No. 03-1237

In The Supreme Court Of The United States

MERCK KGAA
PETITIONER

v.

INTEGRA LIFE SCIENCES, INC.
RESPONDENT

ON WRIT OF CERTIORARI
TO THE UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

BRIEF OF EON LABS, INC. AS *AMICUS CURIAE* IN SUPPORT OF PETITIONER

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BRIEF OF EON LABS, INC. AS *AMICUS CURIAE* IN SUPPORT OF THE PETITIONER, MERCK KGaA.

With the consent of the Petitioner and the Respondent, *amicus curiae,* Eon Labs, Inc. ("Eon") respectfully submits this brief in support of the Petitioner, Merck KGaA.[*]

INTEREST OF *AMICUS CURIAE*

Eon is a generic drug company having its principal place of business in Lake Success, NY. Eon is one of the nation's largest suppliers of generic pharmaceuticals, is committed to providing high quality, affordable products. Eon produces a broad range of pharmaceuticals in a wide variety of therapeutic categories. Our diverse product line consists of more than two hundred products representing various dosage strengths for over sixty drugs; many of which are generics of the leading drugs currently available in the market today.

For the past four years, Eon has been among the industry leaders in Abbreviated New Drug Application (ANDA) approvals and "first-to-market" products. Our ability to introduce a significant number of timely approvals has yielded a growing product line, with nearly two-thirds of our products ranked either first or second in market share. Eon's ongoing commitment to R&D and significant manufacturing capacity serve as the

[*] Counsel of record for the parties consented to the filing of this amicus brief. In accordance with this Court's Rule 37.3(b), those letters have been filed with the Clerk.

In accordance with Rule 37.6, *amicus* states that this brief was authored in its entirety by the counsel listed on the cover, and no person or entity other than the *amicus* listed on the cover made a monetary contribution to the preparation or submission of this brief.

springboard for future growth of new generic drugs.

Accordingly, by virtue of the patent and FDA laws that govern the approval and introduction of generic drugs into the market, the Federal Circuit's decision has an impact on the generic drug industry as a whole and on Eon in particular.

QUESTION PRESENTED

To encourage development and expedite introduction of pharmaceuticals, Congress amended the patent laws in 1984 to insulate drug research from charges of infringement so long as the research is "reasonably related to the development and submission of information" to the Food and Drug Administration. Did the Federal Circuit err in concluding that this drug-research safe harbor does not protect animal studies of the sort that are essential to the development of new drugs, where the research will be presented to the FDA, and where barring the research until expiration of the patent could mean years of delay in the availability of life-saving new drugs?

SUMMARY OF THE ARGUMENT

The plain text of the statute allows for a liberal interpretation of the safe harbor exemption. Congress chose to use the words "reasonably related" and the word "information" to describe the scope of the exemption. The exemption does not regulate conduct, *per se*, rather it regulates the type of information that is generated. Therefore, to the extent that the Federal Circuit focused on conduct, this was erroneous.

Since this Court's decision in *Eli Lilly v. Medtronic*, 496 U.S. 661 (1990), the lower courts have applied a

liberal interpretation to the scope. The lower courts, including the Federal Circuit have held various activities ostensibly unrelated directly to the FDA approval process as being safe harbored.

Because the plain text refers to information, logically then the exemption applies to any information that the FDA would normally request or that it mandates be submitted. FDA has promulgated regulations that mandate certain pre-clinical or screening information be submitted.

Given the volume of case law applying the safe harbor exemption, Congress has yet to do amend § 271(e)(1) to correct any perceived problem.

Finally, generic drug companies will often engage in the same kind of screening activities that Merck KGaA did in order to find a bioequivalent product. This activity is shielded.

In examining the scope of the safe harbor exemption, it is important to recognize that it covers two distinct regimes. The first regime is the testing and information collected related to developing a brand new drug and proving that it is safe and efficacious. 21 U.S.C. §355(a) and (b). This is normally associated with the animal testing, the Phase I, II, and III clinical trials that eventually produce a new drug for which a New Drug Application (NDA) is approved.

The second regime is the testing and information collected related to approving a generic version of a pre-approved drug. 21 U.S.C. §355(j). Whereas a new drug must prove that it is safe and efficacious, the abbreviated new drug application (ANDA) must show that the putative generic version is bioequivalent to the new drug. 21 U.S.C. §355(j)(2)(A)(iv). Thus, the ANDA applicant may test and experiment to derive information showing bioequivalency.

