Nos. 03-1227 & 03-1258

United States Court of Appeals
For The Federal Circuit

PFIZER INC.
Plaintiff - Appellant,

v.

DR. REDDY'S LABORATORIES, INC. AND
DR. REDDY'S LABORATORIES LTD.
Defendants - Appellees.

On Appeal from the United States District Court for the District of New Jersey

BRIEF OF AMICUS CURIAE WASHINGTON LEGAL FOUNDATION IN SUPPORT OF APPELLANT PFIZER, INC.

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IDENTITY AND INTEREST OF *AMICUS CURIAE*

The Washington Legal Foundation (WLF) is a public interest law and policy center located in Washington, D.C. with supporters in all fifty States. WLF's mission is to promote legal policies that preserve the Nation's free enterprise system. WLF has participated as a party or as *amicus curiae* in numerous cases before the Supreme Court, this Court and other federal and state appellate courts, including specifically cases involving health-care delivery. *E.g.*, *PhRMA* v. *Concannon*, No. 01-188, *cert. granted*, 122 S. Ct. 2657 (2002); *WLF* v. *Friedman*, 13 F. Supp. 2d 51 (D.D.C. 1998), *appeal dismissed*, 202 F.3d 331 (D.C. Cir. 2000) (WLF's successful challenge to constitutionality of FDA's restrictions on off-label use of FDA-approved products).

WLF believes that both innovator and generic pharmaceutical manufacturers play important roles in the health care system. If advances in health care are to continue, innovator companies must have a substantial and meaningful period of exclusivity during which potential competitors may not market the new therapeutic substances the innovators invented and patented. This period of exclusivity provides the economic incentive and the flow of capital necessary to promote further innovation.

Congress balanced the innovators' interests against the legitimate goal of lowering drug prices through competition *after* patents expire. WLF has filed

briefs urging that the balance be maintained. *E.g.*, *Mylan Laboratories, Inc.* v. *Thompson*, 268 F.3d 1323 (Fed. Cir. 2001), *cert. denied*, 123 S. Ct. 340 (2002); *Allergan, Inc.* v. *Alcon Laboratories, Inc.*, No. 02-1449 (Fed. Cir.) (pending).

WLF submits this brief to explain why a sound interpretation of the patent extension statute is necessary to implement Congress's objective of stimulating adequate capital investment in the invention and marketing of new medicines.

INTRODUCTION

The patent term extension (PTE) provision in the Drug Price Competition and Patent Term Restoration Act of 1984, 35 U.S.C. § 156 ("Hatch-Waxman"), reflects the "economic philosophy" behind the constitutional clause empowering Congress to grant patents: "the conviction that encouragement of individual effort by personal gain is the best way to advance public welfare through the talents of … inventors in 'Science and useful Arts.'" *Mazer* v. *Stein*, 347 U.S. 201, 219 (1954). As the Supreme Court recently explained in *Eldred* v. *Ashcroft*, 123 S. Ct. 769, 787 (2003), Congress many times has recognized that lengthening patent terms may be necessary to achieve the goal of encouraging investment in creative scientific innovation.

Indeed, "patents are generally thought to be more important to foster innovation in the pharmaceutical industry than in most other industries." K. Viscusi *et al.*, THE ECONOMICS OF ANTITRUST & REGULATION 820 (3d ed. 2000). In

enacting the patent term extension under Hatch-Waxman, Congress recognized that the need to provide incentives for innovative drug research to improve the current drug inventory was at least as important as making more of the current inventory available at the lower prices offered by generics.

The district court's decision sharply reduced the economic value of Pfizer's extended patent by restricting its coverage to only a single salt form of a compound while allowing a generic competitor to make and sell a different salt form of a compound using the exact same active ion that Pfizer invented and patented. That decision significantly undercuts these R&D incentives by effectively nullifying the patent term extension as a protection against a class of products that come within the extended patent and are designed to compete with the pioneer drug. The district court's approach legitimizes poaching on patented drug innovation, allowing a competitor to make and sell a product that contains the same patented, pharmacologically active substance, has the same therapeutic use, and varies only in the substitution of one non-therapeutic "counter-ion" for another. That result cannot be reconciled with the policy judgment Congress made in promising *meaningful* patent extensions to pharmaceutical companies that invent and patent new therapeutic agents.

ARGUMENT

I. THE COMPLEXITY OF DRUG DEVELOPMENT AND THE ECONOMICS OF THE INNOVATOR PHARMACEUTICAL INDUSTRY REQUIRE A SUBSTANTIAL AND EFFECTIVE PERIOD OF PATENT PROTECTION FOR NOVEL THERAPEUTIC SUBSTANCES

A. The Chemistry of Drug Development Shows That Protection Of The Therapeutically Active Ion Is Central

1. The process of inventing and developing a new drug generally begins with identifying an appropriate therapeutic target (such as an enzyme implicated in a disease) and assaying thousands of chemical compounds against it. For each compound that demonstrates biological activity, numerous chemical analogs are developed and tested. From a library of thousands of compounds, only one or two will be selected for preclinical development. The compounds that are synthesized at this stage usually are still in the free acid or base form, *i.e.*, not yet compounded as a salt or ester. While the free acid or base form may provide the sought-after pharmacological activity, certain chemical and physical characteristics (*e.g.*, problems with solubility, stability and bio-availability) generally make free acids or bases unsuitable for *in vivo* pharmaceutical use.

