IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

MYLAN LABORATORIES INC. 1500 Corporate Drive Canonsburg, PA 15317 and MYLAN PHARMACEUTICALS INC. 781 Chestnut Ridge Road Morgantown, WV 26505 Plaintiffs, v. MICHAEL O. LEAVITT, in his official capacity as SECRETARY OF HEALTH AND HUMAN SERVICES 200 Independence Ave., S.W. Washington, DC 20204, ANDREW C. VON ESCHENBACH, M.D., in his official capacity as COMMISSIONER OF FOOD AND DRUGS, 200 C Street, S.W. Washington, DC 20204, and UNITED STATES FOOD AND DRUG ADMINISTRATION, et al., 5600 Fishers Lane Rockville, MD 20857 Defendants.	)	Civil Action No.

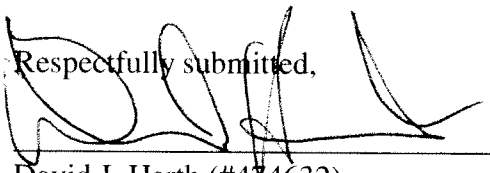
MYLAN'S EMERGENCY APPLICATION FOR A
TEMPORARY RESTRAINING ORDER AND/OR PRELIMINARY INJUNCTION

Mylan Laboratories Inc. and Mylan Pharmaceuticals Inc. (collectively, "Mylan") respectfully submit this emergency application for a temporary restraining order and/or preliminary injunction enjoining defendants, the U.S. Food and Drug Administration ("FDA") and Andrew C. von Eschenbach, M.D., in his official capacity as Commissioner of Food and Drugs (collectively, "FDA") from taking any action to issue an approval of any Abbreviated New Drug Application for amlodipine besylate products pending the determination of the scope and duration of Mylan's 180-day generic exclusivity.

The bases for the present emergency application for a temporary restraining order are fully set forth in the accompanying Statement of Points and Authorities and Declaration of Brian Roman.

Dated: March 26, 2007

Respectfully submitted,



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MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF PLAINTIFFS' EMERGENCY APPLICATION FOR A TEMPORARY RESTRAINING ORDER AND/OR PRELIMINARY INJUNCTION

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INTRODUCTION

Plaintiffs Mylan Laboratories Inc. and Mylan Pharmaceuticals Inc. ("Mylan") seek an injunction from this Court to prevent the FDA from approving – without any statutory authority – its competitors' amlodipine besylate products until the merits of Mylan's claim to 180-day exclusivity can be heard.

This case arises under the Hatch-Waxman statutory scheme, enacted by Congress to promote the expedited entry of generic drugs to market. Mylan was the first ANDA applicant to challenge Pfizer's patent covering the brand name drug, Norvasc®, U.S. Patent No. 4,879,303 ("the '303 patent"). Mylan was sued by Pfizer for infringement of the '303 patent, and Mylan's defense of that suit has stretched out over the last five years.

The '303 patent was set to expire on March 25, 2007. Last Thursday, March 22, the Court of Appeals for the Federal Circuit held the '303 patent invalid. The next day, Mylan began marketing amlodipine besylate tablets. Under the express terms of the Hatch-Waxman Act, Mylan's commercial marketing of amlodipine besylate triggered a 180-day period of exclusive marketing – free from competition by other ANDA applicants. As we will see, this is an enormously valuable right.

In the past, the FDA has taken the position that 180-day generic exclusivity does not survive patent expiration. There is no basis in the Hatch-Waxman Act for such a limitation. Mylan has learned that the FDA is considering issuing immediate final approvals for amlodipine besylate applications filed by other generic manufacturers. Should the FDA take such action, it would not only destroy Mylan's 180-day exclusivity, but also fundamentally undermine the Hatch-Waxman Act, which provides 180-day exclusivity as an incentive for generic drugmakers to challenge invalid patents. In short, the FDA's threatened action is unlawful.

Because Mylan will be irreparably harmed if the FDA acts to approve its competitors' applications, and because Mylan can establish the other prerequisites for preliminary injunctive relief, the Court should enter an order enjoining the FDA from taking any action to approve other generic applicants during the pendency of this action or until expiration of Mylan's 180-day exclusivity period on September 23, 2007.

BACKGROUND

Amlodipine besylate is a drug approved by the FDA for treating hypertension and chronic stable and vasospastic angina. The large pharmaceutical company, Pfizer, held two patents that it contended covered different aspects of amlodipine besylate, U.S. Patent No. 4,572,909 ("the '909 patent") and U.S. Patent No. 4,879,303 ("the '303 patent"). The '909 patent expired on July 31, 2002; the '303 patent expired on March 25, 2007.

Since 1992, Pfizer has commercially marketed amlodipine besylate under the brand name Norvasc®. In May of 2002, Mylan filed with the FDA an Abbreviated New Drug Application (ANDA) on generic 2.5 mg, 5 mg and 10 mg amlodipine besylate tablets. Mylan's ANDA was and is governed by the provisions of the Hatch-Waxman Act.[1]

By letter dated July 23, 2002, Mylan certified pursuant to § 505(j)(2)(A)(vii)(IV) of the Hatch-Waxman Act that the manufacture, use and sale of Mylan's 2.5 mg, 5 mg and 10 mg amlodipine besylate tablets would not violate the '909 patent and the '303 patent because they were invalid, unenforceable, or not infringed. Mylan was the first to file a paragraph IV certification with respect to amlodipine besylate. On September 20, 2002, Pfizer sued Mylan for

[1] *Drug Price Competition and Patent Term Restoration Act of 1984*, P.L. 98-417, 98 Stat. 1585 (Sept. 24, 1984), amending the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 501 *et seq.*

patent infringement in the United States District Court for the Western District of Pennsylvania (the "Pennsylvania action").

By letter dated October 3, 2005, the FDA notified Mylan that its amlodipine besylate ANDA was approved. *Declaration of Shannon M. Bloodworth in Support of Mylan's Emergency Application for a Temporary Restraining Order* (*hereinafter "Bloodworth Decl."*), at Exh. A. In that same letter, the FDA provided the following notice:

> With respect to 180-day generic drug exclusivity, we note that Mylan was the first ANDA applicant to submit a substantially complete ANDA with a paragraph IV certification for Amlodipine Besylate Tablets . . . Therefore, with this approval, Mylan is eligible for 180-days of market exclusivity. This exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the Act will begin to run from the earlier of the commercial marketing or court decision dates identified in section 505(j)(5)(B)(iv).

Id., at Exh. A. The FDA approved Mylan's amlodipine ANDA despite the fact that in November, 2001 the FDA granted Pfizer so-called pediatric exclusivity pursuant to 21 U.S.C. § 355a.

In May 2003, generic pharmaceutical company Apotex, Inc. ("Apotex") filed an ANDA with the FDA seeking approval to sell amlodipine besylate tablets prior to the expiration of Pfizer's '303 patent and certifying pursuant to § 505(j)(2)(A)(vii)(IV) of the Hatch-Waxman Act that the manufacture, use and sale of Apotex's amlodipine besylate tablets would not violate the '303 patent. On July 30, 2003, Pfizer sued Apotex for patent infringement in the United States District Court for the Northern District of Illinois (the "Illinois action"). The FDA has not to date approved Apotex's amlodipine besylate ANDA.

Following a bench trial in the Illinois action, on January 29, 2006, the district court entered judgment dismissing Apotex's invalidity and unenforceability defenses and declaring that Apotex's amlodipine besylate tablets infringed the '303 patent. In addition, the district court ordered that the effective date of Apotex's ANDA be no earlier than September 25, 2007 (patent

expiration plus six months pediatric exclusivity) and enjoined Apotex from engaging in commercial activities with respect to amlodipine besylate. Apotex appealed the district court judgment to the Federal Circuit.

On February 27, 2007, following a bench trial in the Pennsylvania action, the district court entered judgment dismissing Mylan's invalidity and unenforceability defenses and declaring that Mylan's amlodipine besylate tablets infringed the '303 patent. *See Bloodworth Decl.,* at Exh. B. In addition, the district court ordered that the effective date of Mylan's ANDA be no earlier than March 25, 2007 and enjoined Mylan from engaging in commercial activities with respect to amlodipine besylate until patent expiration on March 25, 2007. *See id.,* at Exh. C. Mylan appealed the district court judgment to the Federal Circuit.

On March 22, 2007, the Federal Circuit issued its decision in the Illinois action, holding the '303 patent invalid for obviousness under 35 U.S.C. § 103. *See Pfizer, Inc. v. Apotex, Inc.,* No. 06-1261, 2007 U.S. App. LEXIS 6623 (Fed. Cir. Mar. 22, 2007). The following day, the Federal Circuit issued a stay of the district court's order in the Pennsylvania action. *See Bloodworth Decl.,* at Exh. D. Later that same day, Mylan began commercial marketing of amlodipine besylate tablets, thereby triggering the 180 days of exclusivity pursuant to § 505(j)(5)(B)(iv) of the Hatch-Waxman Act and the FDA's approval letter. *See id.,* at Exh. D.

In addition to Mylan and Apotex, there are at least six other generic pharmaceutical companies who have filed ANDAs on amlodipine besylate. All filed after Mylan. None have received final FDA approval. Mylan has learned that the FDA may issue final approvals to Apotex and the other generic ANDA filers before the expiration of Mylan's 180-day exclusivity. *See Declaration of Brian S. Roman in Support of Mylan's Emergency Application for a Temporary Restraining Order* (*hereinafter* "*Roman Decl.*"), at ¶ 5.

Mylan will be irreparably harmed if the FDA grants additional approvals during its 180-day period of exclusivity. *See* Roman Decl., ¶ 6. Generic exclusivity is a valuable right that the Hatch-Waxman Act provides as an incentive for generic manufacturers to challenge invalid patents, such as Pfizer's '303 patent. *See id.* If the FDA permits other generics into the market during Mylan's 180-day exclusivity period, Mylan will incur substantial losses, losses which it will never be able to recoup, even if the FDA's actions are later overturned. *See id.*

ARGUMENT

To obtain a temporary restraining order, a plaintiff bears the burden of demonstrating: "1) a substantial likelihood of success on the merits, 2) that [plaintiff] would suffer irreparable injury if the injunction is not granted, 3) that any injunction would not substantially injure other interested parties, and 4) that the public interest would be served by the injunction." *Canales v. Paulson*, No. 06-1330, 2006 U.S. Dist. LEXIS 61915, at *8 (D.D.C. August 30, 2006) (granting temporary restraining order to preserve the status quo pending court's ruling on an application for a preliminary injunction) (quoting *Katz v. Georgetown Univ.*, 246 F.3d 685, 687-88 (D.C. Cir. 2001)). Plaintiffs do not need to prevail on each of these four factors because the factors "'interrelate on a sliding scale and must be balanced against each other.'" *Id.* (quoting *Serono Lab. v. Shalala*, 158 F.3d 1313, 1318 (D.C. Cir. 1998)). Furthermore, "'[i]f the arguments for one factor are particularly strong, a temporary restraining order may issue even if the arguments in other areas are rather weak.'" *Id.* (quoting *CityFed Fin. Corp. v. Office of Thrift Supervision*, 58 F.3d 738, 747 (D.C. Cir. 1995)). Therefore, injunctive relief may be granted "'where there is a particularly strong likelihood of success on the merits even if there is a relatively slight showing of irreparable injury.'" *Id; see also Zantop Int'l Airlines, Inc. v. Engen*, 601 F. Supp. 667, 669 (D.D.C. 1985) (ordering existing temporary restraining order to "remain in effect . . . to

preserve the status quo until such time as the Court of Appeals is able to rule on a motion for stay."). "When the balance of hardships tips decidedly toward the movant, it will 'ordinarily be enough that the [movant] has raised questions going to the merits so serious, substantial, difficult and doubtful, as to make them a fair ground for litigation and thus for more deliberative investigation.'" *Al-Marri v. Bush*, No. 04-2035, 2005 U.S. Dist. LEXIS 6259, at *10 (D.D.C. April 4, 2005) (internal citations omitted).

I. MYLAN HAS A SUBSTANTIAL LIKELIHOOD OF SUCCEEDING ON THE MERITS OF ITS CLAIM AGAINST THE FDA

In light of the FDA's threatened actions, which would directly contravene statutory protections that Congress established to protect the 180-day exclusivity of the first ANDA filer, Mylan's request for injunctive relief raises questions going to the merits that are undeniably "so serious, substantial, difficult, and doubtful, as to make them fair ground for litigation and thus more deliberate litigation." *Al-Marri*, 2005 U.S. Dist. LEXIS 6259, at *10.

A. The Hatch-Waxman Act Entitles Mylan to 180-Days Exclusivity, Even Though the Underlying Patent Would have Expired had It Not been Found Invalid

The purpose of the Hatch-Waxman Act was to "make available more low cost generic drugs by establishing a generic drug approval procedure." H.R. Rep. No. 98-857 (Part I), at 14-15 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647, 2647. To achieve the goals of "quickly getting lower-cost generic drugs to market," the Hatch-Waxman Act lowered the regulatory barriers and created other incentives to encourage generic drug companies to file generic drug applications in the face of the risk that brand drug companies would then bring patent infringement suits against them. *Teva Pharms. Indus. Ltd. v. Crawford*, 410 F.3d 51, 54 (D.C. Cir. 2005). At the same time, to achieve the goal of encouraging innovation by brand drug companies, the Act provided brand companies with enhanced litigation options as well as potential eligibility for a range of

market exclusivity periods. In this manner, Congress sought to balance the statutory rights and responsibilities of generic drug applicants and brand drug companies.

To provide generic drug companies with an incentive to file ANDAs in the face of the risks and costs of being sued for patent infringement, Congress promised 180 days of market exclusivity to the first generic company to submit a substantially complete ANDA with a so-called "paragraph IV" certification challenging the brand company's patent.[2] During this 180-day exclusivity period, the FDA is proscribed from granting any other generic producers approval for the same drug, thereby giving the first filer a "head start" in the marketplace vis-à-vis other generic drug companies. *See* 21 U.S.C. § 355(j)(5)(B)(ii). 180-day exclusivity is a cornerstone of the Hatch-Waxman framework because it is the primary incentive for generic companies to file their ANDAs in the face of the risks and costs of patent infringement litigation. *See Mylan Pharms. v. Shalala,* 81 F. Supp. 2d 30, 33 (D.D.C. 2000) (explaining that Congress created the 180-day exclusivity provision to "encourage generic drug makers to incur the potentially substantial litigation costs associated with challenging pioneer drug marker' patents").

The Hatch-Waxman Act specifically provides that, once granted, Mylan's 180-day exclusivity rights will not begin to run – much less lapse – until the start of commercial marketing or a favorable court decision:

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[2] The ANDA applicant must make one of four possible certifications for each patent that covers the relevant brand drug listed in an FDA's publication, *Approved Drug Products with Therapeutic Equivalence Evaluations*, commonly called the "Orange Book." *See* 21 U.S.C. § 355(j)(2)(A)(vii)(I)-(IV). If the applicant challenges an Orange Book patent, he must file a so-called "paragraph IV" certification, certifying that the listed patent – "in the opinion of the applicant and to the best of his knowledge" – is "invalid or will not be infringed by the manufacture, use, or sale of the new [generic] drug." 21 U.S.C. § 355(j)(2)(A)(vii)(IV). The applicant must notify the patentee of its paragraph IV certification and describe the basis for his belief that the patent is invalid or not infringed. *See* 21 U.S.C. § 355(j)(2)(B).

> [I]f the application contains a certification described in subclause IV of paragraph (2)(A)(vii) and is for a drug for which a previous application has been submitted under this subsection ... [containing] such a certification, the application *shall be made effective not earlier than one hundred and eighty days after* ...
>
> > (I) the date the Secretary receives notice from the applicant under the previous application of the first commercial marketing of the drug under the previous application, or
> >
> > (II) the date of a decision of a court in an action described in clause (iii) holding the patent which is the subject of the certification to be invalid or not infringed, whichever is earlier.