This case involves the first regime; Merck KGaA used the patented inventions to screen for a molecule candidate that itself would become the basis for a new drug *vis a vis* the NDA approval process. The distinction between first and second regime interpretations plays an important role in the scope of the 271(e)(1) interpretation.

To the extent, therefore, the Federal Circuit fixated on policy of the safe harbor applying to generic drugs only (*vis a vis* the ANDA approval process), *Integra Life Sciences I v. Merck KGaA*, 331 F.3d 860, 867 (Fed. Cir. 2003) ("the context of this safe harbor originally *keyed* its use to facilitating expedited approval of patented pioneer drugs already on the market")(emphasis added), this was erroneous.

ARGUMENT

I. The Safe Harbor Provision of § 271(e)(1) Has A Scope – One Defined By Its Plain Text.

Statutory interpretation necessarily begins with the text of the statute. *Hughes Aircraft Co. v. Jacobson*, 525 U.S. 432, 438 (1999) ("As in any case of statutory construction, our analysis begins with the language of the statute."). The task is to determine whether the statutory language "has a plain and unambiguous meaning with regard to the particular dispute in the case. Our inquiry must cease if the statutory language is unambiguous and 'the statutory scheme is coherent and consistent.' " *Robinson v. Shell Oil Co.*, 519 U.S. 337, 340 (1997). As the Federal Circuit's decision and the briefs submitted in the *certiorari* stage demonstrate, the parties and the courts rely on the self-serving portions of the legislative history as opposed to the plain language. But where the legislative history is ambiguous or not definitive, it is not improper to look at the plain text of the statute that Congress promulgated to determine the scope of the exemption. This section examines just that.

I.A. The Plain Text of § 271(e)(1) Expressly Relates to "Information" Development and "Information" Submission to the FDA.

Truncated, the statute says: "[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… ." At the outset, therefore, the plain text says nothing about clinical trials, pre-clinical trials, research tools, "biotechnological inventions", etc. Rather, the plain text expressly speaks to information *development* and then information *submission*. The plain text does not say that this safe-harbored information must be the very information submitted to the FDA. *But see*, *Integra,* 331 F.3d at 867 ("The exemption viewed in this context does not endorse an interpretation of § 271(e)(1) that would encompass drug development activities far beyond those necessary to acquire information for FDA approval of a patented pioneer drug already on the market.").

Indeed the universe of information developed far exceeds the information actually submitted; information submitted is a subset of information developed. This is because at the time of and during *development*, it can never be known with certainty just what information FDA will require for *submission* until the relevant applications are made. Not only does the statute describe the genesis of the information (information derived from development), the statute specifically denominates the type of information; the *information* relates to *any* information related to *a* Federal law that regulates the make, use, or sale of the patented invention. To the extent that the Federal Circuit fixated on clinical trial versus pre-clinical trial conduct, *Integra*, 331 F.3d at 866, 867, this was an error as a matter of law because it was supposed to focus on the information.

Because the plain text is not limited to specified information to the FDA, the next question in the analytical construct concerns the scope of § 271(e)(1).

I.B. The Plain Text Contemplates A Reasonable Scope To The Exemption.

It is true that the plain text uses the term "reasonably" in relation to the term "related." It is true that this word is a word of degree and has a sense of elasticity to it. When words of elasticity are used, this Court "construe[s] language in its context and in light of the terms surrounding it." *Leocal v. United States*, 125 S.Ct. 377, 382 (2004)(interpreting the elastic word "use" in relation to deportation of immigrant for drunk driving). It is also true that the plain text uses the term "solely" that imbues a limitation to the statute. It is also true that statutes must be construed to give fidelity to each term in the statute as opposed to interpreting it to render any one particular term meaningless. The Federal Circuit violated these rules by focusing on the term "solely" as opposed to interpreting this term in conjunction with the term "reasonably" for when one does so, the statutory construction results in a more liberal interpretation than what the Federal Circuit gave. If Congress had intended that the scope be so narrow, then why did Congress insert the term "reasonably" into the statute? *Integra*, 331 F.3d at 866-67. Congress chose to use the term "reasonably" as a word of degree and thus fidelity ought to be given to that choice. Over 120 years ago, this Court stated the then well-accepted axiom that "[i]t is the duty of the court to give effect, if possible, to every clause and word of a statute, avoiding, if it may be, any construction which implies that the legislature was ignorant of the meaning of the language it employed." *Inhabitants of Montclair Tp. v. Ramsdell*, 107 U.S. 147, 152 (1883).