By the time a promising new drug candidate emerges from preclinical testing, it includes more than the therapeutic agent in free acid or base form. Instead, the active ion is combined with an acid or base counter-ion ("anion") to produce an "addition salt." (An alternative is to use alcohol, which may react with

the active ion to produce an "ester.") An acid-addition salt is used to improve such characteristics for *in vivo* use as solubility, stability, and processing.[1] One goal of salt selection is improving oral absorption of the active ion, as salt forms generally dissolve faster in water. For many decades, the vast majority of drug products that reach patients have not been free acids or free bases, but generally salts or esters.

The two anions involved in this case, maleate and besylate, are commonly used by manufacturers of pharmaceutical products to combine with the active ion to form a salt. The salts do not change the intrinsic properties of the active agent.[2] In all cases, it is the newly invented molecule that has the therapeutic activity. The standard anions used to form the salts have simpler structures than therapeutic ions. They are common, "off the shelf" items. Testing this limited universe of compounds is a far less challenging exercise than discovering the initial therapeutic agent itself. Once an innovator company identifies a therapeutically active ion and selects a salt formulation for it, it is relatively simple for a copycat manufacturer to take that same new drug compound and formulate it as a different salt. Without investing a dollar for independent research, a copycat manufacturer thus could obtain a variant of the same exact drug compound that is offered for the same

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[1] Hoff, *Preserving the Environment for Innovation: The Challenge to Society and Industry*, 29th Annual Meeting of Pharmaceutical Manufacturers' Association 11-12 (May 1987).

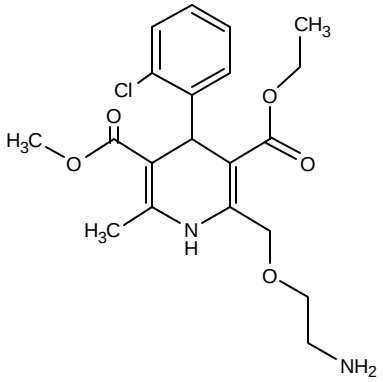
[2] Remington, THE SCIENCE AND PRACTICE OF PHARMACY 704 (20th ed. 2000).

medical use—unless, of course, the innovator's patent as extended prohibits such copying.

2. The patent in this case and the two products at issue, each of which practices the patent, illustrate these principles. Pfizer's Patent No. 4,572,909 claims the amlodipine molecule (claim 8) with the following structure:

Amlodipine

3-ethyl-5-methyl-2-(2-aminoethoxymethyl)
-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-
3,5-pyridinecarboxylate



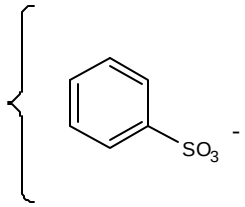
Claim 1 claims all "pharmaceutically acceptable acid addition salts" of a generic structure that encompasses amlodipine.

Maleate and besylate are among the many common counter-ions. Pfizer chose to use besylate in manufacturing and selling amlodipine under the trade name Norvasc®. Dr. Reddy's Laboratories proposes to use maleate in manufacturing and marketing amlodipine during the period covered by the extended patent. The patent, however, expressly states that the "pharmaceutically acceptable acid salts" for its patented amlodipine ion include "maleate." *See* '909 patent, col. 2, lines 4-11. The anions themselves do not have therapeutic activity.

Rather, it is the amlodipine ion present in the salt that benefits the patient suffering from heart disease.

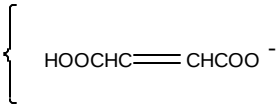
The structure of the besylate counter-ion is:

Besylate

besylate = benzenesulphonate 

The structure of the maleate counter-ion is:

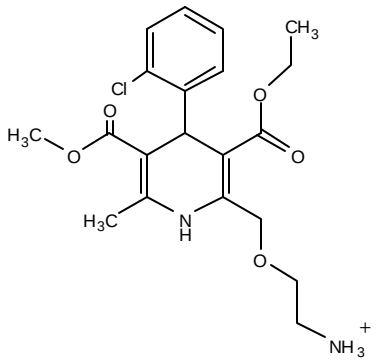
Maleate

maleate = maleic acid 

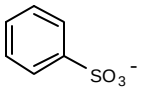
Thus, the structure of Pfizer's amlodipine besylate and Dr. Reddy's amlodipine maleate both contain the same amlodipine ion in addition to the non-therapeutically active acid counter-ions:

AB: Amlodipine besylate

3-ethyl-5-methyl-2-(2-aminoethoxymethyl)
-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-
3,5-pyridinecarboxylate



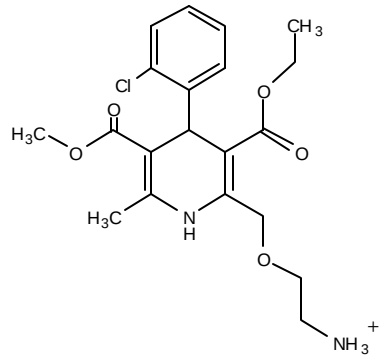
besylate = benzensulphonate



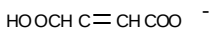
NORVASC — 3-ethyl-5-methyl-2-(2-aminoethoxymethyl)
-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-
3,5-pyridinecarboxylate benzenesulphonate

AM: Amlodipine maleate

3-ethyl-5-methyl-2-(2-aminoethoxymethyl)
-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-
3,5-pyridinecarboxylate



maleate = maleic acid



Dr. Reddy's Drug — 3-ethyl-5-methyl-2-(2-aminoethoxymethyl)
-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-
3,5-pyridinecarboxylate maleic acid

Chemically and therapeutically, therefore, Dr. Reddy's proposes to use the same active substance, the amlodipine ion, that Pfizer patented.

