and they should not be denied

the protection against infringement that the statute confers on *all* developers and submitters of FDA information – generic and innovative alike.

This Court should not wait to review the Federal Circuit's erroneous and harmful ruling. The decision is already being cited by lower courts to shrink the safe harbor. *See, e.g.*, *Momenta Pharms., Inc. v. Amphastar Pharms., Inc.*, Civ. A. No. 11-11681-NMG, 2011 U.S. Dist. LEXIS 125184, at *27 (D. Mass Oct. 28, 2011) (denying safe harbor status to post-approval activity). Amicus PhRMA accordingly urges this Court to grant review and reverse.

ARGUMENT

REVIEW IS WARRANTED BECAUSE THE DECISION BELOW DRAMATICALLY LIMITS THE STATUTORY SAFE HARBOR IN VIOLATION OF THE PLAIN LANGUAGE OF THE STATUTE AND THIS COURT'S TEACHINGS

A. The Federal Circuit's Decision Could Improperly Deprive Innovators Of The Protections Of The Statutory Safe Harbor.

GlaxoSmithKline's petition ably demonstrates why the decision below is incorrect on the merits. Pet. 16-22. PhRMA fully concurs in the conclusion that the decision's crabbed reading of the safe-harbor provision is wholly untenable as a matter of statutory construction.

According to the Federal Circuit, to the extent the safe harbor offers any protection at all, it should reach only actions undertaken in connection with the "*premarketing* approval of *generic* drugs." Pet App. 27a (emphasis added). Such a reading could deprive

innovators of the safe harbor's protection for the myriad activities they undertake to develop and submit information to the FDA – pursuant to federal law – *after* a drug has been approved for marketing. It also suggests that innovators, but not generic manufacturers, should be denied protection for even their *pre-approval* undertakings.

But there is not a word in the statute suggesting that Congress wanted to impose such limitations. By its plain terms, the safe harbor's scope is defined not in terms of *who* engaged in certain actions, or *when* those actions took place, but rather in terms of *whether* the actions are sufficiently related to the development and submission of information under *any* federal drug law, whether or not that law governs initial marketing approval. *See* 35 U.S.C. § 271(e)(1) (safe harbor extends to actions undertaken "solely for uses reasonably related to the development and submission of information" under federal law regulating the manufacture, use, or distribution of drugs).

The Federal Circuit's contrary conclusion is particularly inexplicable given that this Court has twice rejected extra-textual limitations on the safe harbor and found that actions taken by innovators fall within the safe harbor's scope. In *Merck*, this Court found that information submitted in connection with an investigational new drug application by Merck was not outside that scope. 545 U.S. at 199, 207. And in *Eli Lilly*, the Court held that the safe harbor extended to the submission of information for medical devices, which do not have generic counterparts. Both decisions would have come out the other way if

the statute provided protection only for activities undertaken in connection with "premarketing approval of generic drugs." Pet App. 27a.

The Federal Circuit's decision acknowledged these precedents, but found that they engaged in a "purposive" analysis that supported the court's conclusion in this case. That is incorrect. To be sure, this Court discussed the purpose of the safe harbor in *Merck* and *Eli Lilly* – but it identified that purpose on the basis of what the statutory language actually *says*. Thus, in refusing to read the statute's purpose narrowly, the Court explained in *Merck* that

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

545 U.S. at 206 (quoting § 271(e)(1)).

In contrast, the Federal Circuit's analysis was driven primarily by the statute's legislative history, which it treated as containing an exhaustive account of the statute's intended goals. *See, e.g.*, Pet. App. 27a-28a (asserting that the legislative history is "replete with statements that the legislation concerns premarketing approval of generic drugs"). This Court has expressly rejected that approach, explaining that

"[i]t is not the law that a statute can have no effects which are not explicitly mentioned in the legislative history." *Eli Lilly*, 496 U.S. at 669 n.2; *see also, e.g.*, *New York v. FERC*, 535 U.S. 1, 21 (2002) (stating that the issue that "catalyzed the enactment" of a statute "does not define the outer limits of the statute's coverage"). The Federal Circuit therefore erred in allowing certain objectives mentioned in the legislative history to trump the statute itself.