Another way to examine the safe harbor exemption is to examine what it does not textually prohibit. As

seen, the statute applies to information relating to patented inventions. It does not, as the Federal Circuit suggests, limit the safe harbor only to generic versions of pre-approved pioneer drugs. *Integra,* 331 F.3d at 867 ("The exemption viewed in this context does not endorse an interpretation of § 271(e)(1) that would encompass drug development activities far beyond those necessary to acquire information for FDA approval of a patented *pioneer drug already on the market*.")(emphasis added). It equally applies to the development of new drugs for the language of the statute does not limit it to generic versions. For it only applied to generic drugs, that would be inconsistent with this Court's *Eli Lilly* decision and other Federal Circuit ones. Rather than using the more open ended language Congress used, Congress could have expressly limited it to generic versions by limiting the application to drugs developed under 21 U.S.C. 355(j) (§ 505(j) of the Food Drug Cosmetic Act). As such, if Congress intended to limit the safe harbor to the approval of true generics only (as opposed to new drug development), then Congress can so make the appropriate amendment.

Once this Court adopts this interpretation, then contrary to the Federal Circuit's interpretation, § 271(e)(1) is intended to reach down the chain of experimentation. *Integra,* 331 F.3d at 865-66.

II. The Scope Of § 271(e)(1) Plainly Reaches Down The Chain

In 2000, one author predicted this situation. In posing hypotheticals, the author stated:

> How far down the chain of infringement may a defendant go in order to get FDA approval of the [device] in question? Stated another way, does § 271(e)(1) only protect infringement of the patent that is the sole subject of the intended FDA application? Can a defendant infringe many totally

> unrelated patents if the infringement of each patent is somehow reasonably related to gaining FDA approval of the [device] in question? Shashank Upadhye, *Understanding Patent Infringement Under 35 U.S.C. 271(e): The Collisions Between Patent, Medical Device, and Drug Laws*, 17(1) Santa Clara Comp. & High Tech. L.J. 1, 23 (2000)("Upadhye")(also available here: http://www.lordbissell.com/Newsstand/UPIU-SUpadhye-1999.pdf).

II.A. Federal Circuit Case Law Has Consistently Applied A Liberal Interpretation To Include Medical Devices And Other Ostensibly Unrelated Activities

Since this Court affirmed the Federal Circuit that § 271(e)(1) applied to medical devices even though the plain text does not even mention "devices", *Eli Lilly v. Medtronic*, 872 F.2d 402 (Fed. Cir. 1989), *aff'd* 496 U.S. 661 (1990), the Federal Circuit has reaffirmed the vitality of liberal interpretations. See e.g., *Chartex Int'l v. MD Personal Products*, 5 F.3d 1505 (Fed. Cir. 1993)(unpublished)(applying § 271(e)(1) to Class I and II medical devices); *Abtox v. Exitron*, 122 F.3d 1019 (Fed. Cir. 1997)(precedential opinion involving Class I and II medical devices).

It stands to reason, therefore, the overall scope of § 271(e)(1) has been liberally expanded to include medical devices when the statute did not expressly do so.

The case law is replete that many ostensibly unrelated activities have been shielded by the safe harbor provision. In *Upadhye*, that article collects the various cases in which the scope of safe harbor has been litigated. See, *Upadhye*, *supra*, 17(1) Santa Clara Comp. & High Tech. L.J. at 35-39 (discussing demonstrating device at trade show; disseminating information to non-medical personnel; demonstrating device to physicians; etc.).

II.B. § 271(e)(1) Protection Logically Applies To Information That The FDA Requires

More recently, in *Wesley Jessen v. Bausch and Lomb*, 235 F. Supp.2d 370, 375-76 (D. Del. 2002), the court held that because the FDA requested certain information and testing, even though the accused device was conditionally FDA approved, the safe harbor applied with full force to the post-approval testing. This is consistent with the view that the measure of reasonableness to gain FDA approval can indeed be predicated on if the FDA so requires or mandates that information. To this end, the FDA may require preclinical testing because that is statutorily expressly required under 21 U.S.C. §355(i)(1)(A).