B. Few Potential Innovator Drugs Survive Testing And Lengthy FDA Review

The process of drug development begins with pure scientific research in the screening and discovery phase described above, followed by toxicity testing in animals.[3] An inventor must apply for a patent immediately after the discovery phase or risk not getting a patent. The clock runs on the patent protection period during ensuing testing and regulatory review.

If preclinical testing is successful, the company must file an Investigational New Drug application (IND) with the FDA, which allows it to conduct human testing and clinical trials of safety and efficacy. Those trials take place in three phases: first, testing safe dosage levels and toxicity on fewer than 100 healthy volunteers; second, testing for both safety and efficacy on 50 to 200 people who have the targeted disease; third, drugs that pass both hurdles then are subjected to two controlled clinical trials on thousands of subjects, testing for statistically significant results.

As the history of Pfizer's amlodipine drug indicates, a manufacturer may switch from one salt to the other during testing. Pfizer conducted preclinical and

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[3] *See generally* Congressional Budget Office, *How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry* 15-19 (July 1998) ("*CBO Study*"); DiMasi, *Cost of Innovation in the Pharmaceutical Industry*, 10 J. HEALTH ECON. 107, 110-111 (1991).

clinical trials using both the besylate salt and the maleate salt. The FDA properly considers the drug to have undergone a single continuous review, regardless of such a switch. The drug it ultimately approved, Pfizer's drug Norvasc®, happens to use besylate.

If all trials have been completed successfully, the company files a New Drug Application (NDA). The FDA then subjects the trial data to extensive review and may require additional testing. The drug can be marketed only after the NDA is approved. Although the FDA has accelerated the NDA review process, those gains have been offset by longer periods of clinical testing.

C. The Economics of the Innovator Pharmaceutical Industry Show Why Patents Must Have A Term That Protects Commercially Valuable Drugs Against Competition From Generic Substitutes Using The Same, Novel Active Substance

1. During the period of testing and review, the life of any patent the inventor has obtained is winding down. The Congressional Budget Office explains:

> "For drug manufacturers to be successful, the present value of their future profits from the sale of new products (discounted to the date the products were introduced) must exceed the capitalized cost of their original R&D investment (capitalized to the date of market introduction), including investment in drugs that never make it to market." *CBO Study,* 3.

The costs that must be recovered are substantial, but the drugs that can provide sufficient rewards to cover all the failures are few. On average, developing a single innovative drug that makes it to market takes 10 to 12 years

and costs more than $800 million.[4] The costs account for the expenses associated with developing and testing drugs that never receive marketing approval.

The high cost of pharmaceutical R&D has several causes, including the extensive regulatory testing regime. The complexity of the human body and the need for safety require the involvement of specialists in organic chemistry, physical chemistry, biology, biochemistry, physics, toxicology, pharmacology, pharmacy, statistics, medicine, engineering, and physiology. Innovator pharmaceutical manufacturers spend nearly 20% of sales revenue on R&D. *CBO Study*, 4. That sum now exceeds $30 billion annually. PhRMA, *Pharmaceutical Industry Profile 2002*, 12 (2002).

This system depends on adequate patent protection for the new chemical entity ("NCE") the innovator company invented. As the FTC was told, "about 98

[4] *See* Tufts Center for the Study of Drug Development ("Tufts Center"), *Backgrounder: A Methodology for Counting Costs for Pharmaceutical R&D*, http://csdd.tufts.edu/NewsEvents/RecentNews.asp?newsid=5 (Nov. 2001); DiMasi, *New Drug Development in the United States from 1963 to 1969*, 69 CLINICAL PHARMACOLOGY & THERAPEUTICS 286, 295 (2001); Viscusi, 817; *CBO Study*, 14. Earlier estimates placing the cost of drug development around $200 million derived from DiMasi's 1991 study (see n.3, *supra*); his 2001 Tufts Center study produced the $800 million figure.

percent of the net present value of the pharmaceutical innovation at the time you launch it is tied up in the NCE patent."[5]

The profit stream to support this huge R&D effort follows a predictable pattern. *See CBO Study*, 15-16 & Fig. 3. For the 10-12 years that the drug is under development, it shows a loss, as there is no revenue. After market introduction, returns increase up to the 9th or 10th year (if the patents have not expired), and generally plateau there. *Id.*, 40, 45. Once the patents expire, however, the return declines precipitously, as 40% to 80% of sales shift to generics within the first year.[6] Thus, any judicial decision that effectively shortens the period of patent protection and permits immediate generic competition dramatically reduces the investment capital available to finance further innovation.