Because the Federal Circuit entirely ignored the plain language of the safe harbor, and because the Federal Circuit's decision may impose limits on the scope of the safe-harbor infringement defense, this Court should grant review to correct the lower court's error.

B. By Adding Limitations To The Safe Harbor That Are Not Found In The Statutory Text, The Ruling Below Will Hinder The Development Of New Drugs And New Uses For Drugs.

The ruling below is not just incorrect as a matter of statutory interpretation; it is fundamentally inconsistent with the legal regime governing development and submission of information to the FDA, and could have a substantial detrimental effect on the development of medications in this country. Under the Federal Circuit's decision, various FDA-*mandated* studies directed toward improving drug safety and protecting patient health appear to fall outside the safe harbor. So, too, do certain exploratory studies for new indications for existing drugs. Subjecting manufacturers to infringement liability for undertaking such studies flies in the face

of the FDA's requirements and inhibits research that ultimately benefits the public.

1. Pharmaceutical development does not end with the FDA's approval for marketing. Federal law contains a raft of provisions that require pharmaceutical companies – both innovators and generic companies – to develop and submit information *after* the FDA has approved a drug. These provisions serve highly valuable purposes, permitting regulators and manufacturers to review the efficacy and safety of drugs on an ongoing basis and to improve drug labeling.

First, the FDA can require manufacturers to conduct post-approval safety studies to ensure that a new drug does not have detrimental effects. Under § 355(o)(3)(B) of Title 21, the FDA may require a holder of an approved New Drug Application (NDA) or Biological License Application (BLA) to conduct post-approval studies to "assess a known serious risk" related to the use of the drug involved, or to assess "signals" or a "potential" of risk concerning the drug. 21 U.S.C. § 355(o)(3)(B). By definition, such studies require the development and submission of information to the FDA. Indeed, they serve much the same purpose as pre-approval studies in that they provide the FDA with information about the safety of a medication.

The FDA often exercises its authority under § 355(o)(3)(B). In 2011 alone, the FDA required at least 31 NDA and BLA holders to conduct post-approval safety studies or clinical trials. *See* http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm.

These studies are not in any way optional; a manufacturer who declines to perform a required study faces a host of penalties. Among other sanctions, the manufacturer may be civilly fined up to $250,000 per violation, 21 U.S.C. § 333(f)(4)(A)(i), and the FDA may designate the drug in question as "misbranded," barring the manufacturer from selling it on pain of criminal penalties and allowing the FDA to seize the drug, *id.* § 352(z); § 355(o)(1) (providing that misbranded drugs may not be introduced "into interstate commerce").

Second, the FDA frequently requires manufacturers to conduct post-approval clinical trials to further assess the efficacy of an approved drug. Such trials are used to evaluate drugs that treat serious or life-threatening diseases, since it may be undesirable to wait to complete all testing before approving the drug in the first instance. In such cases, the FDA will approve the drug based on a "surrogate endpoint" (such as the product's ability to shrink cancerous tumors), but will then require post-approval testing to measure other aspects of the drug's efficacy (such as increased survival rates). *See* 21 C.F.R. §§ 314.510, 601.41; *see generally* 21 U.S.C. § 356; 21 C.F.R. pt. 314, subpt. H; *see also id.* pt. 601, subpt. E (same process for biological products).

As with post-approval safety trials, there are substantial penalties facing a manufacturer who fails to answer the FDA's call for a post-approval efficacy study. The FDA is empowered to withdraw the new drug application altogether, thereby preventing the manufacturer from selling the product. *See* 21 U.S.C. § 356(b)(3); 21 C.F.R. §§ 314.530, 601.43. The FDA

also may determine that the product is misbranded, subjecting the application holder to possible criminal prosecution and an injunction or seizure action. *See* 21 U.S.C. § 355(p)(2) (providing that a drug or biological product is misbranded if application holder failed to conduct post-approval studies required under Subpart H or Subpart E); *id.* § 331(a), (d) (stating that it is a prohibited act to introduce or deliver for introduction into interstate commerce a misbranded drug or biological product or such a product that is in violation of Section 505 of the FDCA).

