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* SEPRACOR INC. IN SUPPORT OF NEITHER PARTY

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Sepracor Inc. respectfully submits this brief as *amicus curiae* in support of neither party. This brief is filed with the written consent of all parties.[1]

INTEREST OF THE *AMICUS CURIAE*

Sepracor Inc. is a product-based pharmaceutical company dedicated to treating and preventing human disease through the discovery, development, and commercialization of innovative pharmaceutical products that are directed toward serving unmet medical needs. Sepracor's drug development program has yielded an extensive portfolio of pharmaceutical compound candidates, with a focus on respiratory and central nervous system disorders. Sepracor has launched one product, XOPENEX®-brand levalbuterol, and recently received an approval letter for an NDA on another product, LUNESTA™-brand eszopiclone. Sepracor has a strong interest in ensuring that the scope of 35 U.S.C. § 271(e)(1) is not unduly limited thereby potentially quashing pharmaceutical research, development, and activities directed toward approval of new, beneficial drugs.

SUMMARY OF ARGUMENT

The Court of Appeals misinterpreted the scope of the exemption from infringement under § 271(e)(1), by suggesting that this statutory immunity is limited to activities relating to FDA approval of a generic version of a drug

1. The Parties' letters of consent are attached hereto and have been filed with the Clerk of the Court. This brief was not authored, in whole or in part, by counsel to any party, and none of the parties to this case or their counsel has contributed either substantively or monetarily to the preparation of this brief. Specifically, only the *amicus* and its counsel have made a monetary contribution to the preparation or submission of this brief.

already on the market. The statutory immunity encompasses activities reasonably related to the development and submission of information to the FDA in connection with an Investigational New Drug Application ("IND") or a New Drug Application ("NDA"), as well as an Abbreviated New Drug Application ("ANDA").

Prior to the Court of Appeals' decision in this case, lower courts, including the Federal Circuit, had broadly interpreted the requirement that exempt activities be "reasonably related" to the development and submission of information to the FDA, in accordance with this Court's direction in *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661 (1990).

The Federal Circuit earlier recognized that this Court in *Eli Lilly* did not limit the statutory exemption from infringement under § 271(e)(1) to patents for which a term extension is available under § 156. *Abtox, Inc. v. Exitron Corp.*, 122 F.3d 1019 (Fed. Cir. 1997), *amended on reh'g*, 131 F.3d 1009 (Fed. Cir. 1997). Although the safe harbor includes at least activities covered by all patents which are eligible for extension under § 156, the scope of the immunity conferred by § 271(e)(1) is not limited to subject matter also encompassed by § 156, which is far narrower in scope.

The Federal Circuit in the present case has unduly restricted the scope of the § 271(e)(1) exemption by artificially limiting its application to *clinical* testing of a drug candidate following FDA acceptance of an IND. Neither the language of § 271(e)(1), nor the Hatch-Waxman Act as a whole, defines the outer contours of the § 271(e)(1) exemption solely by reference to clinical testing activities.

The FDA requires many types of data prior to permitting dosing in humans after submission of an IND, and ultimately, to approve a drug. Those data include preclinical or nonclinical data generated before and after IND submission, and even after an NDA submission, as well as human or clinical data generated after an IND is submitted and accepted by FDA.

All of these data, nonclinical and clinical alike, are developed or generated by the applicant in order to seek approval to first test the drug product in humans, and if those tests are successful, to submit an NDA and receive approval from the FDA to launch and commercialize the drug product, and, thus, are activities that should be within the § 271(e)(1) exemption.

ARGUMENT

I. The Safe Harbor Of § 271(e)(1) Encompasses New Drugs

In construing the scope of the § 271(e)(1) infringement exemption, the Federal Circuit misinterpreted the legislative history of the statute in concluding that the policies underlying the Drug Price Competition and Patent Term Restoration Act of 1984 (the "Act" or the "Hatch-Waxman Act")[2] require a narrow interpretation of this provision. The Court of Appeals considered that Scripps' research activities were not exempt because "the § 271(e)(1) safe harbor clearly covers those pre-expiration activities 'reasonably related' to acquiring FDA approval of a drug already on the market." *Integra Lifesciences I, Ltd. v. Merck*