21 U.S.C. § 355(j)(5)(B)(iv) (2002) (emphasis added).[3]

Mylan started commercial marketing of amlodipine besylate on March 23, 2007. Under the plain language of § 355(j)(5)(B)(iv), all other ANDAs for amlodipine besylate "shall be made effective not earlier than one hundred and eighty days after" that date, or in this case, September 23, 2007. The FDA cannot make a subsequent application effective – i.e., issue final approval to a subsequent application before September 23, 2007 – because this would nullify Mylan's 180-day exclusivity. *See Lamie v. United States Trustee,* 540 U.S. 526, 534 (2004) ("'[W]hen the statute's language is plain, the sole function of the courts – at least where the disposition required by the text is not absurd – is to enforce it according to its terms.'") (quoting *Hartford Underwriters Ins. Co. v. Union Planters Bank, N.A.*, 530 U.S. 1, 6 (2000)).

Other provisions in the Hatch-Waxman amendments also make clear that a generic producer's 180-day exclusivity rights cannot be divested, *even if* the underlying patent would have already expired. In 21 U.S.C. § 355a(k), Congress provided that any period of overlap between the 180-day generic exclusivity period and the so-called pediatric exclusivity period,

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[3] The 180-day exclusivity provisions cited above apply to ANDAs – like Mylan's – filed before December 8, 2003. *See Medicare Prescription Drug, Improvement and Modernization Act of 2003* ("MMA"), at § 1102(b)(1), Pub. L. 108-173, 117 Stat. 2066 (Dec. 8, 2003).

which only is triggered *after* patent expiration, must be tolled for purposes of preserving the entire 180-day period of generic drug exclusivity.[4] Section 355a(k) is thus an express recognition by Congress that 180-day generic exclusivity is *not* exhausted by the expiration of the patent.

At a minimum, as long as the '303 patent remains listed in the Orange Book, Mylan's 180-day exclusivity applies. It is the FDA's policy that "the Agency may approve the ANDA on the date the district court issues a judgment that the patent is invalid, unenforceable, or not infringed pursuant to a mandate issued by a court of appeals." *Bloodworth Decl.*, at Exh. E, *Guidance for Industry: Court Decisions, ANDA Approvals, and 180-Day Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act* (March 2000) at 4. Therefore, at a minimum, Mylan is entitled to be the exclusive marketer until the mandate is issued to the district court.

In view of the mandatory language of § 355(j)(5)(B)(iv) that ANDAs other than the first-to-file "shall" be given an effective date "no earlier than" the expiration of 180-day generic exclusivity, Congress' direction to the FDA could hardly be clearer.

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[4] This provision states as follows:

> (k) Clarification of interaction of market exclusivity under this section and market exclusivity awarded to an applicant for approval of a drug under section 355(j) of this title [*21 USCS § 355(j)*]. If a 180-day period under section 505(j)(5)(B)(iv) [*21 USCS § 355(j)(5)(B)(iv)*] overlaps with a 6-month exclusivity period under this section, so that the applicant for approval of a drug under section 355(j) [*21 USCS § 355(j)*] entitled to the 180-day period under that section loses a portion of the 180-day period to which the applicant is entitled for the drug, the 180-day period shall be extended from—
>
> (1) the date on which the 180-day period would have expired by the number of days of the overlap, if the 180-day period would, but for the application of this subsection, expire after the 6-month exclusivity period; or
>
> (2) the date on which the 6-month exclusivity period expires, by the number of days of the overlap if the 180-day period would, but for the application of this subsection, expire during the six-month exclusivity period.

B. FDA Can Cite to No Authority that Would Allow It to Deprive Mylan of Its Right to 180-Day Exclusivity

Although the FDA has expressed the view that eligibility for 180-day exclusivity cannot extend beyond the expiration date of the patent from which that exclusivity derives, that policy does not and cannot apply in situations where the 180-day exclusivity has already been awarded and triggered. Mylan does not request that the FDA reverse any position that it has publicly announced with respect to the effect of the 180-day exclusivity after patent expiration. Instead, the situation presented in this case is one that, to Mylan's knowledge, has never been addressed by the FDA.

In *Dr. Reddy's Laboratories, Inc. v. Thompson*, 302 F. Supp. 2d 340 (D.N.J. 2003) ("*DRL*"), the district court approved the FDA's interpretation of § 355(j)(5)(B)(iv) insofar as it relates to *tentatively* approved ANDAs. The court accepted the rationale that, upon patent expiration, a paragraph IV certification in a tentatively approved ANDA is no longer accurate and it converts *de facto* or *de jure* to a paragraph III certification at the moment the patent expires. *Id.* at 351. However, the FDA has made clear that a holder of a fully *approved* ANDA, like Mylan's, is under no obligation to amend a patent certification upon patent expiration. *See Bloodworth Decl.*, at Exh. F, Letter from Gary Buehler dated June 22, 2004 at 3 ("An application with full effective approval has no continuing obligation to update its patent certifications. *See* 21 C.F.R. § 314.94(a)(12)(viii)(C) (obligation to amend certification applies before effective date of approval)". The FDA's prior administrative rulings in situations like cisplatin (August 6, 1999) or omeprazole (November 16, 2001), involved ANDAs that were *tentatively-approved* when a patent expired, and the FDA was deciding whether a first-filer retained *eligibility* for 180-day exclusivity. *See also Ranbaxy Labs v. FDA,* 307 F. Supp. 2d 15 (D.D.C. 2004) (explaining FDA policy regarding patent certifications upon patent expiration).

Unlike the situations that the FDA has addressed previously, Mylan's ANDA was fully approved and the 180-day exclusivity period had been triggered before patent expiration. As the FDA has previously concluded, Mylan's paragraph IV certification did not change when the patent expired. Therefore, Mylan's ANDA fully complies with the language of § 355(j)(5)(B)(iv), as it "is for a drug for which a previous application has been submitted under this subsection [containing] such [subclause IV] certification[.]" This makes a significant difference, because § 355(j)(5)(B)(iv) makes it clear that once exclusivity has been triggered, the FDA may not approve additional ANDAs for 180 days. The FDA's previously announced positions do not and should not preclude Mylan's 180-day exclusivity extending beyond the expiration of Pfizer's patent.

Mylan anticipates that the FDA will argue that *DRL* upholds its authority to terminate Mylan's 180-day exclusivity rights upon patent expiration. *DRL*, however, is factually distinguishable because in that case the generic applicant was merely *eligible* for 180-day exclusivity, but had not received final approval before patent expiration and, critically, had not triggered generic exclusivity under § 355(j)(5)(B)(iv). 302 F. Supp. 2d at 346. The *DRL* court held that the Hatch-Waxman Act is silent regarding whether *eligibility* for generic exclusivity in these circumstances survives patent expiration, and, applying *Chevron* deference, found permissible the FDA's regulations terminating such eligibility after patent expiration.

But *Chevron* also holds that if a statute speaks clearly to "the precise question at issue," a court must "give effect to the unambiguously expressed intent of Congress." *Chevron U.S.A., Inc. v. Natural Resources Defense Council*, 467 U.S. 837, 842-43 (1984). In this case, § 355(j)(5)(B)(iv) could not be clearer, once 180-day exclusivity is triggered, any subsequent FDA approvals "shall be made effective no earlier than" the expiration of the 180-day

exclusivity period. Under *Chevron*, the FDA's decision to grant approvals *before* expiration of the 180 days is entitled to no deference and, and because that decision is contrary to law, should be enjoined by this Court.

II. MYLAN WILL SUFFER IRREPARABLE HARM ABSENT IMMEDIATE INJUNCTIVE RELIEF FROM THIS COURT

If the FDA is not enjoined from granting final approval to other generic drug producers, Mylan will suffer tremendous harm, which cannot be remedied even should Mylan prevail on the merits.

A. Mylan's Loss of Its 180-Day Exclusivity Would Constitute Irreparable Harm *Per Se*

Any FDA actions to grant final approval to other generic drug producers would wipe out the 180-day exclusivity period that Mylan has been working for years to obtain – and can now finally enjoy. Courts have repeatedly acknowledged that a generic drug manufacturer is irreparably harmed when wrongfully deprived of its 180-day period of marketing exclusivity vis-à-vis other generic manufacturers. *See Mova Pharm. Corp. v. Shalala,* 955 F. Supp. 128, 131 (D.D.C. 1997) (finding irreparable harm where FDA deprives a party of its "180-day statutory grant of exclusivity. ... All parties recognize that the earliest generic drug manufacturer in a specific market has a distinct advantage over later entrants."); *aff'd by* 140 F.3d 1060, 1067, n. 6 (D.C. Cir. 1998) (confirming that Mova's loss of its "'officially sanctioned head start' ... suffices to show a severe economic impact to Mova," for purposes of satisfying the irreparable harm standard); *Mylan Pharms, Inc.,* 81 F. Supp. 2d at 44 (denying requested injunctive relief where the balances of harms weighed in favor of Geneva, who would otherwise be "depriv[ed] ... of the full benefits of exclusivity"); *Bracco Diagnostics, Inc. v. Shalala,* 963 F. Supp. 20, 29 (D.D.C. 1997) (granting preliminary injunction and acknowledging that "there is a significant economic advantage to receiving first approval and being the first company to enter the market,

an advantage that can never be fully recouped through money damages or by 'playing catch-up'"); *Boehringer Ingelheim Corp. v. Shalala,* 993 F. Supp. 1, 2 (D.D.C. 1997) (denying injunctive relief, while recognizing that losing "the advantage of being the first to market" amounts to significant harm for purposes of balancing hardships).

Acknowledging the harm to companies deprived of their 180-day exclusivity, courts have frequently issued injunctions in these circumstances – especially where the plaintiff also shows likelihood of success on the merits. *See TorPharm, Inc. v. Shalala,* No. 97-1925, 1997 U.S. Dist. LEXIS 21983, at *14 (D.D.C. Sept. 15, 1997) (issuing injunction where, among other things, generic company was improperly denied timely access to market, which the brand company acknowledged to be "critical for success in [the] marketplace"); *see also Bracco Diagnostics*, 963 F. Supp. at 29 (issuing an injunction in favor of generic company that faced wrongful deprivation of the "significant economic advantage" that would have resulted from its ability to enter the market with 180-day exclusivity); *Mova Pharm.*, 955 F. Supp. at 131 (issuing injunction in light of threatened deprivation of 180-day exclusivity period).

B. By Any Measure, the Impact of the FDA's Deprivation of Mylan's 180-Day Exclusivity Constitutes Irreparable Harm

If Mylan is deprived of its opportunity to enjoy its priority final approval status and its 180-day exclusivity, it will suffer tremendous harm. Because Mylan possesses 180-day exclusivity and an officially sanctioned "head start" over other generic producers, those producers should not receive final approval to market amlodipine besylate until Mylan's exclusivity period expires – provided, of course, that the FDA does nothing to undermine or nullify that exclusivity at this time. This "head start" will permit Mylan to secure distribution channels and access to customers, enter into long-term sales agreements, and retain greater market share in the long term. *See Roman Decl..,* ¶ 6. Granting final approval to Mylan's

generic competitors would deprive Mylan of the benefits of its 180-day exclusivity, impairing its access to customers and diminishing its ability to establish or retain market share. *See id.*, ¶ 6. *See also, TorPharm,* 1997 U.S. Dist. LEXIS 21983, at *14 (recognizing that "early market entry is critical to success in the ... market because competitors will vie for a small number of long-term contracts").

In the absence of injunctive relief, Mylan will be substantially deprived of several million dollars per day in estimated sales of its amlodipine products that it had projected based on its status as the sole approved generic manufacturer at this time. *See id.*, ¶ 6. In the absence of an injunction, Mylan will lose many of these sales opportunities.

The harm to Mylan if the FDA deprives it of its 180-day exclusivity is irreparable. Mylan will not be able to recoup its monetary damages from the FDA. Mylan would also likely be barred from recovering damages against Pfizer. Because the economic damages are unrecoverable, they are irreparable, thus justifying immediate injunctive relief. *See, e.g., Express One Int'l, Inc. v. United States Postal Serv.*, 814 F. Supp. 87, 91 (D.D.C. 1992) (finding irreparable harm supported where the "non-recoverable monetary losses [movant] faces are therefore real and present" and damages exist "for which there is no recourse"; *Hoffman-Larouche, Inc. v. Califano*, 453 F. Supp. 900, 903 (D.D.C. 1978) (noting that "[i]f the order goes into effect, plaintiff will suffer loss of sales and good will for which it would have *no right or recourse*, and thus its injury will be irreparable" (emphasis added)).

III. THE BALANCE OF RELATIVE HARMS FAVORS ENTRY OF AN INJUNCTION

Unless Mylan receives injunctive relief, it will suffer a substantial and complete loss of its priority final approval status and its 180-day exclusivity, along with the first-mover advantage

that accompanies that exclusivity. The FDA, on the other hand, has no commercial stake in the outcome of this litigation. The balance of harms inquiry should end there.

IV. THE PUBLIC INTEREST WILL BENEFIT FROM AN INJUNCTION

The overwhelming weight of public interests favors preliminary injunctive relief in this case. The public's interest lies, first and foremost, in the FDA's "faithful application of the laws" consistent with the will and intent of Congress. *See Mylan Pharms.*, 81 F. Supp. 2d. at 45 ("It is in the public interest for courts to carry out the will of Congress and for an agency to implement properly the statute it administers."); *Mova Pharm.*, 140 F.3d at 1066 (holding that the public interest is served by a "faithful application of the laws"). It is appropriate to enjoin the FDA from taking action that is self-evidently contrary to statutory authority – at least to preserve the status quo while the court can make a determination regarding the proper application of the FDA's authority.

Moreover, Congress has determined that the public is served by encouraging generic manufacturers to challenge invalid patents, such as the Pfizer '303 patent in this case. If a generic manufacturer is unable to enjoy its 180-day exclusivity because the patent has expired, the value of the statutory incentive to challenge invalid patents will be materially diminished. To protect all of the aforementioned public interests – including public health concerns – the FDA should grant the requested preliminary injunction.

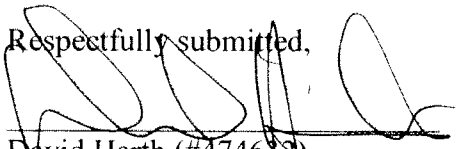
CONCLUSION

For these reasons, Mylan seeks a temporary restraining order and/ or preliminary injunction to enjoin the FDA from taking any action to issue an approval of any Abbreviated

New Drug Application for amlodipine besylate products pending the determination of the scope and duration of Mylan's 180-day generic exclusivity

Dated: March 26, 2007

Respectfully submitted,



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Attorneys for Plaintiffs
MYLAN LABORATORIES INC. and
MYLAN PHARMACEUTICALS INC.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

MYLAN LABORATORIES INC. 1500 Corporate Drive Canonsburg, PA 15317 and MYLAN PHARMACEUTICALS INC. 781 Chestnut Ridge Road Morgantown, WV 26505 Plaintiffs, v. MICHAEL O. LEAVITT, in his official capacity as SECRETARY OF HEALTH AND HUMAN SERVICES 200 Independence Ave., S.W. Washington, DC 20204, ANDREW C. VON ESCHENBACH, M.D., in his official capacity as COMMISSIONER OF FOOD AND DRUGS, 5600 Fishers Lane Rockville, MD 20857, and UNITED STATES FOOD AND DRUG ADMINISTRATION, et al., 5600 Fishers Lane Rockville, MD 20857 Defendants.	)	Civil Action No. _____

DECLARATION OF SHANNON M. BLOODWORTH
IN SUPPORT OF MYLAN'S EMERGENCY APPLICATION
FOR A TEMPORARY RESTRAINING ORDER

I, Shannon M. Bloodworth, declare and state as follows:

1. I am an attorney with the law form of Heller Ehrman LLP, counsel to Mylan Laboratories Inc. and Mylan Pharmaceuticals Inc. (collectively "Mylan"), in the above-captioned proceeding. I submit this declaration in support of Mylan's emergency application for a temporary restraining order and/or preliminary injunction.

2. Annexed hereto as Exhibit A is a true and correct copy of the letter from Gary Buehler to Wayne Talton issuing final approval to ANDA No. 76-418 (dated October 3, 2005).

3. Annexed hereto as Exhibit B is a true and correct copy of *Findings of Fact and Conclusions of Law* (dated February 27, 2007).

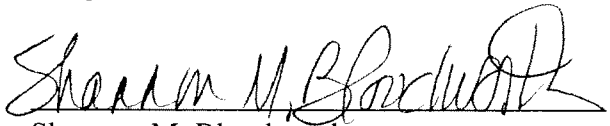
4. Annexed hereto as Exhibit C is a true and correct copy of *Amended Judgment* (dated March 16, 2007).