2. Several factors explain the speed of this shift to generics once a patent expires — or is judicially deprived of practical significance. Most pharmaceuticals are sold through some type of formulary, such as a hospital, health plan or HMO,

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[5] Testimony of Robert Armitage (at 178), submitted *In re Public Hearing on Competition and Intellectual Property Law and Policy in the Knowledge-Based Economy* (March 2002).

[6] *CBO Study*, 28; Grabowski & Vernon, *Longer Patents for Increased Generic Competition in the US: The Waxman-Hatch Act After One Decade*, PHARMACOECONOMICS, Vol. 10, supp. 2, 110, 121 (1996); Hughes, Moore & Snyder, *"Napsterizing" Pharmaceuticals: Access, Innovation, and Consumer Welfare* 9, comment submitted in Federal Trade Commission, *In re Public Hearing on Competition and Intellectual Property Law and Policy in the Knowledge-Based Economy* (March 2002).

or pharmacy benefits manager (PBM) serving several health plans. Sixty percent of retail drug sales are funded by third-party payors, who also have their own formularies. *CBO Study*, 7, 14. Formularies drive pharmaceutical purchasing (and prescribing) decisions. Thus, once a generic appears on a formulary, it is far more likely to be prescribed.

Moreover, benefits managers promote generic substitution. Pharmacists already have incentives to substitute generics, because they can and do impose greater mark-ups on generics than on pioneer drugs. State laws generally give them the ability to substitute in a broad range of circumstances. *Id.*, 7-8; Grabowski & Vernon, *Longer Patents 1996*, 115-118. Mail-order pharmacies have especially high rates of generic substitution. *CBO Study*, 9.

3. The commitment of the pharmaceutical industry to continuing research and development depends on revenues from a few highly successful, patented products while they are free from generic competition. *CBO Study*, xv, 15. Out of 5,000 chemicals tested on animals, only five go to human testing with an IND; of those five, only one goes to market.[7] "[O]nly three out of ten drugs that are

[7] Tufts Center, *Backgrounder; How New Drugs Move Through the Development Process*, http://csdd.tufts.edu/NewsEvents/RecentNews.asp?newsid =4 (Nov. 2001); DiMasi, *Risks in New Drug Development: Approval Success Rates for Investigational Drugs*, 69 CLINICAL PHARMACOLOGY & THERAPEUTICS 297, 300 (2001).

marketed cover their total costs — including their share of failures." Viscusi, 823. Accordingly, any siphoning of sales revenues derived from the small handful of successful products substantially reduces the capital resources available to investigate and formulate new drugs.

The industry's economics show that the decision below strikes at the heart of the pharmaceutical patent system Congress crafted. The inventor of a patented therapeutic agent would lose the economic benefit that a patent is designed to secure, if a free-riding generic manufacturer could switch the salt form used by the innovator and, by that mere sleight of hand, acquire the right to make and market a competing drug using the active ion patented by the inventor.

II. HATCH-WAXMAN BALANCES GENERIC ACCESS TO ESTABLISHED DRUGS WITH INCENTIVES TO INVENT NEW ONES

Hatch-Waxman attempted to preserve economic incentives for the development of new drugs by "innovative drug manufacturers," while easing the way to *eventual* price competition from "generic drug manufacturers." *Warner-Lambert Co.* v. *Apotex Corp.*, 316 F.3d 1348, 1358 (Fed. Cir. 2003); *see* H.R. Rep. No. 98-857 pt. 1, 14-15 (1984). Before Hatch-Waxman, regulatory delay reduced the effective benefit of a standard patent term significantly before the innovator could begin marketing a product covered by the patent. Congress was particularly concerned that, without patent-term extension, pharmaceutical companies would

lose the incentive to invest in R&D. H.R. Rep. No. 98-857(I), 17. On the other side of the system, the need for separate regulatory approvals delayed generic competition for years after patents expired. Competition also was confined to the most successful drugs. Grabowski & Vernon, *Longer Patents for Lower Imitation Barriers: The 1984 Drug Act*, 76 AM. ECON. REV. 195, 195-196 (1986)).

Hatch-Waxman addressed these twin concerns by amending (in Title I) the FDCA, 21 U.S.C. § 301 *et seq.*, and (in Title II) the Patent Code, 35 U.S.C. To "create a new incentive for increased expenditures for research and development of certain products which are subject to pre-market government approval" (H.R. Rep. No. 98-857(I), 15), Hatch-Waxman allows the PTO to extend the patent term for a new drug to compensate for a portion of the period the drug was undergoing clinical testing and regulatory review and could not be marketed. *See* 35 U.S.C. § 156 (c)-(d). Once the FDA certifies the length of the delay in approving the first product covered by the patent, the PTO then issues a formal extension of "the term of the patent" for a period that reflects a portion of the delay. Since the statute's goal is only to protect against direct competition during the extended period, the extended patent may be enforced only by prohibiting a rival from making and marketing a covered product for the same "use"—such as the treatment of heart disease and hypertension—for which the first product the FDA cleared had been approved. Section 156(b)(1).