2. Pub. L. No. 98-417, 98 Stat. 1585 (codified as amended at 21 U.S.C. § 355 (2000); 35 U.S.C. §§ 156, 271, 282 (2000)).

KGaA, Nos. 02-1052, -1065, 2003 U.S. App. LEXIS 27796 at *17 (Fed. Cir., June 6, 2003). Focusing on the context of the safe harbor as originally keyed to facilitating expedited approval of generic versions of commercialized, patented pioneer drugs, the Federal Circuit reasoned that the exemption was confined to activity that "would contribute (relatively directly)" to information the FDA considers in approving a generic drug, and that a further extension would violate any *de minimis* encroachment on the rights of the patentee. *Id*. at *17-18. The Federal Circuit in an amended opinion acknowledged, however, that the exemption was not limited to generic drug approval, citing this Court's decision in *Eli Lilly & Co. v. Medtronic*, *Inc.*, 496 U.S. 661, 674 (1990).[3] Positing that exempt activity is limited to human clinical trials, the Court of Appeals indicated that the exemption does not "embrace all stages of the development of new drugs merely because those new products will also need FDA approval." 2003 U.S. App. LEXIS 27796 at *17.

The Federal Circuit's holding is based on an overly narrow and legally incorrect construction of 35 U.S.C. § 271(e)(1), which is plainly inconsistent with this Court's interpretation of the "reasonably related" language in *Eli Lilly*. The Court of Appeals based its construction on the incorrect factual assumption that "[t]he FDA has no interest in the hunt for drugs that may or may not later undergo clinical testing for FDA approval [and that] . . . the FDA does not require information about drugs other than the compound featured in an Investigational New Drug application."

3. In view of the revisions to the Federal Circuit's published opinion at 331 F.3d 860, citations herein are to the electronic version containing the corrections, *Integra LifeSciences I, Ltd. v. Merck KGaA*, Nos. 02-1052, -1065, 2003 U.S. App. LEXIS 27796 (Fed. Cir., June 6, 2003).

2003 U.S. App. LEXIS 27796 at *15. The language of the Act does not limit the scope of the safe harbor exemption from infringement under § 271(e)(1) to drug patents, nor does the statute distinguish between classes of potential infringers (whether innovator companies or generic manufacturers). The statute provides a general exemption from infringement of "a patented invention" without any subject matter limitation on the *nature* of the patented invention.[4]

Indeed, this Court in *Eli Lilly* construed § 271(e)(1) in the context of the Hatch-Waxman Act as a whole, and concluded that "patented invention" as set forth in § 271(e)(1) was not limited to drug-related inventions alone. 496 U.S. *at* 665-66. Contrary to the Federal Circuit's assumption concerning the public policy expressed in the legislative history, in *Eli Lilly* this Court adopted a broad interpretation of § 271(e)(1), *id.* at 665, noting the lack of clear congressional intent to limit the statute to drug products. *Id.* at 667. This Court did not distinguish among the various beneficiaries of the § 271(e)(1) exemption in *Eli Lilly*, and the language of § 271(e)(1) does not limit the exempt activities to those of generic manufacturers. From the standpoint of new drug innovators such as Sepracor, a central flaw of the Federal Circuit's analysis is the distortion of the safe harbor provision which results when the statute is viewed solely from the perspective of developing the limited information that is necessary for filing an Abbreviated New Drug Application ("ANDA") relating to a generic version of an existing drug.

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4. This Court's decision in *Eli Lilly* foreclosed the possibility that the scope of "patented invention" could be narrowed to limit the exemption to specific categories of invention, such as generic drugs, new drugs, or medical devices, because the Court stated that "[t]he phrase 'patented invention' in § 271(e)(1) is defined to include all inventions, not drug-related inventions alone." 496 U.S. at 665.

In the 15 years following *Eli Lilly*, Congress has not acted to limit this Court's reasoned interpretation of § 271(e)(1), which includes in its safe harbor new drugs as well as generic drugs and medical devices. At issue in the present case is the scope of activities that are "reasonably related" to the development and submission of data to FDA in connection with INDs and NDAs seeking regulatory approval of new drugs.