5. Annexed hereto as Exhibit D is a true and correct copy of the Order issued by Federal Circuit Court Judge Sharon Prost (dated March 23, 2007).

6. Annexed hereto as Exhibit E is a true and correct copy of *Guidance for Industry: Court Decisions, ANDA Approvals, and 180-Day Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act* (March 2000).

7. Annexed hereto as Exhibit F is a true and correct copy of the letter from Gary Buehler to E. Anthony Figg and Peter O. Safir (dated June 22, 2004).

I declare under penalty of perjury that the foregoing is true and correct of my own knowledge. Executed this 26th day of March, 2007 in Washington, D.C.

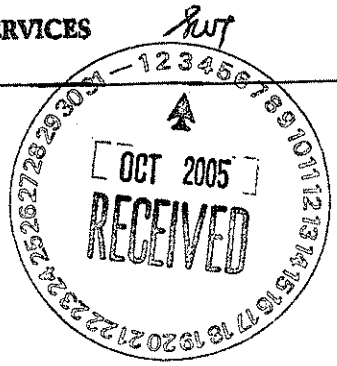


Shannon M. Bloodworth

Exhibit A

Plaintiffs' Emergency Application for a Temporary Restraining Order and/or Preliminary Injunction

DEPARTMENT OF HEALTH & HUMAN SERVICES



Food and Drug Administration
Rockville MD 20857

ANDA 76-418

OCT 3 2005

Mylan Pharmaceuticals Inc.
Attention: S. Wayne Talton
Vice President, Regulatory Affairs
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated May 22, 2002, submitted pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act (Act), for Amlodipine Besylate Tablets, 2.5 mg (base), 5 mg (base) and 10 mg (base).

Reference is also made to your amendments dated October 2, 2002; and January 6, April 1, August 1, and August 4, 2005.

We have completed the review of this ANDA and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the ANDA is approved. The Division of Bioequivalence has determined your Amlodipine Besylate Tablets 2.5 mg (base), 5 mg (base), and 10 mg (base), to be bioequivalent and therefore, therapeutically equivalent to the listed drug, Norvasc Tablets 2.5 mg (base), 5 mg (base), and 10 mg (base), respectively, of Pfizer, Inc. (Pfizer). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

The listed drug product (RLD) referenced in your ANDA, Pfizer's Norvasc® Tablets, is subject to periods of patent protection. As noted in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), U.S. Patent Nos. 4,572,909 (the '909 patent) and 4,879,303 (the '303 patent) are scheduled to expire (with pediatric exclusivity added) on January 31, 2007, and September 25, 2007, respectively.

Your ANDA contains patent certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that both these patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Amlodipine Besylate Tablets, 2.5 mg (base), 5 mg (base) and 10 mg (base), under this ANDA. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an action is brought against Mylan Pharmaceuticals Inc. (Mylan) for infringement of either of the patents that were the subject of the paragraph IV certifications. This action must have been brought against Mylan prior to the expiration of 45 days from the date the notice you provided under paragraph (2)(B)(i) was received by the NDA/patent holder(s). You have notified the agency that Mylan complied with the requirements of section 505(j)(2)(B) of the Act, and that no action for infringement of the '909 patent or the '303 patent was brought against Mylan within the statutory 45-day period, which action would have resulted in a 30-month stay under section 505(j)(5)(B)(iii).[1]

With respect to 180-day generic drug exclusivity, we note that Mylan was the first ANDA applicant to submit a substantially complete ANDA with a paragraph IV certification for Amlodipine Besylate Tablets, 2.5 mg (base), 5 mg (base) and 10 mg (base). Therefore, with this approval, Mylan is eligible for 180-days of market exclusivity. This exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the Act,[2] will begin to run from the earlier of the commercial marketing or court decision dates identified in section 505(j)(5)(B)(iv). Please submit correspondence to the ANDA informing the agency of the date the exclusivity begins to run.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

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[1] Because information on the '909 and '303 patents was submitted before August 18, 2003, this reference to section 505(j)(5)(B)(iii) of the Act is to that section of the Act as in effect prior to December 8, 2003, when the Medicare Prescription Drug, Improvement and Modernization Act (MMA) (Public Law 108-173) was enacted. See MMA § 1101(c)(3). The Agency is aware that Pfizer initiated patent litigation against Mylan shortly after expiration of the statutory 45-day period.

[2] Because your ANDA was filed before the date of enactment of the Medicare Prescription Drug, Improvement and Modernization Act (MMA) (Public Law 108-173) on December 8, 2003, this reference to the 180-day exclusivity provision is to the section of the Act as in effect prior to December 8, 2003. See MMA § 1102(b)(1).

Post-marketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Exhibit B

Plaintiffs' Emergency Application for a Temporary Restraining Order and/or Preliminary Injunction

IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF PENNSYLVANIA

PFIZER, INC.,	)	
	)	
Plaintiff and	)	
Counterclaim Defendant,	)	
	)	
v.	)	02: 02cv1628
	)	
MYLAN LABORATORIES, INC. and	)	
MYLAN PHARMACEUTICALS, INC.,	)	
	)	
Defendants and	)	
Counterclaim Plaintiffs.	)	

FINDINGS OF FACT AND CONCLUSIONS OF LAW

TABLE OF CONTENTS

February 27, 2007

Pfizer Inc. filed this lawsuit against Defendants Mylan Laboratories, Inc., and Mylan Pharmaceuticals, Inc. for infringement of United States Patent Nos. 4,572,909 (the '909 patent) and Patent No. 4,879,303 (the '303 patent).[1] The parties tried this case on the '303 patent before the Court without a jury from November 28, 2006, through December 6, 2006. Following the trial, the parties filed Supplemental Proposed Findings of Fact and Conclusions of Law.

Based on the testimony and evidence presented during the bench trial and the applicable law, the Court finds that Defendants Mylan Laboratories, Inc., and Mylan Pharmaceuticals, Inc., have failed to prove by clear and convincing evidence that the '303 patent is invalid as obvious under 35 U.S.C. § 102. The Court also finds that Defendants have failed to prove by clear and convincing evidence that the '303 patent is unenforceable due to inequitable conduct before the United States Patent and Trademark Office ("PTO").

The Court now enters the following Findings of Fact and Conclusions of Law pursuant to Federal Rule of Civil Procedure 52(a):

FINDINGS OF FACT

I. The Parties and General Information

1. Plaintiff, Pfizer Inc. ("Pfizer"), is a corporation organized and existing under the laws of the State of Delaware. Pfizer has a principal place of business at 235 East 42nd Street, New York, New York. (*Stip. of Uncontested Facts ("Stip. Facts"), ¶ 1.*)

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[1] The '909 patent expired on July 31, 2006, and the claims relating to the '909 patent were dismissed by Order of Court on October 18, 2006.

2. Mylan Laboratories, Inc., is a corporation organized and existing under the laws of the Commonwealth of Pennsylvania and has its principal place of business at 1500 Corporate Drive, Canonsburg, Pennsylvania. (*Stip. Facts, ¶ 2.)*

3. Mylan Pharmaceuticals, Inc., is a corporation organized and existing under the laws of the State of West Virginia and has its principal place of business at 781 Chestnut Ridge Road, Morgantown, West Virginia. Mylan Pharmaceuticals, Inc. is a wholly-owned subsidiary of Mylan Laboratories, Inc.[2] *(Stip. Facts, ¶ 3.)*

4. The '909 patent, entitled "2-(Secondary Aminoalkoxymethyl) Dihydropyridine Derivatives as Anti-Ischaemic and Antihypertentive Agents," was issued by the PTO on February 25, 1986. The '909 patent covers a genus of compounds, including amlodipine, the active ingredient in Norvasc®. (*See '909 patent; MTX 1.)*

5. Simon F. Campbell, Peter E. Cross, and John K. Stubbs, are identified in the '909 patent as the inventors. Pfizer is identified as the owner of the '909 patent. *(Id.)*

6. The '303 patent, entitled "Pharmaceutically Acceptable Salts," was issued by the PTO on November 7, 1989. The '303 patent covers the besylate salt of amlodipine. *(Stip. Facts, ¶ 5.)*

7. Dr. James I. Wells ("Dr. Wells") and Mr. Edward Davison ("Mr. Davison") are identified in the '303 patent as the inventors. *(Stip. Facts, ¶ 7.)* Both Dr. Wells and Mr. Davison were employees of Pfizer in its Pharmaceutical Research & Development Group

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[2] The defendants, Mylan Laboratories, Inc. and Mylan Pharmaceuticals Inc., are hereinafter collectively referred to as "Mylan."

("Pharm. R&D") during the time that the tests described in the '303 patent were performed. *(Stip. Facts, ¶ 28.)*

8. Pfizer is identified as the owner of the '303 patent. *(See '303 patent, PTX 2 and MTX 2.)*

9. Mr. Keith Ruddock was the Pfizer in-house patent agent who oversaw the drafting and prosecution of the '303 patent. Mr. Ruddock was supervised by Dr. David Wood. James McManus was the Pfizer U.S. patent agent responsible for the prosecution of the '303 patent before the PTO. *(See Depo. of James McManus, Pfizer v. Mylan, at 99.)*

10. Typically, the Pfizer U.S. patent agents would not talk to the Pfizer U.K inventors before filing a U.S. patent application. *(See Depo. of James McManus, Pfizer v. Mylan, at 24.)* The U.S. patent agents would rely on the U.K patent lawyers or U.K patent agents to provide the information which needed to be submitted to the PTO. *(Id. at 34.)*

11. Pursuant to the provisions of 21 U.S.C. § 355a, the United States Food and Drug Administration ("FDA") granted Norvasc® a six-month period of pediatric exclusivity, which is applicable to the '303 patent. *(Stip. Facts, ¶ 9.)* The expiration date of the '303 patent is March 25, 2007, and the six-month period of pediatric exclusivity for the '303 patent, to the extent applicable, expires on September 25, 2007. *(Stip. Facts, ¶¶ 8, 10.)*

12. Pfizer filed a New Drug Application ("NDA") for Norvasc® (amlodipine besylate) tablets with the FDA on December 23, 1987. In the application, Pfizer advised the FDA that it had switched from maleate salt to besylate salt because the besylate salt had significantly better chemical stability and less sticking to processing equipment than the maleate salt. *(See Stip. Fact, ¶ 14.)*

13. The FDA approved Pfizer's NDA for amlodipine besylate tablets in late 1991. Thereafter, Pfizer proposed, and the FDA approved a four-year shelf life for amlodipine besylate tablets based on Pfizer's long-term stability data for the tablets. The current shelf life for Norvasc® tablets in bottles is 5 years. *(Stip. Facts, Trial Transcript V, at 2.)*

14. Norvasc® is approved by the FDA for treating hypertension and chronic stable and vasospastic angina. Norvasc® was launched as a commercial product by Pfizer in the United States in November 1992. *(See Stip. Facts, ¶¶ 15 and 54.)*

15. Pursuant to 21 U.S.C. § 355(b)(1) and the regulations of the FDA promulgated pursuant thereto, Pfizer listed the '909 patent and the '303 patent in the FDA's publication "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book") as covering the drug substance, amlodipine besylate, in Norvasc®. *(Stip. Facts, ¶ 6.)*

16. On May 22, 2002, Mylan filed with the FDA an Abbreviated New Drug Application ("ANDA") No. 76-418, in which it sought approval to commercially sell 2.5 mg, 5 mg, and 10 mg dosage strength generic amlodipine besylate tablets (the "ANDA products"), before the expiration of the terms of the Pfizer '909 and '303 patents. *(Stip. Facts, ¶ 4.)*

17. By letter dated July 23, 2002, Mylan certified pursuant to 21 C.F.R. § 314.94(a)(12(i)A)(4) that it was seeking approval to market a generic version of Norvasc®.

18. Mylan has received final approval from the FDA of its ANDA No. 76-418, and plans to commercially sell the ANDA products in the United States, pursuant to 21 U.S.C. § 355(j)(2). *(Stip. Facts, ¶ 21.)*

19. On September 22, 2002, Pfizer commenced this patent infringement action against Mylan pursuant to 35 U.S.C. § 271(e)(2)(A), which makes it an act of infringement to file an ANDA for a drug claimed in a patent.

20. Pfizer seeks, *inter alia*, an order "permanently enjoining [Mylan]" from making, using, selling, offering to sell, or importing into the United States the Mylan Amlodipine Tablets described in ANDA No. 76-4618 until the expiration of the '909 patent term, . . . , and after the expiration of the '303 patent term . . . ."

21. The '909 patent expired on July 31, 2006. Thereafter, by Order of this Court dated October 18, 2006, the claims relating to the '909 patent were dismissed from this action for lack of subject matter jurisdiction.

22. Pfizer is asserting infringement only of claims 1, 2 and 3 of the '303 patent. Mylan does not contest infringement of these claims. However, Mylan alleges that claims 1, and 3 of the '303 patent are invalid under 35 U.S.C. § 103 as obvious and that the '303 patent is unenforceable for inequitable conduct before the PTO. (*See Stip. Facts, ¶ 22.)*

23. Claim 1 of the '303 patent is "[t]he besylate salt of amlodipine," which is generally known as "amlodipine besylate."

24. Claim 2 of the '303 patent is "[a] pharmaceutical composition comprising an anti-hypertensive, antiischaemic or angina-alleviating effective amount of the besylate salt of amlodipine as claimed in claim 1 together with a pharmaceutically acceptable diluent or carrier."

25. Claim 3 of the '303 patent is "[a] tablet formulation comprising anti-hypertensive, antiischaemic or angina-alleviating effective amount of the besylate salt of amlodipine as claimed in claim 1 in admixture with excipients."

26. If the Court holds that the '303 patent is valid and enforceable, the Mylan ANDA products, if manufactured, used, sold, or offered for sale in the United States, or imported for sale into the United States, will literally infringe claims 1, 2, and 3 of the '303 patent. *(Stip. Facts, ¶ 22.)*

II. Pharmaceutical Salts

27. A "base," such as amlodipine, is a compound which can become a positively charged ion. The positively charged ion of a base is called a "cation." An "acid" is a compound which can become a negatively charged ion. The negatively charged acid ion is called an "anion." *(Stip. Facts, ¶ 20.)*

28. A salt is the product of the reaction of a base and an acid. *(Stip. Facts, ¶ 19.)*

29. Acid addition salts may form as crystalline or amorphorous solids, or as liquids, such as oils. *(See Testimony of James I. Wells, Trial Transcript I, at 196.)*

30. A finished drug product consists of an active pharmaceutical ingredient together with inactive ingredients, known as excipients, in a dosage form such as a tablet, capsule, or injectable solution. *(See Testimony of Stephen W. Hoag, Trial Transcript V, at 165.)*

31. A pharmaceutically acceptable salt is any salt of an active drug molecule that can be used to make a finished drug product suitable for administration of the drug to a patient.

32. Pharmaceutical salts are evaluated for use in drug products based on their physicochemical or formulation properties which include aqueous solubility, chemical stability, hygroscopicity, and processability (*i.e.,* the ability to be manufactured into commercial dosage forms through the use of typical processing machinery).

33. The maximum amount of a compound that will dissolve at a specific temperature in a fixed amount of water, or water-based solvent, is called the aqueous solubility of the compound at that temperature. *(Stip. Fact, ¶ 23.)*

34. Pharmaceutical scientists, or formulators, use a rule of thumb for good solubility. Aqueous (in water or water-based solvent) solubility greater than 1 mg/ml at 37◦C is good solubility. *See '303 patent, Col. 2: 22-27.* Drug compounds having solubilities greater than the 1 mg/ml threshold or baseline generally have good bioavailability in oral dosage form.

35. Chemical stability relates to the resistence of a drug substance to chemically breakdown. Chemical stability may be determined for the drug substance alone ("bulk stability") or for the drug substance in combination with biologically inactive compounds known as excipients ("formulation stability"). *(Stip. Fact, ¶ 24.)*

36. The breakdown of the drug substance is known as degradation and the products from the breakdown of the drug substance are called "degradants." *(Stip. Fact, ¶ 25.)*

37. Chemical stability testing is also necessary to determine the shelf-life of the product.

38. Drug manufacturers assess chemical stability of an active drug compound alone and in admixture with excipients, *e.g.*, as the finished product.

39. Both the number and concentration of degradants in finished drug products are monitored closely as part of the drug development and approval process.