Based on the plain language of §355(i)(1)(A) and the statutory mandate to promulgate regulations to that effect, the FDA promulgated 21 C.F.R. §312.20 *et seq*. to handle the preclinical testing so that an applicant can apply for an Investigational New Drug (IND) permit. Those regulations, see e.g., 21 C.F.R. §§312.21(a)(2) (discussing studies "in which investigational drugs are used as research tools to explore biological phenomena or disease processes"); 312.22(b)(IND should include the "developmental phase of drug" information to be submitted in the IND); 312.23(a)(3)(iv), 312.23(a)(5)(ii), and 312.23(a)(8), each effectuate the FDA requirement of preclinical testing. Accordingly, where, as here, it would be illogical on hand to have the FDA mandate certain preclinical testing yet on the other hand deny safe harbor to that testing as not being related to an FDA requirement. It simply does not make any sense.

To this end, the Federal Circuit erred when it stated that the FDA is not interested in the hunt for new drugs. *Integra*, 331 F.3d at 866. Quite the contrary, the FDA is interested in any information that may ultimately end up in the IND and has the right to ask for it. As such, because the IND applicant cannot know just what

information the FDA may require, it stands to reason that the IND applicant be permitted to expand the universe of available information and have it ready for submission should the FDA so require.

II.C. Congress Has Amended § 271(e)(1) Many Times But Has Not Corrected The Perceived Problem.

Congress promulgated § 271(e)(1) in 1984. In 1985, the district court in *Eli Lilly v. AH Robbins*, 228 U.S.P.Q. 757 (E.D. Va. 1985) stripped § 271(e)(1) protection to commercial activity. In 1988, Congress amended that section to add the recombinant DNA provisions. Pub. L. 100-670, §201(i)(1). In 1989, the District of Delaware ruled in *American Standard v. Pfizer*, 722 F.Supp. 86 (D. Del. 1989) that dual use – that is, use that is investigational and commercial – stripped immunity. In 1990, this Court ruled in *Eli Lilly v. Medtronic* that the safe harbor applied to medical devices. In 1991, the court ruled in *Intermedics* that allowed safe harbor to ostensibly unrelated uses. *Intermedics v. Ventritex*, 775 F. Supp. 1269 (N.D. Cal. 1991), *aff'd without op.* 991 F.2d 808 (Fed. Cir. 1993). In 1992, the court decided *Telectronics Pacing Systems v. Ventritex*, 19 U.S.P.Q.2d 1960 (N.D. Cal. 1991), *aff'd* 982 F.2d 1520 (Fed. Cir. 1992), which permitted demonstrations of the device and disseminating data. Also in 1992, *Elan Transdermal v. Cygnus Therapeutics*, 19 U.S.P.Q.2d 1926 (N.D. Cal. 1992) held that circulating test data and results was permissible. In 1993, *Chartex Int'l v. MD Personal Products*, 5 F.3d 1505 (Fed. Cir. 1993)(unpublished opinion) held that Class I and II devices were within the ambit of safety.

Against this backdrop of cases that applied the safe harbor provisions to activities that were at best, ancillary, to the FDA approval process, in 1994 Congress amended § 271(e)(1) yet again. This time, rather than correcting what the patent holders decried as being a perversion of § 271(e)(1), Congress did not address that

concern. Rather it amended to the statute to include the offer-for-sale provisions. Pub. L. 103-465, §533(a)(3)(A) (08 Dec. 1994). Congress gave the statute broad interpretation and knew how to limit the scope if it desired to do so. *Ohio v. Kovacs*, 469 U.S. 274, 279 (1985). Congress legislates against the backdrop of judicial decisions. *FDA v. Brown & Williamson Tobacco*, 529 U.S. 120, 144 (2000)(interpreting the scope of the tobacco regulation under the Food, Drug Cosmetic Act given six subsequent statutes regulating tobacco separately). If Congress was so concerned that the exemption was being too broadly interpreted by this Court in *Eli Lilly* and by the lower courts, Congress can change the law as it desires. *See* also, *TVA v. Hill*, 437 U.S. 153, 185 (1978) ("It is not for us to speculate, much less act, on whether Congress would have altered its stance had the specific events of this case been anticipated").