II. Courts Have Interpreted "Reasonably Related" Broadly In View Of *Eli Lilly*

Since this Court's decision in *Eli Lilly*, lower courts have broadly construed the contours of the exemption in a manner consistent with *Eli Lilly* and the language of the statute, holding that § 271(e)(1) is not limited solely to generic drug products,[5] or to clinical research,[6] or to infringement of a patent for which an extension is available under § 156.[7] Rather, when the statute is construed in view of the entirety of the Hatch-Waxman Act, the exemption is available to *all*

5. *See*, *e.g.*, *NeoRx Corp. v. Immunomedics*, *Inc.*, 877 F. Supp. 202, 205 (D.N.J. 1994) (process for labeling antibodies with radioactive metal isotopes to detect and treat cancer); *Nexell Therapeutics*, *Inc. v. Amcell Corp.*, 199 F. Supp. 2d 197, 205 (D. Del. 2002) (method for preparing purified suspensions of human stem cells using patented antibodies, and patented magnetic cell separation device).

6. *See*, *e.g.*, *Intermedics*, *Inc. v. Ventritex*, *Inc.*, 775 F. Supp. 1269 (N.D. Cal. 1991), *aff'd*, 991 F.2d 808 (Fed. Cir. 1993); *Telectronics Pacing Systems*, *Inc. v. Ventritex*, *Inc.*, 982 F.2d 1520 (Fed. Cir. 1992).

7. *See*, *e.g.*, *Abtox*, *Inc. v. Exitron Corp.*, 122 F.3d 1019 (Fed. Cir. 1997), *amended on reh'g*, 131 F.3d 1009 (Fed. Cir. 1997).

uses of *any* "patented invention" that are "reasonably related" to development of data and submission of data under a Federal law regulating drugs.

A year after *Eli Lilly* was decided, the district court in *Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269 (N.D. Cal. 1991), *aff'd*, 991 F.2d 808 (Fed. Cir. 1993) (unpublished opinion), considered whether the statutory exemption was limited to activities of infringers who intended to commercialize an infringing product *after* the expiration of a patent, or whether commercial activities commenced *before* patent expiration could be "reasonably related" to regulatory approval. *Id.* at 1273-75. In construing the scope of "reasonably related," the court reasoned that "Congress . . . intend[ed] that the courts give parties some latitude in making judgments about the nature and extent of the otherwise infringing activities they would engage in as they sought to develop information to satisfy the FDA." *Id.* at 1280. The court thus framed its inquiry as to whether it

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

Id. This broad interpretation of "reasonably related" has been widely followed,[8] and was cited by the Federal Circuit in

8. *See, e.g., Abtox, Inc. v. Exitron Corp.*, 888 F. Supp. 6, 8 (D. Mass. 1995), *aff'd*, 122 F.3d 1019 (Fed. Cir. 1997); *NeoRx Corp. v. Immunomedics, Inc.*, 877 F. Supp. 202, 205 (D.N.J. 1994); (Cont'd)

the present case, although the court incorrectly restricted the scope of activity that uniformly has been considered to be exempt under this standard. 2003 U.S. App. LEXIS 27796, at *17 ("Within this framework and language of the 1984 Act, the district court correctly confined the § 271(e)(1) exemption to activity that "would contribute (relatively directly)" to information the FDA considers in approving a drug. *Intermedics*, 775 F. Supp. at 1280.").

The Federal Circuit's restrictive interpretation of § 271(e)(1) in the present case contrasts markedly with its earlier decisions, which correctly followed this Court's decision in *Eli Lilly*, and adopted an expansive interpretation of the immunity from infringement conferred by the safe harbor provision. In *Telectronics Pacing Systems*, *Inc. v. Ventritex*, *Inc.*, 982 F.2d 1520 (Fed. Cir. 1992), the Federal Circuit's first published decision addressing the "reasonably related" language of § 271(e)(1), the court confirmed that the demonstration of a defibrillator at medical conferences was "solely for uses reasonably related to clinical trial purposes," and was exempt from infringement under § 271(e)(1). The Federal Circuit thus rejected the view that

(Cont'd)