40. It is standard practice to use accelerated chemical stability testing in the pharmaceutical industry. Accelerated stability tests expose the active drug compound and finished product to high temperatures or high relative humidity in an effort to accelerate degradation that may occur over longer time periods at normal temperatures and relative humidities.

41. "Hygroscopicity," in the context of drug development, is a measure of the amount of water (moisture) that a drug compound absorbs when the drug compound is exposed to specified conditions of temperature, relative humidity, and time.

42. Hygroscopic drug compounds complicate the manufacturing process because precise measurement of the amount of active drug compound to be incorporated into a drug product is required. Absorption of moisture changes the weight of the active drug compound. Variation in the amount of the drug compound because of absorbed moisture may result in incorporating too little active drug into a drug product which will lead to variable dosing.

43. Nonhygroscopicity of a drug compound is also an important formulation property because absorbed water may promote chemical instability of a drug compound or drug product, or lead to changes in processability of the drug product.

44. "Processability" describes the ability of a formulation to be manipulated during the process of manufacturing a commercial dosage form, such as a tablet or capsule.

45. Stickiness, one aspect of processability, refers to adherence of the drug substance to the surfaces of manufacturing equipment, such as the metal surface of the punch face of a tablet press.

46. Stickiness is a problem when manufacturing a drug product because adherence of the drug substance to the surface of manufacturing equipment can interrupt production and/or cause a defective product to be made. In commercial tablet manufacturing very large quantities of tablets are produced on extremely high speed tablet presses. If a drug compound sticks to the punch faces of tablet presses while tablets are being made, the punch faces will require cleaning during tablet runs which would interrupt and slow production. Sticking to the punch face is referred to as "punch filming." Also, sticking may result in tablets having surfaces that are "picked" or pitted in appearance. *(See Testimony of Stephen W. Hoag, Trial Transcript V, at 170-78.)*

47. Manufacturing deficiencies, such as sticking, when observed in small experimental tablet operations will be more significant when using extremely high speed tablet presses. For that reason, pharmaceutical formulators strive to achieve "robust" tablet formulations, *i.e.,* formulations that can be tableted without production problems in a variety of conditions.

48. Pharmaceutically acceptable salts are those which are non-toxic and have no significant impurities or degradation products formed as a result of chemical breakdown of the salt, alone or in combination with excipients, over extended time periods, and which are suitable for making a dosage form that is administrable to a patient. The term

"pharmaceutically acceptable salt" does not convey any information about a particular salt or its chemical structure.

III. Amlodipine and Amlodipine Maleate

49. Amlodipine is the common name for the chemical compound 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine, which is a member of the class of compounds referred to as "1,4-dihydropyridines." *(Stip. Fact, ¶ 16.)*

50. Amlodipine is a biologically active chemical compound that has anti-hypertensive and anti-ischaemic activity in the body. *(Stip. Fact, ¶ 26.)* Anti-hypertensive activity means that amlodipine lowers the blood pressure of a patient. Antiischaemic activity means that amlodipine reduces angina, the pain associated with a lack of blood flow to the heart muscle.

51. Amlodipine maleate is an acid addition salt, formed from the reaction of amlodipine and maleic acid. *(Stip. Fact, ¶ 27.)*

52. During the 1980's, each new active moiety made at Pfizer's Sandwich, England research facility was assigned a code beginning with the prefix "UK", for the United Kingdom, followed by a five-digit number. *(Stip. Fact, ¶ 29.)*

53. Amlodipine was assigned compound number "UK-48,340." *(Stip. Fact, ¶ 30.)*

54. During the 1980's, salts made from a particular acid anion were assigned a code by Pfizer which consisted of the code for the active moiety followed by a two-digit or two-letter code used for all salts made from that acid anion. *(Stip. Fact, ¶ 31.)*

55. The Pfizer two-digit code for the maleate anion was "11," and amlodipine maleate was assigned code "UK-48,340-11." *(Stip. Fact, ¶ 32.)*

56. The two-digit Pfizer codes for the anions listed in the '303 patent are as follows: Hydrochloride anion was "01"; Acetate anion was "14"; Tosylate anion was "15"; Succinate anion was "24"; Besylate anion was "26"; Mesylate anion was "27"; Lactate anion was "50"; Salicylate anion was "AB." *(Stip. Fact, ¶¶ 33-40.)*

57. On or about July 14, 1982, the Pfizer Discovery Chemistry Group located at the Pfizer Central Research Laboratories in Sandwich, England, recommended that an effort be made to develop amlodipine into a commercial product. Clinical studies on amlodipine maleate were planned for 1983.

58. The finished commercial product was intended to be an 20 mg amlodipine maleate tablet. *(See Deposition of Edward Davison, Pfizer v. Apotex, at 128; Deposition of Edward Davison, Pfizer v. Synthon, at 38.)* Tablets are the preferred oral dosage form for several reasons, which include patient acceptance, self-administration, and tablets are the optimum economic commercial dosage form to manufacture. *(Id.; See Testimony of Stephen W. Hoag, Trial Transcript V, at 179.)*

59. In 1982, the Pfizer Pharm. R&D Group, also located in Sandwich, England, was responsible for developing commercial dosage forms (drug products) of pharmacologically active compounds discovered and recommended by the Pfizer Discovery Chemistry Group.

60. Neither Dr. Wells nor anyone in Pharm. R&D participated in selecting amlodipine maleate as the amlodipine salt to be developed to a commercial dosage form. The salt form was selected by the Discovery Chemistry Group. *(See Testimony of James I. Wells, Trial Transcript I, at 189; see also Deposition of Edward Davison, Pfizer v. Apotex, at 5.)*

61. In 1982, the head of Pharm. R&D was Mr. J.E. Jeffries. His deputy, Dr. J.R. Davidson, assigned Dr. Wells, a group development leader in Pharm. R&D, the primary responsibility to develop a commercial tablet formulation of amlodipine maleate. *(See Testimony of James I. Wells, Trial Transcript I, at 192.)*

62. Dr. Wells assigned Mr. Davison, a physical chemist within Pharm. R&D,[3] to assist him in developing the formulation properties of amlodipine maleate. Ms. Teresa Cutt, Mr. David Smith, and Ms. Sally Darling, also members of the Pharm. R&D, were also assigned to the project of developing a commercial amlodipine maleate tablet.

63. At the time that Dr. Wells and Mr. Davison were given this assignment, neither scientist expected that formulating a commercial dosage form of amlodipine maleate would present any problem in terms of stability or processability. It did not occur to Dr. Wells that the amlodipine and the amlodipine maleic acid would react and produce a degradation problem. *(See Testimony of James I. Wells, Trial Transcript I, at 197.)*

64. Dr. Wells and Mr. Davison worked closely with the Pfizer Process Research & Development Group ("Process R&D") and the Analytical Chemistry Department.

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[3] Mr. Davison received his Bachelor of Science in chemistry and physics. *See Deposition of Edward Davison, Pfizer v. Apotex, at 2.*

65. Dr. Wells decided that amlodipine maleate tablets should be manufactured using the direct compression process. *(Id. at 194.)*

66. "Direct compression" is a method of tablet making which is desirable for manufacturing purposes on a commercial scale because it has fewer processing steps, reduces the potential for hydrolytic breakdown, and is more cost effective than other tablet manufacturing processes. (*See Testimony of Stephen W. Hoag, Trial Transcript V, at 179.)* Water or other liquid excipients are not used in the direct compression process. *(Id. at 179-81).*

67. In the mid-1980's, as today, "direct compression" tablet manufacturing was the method of choice when the active drug compound in the finished drug product is less than about twenty-five per cent (25%) of the total tablet weight or when hydrolytic instability of the active drug compound is a concern. **(***Id.*)

68. Amlodipine maleate was stable in bulk form (*i.e.,* before being mixed with excipients and processed into a useable dosage form.) However, when Dr. Wells and Mr. Davison began trying to formulate a direct compression amlodipine maleate tablet, they discovered two significant and interrelated problems: (i) the sticking of the amlodipine maleate salt to the metal punch face of the tablet making press and (ii) the chemical instability of the amlodipine maleate salt.

69. The sticking problem became exacerbated when tablets were made on a high speed commercial production press. *(See Testimony of James I. Wells, Trial Transcript I, at 216.)*

70. Toward the end of 1983, Pfizer's Analytical Chemistry Department "diagnosed" that the instability of the amlodipine maleate was caused by the Michael Addition

Reaction ("MAR"), which was generating two percent (2%) of a new degradant compound identified as UK-57,269 in the maleate formulations. *(Id. at 164, 216; see also Testimony of Robin V. Platt, Trial Transcript V, at 4; see also Deposition of Edward Davison, Pfizer v. Apotex, at 37.)* Two percent (2%) of the MAR compound was not acceptable to Dr. Wells for a commercial product. *(See Testimony of James I. Wells, Trial Transcript I, at 223).* Dr. Robin Platt ("Dr. Platt"), a member of Pfizer's Analytical Chemistry Department, was assigned the responsibility for testing the stability of amlodipine maleate in tablet and capsule formulations. He discovered that in the capsule formulation, the degradation of amlodipine maleate was dominated by one main degradation product, UK-57,269. (*See Testimony of Robin V. Platt, Trial Transcript V, at 24.)*

71. Dr. Platt also discovered that in the amlodipine maleate tablet formulation the pattern of degradation was more complex in that degradation products included not only the formation of UK-57,269, but at least another ten unknown degradation products were also produced. *(Id.; see PTX 120 at P0177100-102.)*

72. Initially, Dr. Wells speculated that the ten unknown degradation products may be derivatives of UK-57,269 *(see PTX 123 at P0187936-7)*; however, it was ultimately determined that those unknown degradants in the amlodipine maleate tablet formulations were not by-products of the degradant UK-57,269. *(PTX 284 at P0190403-4; Trial Tr. December 4, 2006 at 42: 1-17.)*

73. The development of the MAR in the capsule and tablet formulations of amlodipine maleate was not expected. *(Trial Tr. December 4, 2006 at 33:6-11).* It could not have been predicted from the structures of the amlodipine and maleic acid molecules. The

Pfizer Discovery chemists, who were skilled synthetic organic chemists, knew about the MAR generally, i.e., as an abstract reaction such as oxidation. Nevertheless, they designated the amlodipine maleate salt as the development candidate. Had the Pfizer Discovery chemists expected that amlodipine maleate, in formulation, would undergo a MAR, they would not have designated that salt as the development candidate. *(Id. at 34:25-37.9.)*

74. A synthetic organic chemist would not expect the MAR to occur in solid state formulations of amlodipine maleate, but would have expected the reaction to occur only in solution at high temperature. Additionally, he or she would not have expected that a neutral (uncharged) primary amine (NH_2) must be present for a MAR to occur. *(Trial. Tr., Dec. 5, 2006 at 143:12-146:3.)*

75. The conditions that one of ordinary skill would have expected to be necessary for a MAR are not present in a solid state formulation of amlodipine maleate. The primary amine is present as a nonreactive cation, i.e., a positively charged species (NH_3+) and not a reactive neutral species (NH_2). The amlodipine cation and maleate anion are locked in place in the crystal lattice, not free to move and reorient themselves to participate in a MAR.

76. The references Dr. Burgess identified which describe a MAR between a primary amine and maleic acid teach reaction conditions that are vastly different from those in a solid state formulation of amlodipine maleate. The conditions taught require putting the reactants in solution at high temperatures, boiling water, for example, for long periods of time, in the presence of excess amine or the addition of base to make the solution alkaline. None of these conditions is present in a solid state formulation of amlodipine besylate, and those

references would not have been ones that a person of ordinary skill would have considered in attempting to make a tablet of an amlodipine salt. *(Id. at 146:12-147:22.)*

77. Just as it had not been predicted by the Pfizer Discovery chemists, the MAR was not predicted by Pfizer analytical or process chemists. It was identified only by hindsight after the UK-57,269 degradant had been isolated and its chemical structure had been determined by sophisticated analytical techniques. From the chemical structure of UK-57,269, Pfizer chemists, after months of investigation, were able to determine that a MAR had caused the degradant to be formed. *(Trial Tr., Nov. 28, 2006 at 223: 12-225:11.)*

78. Dr. Burgess pointed to a statement in a quarterly report of ACD in May 1985 and the fact that a MAR cannot occur in amlodipine besylate - the besylate anion has no carbon double bond - as evidence that the MAR was predictable from the structure of amlodipine. The statement, referring to a comparative stability study of amlodipine besylate and maleate tablets, is: "As expected the besylate demonstrated a superior stability profile over the maleate." The stated expectation has nothing to do with the MAR. The expected superiority of the amlodipine besylate salt is based not on the absence of a MAR, but on the stability study that had been conducted by Pfizer. During the second half of 1984, Dr. Platt had extensively studied the stabilities of amlodipine salts and he had concluded that the besylate salt in formulation is significantly more stable than the maleate salt. Accordingly, the May 1985 report states that the same result in the follow-up comparative tablet study was expected. *(Trial Tr., Dec. 4, 2006 at 98:4 - 101: 25.)*

79. Dr. Wells and Mr. Davison's first strategy to control the sticking and instability of amlodipine maleate was to change the excipients in the formulations. The fact

that the sticking and instability problems were interrelated, *i.e.*, excipients that reduced sticking exacerbated instability and increased the difficulty of finding a formulation that controlled the problems exhibited by the maleate salt of amlodipine.

80. Amlodipine maleate was also discovered to be very unstable in a liquid formulation and required the addition of cosolvents in order to increase stability. *(See Testimony of James I. Wells, Trial Transcript I, at 225-26.)*

81. As a result of these difficulties, Dr. Wells became concerned that he could not produce a commercially viable direct compression amlodipine maleate tablet formulation. On April 24, 1984, Dr. Wells proposed to Dr. Davidson, his supervisor and the head of Pharm. R&D, that other salts of amlodipine be considered for development and as replacements for amlodipine maleate. Dr. Wells identified several acids which could be used to attempt to make a new salt for testing. *(See PTX 123 / MTX 293; Testimony of James I. Wells, Trial Transcript I, at 231.)*

82. Dr. Wells predicted that amlodipine acetate and amlodipine free base[4] would have the greatest likelihood to overcome the instability problems exhibited by amlodipine maleate. These predictions turned out to be wrong, as both amlodipine acetate and amlodipine free base were much more unstable than amlodipine maleate. (*See Testimony of Robin V. Platt, Trial Transcript V, at 44.)*

[4] Amlodipine base or amlodipine free base refers to the amlodipine molecule alone without reaction with an acidic molecule.

83. Dr. Wells also stated in his memorandum that if management was unwilling to consider making and testing new amlodipine salts, then a different 1,4-DHP compound than amlodipine should be considered for development. *(See PTX 123.)*

84. Dr. Platt expressed reservations about Dr. Wells' proposal to try to find a new amlodipine salt because of the potential high risk of failure. *(See PTX 120; Memorandum from R. V. Platt to P. F. Wadsworth, dated May 3, 1984; see also Testimony of Robin V. Platt, Trial Transcript V, at 51, 80.)* He cautioned that new salts of amlodipine would not necessarily have better stability than amlodipine maleate, as each acid could result in a salt with its own unique degradation pathways or other problems. (*See Testimony of Robin V. Platt, Trial Transcript V, at 26-27.)*

85. At the time Dr. Wells made his proposal, the amlodipine maleate salt, in the form of capsules and intravenous injections, was being tested by Pfizer on human beings in clinical trials. *(Stip. Fact, ¶ 41.)*

86. Soon after Dr. Wells' April 24, 1984 recommendation was approved, he asked Pfizer's Process R&D scientists to attempt to make new acid addition salts of amlodipine. Process R&D created the following salts, based upon the acids that Pfizer had on hand at the time: amlodipine besylate, amlodipine tosylate, amlodipine mesylate, amlodipine succinate, amlodipine salicylate, amlodipine acetate, amlodipine hydrochloride, and amlodipine naphthsylate. *(See Testimony of Robin V. Platt, Trial Transcript V, at 54; see also PTX 75.)*

87. Dr. Wells also requested that Process R&D try to make additional amlodipine salts that he identified in order to test their physicochemical properties and compare those properties with amlodipine maleate. All of the salts selected by Dr. Wells had previously been

used in pharmaceutical formulations. *(See Testimony of James I. Wells, Trial Transcript I, at 175.)*

88. Dr. Wells chose these candidates from a larger number of pharmaceutically acceptable acids of which he was aware from various sources. However, he could not predict whether any particular salt of amlodipine would form as a crystalline salt, or what the physicochemical properties would be of any salts that did form. Dr. Wells proposed a broad range of salts, including sulfonates, carboxylates, and inorganic salts. *(See Testimony of James I. Wells, Trial Transcript I, at 176, 178; see also Testimony of Robin V. Platt, Trial Transcript V, at 75.)*

89. Dr. Wells did not know prior to testing whether any salt which he proposed would be an improvement over amlodipine maleate. However, Dr. Wells had "high hopes" that besylate would be a possible alternative to the maleate. *(See Testimony of James I. Wells, Trial Transcript I, at 176, 178.)*

90. Dr. Platt did not know prior to testing whether any salt proposed by Dr. Wells would be an improvement over amlodipine maleate. *(See Testimony of Robin V. Platt, Trial Transcript V, at 49.)*

91. Dr. Wells and Mr. Davison, together with other members of Pharm R&D and Dr. Platt, established testing protocols and tested the new amlodipine salts made by Process R&D for the physicochemical properties of solubility, hygroscopicity, chemical stability in formulations, and processability, *i.e.*, sticking to the tablet-making equipment. Amlodipine maleate, which exhibited unacceptable sticking and stability, was used as the control in the experiments. **(***See Testimony of Robin V. Platt, Trial Transcript V, at 62.)*

92. Pfizer scientists used methods routinely employed by Pfizer and the pharmaceutical industry in general to test the new amlodipine salts for solubility, hygroscopicity, and instability. For sticking, Mr. Davison adapted a test previously used by another member of Pharm R&D to measure sticking of a different active compound.