Finally, although safety and efficacy studies are the most common post-approval FDA requirements, a host of other post-approval obligations are found throughout "Federal law which regulates the manufacture, use, or sale of drugs." 35 U.S.C. § 271(e)(1). For example, the sponsor of a new drug or biological product can be required to generate information from clinical studies in pediatric populations and to submit those data to the FDA. *See* 21 U.S.C. § 355c(a)(2)(A). The FDA will often defer these pediatric study requirements until after approval in view of the ethical or practical limitations of testing new drugs on children. *See id.* § 355c(a)(3). Additionally, the FDA may require post-approval clinical efficacy studies for drugs or biological products intended to prevent or treat conditions associated with exposure to biological, chemical, radioactive, or nuclear substances. *See* 21 C.F.R. pt. 314, subpt. I (drugs); *id.* pt. 601, subpt. H (biological products). Conducting clinical trials for efficacy on humans prior to approval of such products would be infeasible or unethical, as it would require exposing healthy human subjects to harmful or lethal

conditions. In these situations, the FDA may approve these products based on adequate and well-controlled animal efficacy studies, *see* 21 C.F.R. §§ 314.610(a), 601.91(a), and only after approval require the application holder to conduct clinical studies to confirm the drug's efficacy and safety in humans, *see id.* §§ 314.610(b)(1), 601.91(b)(1). If the application holder "fails to perform the post-marketing study with due diligence," the FDA may withdraw approval of the product. *Id.* § 314.620(a)(2), 601.92(a)(2).

If the Federal Circuit's decision is permitted to stand, then manufacturers could be subject to infringement liability for the actions they take in order to comply with their various *mandatory* post-approval obligations. It simply makes no sense to interpret the statute to make these obligations more difficult, expensive, and burdensome than manufacturers' pre-approval obligations, since *both* sets of FDA requirements are equally critical to the protection and promotion of public health and safety.

2. Wholly apart from situations in which the FDA *requires* the development and submittal of post-approval information on pain of penalty, there are many scenarios in which a manufacturer will develop and present additional information to the FDA after obtaining approval to market a drug in order to obtain authorization under federal law for a new use of that drug. *See* 21 U.S.C. §§ 355(a), (b)(2), 321(p); 21 C.F.R. § 310.3(h). For example, a company that owns a drug approved as monotherapy may wish to study its potential as part of a combination therapy with a compound patented by someone else, with the aim of obtaining approval for an additional indication

for combination therapy. In the field of oncology, such studies are common, as are studies directed toward developing improved treatment protocols. *See* Catherine Arnst, *Same Cancer Drugs, New Applications*, Bus. Week Online, June 3, 2007, *available at* http://www.businessweek.com/technology/content/jun2007/tc20070603_510760.htm. Likewise, work is routinely done in the field of genotype research to find drug response genotypes or genotypes that could lead to adverse events.

This research is important and beneficial to the public. Indeed, one recent empirical study found that in some classes of medicines, 70-80% of total patient use is attributable to indications developed and approved after the drug first came to market. Ernst R. Berndt et al., *The Impact of Incremental Innovation in Biopharmaceuticals*, 24 Pharmacoeconomics (Supp. 2d) 69, 81 (2006); *see also* Maya Said et al., *Continued Development of Approved Biological Drugs: A Quantitative Study of Additional Indications Approved Postlaunch in the United States* 6 (Boston Consulting Group, White Paper, Dec. 2007), *available at* http://www.bcgsea.com/documents/file15138.pdf (noting that 47% of biologics approved between 1986 and 2006 had at least one additional indication).