Amgen, *Inc. v. Hoechst Marion Roussel*, *Inc.*, 3 F. Supp. 2d 104, 108 (D. Mass. 1998); *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer*, *Inc.*, No. 95 Civ. 8833 (RPP), 2001 U.S. Dist. LEXIS 19361, at *12 (S.D.N.Y. Nov. 28, 2001); *Nexell Therapeutics*, *Inc. v. Amcell Corp.*, 199 F. Supp. 2d 197, 205 (D. Del. 2002); *Elan Transdermal*, *Ltd. v. Cygnus Therapeutic Sys.*, No. C-91-1413 (WHD), 1992 U.S. Dist. LEXIS 20004, at *20 (N.D. Cal. June 23, 1992). As the district court in *Amgen* observed, "[t]he test is prospective, in that it evaluates the potential infringer's activities at the time they were undertaken, and objective, in that it does not concern itself with the potential infringer's state of mind. It thus acknowledges the inherently unpredictable nature of the FDA approval process." *Amgen*, 3 F. Supp. 2d at 108.

the word "solely" in § 271(e)(1) "requires that the original exemption of the making, using and selling activities be revoked when the resulting data is later used for non-FDA reporting purposes." *Id.* at 1524.

The Court of Appeals further extended the reasoning of *Eli Lilly* in *Abtox, Inc. v. Exitron Corp.*, 122 F.3d 1019 (Fed. Cir. 1997), *amended on reh'g*, 131 F.3d 1009 (Fed. Cir. 1997), in considering (as a matter of first impression) whether Class II medical devices were subject to the exemption of § 271(e)(1).[9] Abtox argued that the § 271(e)(1) exemption did not include a Class II device, because it was not eligible for patent term extension under § 156.[10] The Federal Circuit rejected this argument, reasoning that although only Class

9. In an earlier nonprecedential decision in *Chartex Int'l PLC v. M.D. Personal Prods. Corp.*, No. 92-1556, 1993 U.S. App. LEXIS 20560, at *5 (Fed. Cir. Aug. 12, 1993), the court declined to read limitations that might have applied to § 156 into § 271(e)(1). The patent owner in that case alleged that its female condom, which was a Class I or Class II medical device, was outside the scope of § 271(e)(1) because neither a Class I nor a Class II medical device is eligible for a patent extension under § 156. *Id*. at *2-5.

10. *Abtox*, 122 F.3d at 1027-28. 35 U.S.C. § 156(g)(3)(B) limits the regulatory review period for medical devices to those that require review under § 515 of the Federal Food Drug and Cosmetic Act ("FDCA") (21 U.S.C. § 360e), which applies only to Class III devices. *Id*. In *Eli Lilly*, this Court reasoned that the symmetry between § 156 (patent term extension) and § 271(e)(1) (infringement exemption) was preserved for Class III devices, stating that "[i]nterpreting § 271(e)(1) as the [Federal Circuit] did here appears to create a perfect 'product' fit between the two sections. All of the products eligible for a patent term extension under [§ 156] are subject to [§ 271(e)(1)], since all of them . . . are subject to premarket approval under various provisions of the FDCA." 496 U.S. at 673-74.

III devices fell within the § 271(e)(1) exemption under this Court's "narrower justification of statutory symmetry" in *Eli Lilly*, all classes of medical devices fell within the plain meaning of section 271(e)(1) under the broad holding of *Eli Lilly*. *Abtox*, 122 F.3d at 1029. Citing "potential conflict" between *Eli Lilly*'s "broader holding" and "its own narrower reasoning," the Federal Circuit stated:

> Section 271(e)(1) makes no distinctions based upon the different FDA classes of medical devices or drugs. Moreover, the Court explicitly accepted a statutory interpretation "in which a patentee will obtain the advantage of the [section 156] extension but not suffer the disadvantage of the [section 271(e)(1)] noninfringement provision, and others in which he will suffer the disadvantage without the benefit." 496 U.S. at 671-72. In other words, the Supreme Court commands that statutory symmetry is preferable but not required.

Abtox, 122 F.3d at 1029 [brackets in original]. The issue of whether symmetry between § 271(e)(1) and § 156 restricts the safe harbor to those patents covering products and methods specified in § 156 has seldom arisen following the Federal Circuit's decision in *Abtox*.

III. The Statute Does Not Limit The § 271(e)(1) Safe Harbor To Patents For Which A Term Extension Is Available Under § 156

Section 271(e)(1) was enacted as part of the Hatch-Waxman Act and was intended to remedy two opposing distortions of a patent term associated with FDA's regulatory approval process for drugs: (1) the time required for

premarketing approval of generic versions of innovator drugs (creating a *de facto* patent term extension); and (2) the effective patent term reduction based on the lengthy FDA approval process for innovator drugs. *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. at 669-73.