Balancing this extension of the innovator's period of exclusivity are amendments making it easier for generic manufacturers to make and sell drugs covered by the patent as soon as the extended term expires. There is an exemption from patent infringement liability for new experimentation and tests with a patented drug. 35 U.S.C. § 271 (e)(1). Amended FDA procedures permit generic entry with significantly less regulatory review than a new drug requires. If a prospective generic entrant's product is "bioequivalent"—having the same effect in the body as an approved drug—the generic can free-ride on the innovator's safety and efficacy studies by filing an Abbreviated New Drug Application ("ANDA"). *See* 21 U.S.C. § 355 (j). Bioequivalence testing is much less expensive than full safety and efficacy testing, and takes only about a year. *CBO Study*, 44; Hughes, Moore & Snyder, 7, 10.

Also amended and liberalized were provisions for "paper NDAs," *see* 21 U.S.C. § 355(b)(2), which rely on published safety and efficacy results. *CBO Study*, 44. Current FDA draft guidance treats "paper NDAs" virtually the same as ANDAs, not only permitting the applicant to free-ride on earlier data about the efficacy of the therapeutic agent, but also on safety data *compiled for a different salt or ester* of the chemical. *See* FDA Center for Drug Evaluation & Research, *Applications Covered by Section 505(b)(2)*, 5 (Draft Guidance for Industry) (Oct. 1999) ("*FDA 505(b)(2) Draft Guidance*"). Dr. Reddy's Laboratories appears to

assume a fully streamlined approval process for its paper NDA for amlodipine maleate, relying on the work that Pfizer did in testing both the besylate and maleate compounds of amlodipine.

The PTE provisions, on average, have added three years to patent life. *CBO Study* 38, 40. But Hatch-Waxman also eliminated what had been, on average, a three-year delay between patent expiration and introduction of the first generic competitor. *Id.*, 38. This accelerated introduction of generics has reduced the average total returns from marketing a new drug by roughly 12%. *Id.*, 38. While the PTE provisions preserved "most of the returns from marketing a new drug" that were available before Hatch-Waxman, they have not fully preserved incentives for innovation. *Id*., 45.

III. LIMITING THE EXTENDED PATENT TO THE PRECISE FORMULA IN THE FIRST APPROVED COMPOUND WOULD UNDERMINE THE INCENTIVES TO INNOVATE THAT SECTION 156 WAS DESIGNED TO PROVIDE

1. The interpretation of the PTE provision should reflect the societal and economic benefits driving its creation. "If Congress had only instituted ANDAs under the 1984 Act, without also addressing the reductions that had occurred in effective patent life because of increased regulation and other factors, there would have been significant adverse consequences for drug innovation incentives." Grabowski & Vernon, *Longer Patents 1996*, 118. Whatever short-lived benefits might result from lowered prices for the current inventory of drugs would be

outweighed by decreased incentives to invest in new, innovative drugs to benefit future consumers. The district court took a dangerous step in this direction.

Hatch-Waxman aimed to achieve dynamic efficiency by balancing the incentive to innovate and achieve desirable future outcomes against the desirable present outcome of lower-cost access to innovative products *after* patents expire. Congress's effort to protect economic incentives to invest for innovation, however, has not been entirely successful. Although patent periods have increased, so have the periods consumed by clinical trials.[8] In addition, despite longer patent terms, product life-cycles are shortening, largely because of rapid rates of sales decay upon generic entry. Grabowski & Vernon, *Longer Patents*, 121.

As a result, the balance is again tipping against innovation. The Congressional Budget Office concluded that incentives to innovate, measured by the returns from marketing a new drug, have decreased by 12% since Hatch-Waxman was passed. *CBO Study*, 38.

Against this background, the district court's judicially prescribed erosion in the effect of patent term extensions represents a substantial loss of already-weakened incentives and threatens to deprive future consumers of new and

[8] Grabowski & Vernon, *Longer Patents 1996*, 121-122; Hughes, Moore & Snyder, 7 (Oct. 2002); *CBO Study*, 49.

valuable medicines. That is especially so here, where the decision lays out a roadmap for generic manufacturers to nullify the effect of a patent term extension.

2. Discouraging investment in new drug R&D has substantial social welfare costs. Eliminating patent protection for new drugs would cost consumers $3 in benefits from foregone innovation in new drugs for every dollar gained in reduced prices for the current stock of prescription drugs. Hughes, Moore & Snyder, 33. Similar effects may be extrapolated from piecemeal weakening of patent protection. One may anticipate that the "number of new molecular entities would fall proportional to the drop in profits."[9]

This is not a mere reallocation of fixed resources among businesses; it produces a disproportionately anti-consumer result. Pharmaceutical R&D provides one of the best cost-benefit ratios of any health care program, and is particularly effective in increasing human longevity.[10] It costs $11,000 in medical expenditures to gain one life-year, but "$1,345 in pharmaceutical research and develop-

[9] Testimony of Prof. Edward Snyder before Federal Trade Commission, *In re Public Hearing on Competition and Intellectual Property Law and Policy in the Knowledge-Based Economy* 211 (March 19, 2002).

[10] The disproportion is exacerbated because the decrease in wholesale prices after generic entry is not fully passed on to consumers; rather, pharmacists *increase* their markup, in absolute terms, when they shift consumers from branded drugs to generics. *See* Grabowski & Vernon, *Longer Patents 1996*, 115-118.

ment...yield[s] the same benefit."[11] These benefits result from using *new* drugs instead of older drugs like generics. "[S]ubstitution of new drugs for older drugs led to significant reductions in patient mortality and morbidity, as well as in total medical expenditure."[12] Replacing older drugs with newer drugs in patient use reduces non-drug expenditure 7.2 times as much as it increases drug expenditure.[13] The reductions come primarily from reduced hospital stays, physician office visits, and home health care—and this does not even account for improved quality of life.