Solubility Findings

93. The aqueous solubility of amlodipine besylate, as well as all of the other new amlodipine salts, was tested and measured. All of the new amlodipine salts, except amlodipine tosylate, had solubilities above the 1 mg/ml threshold preferred by formulation scientists. The new salts were not rank-ordered according to their solubility values. None of the new amlodipine salts was eliminated from consideration based on solubility testing.

94. The solubility of each new batch of salt that Process R&D made was measured. Multiple batches were made and the solubility of each batch, along with the original development candidate, amlodipine maleate, and the eventual commercial product, amlodipine besylate, were measured.

95. The solubility of the amlodipine besylate fell in the mid-range of solubilities of the amlodipine salts tested. *(See '303 patent, col. 2, Table 1.)*

96. The solubility value for amlodipine besylate reported in the '303 patent, 4.6 mg/ml, is consistent with the aqueous solubility that Pfizer's formulation scientists measured for amlodipine besylate in an experiment conducted in September 1985. That experiment, in which a pH/solubility profile for amlodipine besylate was produced, reports that the solubility of amlodipine besylate is between 4.6 and 4.7 mg/ml over a range of pH values from 1 to 7. *(PTX 635 at P0056829-30; Trial Tr., Dec. 5, 2006 at 169:1 - 172:10.)* The experiment was

carried out just two months before Dr. Wells submitted to the Pfizer patent department in Sandwich, the invention disclosure that became the '303 patent application. *(PTX 611 at P0085952.)* Moreover, the tosylate solubility value that is set out in the patent, 0.9 mg/ml, is recorded in the very next experiment in the same laboratory notebook. *(PTX 635 at P0056831.)*

97. There are different aqueous solubility values reported for amlodipine besylate in other Pfizer documents prepared during the development of amlodipine tablets. In Dr. Wells' October 11, 1984 memo to Dr. Davidson, he reports a solubility value of 3.6 mg/ml for amlodipine besylate. *(PTX 76 at P0152406.)*

98. Solubility values can vary from batch to batch based on any number of variables in experimentation as reflected in the above referenced finding. Such variations are not unexpected and do not mean that one or the other is incorrect. The '303 patent states that any solubility greater than 1 mg/ml is acceptable and, therefore, the difference between 3.6 mg/ml and 4.6 mg/ml is immaterial under the circumstances.

99. The solubility of the amlodipine besylate could not have been predicted; it had to be made and tested. *(See Testimony of Robin V. Platt, Trial Transcript V, at 72.)*

Hygroscopicity Findings

100. Mr. Davison and members of the Pharm. R&D tested all of the newly created amlodipine salts for hygroscopicity, which was measured by subjecting each of the amlodipine salts to controlled temperatures, relative humidity, and time conditions that may be encountered during the manufacturing, storage, or transportation processes, *e.g.*, 75% relative humidity ("RH") at 37◦ for 24 hours, and 95% RH at 30◦ for three days.

101. Amlodipine besylate, amlodipine tosylate, and amlodipine maleate were the only amlodipine salts that were nonhygroscopic at 75% RH and 37◦ for 24 hours. Amlodipine besylate and amlodipine maleate were the only amlodipine salts that were nonhygroscopic at 95% RH and 30◦ for three days. With the exception of the besylate salt and the maleate salt, all of the amlodipine salts that were tested proved to be hygroscopic at test conditions. All of the sulfonic acid salts other than besylate that were tested were hygroscopic.

102. The fact that the besylate salt of amlodipine was capable of remaining nonhygroscopic through the range of conditions used in the tests could not have been predicted.

Formulation Stability Findings

103. To determine formulation stability, Mr. Davison and other members of the Pharm. R&D, as well as Dr. Platt, had to test all of the newly created amlodipine salts. Multiple formulation blends of each of the newly created amlodipine salts, with different excipients, were made and tested. Tablets were also made by compressing some of the blends.

104. For testing purposes, the tablets were exposed to a range of elevated temperatures to promote degradation. Dr. Platt used the analytical procedure known as thin-layer chromatography ("TLC") to measure the chemical stability of multiple blends and tablets which contained amlodipine salts at multiple time intervals after they had been stored at a fixed temperature. *(See Testimony of Robin V. Platt, Trial Transcript I, at 16-20.)* TLC was a well accepted technique in the pharmaceutical industry for studying the chemical stability of drug compounds. It also was the standard analytical method which he used at Pfizer for stability testing of new compounds, and it was suitable to rank order the tested amlodipine salts based on their respective stabilities.

105. Dr. Platt measured the chemical stabilities of the new amlodipine salts and amlodipine free base, and the amlodipine maleate salt in multiple blends and compacts at multiple time intervals after they had been stored at controlled temperatures. He used multiple solvent systems in the TLC analysis to assure that all degradants would be detected.

106. Dr. Platt evaluated the number and relative amounts of degradants produced by each amlodipine salt in each of the multiple formulations after exposing each blend of each amlodipine salt to accelerated temperature.

107. Dr. Platt discovered that the various newly created amlodipine salts degraded at different rates and produced different kinds and amounts of degradation products when exposed to a range of temperatures and measured at different times.

108. Dr. Platt used amlodipine maleate as a control in these experiments. Amlodipine maleate degraded in formulation to create the degradant UK-57,269, a product caused by the "MAR" of the amlodipine ion interacting with the maleic acid ion.

109. Based on chemical stability data which he accumulated, on October 9, 1984, Dr. Platt prepared a rank ordering of all the amlodipine salts he tested. *(Stip. Fact, ¶ 43; PTX 75)*. Dr. Platt concluded that amlodipine besylate was the most stable in formulation of all of the amlodipine salts that he had tested. Based on the rank order, it also appeared to Dr. Wells that amlodipine besylate was the best choice for an alternative to amlodipine maleate. *(See Testimony of James I. Wells, Trial Transcript II, at 3.)*

110. Despite the fact that acetic acid and hydrochloric acid could not undergo a MAR, the salts made from those acids exhibited significantly worse formulation stability than

amlodipine maleate. Amlodipine free base, which also could not undergo a MAR, had significantly worse stability in formulation than amlodipine maleate.

111. The formulation stability of the besylate salt of amlodipine was not expected and could not have been predicted either from the elimination of the MAR or otherwise. *(See Trial Transcript; December 4, 2006 at 48: 25 - 50: 7.)*

Processability Findings

112. In 1984, Mr. Davison designed and developed a study to compare the punch filming properties of each of the newly created amlodipine salts to measure sticking by making tablets with blends of the salts and measuring the amount of amlodipine that adhered to the tablet punch face as a function of the number of tablets made. *(See '303 patent, col. 3, Lines 50 - 65; PTX 76 at P0152404.)*

113. Mr. Davison tested the amlodipine salts for sticking by making tablets of the different amlodipine salts in the same tablet formulation. The principal excipient of the formulation was calcium dihydrate (Compactrol®) and it also included the lubricant magnesium stearate, at one percent (1%) of the weight of the formulation. The amlodipine maleate salt was again used as the control in the sticking experiments.

114. The sticking studies measured the rate at which amlodipine stuck to the tablet punch face. Mr. Davison measured the rate of sticking for each salt by calculating the slope of the best-fit straight line for a plot of amount of salt per unit area stuck to the punch face against number of tablets made.

115. Mr. Davison's studies were well designed, controlled, and properly carried out.

116. These tests demonstrated that the amlodipine besylate was forty-one percent (41 %) less sticky than amlodipine maleate. The tests also showed that amlodipine besylate was less sticky than all but one of the other amlodipine salts, the amlodipine mesylate, which was forty-two percent (42%) less sticky than amlodipine maleate.

117. To confirm his results with the Compactrol® formulation, Mr. Davison also did a head-to-head study of only amlodipine besylate and amlodipine maleate in the then-lead tablet formulation, known as FID 0650. The principal ingredients of each of the formulations were microcrystalline cellulose (Avicel®) and anhydrous dibasic calcium phosphate with the lubricant magnesium stearate at one percent (1%) of the total weight of the formulation. The study confirmed that on longer runs of tablets, amlodipine besylate was significantly less sticky than amlodipine maleate.[5]

118. Based on all the test results of the amlodipine salts, Dr. Wells concluded that the besylate salt had a combination of outstanding formulation properties.

119. The fact that one salt would have outstanding properties in all of the categories tested could not have been predicted.

120. On or about October 11, 1984, Dr. Wells recommended to Dr. J. R. Davidson, the head of Pharm. R&D, that the amlodipine besylate salt be substituted for the

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[5] The decreased stickiness of amlodipine besylate was also demonstrated by amlodipine besylate scale-up studies carried out by Ms. Teresa Cutt in 1985, after Mr. Davison had determined that besylate was significantly less sticky than maleate.

amlodipine maleate salt in the commercial amlodipine tablet product. *(Stip. Fact, ¶ 44; MTX 310.)*

121. At the time Dr. Wells made his recommendation to switch salts, Pfizer was conducting Phase II clinical trials of amlodipine maleate (using capsules and intravenous injections). *(Stip. Fact, ¶ 45.)*

122. Dr. Wells' recommendation to switch salts late in the development cycle, while Phase II clinical trials were underway, was very unusual and a direct result of the seriousness of the chemical instability and sticking problems that Pharm R&D had experienced in attempting to develop a direct compression commercial tablet formulation of amlodipine maleate.

123. Based on the test results of Wells, Platt, and Davison, Pfizer's senior research and development management decided to switch from amlodipine maleate to amlodipine besylate for the direct compression amlodipine commercial tablet.

124. At the time Pfizer senior research and development management decided to switch salts, Pfizer had begun Phase II clinical trials of amlodipine maleate. Switching salt forms of a drug candidate in the Phase II clinical trial phase was unprecedented at Pfizer.

125. Pfizer filed an amended Investigatory New Drug ("IND") application with the FDA which reflected a switch in salts from amlodipine maleate to amlodipine besylate on or about May 5, 1986. Pfizer submitted additional test data to the FDA for the besylate salt with its amendment. (*Stip. Fact, ¶ 46.)*

126. On or about November 25, 1985, more than a year after he recommended switching salts from amlodipine maleate to amlodipine besylate, Dr. Wells submitted to

Pfizer's patent group in Sandwich, England, the invention disclosure that led to the preparation and filing of the '303 patent and its foreign counterparts. *(See Stip. Fact, ¶ 47.)*

IV. The Discovery of Amlodipine Besylate

127. Amlodipine besylate is an acid addition salt, formed from the reaction of the chemical base amlodipine and benzene sulphonic acid. *(Stip. Fact, ¶ 18.)*

128. After Pfizer switched to amlodipine besylate, it took only three efforts to solve the problems associated with maleate. Pharm R&D was able to produce a chemical size batch within a year of the switch. *(See Testimony of James I. Wells, Trial Transcript II, at 7.)*

129. Dr. Wells' preference is to use one-half percent (0.5%) of lubricant in a formulation; however with the amlodipine besylate formulation he chose to use one percent (1%) because of an "extreme sticking problem" which he had with maleate, "but we had clearly improved with the besylate . . . one percent was a sensible position . . . [i]t left us with a margin of safety." *(Id.)*

130. Since 1997, Norvasc® has been the largest selling branded cardiovascular drug product in the world.

131. In 2003, Norvasc® sales in the United States exceeded $2.1 billion. *(Stip. Fact, ¶ 56.)*

132. The worldwide sales of Pfizer's amlodipine besylate drug product are approximately $4 billion annually. *(Stip. Fact, ¶ 57.)*

133. Pfizer's amlodipine besylate drug product is its second-largest selling product in terms of worldwide annual dollar sales. *(Stip. Fact, ¶ 58.)*

V. The '303 Patent Prosecution

A. The '303 Patent Application

134. On April 4, 1986, Pfizer filed its first patent application in which it claimed amlodipine besylate, British Patent Application No. 8,608,335 (the " British priority application"). *(Stip. Fact, ¶ 13.)* The British priority application was filed almost two years after Dr. Wells had first recommended making and testing new amlodipine salts (April 24, 1984) and approximately 1-½ years after he recommended switching the amlodipine salt from maleate to besylate (October 11, 1984).

135. The '303 patent issued from the United States Patent Application Serial No. 256,938 (the " '938 application"), which was filed in the PTO on October 13, 1988. *(Stip. Fact, ¶ 11.)*

136. The '938 application is a continuation of United States Patent Application Serial No. 30,658 (the " '658 application"), which was filed in the PTO on March 25, 1987. *(Stip. Fact, ¶ 12.)*

137. Pursuant to 35 U.S.C. § 119, the '303 patent claims, and is entitled to, priority based on the April 4, 1986 filing date of the British priority application. *(Stip. Fact, ¶ 13.)*

138. In an Office Action dated October 6, 1987, the PTO examiner found Pfizer's claims to amlodipine besylate to be unpatentable and rejected them as *prima facie* obvious under 35 U.S.C. § 103 over Pfizer's earlier '909 patent on amlodipine and two prior art patents - the Schmidt patent and the Spiegel patent.

139. The PTO Examiner rejected the '658 application as *prima facie* obvious three separate times. On June 17, 1988, the PTO Examiner issued a final rejection.

140. The '303 patent applicants let their patent application go abandoned and filed a continuation application (the ' 938 application) on October 13, 1988, pursuant to 35 U.S.C. § 103.

141. Along with the '938 application, Pfizer submitted to the PTO a Preliminary Amendment of the claims and the Declaration of Dr. Wells dated October 3, 1988 (the "Wells Declaration"), in support of the patentability of the claims in the '938 application. *(See MTX 435.)* The Wells Declaration opines regarding the four characteristics of an active ingredient that are relevant to whether the active ingredient can be made into a pharmaceutical formulation. *(See Depo. of James McManus, Pfizer v. Mylan, at 105.)*

142. The Wells Declaration was submitted under 37 C.F.R. § 1.132 and the declarant, Dr. Wells, swore that the statements made therein were true. (*See MTX 436.*)

143. On November 7, 1989, the Patent Examiner allowed the claims of the '938 application. She did not state whether, in allowing the claims, she had relied on the data in the Wells Declaration which demonstrated amlodipine besylate's unexpected combination of advantageous formulation properties or the arguments of the Pfizer patent attorney that there was no *prima facie* case of obviousness.

144. On November 7, 1989, the PTO issued the '303 patent.

B. Obviousness

i. The Scope and Content of the Prior Art

145. It is undisputed that the following references are prior art to the '303 patent: the '909 patent; a publication by Berge, S.M., et al, "Pharmaceutical Salts," (Jan. 1977) *J.*

Pharm. Sci. 66:1-19 ("Berge"); United States Patent No. 4,432,987 ("Barth"); United States Patent No. 3,816,612 (1974) ("Schmidt"); United States Patent No. 4,032,637 (1977) ("Spiegel"); United States Patent No. 4,346,099 (1982) ("Tanouchi"); United States Patent No. 3,982,007 (1976) ("Laber"), as well as other references are prior art to claims 1 through 3 of the '303 patent. *(Stip. Fact, ¶ 48.)* The Berge, Speigel, and Schmidt references were before the PTO during the prosecution of the '303 patent.