Although the legislative history of the Hatch-Waxman Act undoubtedly contemplates a relationship between the § 156 extension and § 271(e)(1) exemption, the language of § 271 does not require symmetry, and neither this Court nor the Federal Circuit has grafted a symmetry requirement into the language of § 271(e)(1). Nor has Congress chosen to modify the language of § 271(e)(1) to incorporate such a requirement. The exemption has been available to uses of a patented invention without regard to whether the patented invention is eligible for patent term extension under § 156, since the Federal Circuit's decision in *Abtox v. Exitron*, 122 F.3d 1019 (Fed. Cir. 1997), *amended on reh'g*, 131 F.3d 1009 (Fed. Cir. 1997).[11]

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11. In *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*, No. 95 Civ. 8833 (RPP), 2001 U.S. Dist. LEXIS 1936, at *12 (S.D.N.Y. Nov. 28, 2001), the court followed *Eli Lilly* and *Abtox* in holding that "[n]othing in the text of Section 271(e)(1) indicates that Congress intended to restrict the scope of the term 'patented invention' to those products covered by Section 156." *Id.* at *6. *But see Infigen, Inc. v. Advanced Cell Tech., Inc.*, 65 F. Supp. 2d 967, 980 (W.D. Wis. 1999) ("§ 271(e)(1) applies only to those patents identified in § 156(a)(4) and (5) that, among other things, cover certain specified products (including drug products, *see* § 156(f)) that were subject to a regulatory review period before their commercial marketing or use."); *Baxter Diagnostics, Inc. v. AVL Scientific Corp*, 798 F. Supp. 612, 619-20 (C.D. Cal. 1992) (relying on *Eli Lilly* in holding that the scope of the § 271(e)(1) exemption was limited to products that are also subject to a regulatory review period under § 156).

In *Eli Lilly*, this Court noted a symmetry between the infringement exemption under § 271(e)(2) and the patent term extension provisions of § 156, both of which were enacted as a compromise between the interests of drug patent owners and generic manufacturers, and construed the safe harbor provision based on "the structure of the 1984 Act taken as a whole." 496 U.S. at 669. The Court considered that

> [i]nterpreting § 271(e)(1) as the Court of Appeals did here appears to create a perfect 'product' fit between the two sections. All of the products eligible for a patent term extension under [§ 156] are subject to [§ 271(e)(1)], since all of them – medical devices, food additives, color additives, new drugs, antibiotic drugs, and human biological products – are subject to premarket approval under various provisions of the FDCA.[12]

Although the Court contemplated the possibility that "there may be some relatively rare situations in which a patentee will obtain the advantage of the [§ 156] extension but not suffer the disadvantage of the [§ 271(e)(1)]

12. 496 U.S. at 673-74. This Court also acknowledged that the correlation between § § 156 and 271(e)(1) was destroyed in 1986, when, without adding "new infant formula" to the defined products eligible for the patent-term extension under § 156, Congress established a premarket approval requirement for that product, and thus automatically rendered it eligible for the § 271(e)(1) exemption from patent infringement. 496 U.S. at 674 n.6. This Court stated "[t]hat subsequent enactment does not change our view of what the statute means," considering that this "isolated lack of correlation between § 156 and § 271(e)(1) is in any event contradicted by the 1988 amendment that added most new animal drugs and veterinary biological products to § 156 and simultaneously deleted from § 271(e)(1) the infringement exception for those products." *Ibid.*

noninfringement provision, and others in which he will suffer the disadvantage without the benefit" it observed that "[w]e cannot readily imagine such situations (and petitioner has not described any) except where there is good enough reason for the difference." 496 U.S. at 671-72 and n.4. Since this Court's decision in *Eli Lilly*, such situations have been illustrated by decisions including *Abtox*[13] and the present case, in which none of the patents at issue claims a drug product, or method of making or using a drug product, that was subject to regulatory review, as required for a term extension under § 156(a)(4).