A judicial decision increases total treatment costs while worsening medical outcomes, if the decision discourages development of newer, innovative drugs in favor of older, generic drugs and thus reduces consumer access to newer drugs.[14] It makes no sense for judicial intervention to reduce further the modest incentives to innovation contained in Hatch-Waxman.

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[11] Hughes, Moore & Snyder, 15 (citing Lichtenberg, *Sources of the U.S. Longevity Increase, 1960-1997*, NBER Working Paper No. 8755 (Feb. 2002).

[12] Hughes, Moore & Snyder, 15 (citing Lichtenberg, *Are the Benefits of Newer Drugs Worth Their Cost?: Evidence from the 1996 MEPS*, HEALTH AFFAIRS, 241 (Sept.-Oct. 2001).

[13] Lichtenberg, *Benefits and Costs of Newer Drugs: An Update*, Nat. Bur. of Econ. Research Working Paper No. 8996, 1, 5-7 (June 2002).

[14] *See* Hughes, Moore & Snyder, 11-12; *see also* Lichtenberg, *Pharmaceutical Innovation, Mortality Reduction, and Economic Growth*, Nat. Bur. of Econ. Research Working Paper No. 6569, 16-17 (May 1998).

3. In proposing to market a competing compound using Pfizer's patented invention of amlodipine, Dr. Reddy's highlights the perverse disruption of the incentive system. Without conducting any novel research itself, Dr. Reddy's is taking advantage of Hatch-Waxman's accelerated paper NDA approval process. This process uses any published data arising from Pfizer's trials of the patented amlodipine maleate and amlodipine besylate compounds, and similar confidential data submitted with the NDA for Norvasc®. It is absurd to construe the patent laws and the FDA's approval processes to *penalize* manufacturers who publish clinical results for a variety of salts and esters covered by their patent or submit such results in a confidential NDA. The patent laws in particular should be interpreted to *encourage* the dissemination of useful data, in accord with the most fundamental policy of those laws, which require "disclosure" as "the *quid pro quo* of the right to exclude." *J.E.M. AG Supply, Inc.* v. *Pioneer Hi-Bred Int'l, Inc.*, 534 U.S. 124, 142 (2001). The idea that disclosing a safety aspect of an already patented invention could limit patent protection for the invention is worthy of *Alice in Wonderland*, but is foreign to our intellectual property regime.

Where the plain language of the statute accords with sound economics and public policy, and an artificially restrictive reading would have deleterious effects, the Court's choice should be easy. The patent term extension should extend to the full scope of the patent, enforceable against any infringing compound intended for

the same use as the drug that underwent regulatory review. That is the situation here.

IV. THE PLAIN LANGUAGE OF SECTION 156 EXTENDS THE ENTIRE PATENT AS AGAINST ANY INFRINGING PRODUCTS, NOT JUST A SINGLE CLAIMED COMPOUND, IF INTENDED FOR THE SAME USE

1. The language of the statute should provide both the starting point and the end-point of the analysis. Congress chose to extend the "term of a *patent* which claims a product." 35 U.S.C. § 156(a) (emphasis added). It did not merely extend the term of a particular embodiment of a particular claim within the patent. As this Court has recognized, Congress intended Section 156 "to restore *patent* time lost during testing and regulatory approval," *Warner-Lambert*, 316 F.3d at 1357 (emphasis added), not something less. There is no room to constrict the meaning of the word "patent" or to subdivide the "term" for which it is extended by distinguishing, as the district court did, one covered compound from another.

The only limit on the *scope* of the "patent" to be extended appears in Section 156(b). That section provides that the "rights" derived from the extended patent term are "limited to any *use* approved for the product" in question. Section 156(b)(1) (emphasis added).

2. The district court nonetheless added to the *use* limitation a separate limitation, confining the rights to the single *compound* that underwent regulatory review. That spurious limit rested on a misunderstanding of the statute's reference

to an "approved product." Although the district court seemed to believe that Section 156 extended protection only for a single "approved product"—which the court erroneously believed means a *single compound*—the statute speaks more broadly about extending the term of "the patent." Reference to the "approved product" in Section 156(a) is germane only to determine the propriety and length of the extension, and the uses against which the extended patent can be enforced. Thus, a patent qualifies for an extension only on the basis of the regulatory delay that affected the first commercial exploitation of the patent. *See* § 156 (a)(4). But once the patent qualifies for extension, as Pfizer's patent here did, it is the *patent* that is extended, subject only to the approved "use" restriction in § 156(b)(1).

3. This distinction makes perfect sense. This Court recently made clear the importance of "use" as a limitation in the FDA approval process. *See Warner-Lambert*, 316 F.3d at 1360-1362. A patent that covers more than one potential "product" for the same *use* protects the approved product from competition by *any* infringing product, not just perfect copies. Similarly, under Hatch-Waxman, the patent must remain in force as against *all* infringing products—if they are proposed for the *same use* as the product that first commercialized the patent. Otherwise the extended patent protection *as to the approved product itself* is significantly weaker than the original patent protection, which barred all infringing imitations. Nothing

in Hatch-Waxman's "use" limitation justifies scaling back the scope of the products that *infringe* the patent that has been extended.