146. Pfizer internal memoranda which relate to its own development of amlodipine maleate and its having identified, made, and tested new amlodipine salts are not prior art to the '303 patent.

147. The compound amlodipine is described in the prior art to the '303 patent. *(Stip. Fact, ¶ 49.)*

148. The '909 patent issued on February 25, 1986. At the time the '909 patent issued, the patent term was seventeen (17) years from the date of issuance.

149. The '909 patent contains a specific claim (claim 8) to amlodipine.

150. The '909 patent identifies maleic acid as the preferred acid used to form salts (maleate salts) with the compounds disclosed and claimed by the patent. The only salt of amlodipine described in the '909 patent is amlodipine maleate. No information concerning the solubility, hygroscopicity, stability, or processability of amlodipine maleate is provided in the '909 patent. *(See '909 Patent, MTX 1.)*

151. The '909 patent recites twelve (12) acid anions that may be combined with the '909 claimed compounds in order to try to make pharmaceutically acceptable acid addition

salts. Neither benzene sulphonic acid, nor any other sulphonic acid, is identified, disclosed, or mentioned in any way in the '909 patent.

152. The '909 patent teaches that amlodipine salts are useful for treating high blood pressure and preventing a variety of heart conditions including angina pectoris, cardiac arrhythmia, heart attack, cardiac hypertrophy, and coronary vasospasm.

153. The Berge article sets the tone for the theme that the properties of salt(s) are unpredictable. ("Choosing the appropriate salt, however, can be a very difficult task, since each salt imparts unique properties to the parent compound." Berge, at 1.) (*See PTX 266*; *Testimony of Bradley Anderson, Trial Transcript VI, at 113 - 14.)*

154. The Schmidt patent teaches that aryl sulfonic acid salts improve the solubility of nitrogen-containing pharmaceutical compounds and, thus, are preferred over other salts. Benzene sulfonic acids are identified as "especially suited examples of such sulfonic acids." (*See PTX 511 / MTX 81.)*

155. The Speigel patent describes the use of mesoridazine as a sleep promoting agent, *(See Testimony of Bradley Anderson, Trial Transcript VI, at 119),* and teaches that the preferred pharmaceutically acceptable acid-addition salt is besylate. *(See PTX 513.)*

156. The Tanouchi patent refers to carboxy-imidazole derivatives and uses for treating patients for diseases caused by thromboxane A2. *(See Testimony of Bradley Anderson, Trial Transcript VI, at 133-34; PTX 514.)*

157. The Tanouchi patent teaches that certain imidazole derivatives are useful in treating inflammation, cerebral apoplexy, myocardial infarction, acute cardiac death,

cardiostenosis, and thrombus, and that benzene sulphonate is a pharmaceutically acceptable acid-addition salt.

158. The Laber patent refers to synergistic compositions (anti-microbial agents and antibiotics) (*See Testimony of Bradley Anderson, Trial Transcript VI, at 130.*) The third page of the Laber patent contains a boilerplate list of salts, which includes benzenesulphonate. *(Id. at 131.)*

159. The Laber patent teaches that compositions comprising a benzisothiazolinone derivative are a 2-nitrofuryl or 2-nitrothienyl derivative and are useful microbial agents. The patent discloses that "[t]he compounds . . . may be employed in free base form or in the form of pharmaceutically acceptable acid-addition salts. Suitable acid-addition salts include organic acid salts, such as fumarate, tartrate, or benzenesulphonate, and mineral acid salts, such as the hydrochloride, hydrobromide or sulphate."

160. The Teijin patent pertains to 1,4 dihydropyridine derivatives and their pharmaceutically acceptable acid addition salts. The patent application lists inorganic acids, carboxylic acids and organic sulphonic acids. The patent application describes mineral acids as the preferred acid; benzenesulphonic acid is not a mineral acid. One might have discovered the Teijin reference because of the key word "antihypertensive action." However, the Teijin reference describes hydrochloride salts. *(See Testimony of Bradley Anderson, Trial Transcript VI, at 212; MTX 645.)*

ii. Ordinary Skill in the Art

161. A person of ordinary skill in the art in this case would be a formulation scientist with at least a Bachelor of Science degree, or the equivalent thereof, in chemistry or pharmacy or a related discipline and some relevant experience in the development and formulation of pharmaceutical products. *(See Testimony of Bradley Anderson, Trial Transcript VI, at 78.)*

162. The person of ordinary skill in the art would not have to have had expertise with synthesizing chemical compounds and would not have been able to predict whether organic reactions, such as the MAR, could occur when compounds are combined in the solid state.

163. Dr. Bradley Anderson obtained a Masters and Ph.D. in pharmaceutical chemistry from the University of Kansas in 1978. *(See Testimony of Bradley Anderson, Trial Transcript VI, at 71.)* He is currently the H.B. Kostenbauder professor at the University of Kentucky in the Department of Pharmaceutical Sciences, College of Pharmacy, and also is an adjunct professor at the University of Utah. Between 1971 and 1974, Dr. Anderson worked as a quality control chemist at Cutter-Haver Lockhart, which was involved in the manufacturing and sale of pharmaceuticals for veterinarian use. In 1978, Dr. Anderson joined the Upjohn Company, where he was a member of the pharmacy research group, which was the group that was involved in drug development and drug formulation. Dr. Anderson currently teaches courses to professional students and graduate students.[6] In the professional program, he

[6] " 'Professional students' are pharmacy students training to become pharmacists or Pharm Ds. The 'graduate students are training for their Ph.D. in pharmaceutical (continued...)

participates in a course that involves dosage forms, solutions, solid state, and stability. In the graduate program, he teaches a full semester course on rate processes, which concerns itself with drug stability and drug degradation. He also teaches a hands-on analytical course, which addresses chromatography, HPLC, TLC, capillary electrophoresis, GS, etc. Dr. Anderson also has published over 100 scientific articles during his career. (*Id.* at 70-74.)

164. The Court found Dr. Anderson qualified as an expert in the fields of pharmaceutical sciences and physical organic chemistry. *(Id.* at 77.)

165. A person of ordinary skill in the art at the time of the invention of the claims of the '303 patent could not have predicted whether toxic degradants or reaction products would be produced by amlodipine besylate, or what their clinical structures and amounts would be, without making and testing the salt. *(Id.* at 89.)

166. As of the date of invention of the claims of the '303 patent, a person of ordinary skill in the art would have understood the '909 patent as teaching that maleate salts of the 1,4-dihydropyridine compounds disclosed and claimed in the '909 patent were preferred. *(Stip. Fact, ¶ 52.)*

167. A person of ordinary skill in the art at the time of the invention of the claims of the '303 patent could not have predicted whether a new combination of a chemical base and acid would form a salt that is crystalline and has reproducible stoichiometry. *(See Testimony of Bradley Anderson, Trial Transcript VI, at 90.)*

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[6](...continued)
sciences." *(See Testimony of Bradley Anderson, Trial Transcript VI, at 73)*

168. A person of ordinary skill in the art at the time of the invention of the claims of the '303 patent would have known of the MAR, but would not have expected it to occur in the solid state. (*Id.* at 141).

169. There is no prior art reference that teaches one of ordinary skill in the art that the MAR would occur between amlodipine and maleic acid in the amlodipine maleate salt.

170. A person of ordinary skill in the art at the time of the invention of the claims of the '303 patent would not have been aware of literature that discussed the MAR in a solid state, *e.g.,* tablets and capsule formulation. Moreover, if they had an understanding of the reaction, a person of ordinary skill in the art in 1986 would not have expected it to occur in the solid state. *(See Testimony of Bradley Anderson, Trial Transcript VI, at 143.)*

171. A person of ordinary skill in the art at the time of the invention of the claims of the '303 patent would not have been able to predict the solubility of a salt. *(See Testimony of Bradley Anderson, Trial Transcript Vol. VI, at 160.)*

172. A person of ordinary skill in the art at the time of the invention of the claims of the '303 patent would have known that besylate is a pharmaceutically acceptable acid addition salt.

iii. The Differences Between the Claimed Invention and the Prior Art

The '909 Patent

173. In the '909 patent no sulphonate salts are identified or mentioned. The '909 patent specifically describes the maleate salt of amlodipine. It does not specifically describe any other salts of amlodipine. Amlodipine besylate is not specifically described in the '909

patent nor does the '909 patent describe or suggest combining the besylate anion with any particular base cation to form a besylate salt.

174. A person of ordinary skill in the art would have understood that the '909 patent identifies twelve (12) acid anions, any of which could have been tried with any of the millions of biologically active compounds to try to make a suitable salt.

175. A person of ordinary skill in the art would have understood as of the time of the invention of the claims of the '303 patent that the term "pharmaceutically acceptable acid addition salts" in the '909 patent does not describe or suggest any particular chemical structure of a salt, nor does it describe a chemical genus.

176. The '909 patent does not describe the MAR nor does it describe the instability problems that Pfizer scientists encountered with amlodipine maleate in solid formulations.

177. All but one of the working examples of salts in the '909 patent are either the maleate salt or salts made with other carboxylic acids, of which group the maleate salt is a member. The remaining example is not a salt.

The Berge Article

178. The Berge article does not describe salts of biologically active compounds or the indications for which any such compounds may be used, but lists anions that had been used with other base compounds to make pharmaceutical salts.

179. The Berge article discloses that, as of 1974, only 4.16% of the drugs commercially marketed in the United States were sulphonic acids.

180. The Berge article discloses that, as of 1974, the besylate anion was rarely used to make drugs which were commercially marketed in the United States because it teaches that besylate was used only 0.25% of the time. Only two besylate salts had FDA approval as of 1974, atracurium besylate and mesoridazine besylate. *(Stip. Fact, ¶ 50.)*

181. The chemical structures and biological activities of atracurium and mesoridazine are vastly different from the chemical structure and biological activity of amlodipine. *(Stip. Fact, ¶ 50.)*

182. Neither atracurium nor mesoridazine is a 1,4-dihydropyridine. Neither compound is approved by the FDA for treating either hypertension or ischaemia.

183. Atracurium is a neuromuscular blocking agent used as an aid for anesthesia. Mesoridazine belongs to a class of compounds for antidepressants or antipsychotics. *(See Testimony of Bradley Anderson, Trial Transcript Vol. VI, at 116, 118.)*

The Tanouchi Patent

184. The Tanouchi patent lists examples only with inorganic salts. *(See PTX 514; Testimony of Bradley Anderson, Trial Transcript Vol. VI, at 135.)*

The Laber Patent

185. The chemical structures listed in the Laber patent neither relate in any way nor are similar in any way to the structure of amlodipine. The patent indicates that the preferred salts are hydrochlorides. There are no examples of benzenesulphonate salts listed in the patent. *(See PTX 512; Anderson Test., Vol. VI, at 131-32.)*

186. Neither Berge, Barth, Schmidt, Spiegel, Laber, nor Tanouchi describe amlodipine besylate. Each of these references describe salts that were made or could have been made from bases that are different, structurally and biologically, from amlodipine.

The Teijin Patent

187. The Teijin patent does not provide any examples of besylate salts. Rather, all the examples are hydrochloride salts.

iv. Motivation Provided by the Prior Art

188. A person of ordinary skill in the art who was aware of the compound amlodipine maleate in 1986 would not have considered amlodipine besylate to be an obvious modification of amlodipine maleate because (i) the maleate salt is listed as the preferred salt in the '909 patent; and (ii) beyond maleate, the '909 patent gives no particular direction or no particular guidance in terms of "all the universe of possible choices." *(Testimony of Bradley Anderson, Trial Transcript Vol. VI, at 104.)*

189. The '909 patent, the Berge article, nor the existence of atracurium besylate or mesoridazine besylate, either alone or in combination, would have motivated one of ordinary skill in formulation science art to make amlodipine besylate in 1986. *(See Testimony of Bradley Anderson, Trial Transcript VI, at 117.)*

190. The Schmidt patent has nothing to do with salts in the solid state. Therefore, the Schmidt patent, together with the '909 patent and the Berge article, would not have motivated one of ordinary skill in the art as of April 1986 to make amlodipine besylate. *(See Testimony of Bradley Anderson, Trial Transcript VI, at 125-26.)*

191. The Speigel patent either alone or taken together with the '909 patent and the Berge article would not have provided any motivation for one of ordinary skill in the art of pharmaceutical formulation science in 1986 to make the besylate salt of amlodipine. *(See Testimony of Bradley Anderson, Trial Transcript Vol. VI, at 123.)*

192. The Tanouchi patent, either alone or together with the '909 patent and the Berge article, would not have provided any motivation to one of ordinary skill in the art of pharmaceutical formulation science in 1986 to make the besylate salt of amlodipine. *(See Testimony of Bradley Anderson, Trial Transcript VI, at 135.)*

193. The Laber patent, either alone or together with the '909 patent and the Berge article, would not have provided any motivation to one of ordinary skill in the art of pharmaceutical formulation science in 1986 to make the besylate salt of amlodipine. *(See Testimony of Bradley Anderson, Trial Transcript VI, at 132.)*

194. The Teijin reference, either alone or together with the '909 patent and the Berge article, would not have provided any motivation to one of ordinary skill in the art of formulation science in 1986 to make the besylate salt of amlodipine. *(See Testimony of Bradley Anderson, Trial Transcript Vol. VI, at 129, 212.)*

v. Reasonable Expectation of Success

195. A person of ordinary skill in the art of formulation science in April of 1986 would not have had a reasonable expectation that an acid used to make a salt approved by the FDA would make a salt of the compound amlodipine. *(See Testimony of Bradley Anderson, Trial Transcript , Vol. VI, at 101.*)

196. A person of ordinary skill in the art of formulation science in 1986 would not have been able to predict the properties of a salt formed by amlodipine in an acid other than maleate acid. *(See Testimony of Bradley Anderson, Trial Transcript VI, at 106.*)

197. A person of ordinary skill in the art of formulation science in 1986 would not have expected that another salt existed that had better physicochemical properties than amlodipine maleate. *(See Testimony of Bradley Anderson, Trial Transcript, Vol. VI, at 110.*)

198. Even assuming that the physicochemical properties of amlodipine maleate were described in publicly available references as of April of 1986, a person of ordinary skill in the art would not have had any reasonable basis to expect that a salt having better properties than amlodipine maleate would exist. *(See Testimony of Bradley Anderson, Trial Transcript VI, at 111.)*

199. A person of ordinary skill in the art of formulation science in 1986 would not have been able to predict that an acid anion listed by Berge would form a pharmaceutically acceptable acid addition salt with a particular drug base. *(See Testimony of Bradley Anderson, Trial Transcript VI, at 115.)*

200. The '909 patent, the Berge article, and the existence of atracurium besylate or mesoridazine besylate, either alone or in combination, would not have provided a person of ordinary skill in the art of formulation science in 1986 with a reasonable expectation of success with respect to making amlodipine besylate because one cannot predict what the properties of a new salt will be. *(See Testimony of Bradley Anderson, Trial Transcript VI, at 117.)*

201. The Schmidt patent, either alone or together with the '909 patent and the Berge article, would not have motivated one of ordinary skill in the art of formulation science

in April 1986 with a reasonable expectation of success with respect to amlodipine besylate. *(See Testimony of Bradley Anderson, Trial Transcript VI, at 126.)*

202. The Spiegel patent either alone or together with the '909 patent and the Berge article would not have provided a person of ordinary skill in the art of formulation science in 1986 with a reasonable expectation of success with respect to amlodipine besylate. *(See Testimony of Bradley Anderson, Trial Transcript VI, at 123.)*

203. The Tanouchi patent, either alone or together with the '909 patent and the Berge article, would not have provided a person of ordinary skill in the art in 1986 with a reasonable expectation of success with respect to the besylate salt of amlodipine. *(See Testimony of Bradley Anderson, Trial Transcript VI, at 136.)*

204. The Laber patent, either alone or together with the '909 patent and the Berge article, would not have provided a person of ordinary skill in the art in 1986 with a reasonable expectation of success with respect to the besylate salt of amlodipine. *(See Testimony of Bradley Anderson, Trial Transcript VI, at 133.)*

205. The Teijin patent, either alone or together with the '909 patent and the Berge article, would not have provided a person of ordinary skill in the art of formulation science in 1986 with any reasonable expectation of success with respect to the besylate salt of amlodipine. *(See Testimony of Bradley Anderson, Trial Transcript VI, at 130.)*

vi. Unexpected Superior Formulation Properties of Amlodipine Besylate

206. Amlodipine besylate exhibits good solubility. One of ordinary skill in the art as of the time of the invention of the claims of the '303 patent could not have predicted that amlodipine besylate would have good aqueous solubility without making and testing the solubility of amlodipine besylate.