In *Eli Lilly*, this Court reasoned that the Hatch-Waxman Act was intended to reduce the "dual distorting effects of regulatory approval requirements in this entire area" and concluded that Congress did not intend to provide medical devices with a term extension under § 156, without also granting competitors an exemption from infringement under § 271(e). 496 U.S. at 672. Otherwise, Congress would have enacted "provisions which not only leave in place an anticompetitive restriction at the end of the monopoly term but simultaneously expand the monopoly term itself, thereby not only failing to eliminate but positively aggravating distortion in the 17-year patent protection." *Id.* at 672-73.

Under this Court's analysis, it was necessary to construe the scope of the safe harbor exemption to include *at least* activities covered by all patents which are eligible for term

13. *See also Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*, No. 95 Civ. 8833 (RPP), 2001 U.S. Dist. LEXIS 19361 (S.D.N.Y. Nov. 28, 2001). The patent at issue in that case covered semi-synthetic processes for preparing the drug taxol, and chemical intermediates (taxane derivatives) obtained during and used in the process, none of which was subject to regulatory review by the FDA. *Id.* at *5-*6.

extension under § 156.[14] No similar reasoning requires that § 271(e)(1) should be *limited* to subject matter also encompassed by § 156.

The primary purpose identified by the legislature in enacting § 271(e)(1) was to ensure that generic drug makers could proceed to obtain FDA approval prior to the expiration of "pioneer" drug patents. Since commercialization of generic drugs following FDA approval is not similarly immunized from infringement by § 271(e)(1), Congress concluded that infringing activities reasonably related to securing regulatory approval should be permitted as *de minimis* violations of the patent right. Until a new drug application (either NDA or ANDA) is approved by the FDA, any activities by an applicant relating to testing, manufacturing, or use of a drug candidate compound for purposes of developing information reasonably related to regulatory review are similarly limited in scope, regardless of whether a patent covering the compound is eligible for extension under § 156.

The scope of § 156 is narrowly limited because the term "drug product" used therein means the active ingredient of a new drug, antibiotic drug, or human biological product.[15] Some compounds, such as chemical intermediates that are

14. Section 156(a) provides an extension of patent term for "a patent which claims a product, a method of using a product, or a method of manufacturing a product," but only if the patent is subject to a regulatory review period before its commercial marketing or use. *See* § 156(a)(4).

15. 35 U.S.C. § 156(f)(2)(A). A drug product includes "any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient," and also encompasses certain new animal drug or veterinary products. *Id*. § 156(f)(2)(B).

necessary to synthesize a new drug product, are not themselves the active ingredient of a new drug, and patents covering such compounds are not eligible for extension under § 156. In such circumstances, a patent owner should not be permitted to foreclose all use of the patented compound by electing to sue a company who undertakes the costly development of a new drug, based on the argument that the patent owner is unable to obtain a term extension for a patent covering a chemical intermediate used in synthesizing the new drug. The term extension offset under § 156 was provided to further a quite different public policy, which is to compensate pioneer drug patent owners who are successful in obtaining FDA approval and successfully commercialize a drug, for the loss of enforceable patent term required by regulatory delay at the beginning of the patent term.

A significant difference exists between the single patent eligible for term extension under § 156,[16] and entire "families" of patents that may be infringed in developing information for submission to the FDA in connection with an IND, NDA, or ANDA. A pharmaceutical company generally seeks to obtain a number of patents relating to its brand-name drug,[17] typically directed to at least: (1) the drug

16. Under § 156(a), only *one* patent owned by the NDA holder is eligible for patent term extension, regardless of how many patents the NDA holder may have that cover a drug product. *See*, *e.g.*, *Fisons plc v. Quigg*, 876 F.2d 99 (Fed. Cir. 1989) (patented new uses and doses for active ingredient do not qualify as first permitted use of active ingredient); *see also*, 35 U.S.C. § 156(c)(4).

17. *See*, *e.g.*, *Eli Lilly & Co. v. Barr Lab.*, 251 F.3d 955 (Fed. Cir. 2000) (discussing Eli Lilly's family of patents covering fluoxetine hydrochloride, the active ingredient in Prozac®, and methods of administering this compound to inhibit serotonin uptake in the neurons of an animal's brain).

product or active pharmaceutical ingredient ("API") *per se*; (2) compositions comprising the API; (3) methods of using the API; and (4) methods of making the API. Additional patents may also claim, *e.g.*, polymorphs or metabolites of the API, or intermediate compounds used to produce the API. In addition, each of these categories of claims may be recited in different patents owned by the pharmaceutical company.