The district court relied (A8-9) for its contrary conclusion on a statement by this Court suggesting that the patent term extension applied only to the "product on which the extension was based" rather than "all products protected by the patent." *Merck & Co.* v. *Kessler*, 80 F.3d 1543, 1547 (Fed. Cir. 1996). This dichotomy, however, does not capture the distinction that the statute itself makes critical. The only criterion that the statute uses in determining the scope of the extended patent rights is whether the competitor's product would be offered for the same "use" for which the patent holder's product had been approved. That test is satisfied here, since both Pfizer's Norvasc® and Dr. Reddy's' maleate form are intended to treat heart disease and hypertension.

Moreover, *Merck* was not a patent infringement case, and the Court had no controversy before it over the *scope of the protection* afforded by a patent validly extended under Section 156.[15] The Court made its comment while determining the patent holder's *right to extensions* of various patents under Section 156 (Hatch-

[15] *See*, *e.g.*, No. 96-1068, Schering Corp. Br. 31 n.18; Merck & Co. Br. 24 (noting "product" limitation in passing). Indeed, the parties appear to have understood the "product" limitation to refer to *uses* of patented compounds: if "a patent covers a drug and a pesticide," the "Hatch-Waxman restoration period" would "only appl[y] to the drug." *Id.*, Response of Hofmann-LaRoche Inc. & Syntex (U.S.A.) Inc. to Bracco Diagnostics Inc. Reh'g Pet. 8.

Waxman) or Section 154 (Uruguay Round extensions). Those statutes called for varying lengths of extension under differing conditions. The Court acknowledged that its resolution created an anomaly—some patents would be enforceable only by limited means while extended under the Uruguay Round, but again would be enforceable by a full range of remedies when further extended by Section 156—even if only as to one "product." 80 F.3d at 1551.

The Court, however, viewed its ruling as of limited practical effect, terming the resulting anomaly "more illusory than real." *Id.* The Court surely was not attempting to determine the vastly more significant question posed by this case concerning the impact of an extended patent on a competitor's right to use the same patented molecule while the patent remains in force. Indeed, the Court recognized that the purpose of Hatch-Waxman is to restore to the patentee the "time lost in its patent term by reason of FDA delay, and the statute should be liberally interpreted to achieve this end." *Id.* at 1552.

Accordingly, the Court's comment that extensions apply to "one product" does not prevent the Court from deciding, in a patent infringement case like this one, that Section 156 should be given its plain meaning. That plain meaning extends the "term" of the "patent," limited only by the "use" restriction, which is identified by reference to the originally "approved product."

V. RESTRICTIVE INTERPRETATION OF THE TERM "ACTIVE INGREDIENT" TO MEAN ONLY A SINGLE SALT OF THE PATENTED CHEMICAL ENTITY WOULD UNDERMINE INCENTIVES TO INNOVATE

Even if Section 156 only protected against infringement the "one product" on which the extension was based, the decision below would be wrong. The court gave an artificially narrow meaning to the term "product." Section 156(f)(2) defines the "product" covered by the extended patent as a "drug product," which is in turn defined as

> "the ***active ingredient*** of...***a new drug***, antibiotic drug, or human biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act)...***including any salt or ester of the active ingredient.***" (Emphasis added.)

There is no dispute that amlodipine is the only therapeutically "active" chemical in amlodipine besylate and amlodipine maleate. Nonetheless, the district court held that, for purposes of Section 156, the "active ingredient" (and thus the protected "product") was only the single salt ultimately approved as Norvasc®.

A. Construing "Active Ingredient" As A Single Salt (Or Ester) Disregards Congress's Focus On Providing Incentives For The Development Of New Therapeutic Chemical Entities

1. By focusing not on the pioneering discovery of the *new* and *therapeutic* chemical entity, but rather on the far less scientifically significant version of the particular salt in which that active agent is compounded, the district court's interpretation conflicts with recognition by the Supreme Court and this Court that

the "patent term extension" was intended to apply to "'pioneer' drug products." *Eli Lilly & Co.* v. *Medtronic, Inc.*, 496 U.S. 661, 672 n.4 (1990); *see also Fisons* v. *Quigg*, 8 U.S.P.Q.2d 1491, 1499-1500 (D.D.C 1988) ("Under Section 156(a)(5)(A), only new, pioneer chemical entities were to have their effective lives legislatively restored."), *aff'd* and "endorse[d]," 876 F.2d 99, 102 (Fed. Cir. 1989).[16]

The "pioneer" "new chemical entity" here is amlodipine, irrespective of the salt in which a manufacturer chooses to combine that therapeutic agent. Thus, to protect the statutory goal of encouraging innovation to develop new chemical entities like amlodipine, the patent term extension must cover all compound forms of amlodipine.