207. Amlodipine besylate is nonhygroscopic over a wide range of temperatures, relative humidities, and times, and is the only sulphonic acid salt of amlodipine that was not hygroscopic. One of ordinary skill in the art as of the time of the invention of the claims of the '303 patent could not have predicted that amlodipine besylate would be nonhygroscopic over a wide range of temperatures, relative humidities, and times without making and testing the hygroscopicity of amlodipine besylate.

208. The formulation stability testing conducted by Pfizer demonstrated that the formulation stability of amlodipine besylate is better than amlodipine maleate.

209. One of ordinary skill in the art as of the time of the invention of the claims of the '303 patent could not have predicted that amlodipine besylate would exhibit chemical formulation stability that is superior to that of amlodipine maleate without making and testing the chemical formulation stability of amlodipine besylate.

210. Amlodipine besylate has good processability and is forty-one percent (41%) less sticky than the prior art amlodipine maleate salt.

211. One of ordinary skill in the art as of the time of the invention of the claims of the '303 patent could not have predicted that amlodipine besylate would have good processing

properties which are superior to those of amlodipine maleate without making and testing the processability of amlodipine besylate.

212. It was not predictable as of the time of the invention of the claims of the '303 patent, that one salt of amlodipine would have advantageous properties in each of the physicochemical categories of solubility, hygroscopicity, stability, and processability without any significant disadvantages.

213. The besylate salt of amlodipine is superior to the prior art of amlodipine maleate because it has a superior combination of properties.

214. The superior properties of amlodipine besylate, individually and in combination, were unexpected at the time it was invented.

215. Amlodipine besylate's combination of advantageous formulation properties makes it highly suitable for use as an active drug compound in direct compression tablet formulations of amlodipine.

C. Inequitable Conduct

216. Mylan contends that Dr. Wells made six material misrepresentations and/or omissions with the intent to deceive the PTO in his Declaration to the PTO.

217. First, Mylan contends that the statement that the previously preferred maleate "has unacceptable stability characteristics" is a material misrepresentation because the statement was made with respect to both maleate tablets and capsules and there is no evidence which shows that the capsules had "unacceptable stability characteristics." In support of its

position, Mylan points out that at the time of the Wells Declaration, the maleate capsules were being used in live human clinical trials and their shelf life had increased.

218. In April of 1985, Dr. G. W. McLay reported concerns to Dr. C. A. P.D. Saxton, in Pfizer New York, about problems with the stability and processing of the amlodipine maleate capsules, especially with respect to suboptimal robustness of the maleate capsules ("although this formulation may be marketable its robustness in terms of processing and stability is not optimal."). *(See PTX 566.)* In that same memo, he stated "we may be able to market these, but they're not optimal and they have problems with stability and they're not robust because they're sticking to the dosators." *(Id.)*

219. Pfizer established through its testing and experimentation that amlodipine besylate is superior to amlodipine maleate, based on its superior stability and processability, and advantageous physicochemical properties. Pfizer concluded that amlodipine besylate tablets are superior to amlodipine maleate tablets.

220. Pfizer concluded that the capsule formulation that was most stable had the Mannitol; however, in Dr. Wells' memo of October 11, 1984, he describes that there is processing problems with that formulation because the Mannitol is sticking to the dosators. *See PTX 76.)*

221. Further in May 1985, Pfizer reported that it had processing and stability concerns with the clinical capsule formulations with the maleate salt, which indicated that a more robust formulation should be developed as a potential commercial product using the besylate salt because it was better in capsules than the maleate salt.

222. Such that, Dr. McLay reported that "[w]e have concluded that the poor stability of amlodipine maleate tablet formulation preclude their commercialization." *(See PTX 566.*)

223. Second, Mylan contends that Dr. Wells did not tell the PTO about the experiments Pfizer had conducted with the amlodipine maleate tablet using two percent (2%) magnesium stearate, which solved the sticking problem. *(See PTX 77 / MTX 323 - Figure 3.*)

224. The experiment reflected in Figure 3 is a comparative study which Mr. Davison ran in order to decide how much lubricant to put in his tableting mix to do the study. Mr. Davison testified that he wanted to determine how these salts relate to each other in stickiness. If he puts too much magnesium stearate in the formulation, none of the compounds would stick. Figure 3 deals only with amlodipine maleate. *(See Depo. of Edward Davison, Pfizer v. Apotex, at 113.)* This was not an experiment to evaluate the level of magnesium stearate which would avoid punch-filming in commercial-sized runs of amlodipine maleate tablets, but, rather, to determine the level of magnesium stearate that allows one to tell the difference between the salts and their natural properties while allowing one to run the tableting machine in order to conduct the test.

225. Figure 3 was not given to the PTO because it was not relevant or material to anything the PTO was asked to decide in the '303 patent prosecution. It provides no information regarding the relative stickiness of the seven amlodipine salts tested.. Dr. Wells told the PTO that besylate was superior in that it was much less adherent (sticky) than the maleate. Whether stickiness in the maleate tablets could be eliminated with two percent (2%) of a lubricant was not material or relevant to the actual issue before the PTO.

226. Third, Mylan contends that Dr. Wells did not tell the PTO about the drug loading experiments Pfizer had conducted using amlodipine maleate in two percent (2%) Avicel which produced a "spectacularly flat and highly acceptable" level of stickiness. (*See PTX 77 / MTX 323 - Figure 5.)*

227. Like the Figure 3 experiment, the Figure 5 experiment was a control experiment. The test measured for one salt (amlodipine maleate) the effect of drug loading on sticking. The purpose of the test was to determine a level of drug loading which would permit the observation and measurement of differences in stickiness of the various amlodipine salts.

228. The Figure 5 experiment is not relevant or material to the '303 patent prosecution insofar as it provides no information regarding the relative stickiness of the seven amlodipine salts tested.

229. Fourth, Mylan contends that Dr. Wells submitted a punch-filming test to the PTO which was "irrelevant [and] . . . meaningless" because it did not contain a lubricant. *(See PTX 77 / MTX 323 - Figure 7.)*

230. Fifth, in the alternative, Mylan contends that if in fact a lubricant was used in the punch-filming test, then the patent is wrong, the application is wrong, and the Wells Declaration is wrong because none of those documents reference a lubricant in the amlodipine besylate formulation.

231. Undeniably, during the instant trial, Dr. Wells changed his previous testimony and now testified that the punch-filming test did in fact contain a lubricant. He explained that he was wrong when he previously stated that no lubricant was used. Since his prior testimony in various depositions and at the Apotex trial, Dr, Wells has had the occasion to

review the Studies on Drug Sticking (Punch Filming) Report *(PTX 77 / MTX 323)* in detail and realized that his prior testimony that no lubricant was used was incorrect. The Court finds Dr. Wells' testimony at trial to have been credible.

232. Significantly, Mr. Davison, the scientist who actually conducted the experiments, has consistently and unequivocally maintained that he ran the formulation tests with magnesium stearate as the lubricant. *See Depo. of Davison, at 163* ("It would be highly surprising of me to run a tablet blend with no lubricant in it on a tablet, instrumented tablet press. I mean, it would be looked at as professional incompetent . . . .") Further, the report itself indicates over and over again that the experiments were conducted using magnesium stearate as the lubricant. It is clear that magnesium stearate was used in the test because one would not do an experiment (Figure 3) to determine an appropriate level of magnesium stearate if one were not going to use magnesium stearate in the ultimate test formulation.

233. Lastly, Mylan contends that Dr. Wells misrepresented to the PTO the pH of the amlodipine besylate. In his Declaration, Dr. Wells made the representation that salts which provide solutions having a pH close to that of blood (7.4 pH) are preferred.

234. In October, 1984, Dr. Wells listed the pH of besylate as 4.5 (*see MTX130, at P0152406*); in the patent application the pH of besylate is shown as 6.6; and in a May 1986 memorandum written by Dr. Wells, the pH of besylate is again listed as 4.5. (S*ee MTX 646, at A15289.*)

235. Experts for both Pfizer and Mylan agree that the difference between a 4.5 pH and 6.6 pH is scientifically not material.

236. Dr. Anderson testified that the pH of a salt can easily vary such that these minor differences in pH are of no material significance. Essentially this is a normal variation.

237. All of the problems which developed with the stability and processability of amlodipine maleate arose years before the '303 application. There is no evidence that shows any reference to the thought of applying for a patent application for amlodipine besylate until well after the problems with the maleate salt were discovered and the overall superiority of amlodipine besylate was established.

CONCLUSIONS OF LAW

1. To the extent any of the foregoing findings of fact is a conclusion of law, it is hereby adopted as a conclusion of law. To the extent any of the following conclusions of law is a finding of fact, it is hereby adopted as a finding of fact.

I. Controlling Authority

A. Jurisdiction

2. The court has subject matter jurisdiction over this case pursuant to 28 U.S.C. §§ 1391 and 1338(a).

3. Venue is proper in this district under 28 U.S.C. § 1400(b).

4. This Court has personal jurisdiction over the defendants Mylan Laboratories Inc. and Mylan Pharmaceuticals, Inc.

5. The 1984 Hatch-Waxman amendments to the Federal Food, Drug, and Cosmetic Act regulate the process by which generic drug companies gain approval from the FDA to bring generic pharmaceuticals to market. *21 U.S.C. § 355.*

6. The filing of an application with the FDA under 21 U.S.C. § 355 for a drug claimed in a patent or the use of which is claimed in a patent is an act of patent infringement if the intention of the applicant is the commercial manufacture, use, or sale of the drug before the patent expires. *35 U.S.C. § 271(e)(2)(A).*

7. An applicant must make a certification with respect to the patents that cover the generic drug product which is the subject of the application that the ANDA will not infringe the patents or that the patents are invalid. *21 U.S.C. § 355(j)(2)(A)(vii)(IV).*

8. Upon receiving notice of the applicant's certification regarding the patents, the patent holder may bring an action in the United States District Court for a declaration of whether the applicant will infringe the patent. *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1570-71 (Fed. Cir. 1997).

B. Federal Circuit Law Applies

9. Any appeal in this action, which arises under the patent laws of the United States, must be to the United States Court of Appeals for the Federal Circuit, 28 U.S.C. § 1295(a), whose precedent governs matters of substantive patent law in this Court. The Federal Circuit has adopted decisions of the Court of Customs and Patent Appeals ("C.C.P.A.") as its own precedent, making those decisions binding on this Court. *E.g., Southwire Co. v. Essex Group, Inc.*, 220 U.S.P.Q. 1053, 1056 n.6 (N.D. Ill. 1983) ("The law that controls this action . .

. is the law of the Federal Circuit [, which] has declared that the patent decisions of [the C.C.P.A.] will be considered binding . . . . ") (*citing South Corp. v. United States*, 690 F.2d 1368, 1370 (Fed. Cir. 1982) (en banc)).

C. The Presumption of Validity

10. Issued patents have a strong presumption of validity in infringement proceedings. *35 U.S.C. § 282.*

11. The party asserting the invalidity of a patent bears the burden to prove each element of invalidity by clear and convincing evidence. *Norian Corp. v. Stryker Corp.,* 363 F.3d 1321, 1326 (Fed. Cir. 2004); *Monarch Knitting Mach. Corp. v. Sulzer Morat GmgH*, 139 F.3d 877, 881 (Fed. Cir. 1998).

12. Each patent claim constitutes a separate invention and the validity of each claim must be considered separately. *Ortho Pharm. Corp. v. Smith*, 959 F.2d 936, 942 (Fed. Cir. 1992).

13. "Clear and convincing evidence exists when the movant 'place[s] in the mind of the ultimate fact finder an abiding conviction that the truth of its factual contentions are highly probable." *Teleflex v. KSR Intern. Co.*, 119 Fed. Appx. 282, 285 (Fed. Cir. 2005), *cert. granted,* -- U.S. --, 126 S. Ct. 2965 (June 26, 2006) (*quoting Colorado v. New Mexico,* 467 U.S. 310, 316 (1984)).[7]

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[7] On June 26, 2006, the United States Supreme Court granted certiorari in *Teleflex, Inc. v.. KSR Int. Co.,* 119 Fed. Appx. 282 (Fed. Cir. 2005), *cert. granted,* 126 S. Ct. 2965 (2006), and on November 27, 2006, while the instant matter was being tried, the Supreme Court heard oral arguments in the *Teleflex* case, which may put in

(continued...)

14. It is more difficult to overcome the presumption of validity and meet the burden of proof by clear and convincing evidence when the references relied on in support of the validity challenge were before the patent office examiner at the time the patent issued. *Am. Hoist & Derrick Co. v. Sowa and Sons, Inc*., 725 F.2d 1350, 1358 (Fed. Cir.), *cert. denied*, 469 U.S. 821 (1984).

II. The Validity of the '303 Patent

15. The nonobviousness requirement is set forth in 35 U.S.C. § 103(a) (" § 103"), and reads:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person of ordinary skill in the art having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

35 U.S.C. § 103(a)). *See also Graham v. John Deere Co.,* 383 U.S. 1, 14 (1966).

16. Although the determination of obviousness is ultimately a legal conclusion, it rests on underlying factual determinations. *See Graham*, 383 U.S. at 17-18.

17. These factual elements are: (i) the scope and content of the prior art; (ii) the difference between the prior art and the claims at issue; (iii) the level of ordinary skill in the

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[7] (...continued)
question the continuing vitality of the Federal Circuit's jurisprudence regarding the concept of obviousness. Nevertheless, the Court has tried to analyze the obviousness claim in a manner faithful to current Federal Circuit jurisprudence, including that found in *Teleflex*.

pertinent art; and (iv) objective or secondary considerations, such as whether there was a long-felt but unresolved need for the claimed invention, the failure of others, or whether the invention has enjoyed commercial success. *Id.*; *Alza Corp. v. Mylan Labs., Inc.,* 464 F.3d 1286, 1290 (Fed. Cir. 2006).

18. The claimed invention must be viewed " in the state of the art that existed at the time the invention was made." *Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1050-51 (Fed. Cir.), *cert. denied*, 488 U.S. 825 (1988); see also *Al-Site Corp. v. VSI Intern., Inc.*, 174 F.3d 1308, 1323 (Fed. Cir. 1999).

19. In order to establish a *prima facie* case of obviousness, the party challenging the patent must prove by clear and convincing evidence that: (i) there was a suggestion or motivation in the prior art that would motivate one of ordinary skill in the art to make the claimed invention; and (b) that a person of ordinary skill in the art would have had a reasonable expectation that the invention would be successful at the time the invention was made. *See In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991); *Kaufman Co., Inc. v. Lantech, Inc.,* 807 F.2d 970, 974-75 (Fed. Cir. 1986); *Yamanouchi Pharm. Co. v. Danbury Pharm.,* 231 F.3d 1339, 1343 (Fed. Cir. 2000).

20. "It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." *In re Wesslau,* 353 F.2d 238, 241 (C.C.P.A 1965).

21. What a reference teaches is a question of fact addressed to a "person of ordinary skill in the art." *In re Bell*, 991 F.2d 781, 784 (Fed. Cir. 1993). The person of ordinary

skill in the art is an objective legal construct who is presumed to be aware of all the relevant prior art. *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 963 (Fed. Cir. 1986). This person of ordinary skill in the art is not deemed to be an innovator; rather, he is "presumed to think along the lines of conventional wisdom in the art." *Standard Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985).

22. The motivation to combine references and reasonable expectation of success are also questions of fact. *Alza Corp. v. Mylan Labs., Inc.,* 464 F.3d 1286, 1290 (Fed. Cir. 2006).

23. "The motivation need not be found in the references sought to be combined, but may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself." *DyStar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1360 (Fed. Cir. 2006); *Brown & Williamson Tobacco Corp. v. Phillip Morris Inc*., 229 F.3d 1120, 1125 (Fed. Cir. 2000).