However, only patents containing certain categories of claims relating to the drug product are eligible for term extension under § 156. From the perspective of § 156, there are at least three types of "patented inventions" that could be infringed during the course of developing and submitting information to FDA to support an IND, NDA, or ANDA: the single patent for which patent term extension is requested on an approved drug product; other patents that were once eligible for extension but are no longer eligible due to the selection of the single patent; and patents that were never eligible for extension under § 156, such as patents covering compounds for which regulatory approval was never sought or granted, patents covering polymorphs of an approved drug,[18] intermediates used in the manufacture of the drug,[19] new combinations of active

18. "Polymorphic" forms of a drug compound include different crystalline forms, amorphous forms, as well as solvate forms and hydrate forms of the active ingredient. *See*, *e.g.*, FDA, *Guidance for Industry – ANDAs: Pharmaceutical Solid Polymorphism*, *Chemistry*, *Manufacturing and Controls Information* (November 23, 2004), *available at* http://www.fda.gov/cder/guidance/6154dft.pdf. Under certain circumstances, a polymorphic form of an approved drug may be approved in an ANDA, but a patent covering such a variant is not subject to term extension under § 156 if the variant is not the form in the approved product.

19. *See*, *e.g.*, *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer*, *Inc.*, No. 95 Civ. 8833 (RPP), 2001 U.S. Dist. LEXIS 1936 (S.D.N.Y. Nov. 28, 2001) (patent claiming chemical intermediates, which are not subject to FDA regulation, that are used to produce the drug taxol).

ingredients,[20] new chemical forms of an active ingredient,[21] or metabolites of the drug.[22]

For these reasons, although the public policy underlying the Hatch-Waxman Act requires that all activities that are covered by patents subject to extension under § 156 also be subject to the exemption under § 271(e)(1), it clearly does not imply that the safe harbor exemption should be limited only to activities that are covered by those few patents which may be extended under § 156.

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20. *See*, *e.g.*, *Arnold Partnership v. Dudas*, 362 F.3d 1338 (Fed. Cir. 2004) (term extension under § 156 was properly denied where both hydrocodone and ibuprofen had been marketed previously, alone or in combination with other ingredients).

21. *See*, *e.g.*, FDA, *Frequently Asked Questions on the Patent Term Restoration Program*, at 3 (¶7), http://www.fda.gov/cder/about/ smallbiz/ patent_term.htm (last visited Feb. 20, 2005) ("Active ingredient does not equal active moiety (generally the molecule or ion responsible for the physiological or pharmaceutical action). A new ester or salt of a previously approved acid is eligible for patent extension, but a new acid of a previously approved salt or ester is ineligible.").

22. *See*, *e.g.*, *Hoechst-Roussel Pharmaceuticals, Inc. v. Lehman*, 109 F.3d 756 (Fed. Cir. 1997) (patent claiming the metabolite 1-hydroxy tacrine is not entitled to term extension based on regulatory approval of tacrine hydrochloride, which metabolizes to 1-hydroxy tacrine *in vivo,* because the patent does not claim the approved compound).

IV. The FDA Requires Data Generated In The *Preclinical* Stage For Activities That Are Exempt Under § 271(e)(1)

In the present case, the Court of Appeals strongly suggested that the statutory exemption first arises when an applicant seeks to clinically test a candidate drug compound pursuant to filing an IND. The most serious deficiency in the Federal Circuit's analysis is its suggestion that the § 271(e)(1) exemption does not apply to data obtained in the *preclinical* stage: "[a]ctivities that do not *directly* produce information for the FDA are already straining the relationship to the central purpose of the safe harbor;" 2003 U.S. App. LEXIS 27796, at *14 (emphasis added); "this court has permitted *clinical* trials and demonstrations of medical devices under § 271(e)(1)." *Id*. at *12. (emphasis added); "[t]his court has not considered [] whether the *pre-clinical* research conducted under the Scripps-Merck agreement is exempt from liability for infringement." *Id*. (emphasis added). Sepracor considers that this interpretation of the statute is too narrow, because data developed in the preclinical stage, including data which must be developed prior to submission of an IND, are not merely "reasonably related" to approval, but are *required* by the FDA to submit a complete IND and commence the regulatory approval process.