Because Congress did not provide a definition for the phrase "active ingredient...including any salt or ester of the active ingredient," the Court must consider what the phrase means in context. *Serono Laboratories, Inc.* v. *Shalala*, 158 F.3d 1313, 1319 (D.C. Cir. 1998) (citing *McCarthy* v. *Bronson*, 500 U.S. 136 (1991)). The operative words are "active" and "ingredient." "Ingredient" connotes that the chemical in question is a *part* of something, particularly the compound in

[16] When Congress concluded that "patent time has been lost," it focused solely on "data on so-called class I, new chemical entity drugs." H.R. Rep. No. 98-857, pt. 1, 38, quoted in *Fisons*, 8 U.S.P.Q.2d at 1497.

which that ingredient is the "active" part. "Active" in the pharmaceutical context means having a therapeutic effect. The therapeutic part of a pharmaceutical compound is the active ion—like amlodipine.

2. Moreover, as explained earlier, active therapeutic agents often need to be compounded as salts. Nevertheless, the district court ruled that the "active ingredient" protected by Pfizer's extended patent is only *a particular salt*, amlodipine besylate. But that conclusion cannot be squared with the statutory language. The statute defines the protected drug as the "active ingredient . . . *including any salt or ester of the active ingredient.*" Since the definition includes "any" salt "*of* the active ingredient," the active ingredient itself cannot be a salt. The reason is clear: it is chemically impossible to have a salt of a salt. Therefore, when Congress assumed that an "active ingredient" will have salts, it used the term "active ingredient" in its customary sense: the active ion that has the therapeutic effect on the patient's disease.

This natural reading is further bolstered by the realities of pharmaceutical chemistry. Mere substitution of one salt (or ester) for another would make the protection afforded by patent extensions largely illusory. The alternate compounds are related enough so that a paper NDA applicant often can piggyback on the pioneer's research and trials of another salt or ester. *See FDA 505(b)(2) Draft Guidance*, 2-5.

3. By permitting this circumvention of the patent term extension, the district court's contrary interpretation of the statute distorts the intended economic incentives. An imitator could cut off the innovator's promised return by making a simple, therapeutically trivial change to the salt. That would indeed "convert the protection of the patent" as extended "into a hollow and useless thing." *Graver Tank & Mfg. Co.* v. *Linde Air Products Co.*, 339 U.S. 605, 607 (1950).

The European Court of Justice has recognized that, in order to have practical effect, a patent extension must cover the active substance of a drug, not just the particular salt identified as the active ingredient in a marketing authorization. Case C-392/97, *Farmitalia Carlo Erba Srl.*, 1999 E.C.R. I-5553, [1999] ¶¶ 18-22. The European extension is explicitly limited to the approved "product," defined as its "active ingredient." Council Regulation 1768/92, arts. 1, 4, 1992 O.J. (L 182) 1, 2. Construing the same term used in Hatch-Waxman, the Court ruled that the extension must encompass any forms of the therapeutic substance that come within the protection of the *patent*; otherwise a generic entrant could compete with "therapeutically equivalent" products covered by the original patent, frustrating the extension's purpose. *Farmitalia*, ¶ 18.

B. "Active Ingredient" Should Be Construed Consistently With Its Meaning Elsewhere In The Hatch-Waxman Act, Giving *Chevron* Deference To The FDA's Interpretation

Courts should interpret statutes by harmonizing various interrelated portions of a complex regulatory scheme and by according *Chevron* deference to an expert agency's reasonable construction of any arguably ambiguous term. In order to give the terms a consistent meaning throughout Hatch-Waxman, the phrase "active ingredient . . . including any salt or ester of the active ingredient" should be construed as meaning that the "active ingredient" is the therapeutic agent or "active moiety" in a compound. *Eli Lilly*, 496 U.S. at 669; *Abtox, Inc.* v. *Exitron Corp.*, 122 F.3d 1019, 1028 (Fed. Cir. 1997); *Warner-Lambert*, 316 F.3d at 1355.

Even if the statutory terms and structure did not *compel* interpreting the term "active ingredient" as the molecule capable of having a salt or ester, the views of the expert agency construing this term of art should control. The FDA's interpretation of the cognate provisions in Hatch-Waxman should receive a "high level of deference," because it reflects the agency's understanding of a term used repeatedly in the statute it administers and involves the "agency's evaluations of scientific data within its area of expertise." *Serono*, 158 F.3d at 1319.

In this setting the FDA long has "defined" active ingredients "in terms of pharmacological activity." *Serono*, 158 F.3d at 1319 (citing "regulations pre-dating the Hatch-Waxman amendments"). As Pfizer has explained (Br. 50), the FDA has

construed the term "active ingredient (including any salt or ester of the active ingredient)" in the Hatch-Waxman exclusivity provisions (21 U.S.C. § 355) to mean the therapeutically significant molecule or ion, or "active moiety," regardless of its salt or ester form. Similarly, FDA regulations directed at patent term extensions define "active ingredient" as "any component that is intended to furnish pharmacological activity...or to affect the structure or any function of the body." 21 C.F.R. § 60.3(b)(2). That definition includes the active moiety and its salts and esters, and derives from the manufacturing-practices regulations referenced in *Serono*, 158 F.3d at 1319. *See* 21 C.F.R. § 210.3(b)(7); 53 Fed. Reg. 7298 (1988)).

Properly construed and applied, therefore, Section 156 protects against infringement by any competitor's drug that proposes to use the same active ion–here amlodipine–in any compound that would be offered for the same therapeutic use as the innovator's formulation of that invention.

CONCLUSION

The judgment of the district court should be reversed.

Respectfully submitted.

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