In sum, if Congress is so concerned about the scope of the safe harbor exemption and that the parade of horribles that "exaggerating §271(e)(1) out of context would swallow the whole benefit of the Patent Act for some categories of biotechnological inventions", *Integra*, 331 F.3d at 867-88, then Congress can fix this. If Congress is perturbed that the exemption is now being applied to new drug development, it can fix it so that it only applies to generic drugs or devices. It is also worth noting that the Integra patents are not worthless. The safe harbor protection terminates once the relevant FDA application is filed (unless the FDA requires post-filing information) and thus Integra can bring the full force of 35 U.S.C. §§ 271(a), (b), and (c)'s traditional patent infringement suits against the infringer.

III. Generic Drug Companies Are Significantly Affected By The Merck Decision As It Stifles Generic Drug Development

At its core, Merck used Integra's patented invention to screen various candidates to determine which candidate could later be further developed into an FDA approved drug. Generic drug companies may, in certain situations, perform the same experiments. If the patented invention is for a formulated drug (e.g., the patent covers: (a) the active ingredient; (b) excipient B; (c) excipient C; and (d) excipient D in a certain percentage range by weight), a generic drug company faces certain quandaries. Can it experiment with immunity by formulating a bioequivalent drug that uses the identical ingredients except that it alters the percentage of "D". Clearly under current § 271(e)(1) interpretation, this would be allowed because it is a direct experimentation of the patented – and FDA approved – branded drug.

But often times, a generic drug company can formulate a bioequivalent drug that switches out an excipient, for example, switches out excipient D for excipient E. That is, it applies for generic drug approval for a formulation comprising drug+A+B+C+E. The quandary is that what if the same party or even a third party patents this formulation. The formulation containing E is not the approved branded drug – the one containing D is. The point is that a generic drug company may have to "screen" or formulate many candidates, e.g., drug+A+B+C+F; drug+A+B+C+G; drug+A+B+C+H; etc., before arriving at the one combination that is bioequivalent to the branded drug. It cannot be that § 271(e)(1) prohibits a generic drug company from screening candidates that may be patented (by others too).

Accordingly, this area of precursor screening is one major area of concern for generic drug companies. The second area of major concern is for ancillary activities.

Ancillary activities are those that are performed during the formulation step – that is, taking the active ingredient in bulk drug form and processing it into the

final dosage form (e.g., a tablet or capsule). For example, the bulk drug can be mixed with excipient A first, then mixed in mixer, then mixed with excipient B, then blended, then dried, the formed into inner cores. The inner cores may then be coated with a coating, and then the coated core may then be lacquered. The product would then be packaged and assembled for transport. At each step of the process, the company must observe Good Manufacturing Practices (GMP's). This means that samples are taken at each step and tested to ensure purity, quality, measure residual excipient levels, etc. Indeed even samples of the final packaged product will be analyzed to ensure that the product meets with GMP's and is made in accordance with the generic drug application. In addition, during development, the ANDA applicant may change process steps to arrive at a formulation. Method/process patents may protect any of those process steps.

As such, there is much "side testing" done that is ancillary to the actual formulation. To this end, to the extent that a patent may exist on "side testing" activities, those activities too must be shielded under the safe harbor provision. For example, if a patent exists on a method of purifying a drug product and this method is in widespread use, then that method will undoubtedly be practiced by the ANDA applicant and will be shielded by the safe harbor provisions.

In sum, whereas the *Integra* case in its factual posture deals with precursor screening/testing for molecules that would become a brand new NDA approved drug, the *Integra* case holding has farther reaching implications that may seriously impact the development of generic drugs *vis a vis* the ANDA process. Finally, patent holders are not left without recourse. As mentioned earlier, the safe harbor is a limited provision that generally terminates with the FDA application (in most cases) or FDA application approval (in rare cases).

The patentee may then bring the full fury of the patent rights against the party.

CONCLUSION

For these reasons, this Court ought to reverse the Federal Circuit's decision and order the court to remand for dismissal.

Respectfully submitted,

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