Once a compound is selected "with an eye toward submitting an IND"[23] it enters a preclinical stage that is characterized by a host of studies that are different from

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23. *See, e.g.*, *Brief For the United States as Amicus Curiae*, supporting *Merck's Petition for a Writ of Certiorari*, at 12-13 (December 2004).

(and usually more extensive than) those previously conducted. Typical examples include the following:

(a) studies on the physical, chemical and pharmaceutical properties of the compound and its formulation such as solubility studies and an assessment of storage conditions and shelf life;[24]

(b) nonclinical pharmacology studies to assess potency and safety in various animals;[25]

(c) pharmacokinetics and product metabolism studies in animals to evaluate absorption, metabolism, distribution, metabolism and excretion;[26]

(d) toxicology studies that include in vitro and in vivo genotoxicity and carcinogenicity studies and reproductive and developmental toxicity studies in animals;[27]

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24. *See*, *e.g.*, 21 C.F.R. § 312.23(a)(5); FDA, *Investigational New Drug Application*, *available at* http://www.fda.gov/cder/handbook/indbox.htm (last visited Feb. 19, 2005); FDA, *Chemistry Review*, *available at* http://www.fda.gov/cder/handbook/chemisti.htm (last visited February 14, 2005).

25. *See*, *e.g.*, 21 C.F.R. § 312.23(a)(5), (a)(7), (a)(8).

26. 21 C.F.R. § 312.23(a)(8).

27. *Id.*, *see also* FDA, *Pharmacology/Toxicology Review*, *available at* http://www.fda.gov/cder/handbook/pharmaci.htm (last visited February 14, 2005); FDA, *Pre-Clinical Research*, *available at* http://www.fda.gov/cder/handbook/preclin.htm (last visited February 14, 2005).

(e) safety and efficacy in laboratory models and animals;[28]

(f) bioavailability studies;[29]

(g) formulation studies testing for both physical and chemical stability at accelerated temperatures.[30]

These are studies that are typically not performed until a drug candidate has entered the preclinical stage, and use of patented inventions to perform these activities should be exempt under § 271(e)(1). Other types of nonclinical activities performed by the applicant prior to IND submission through NDA filing may include ADME[31] studies, such as stability, metabolism, dosing, and plasma protein binding studies; chemistry and pharmaceutical studies, such as synthetic method scale-up, chemical stability studies, determination of commercial synthesis route, salt selection, form (*e.g.*, polymorph) screening, particle size studies, and pre-formulation and formulation studies. These tests are described in FDA's Investigator's Brochure, 21 C.F.R. § 312.23(5), [32] and use of patented inventions to obtain data

28. *See* 21 C.F.R. § 312.23(a)(5), (a)(7).

29. 21 C.F.R. § 320.

30. *See* note 28, *supra*.

31. ADME is an acronym for absorption, distribution, metabolism, excretion.

32. An investigator's brochure contains: (i) a description of the drug substance and its formulation; (ii) a summary of the pharmacological and toxicological effects of the drug in animals and, to the extent known, in humans; (iii) a summary of the (Cont'd)

in any of the foregoing categories should be exempt from claims of infringement under § 271(e)(1).

Certainly, generic manufacturers must submit to FDA various types of preclinical or nonclinical data concerning the testing, manufacture, and formulation of generic versions of pioneer drugs as described in some of the above-referenced categories. Thus, it would be anomalous and contrary to clear legislative intent to interpret § 271(e)(1) in any manner other than that such activities are exempt under § 271(e)(1).

(Cont'd)
pharmacokinetics and biological disposition of the drug in animals and, if known, in humans; (iv) a summary of information relating to safety and effectiveness in humans obtained from prior clinical studies; and (v) a description of possible risks and side effects to be anticipated on the basis of prior experience with the drug under investigation or with related drugs, and of precautions or special monitoring to be done as part of the investigational use of the drug. 21 C.F.R. § 312.23(5).

CONCLUSION

For the foregoing reasons, Sepracor urges the Court to confirm that the safe harbor exemption extends to activity prior to commencement of FDA proceedings, and encompasses the use of patented compounds and intermediates which are not themselves subject to a term extension under § 156.

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