There is no reason to deprive such beneficial research of the protection of the safe harbor. Indeed, it is nonsensical to do so given that research of this kind frequently begins *before* approval to market a drug is obtained, and the Hatch-Waxman Act itself expressly encourages such undertakings. That Act provides an innovator with a three-year period of

exclusivity, protecting it from competition in the marketplace, after approval of an application for a new use for an existing compound when that application is based on new clinical investigations. *See* 21 U.S.C. § 355(c)(3)(E)(iv), (j)(5)(F)(iv). The same Congress that wanted to stimulate these kinds of post-approval investigations could not also have intended to deprive innovators who engage in them of protection from infringement liability.

3. Even beyond these problems with the Federal Circuit's decision, any presumption of a strict separation between pre-approval information and post-approval information creates absurd results. The Federal Circuit has ruled that a manufacturer is protected from infringement liability for actions undertaken "solely for uses reasonably related to the development and submission of information under Federal law" governing initial approval of a drug. But under that ruling, a manufacturer could *lose* its safe harbor protection simply by taking information that it developed for purposes of the initial approval process and submitting that information to the FDA under federal law governing some post-approval activity. For example, pre-approval testing information might be submitted alongside post-approval testing information to provide the FDA with a more complete picture of a drug's efficacy and safety. In that circumstance, the information could no longer be said to have been developed and submitted "*solely* for uses reasonably related" to the FDA's original marketing-approval decision. 35 U.S.C. § 271(e)(1) (emphasis added). It is impossible to believe that Congress intended the safe harbor to function in this irrational way.

4. Finally, the decision below is also highly pernicious to the extent that it could be read to suggest that innovator manufacturers, but not generic manufacturers, should be deprived of the benefit of the safe harbor even for *pre-approval* submission of information. As explained above, this Court's existing decisions are not consistent with that limitation, and there is nothing in the statutory text suggesting it. Innovators, just like generic manufacturers, develop and submit reams of information to the FDA in the process of gaining approval of New Drug Applications and Biological License Applications. And innovators, just like generic manufacturers, face exposure to claims of infringement in developing new drugs. It cannot possibly be the case that only generic manufacturers enjoy the protection of the safe harbor for their pre-approval efforts. *See, e.g.*, *Merck*, 545 U.S. at 202 (holding that Merck was eligible for safe harbor protection and explaining that "[t]here is simply no room in the statute for excluding certain information from the exemption on the basis of the phase of research in which it is developed or the particular submission in which it could be included"); *id.* at 206-07 (explaining that Congress did not "create an exemption applicable only to the research relevant to filing an ANDA for approval of a generic drug").

Handicapping the preeminent group of manufacturers of new drugs would risk detrimental effects on the development of medicine. As noted above, PhRMA's members pour tens of billions of dollars a year into medical research and development, with life-saving results. *See supra* p. 1. As Congress has recognized, they should not be constrained in the research avenues they pursue and hindered by claims

of infringement. This Court should act to dispel any doubt created by the Federal Circuit's emphasis on "premarketing approval of *generic* drugs," Pet App. 27a (emphasis added), and ensure that the playing field is not tilted in favor of generic manufacturers.

C. Courts Are Capable Of Determining On A Case-by-Case Basis Which Activities Are Actually Protected By The Safe Harbor.

None of this is to say that *all* activities connected with FDA regulation qualify for protection under the safe harbor. Section 271(e)(1) states on its face the test for entering that harbor: the alleged act of infringement must be undertaken "*solely* for uses *reasonably related* to the development and submission of information" under certain kinds of federal law. 35 U.S.C. § 271(e)(1) (emphasis added). Courts will be able to work out in individual cases whether an alleged act of infringement meets this test. But the ruling below appears to cut off this inquiry before it even begins. In the Federal Circuit's view, it does not matter how "related" an activity is to development or submission of information under federal law unless that information concerns "premarketing approval of generic drugs." Pet. App. 27a. As in *Eli Lilly* and *Merck*, this Court should ensure that Congress's judgment and this Court's prior decisions about the safe harbor's boundaries are respected, and should not allow the Federal Circuit to place extra-textual limits on the statute and the valuable activities that it protects.

CONCLUSION

For the foregoing reasons, the writ of certiorari should be granted.

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