24. In the context of the structural similarity between the claimed chemical compound and the prior art chemical compound(s), the prior art must give, *inter alia*, reason or motivation to make the claimed compound. *See In re Baird,* 16 F.3d 380 (Fed. Cir.1994) (holding that obviousness had not been shown based on a single reference because the PTO had not demonstrated motivation to select claimed species from prior genus of millions of compounds); *see also In re Dillon,* 919 F.2d 688, 692 (Fed. Cir.1990) (en banc) ("structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a *prima facie* case of obviousness . . . ."), *cert. denied*, 500 U.S. 904 (1991).

25. "[T]here is no requirement that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." *DyStar*, 464 F.3d at 1361 (*quoting Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461, 1472 (Fed. Cir. 1997)).

26. The prior art must also provide a reasonable expectation of success. *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp*., 320 F.3d 1339, 1354 (Fed. Cir. 2003) ("A showing of obviousness requires a motivation or suggestion to combine or modify prior art references, coupled with a reasonable expectation of success. . . ."); *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed .Cir. 1988). "Obvious to try" is not sufficient. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1380 (Fed. Cir. 1986).

27. The assessment of obviousness also requires examination of objective evidence of nonobviousness. Such objective evidence, when present, must be considered and includes the extent of commercial success of the patented invention, unexpected properties of the invention compared to the prior art, whether the invention satisfies a long-felt need, whether others have failed to find a solution to the problem plaguing the art, and any copying of the invention by others. *Graham*, 383 U.S. at 17-18. The commercial success of a patented product supports the nonobviousness of a patent only where there is a nexus between the patent and the commercial success of the product patented. *Ormco Corp. v. Align Tech., Inc*., 463 F.3d 1299, 1311-12 (Fed. Cir. 2006).

28. Evidence of unexpected results are but a part of the "totality of the evidence" that is used to reach the ultimate conclusion of obviousness. *Richardson-Vicks Inc. v. The*

Upjohn Co., 122 F.3d 1476, 1483 (Fed. Cir. 1997). "The existence of such evidence, however, does not control the obviousness determination." *Id.*

29. Objective evidence is "often the most probative and cogent evidence in the record." *Stratoflex, Inc. v. Aeroquip Corp,* 713 F.2d 1530, 1538 (Fed. Cir 1983). "It may often establish that an invention appearing to have been obvious in light of the prior art was not. It is to be considered as part of all the evidence, not just when the decisionmaker remains in doubt after reviewing the art." *Id.* at 1538-39.

30. The party alleging obviousnesss has the burden of proof with respect to all of the obviousness factors, including, where relevant, objective evidence of nonobviousness. *See Dennison Mfg Co. v. Panduit Corp*., 475 U.S. 809, 810 (1986).

31. In *Teleflex,* the Federal Circuit Court held that:

> [w]hen obviousness is based on the teachings of multiple prior art references, the movant must also establish some "suggestion, teaching, or motivation" that would have led a person of ordinary skill in the art to combine prior art teachings in the manner claimed.

Teleflex, supra at 285 (internal citations omitted).

32. Once a *prima facie* case has been established, the burden shifts to the patentee to go forward with rebuttal evidence showing facts supporting nonobviousness. *Yamanouchi Pharm.,* 231 F.3d at 1343. Each fact forming the factual foundation upon which the Court bases its ultimate conclusion regarding the obviousness of the claimed subject matter as a whole must be established by clear and convincing evidence. *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc*., 776 F.2d 281, 291-92 (Fed. Cir. 1985) (internal citations omitted).

33. A result is unexpected for the purpose of showing non-obviousness when the result could not have been predicted by a person of ordinary skill in the art at the time of the invention. *See In re May*, 574 F.2d 1082, 1094 (C.C.P.A. 1978).

34. In this case, the Court finds that the unexpected superior properties of the besylate salt of amlodipine (*i.e.,* solubility, stability, hygroscopicity, and processability), compared to the prior art maleate salt of amlodipine are sufficient to overcome any potential case of *prima facie* obviousness. *See Glaxo Group Ltd. v. Apotex, Inc*., 376 F.3d 1339, 1349 (Fed. Cir. 2004).

35. As explained below, Mylan has failed to establish by clear and convincing evidence that the subject matter of any of claims 1, 2, and 3 of the '303 patent would have been obvious within the meaning of § 103 to a person of ordinary skill in the art as of April 4, 1986.

A. The Selection of The Besylate Salt Would Not Have Been Obvious

36. Mylan contends that the prior art, including the '909 patent, would have motivated a person of ordinary skill in the art to make amlodipine besylate. To prevail on its theory that amlodipine besylate was obvious, Mylan must establish by clear and convincing evidence that one of ordinary skill in the art would have been motivated to select the besylate salt. *Yamanouchi,* 231 F.3d at 1344; *see also Dillon*, 919 F.2d at 692 (finding that *prima facie* obviousness is established "where the prior art gives reason or motivation to make the claimed compositions").

37. The Court concludes that Mylan has failed to show by clear and convincing evidence a motivation to create the besylate salt of amlodipine as contained in the prior art.

The '909 patent specifically directed that the maleate salt was the preferred salt. The '909 patent listed a number of other classes of acid(s) to try, none of which were sulphonates, of which benzene sulphonic acid is a member. None of the other prior art references provide a suggestion to combine amlodipine and benzene sulphonic acid in particular. Importantly, the prior art does not teach a reason for one skilled in the art to even try to improve upon the maleate salt.

38. Therefore, the Court finds and rules that Mylan has failed to show, by clear and convincing evidence, that one skilled in the art would have been motivated to create amlodipine besylate based solely upon a reading of the prior art.

B. There Was No Reasonable Expectation of Success

39. Moreover, Mylan has failed to prove by clear and convincing evidence that a person of ordinary skill in the art would have had a reasonable expectation that amlodipine besylate would be successful based on the '909 patent considered in combination with the Berge, Barth, Spiegel, Schmidt, Laber, Tanouchi references, or any other reference. *See Boehringer,* 320 F.3d at 1354.

40. Mylan has failed to prove by clear and convincing evidence that a person of ordinary skill in the art would have had a reasonable expectation that amlodipine besylate would be successful based on the knowledge that besylate salts of biologically active compounds had been made or suggested for chemical structures different than amlodipine, such as the compounds described in the Berge, Barth, Spiegel, Schmidt, Laber, and Tanouchi references.

41. Based on the prior art in 1986, a person of ordinary skill in the art would not have had a reasonable expectation that amlodipine besylate would be superior over the prior art salt, amlodipine maleate, because it was completely unpredictable as to whether a salt would form, much less whether it would form a pharmaceutically acceptable addition salt.

42. For all these reasons, the Court finds that Mylan has failed to establish a *prima facie* case of obviousness by clear and convincing evidence.

C. Unexpected Superior Formulation Properties of Amlodipine Besylate

43. If claims are found to be *prima facie* obvious, the burden shifts to the patentee to come forward with evidence rebutting the finding. The rebuttal may consist of a showing that the claimed invention has an unexpected, superior property compared with the closest prior art. When the patentee comes forward with rebuttal evidence of non-obviousness, all of the evidence for and against obviousness must be evaluated and the burden of proof by clear and convincing evidence that the claims are obvious in light of all the evidence remains on the party challenging the patent. *Hybritech,* 802 F.2d at 1385.

44. Unexpected superior properties from an invention support the conclusion that the invention was not obvious to one of ordinary skill in the art. *In re Baxter Travenol Labs*, 952 F.2d 388, 392 (Fed. Cir. 1991).

45. In order for a showing of unexpected results to be probative of nonobviousness, such evidence must at least establish that: (i) there actually is a difference between the results obtained and those of the closest prior art, and (ii) the difference actually

obtained would not have been expected by one skilled in the art at the time of the invention. *In re Freeman*, 474 F.2d 1318, 1324 (C.C.P.A. 1973).

46. Assessment of the obviousness of a chemical compound cannot, however, be based merely on comparisons between that compound's chemical structure and structures in the prior art. *In re Papesch,* 315 F.2d 381, 391 (C.C.P.A. 1963). The law of § 103 also requires consideration of the respective biological and pharmacological properties of the claimed compound and those in the prior art before a final conclusion of obviousness can be reached. *Id.*

47. One unexpected property superior to the closest prior art is sufficient to overcome a case of *prima facie* obviousness. There is not a need that the invention be unexpectedly superior in all properties. *In re Chupp*, 816 F.2d 643, 647 (Fed. Cir. 1987).

48. A result is unexpected for the purpose of showing non-obviousness when the result could not have been predicted by a person of ordinary skill in the art at the time of the invention. *In re May,* 574 F.2d 1082, 1094-95 (C.C.P.A. 1978.)

49. In the alternative, assuming *arguendo* that a case of *prima facie* obviousness has been established by Mylan, the Court finds and rules that Pfizer has established that amlodipine besylate exhibits an unexpectedly superior combination of formulation properties sufficient to overcome any case of *prima facie* obviousness.

50. Amlodipine besylate was unexpectedly superior to amlodipine maleate in stability which was significant and of practical and important value.

51. Amlodipine besylate was unexpectedly superior to amlodipine maleate in processability which was significant of practical and important value.

52. Amlodipine besylate has a superior and unexpected combination of formulation properties in that it had no shortcomings in any of the essential qualities of solubility, hygroscopicity, stability, and processability. This combination of these highly desirable properties is important and of practical value to a pharmaceutical formulation scientist and to a pharmaceutical manufacturer.

53. The Court finds and rules that the superior combination of formulation properties of amlodipine besylate was unexpected and could not have been predicted.

D. Conclusion Regarding Obviousness

54. An analysis under *Graham,* which considers the scope and content of the prior art, the level of skill in the art, the differences between the prior art and the amlodipine besylate, and the objective evidence of nonobviousness, leads the Court to conclude that Mylan has failed to prove by clear and convincing evidence that the subject matter in claims 1, 2, and 3 of the '303 patent would have been obvious within the meaning of 35 U.S.C. § 103 to a person of ordinary skill in the art as of April 4, 1986, the filing date of the British priority application to which the '303 patent is entitled under 35 U.S.C. § 119.

In the alternative, assuming *arguendo* that a *prima facie* case of obviousness was established by clear and convincing evidence, the Court finds and rules that Pfizer has established that amlodipine besylate exhibits an unexpectedly superior combination of formulation properties sufficient to overcome any case of *prima facie* obviousness.

III. Inequitable Conduct

55. Patent applicants have a duty to prosecute patents in the PTO with candor and good faith, including the duty to disclose information known to the applicants to be material to patentability. *37 C.F.R. § 1.56(a); see also Molins PLC v. Textron, Inc.*, 48 F.3d 1172, 1178 (Fed. Cir. 1995). "[I]nequitable conduct includes affirmative misrepresentation of a material fact, failure to disclose material information, or submission of false material information, coupled with an intent to deceive." *Semiconductor Energy Lab. v. Samsung Electronics Co., Ltd.*, 204 F.3d 1368, 1373 (Fed. Cir. 2000), *cert. denied*, 531 U.S. 1190 (2001); *Molins,* 48 F.3d at 1178.

56. The duty of candor extends throughout the patent's entire prosecution history. *Baxter Int'l v. McGaw, Inc.*, 149 F.3d 1321, 1331 (Fed. Cir. 1998); *Fox Indus. v. Structural Preservation Sys., Inc.,* 922 F.2d 801, 803 (Fed. Cir. 1990).

57. If a patent applicant violates these duties, the patent may be held to be unenforceable due to inequitable conduct. *See Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*, 326 F.3d 1226, 1233 (Fed. Cir. 2003).

58. A party who asserts that a patent is unenforceable due to inequitable conduct must prove materiality and intent by clear and convincing evidence. *Manville Sales Corp. v. Paramount Sys, Inc.,* 917 F.2d 544, 551 (Fed. Cir. 1990); *Kingsdown Med. Consultants, Ltd. v. Hollister, Inc.*, 863 F.2d 867, 872 (Fed. Cir. 1988).

59. "Inequitable conduct entails a two-step analysis: first, a determination of whether the withheld reference meets a threshold level of materiality and intent to mislead, and second, a weighing of the materiality and intent in light of all the circumstances to determine

whether the applicant's conduct is so culpable that the patent should be unenforceable." *GFI, Inc. v. Franklin Corp*., 265 F.3d 1268, 1273 (Fed. Cir. 2001); *see also Molins*, 48 F.3d at 1178.

60. This requires a careful balancing: when the misrepresentation or withheld information is highly material, a lesser quantum of proof is needed to establish the requisite intent. *See N.V. Akzo v. E.I. DuPont de Nemours*, 810 F.2d 1148, 1153 (Fed. Cir. 1987). In contrast, the less material the information, the greater the proof needed to establish a requisite intent must be. *Id.*

61. Thus, to prevail on its allegations of inequitable conduct, Mylan must prove that information that has allegedly been withheld or misrepresented was material to patentability. It must then demonstrate knowledge, chargeable to those responsible for prosecuting the application, of that information and of its materiality. Finally, it must prove that an individual (not "Pfizer" generally) having a duty of disclosure to the PTO, intentionally withheld or misrepresented the information with an intent to mislead the PTO.

A. Materiality

62. In evaluating materiality, the United States Federal Circuit Court has consistently referred to the standard set forth in Patent Trade Office Rule 56. *Bruno Indep. Living Aids, Inc., v. Acorn Mobility Servs., Ltd.*, 394 F.3d 1348, 1352 (Fed. Cir. 2005).

63. Prior to 1992, Rule 56 defined information as being material "where there is a substantial likelihood that a reasonable examiner would consider it important in deciding whether to allow the application to issue as a patent." *37 C.F.R. § 1.56.*

64. Because the '303 patent was filed prior to the date Rule 56 was amended, the Court must look to the pre-1992 version of the Rule.

65. A Declaration submitted to the PTO is highly material. *Ferring B.V. v. Barr Labs, Inc.*, 437 F.3d 1181, 1189 (Fed. Cir.), *cert. denied*, -- U.S. --, 127 S. Ct. 515 (2006).

66. A misrepresentation in a Declaration submitted to the PTO is *per se* material. *Rohm & Haas Co. v. Crystal Chem. Co.*, 722 F.2d 1556, 1571 (Fed. Cir. 1983).

B. Intent to Deceive

67. The Federal Circuit has held that an actual intent to deceive is a required element. A good-faith error in judgment, a mistake, negligence, or even grossly negligent failures are not sufficient to render an otherwise valid patent unenforceable. *Kingsdown Medical Consultants, Ltd. v. Hollister, Inc*., 863 F.2d 867 (Fed. Cir. 1988).

68. Direct evidence of intent to deceive or mislead the PTO is "rarely available but may be inferred from clear and convincing evidence of the surrounding circumstances." *Baxter Int'l, Inc. v McGaw, Inc.,* 149 F.3d 1321, 1329 (Fed. Cir. 1998). "Generally, intent must be inferred from the facts and circumstances surrounding the applicant's conduct." *Molins*, 48 F.3d at 1180.

69. Intent to deceive, however, cannot be "inferred solely from the fact that information was not disclosed: there must be a factual basis for finding of deceptive intent." *Hebert v. Lisle Corp.*, 99 F.3d 1109, 1116 (Fed. Cir. 1996). "Although there may be special circumstances in which intent is appropriately deemed established by inference alone, there

must be sufficient evidence to support such inference." *Huff v. Siroflex of Am., Inc.,* 122 F.3d 1456, 1466 (Fed. Cir. 1997).

70. When determining whether intent has been shown, a court must consider the totality of the circumstances, including evidence of good faith. *Baxter,* 149 F.3d at 1330 ("It is the totality of the applicant's conduct that creates the inference upon which the applicant's intent can be ascertained.").

71. The required intent cannot be proven by evidence of materiality alone. "Inequitable conduct requires an intent to act inequitably. Materiality of an undisclosed reference does not presume an intent to deceive." *Halliburton Co. v. Schlumberger Tech. Corp*., 925 F.2d 1435, 1442 (Fed. Cir. 1991). "Intent is an independent element of inequitable conduct . . . and must be separately established." *Hupp,* 122 F.3d at 1465.

72. However, "[t]he more material the conduct, the less evidence of intent will be required in order to find that inequitable conduct has occurred." *PerSeptive Biosystems, Inc. v. Pharmacia Biotech, Inc*., 225 F.3d 1315, 1319 (Fed. Cir. 2000).

73. A showing of subjective good faith militates against a finding of intent to deceive. *Kingsdown*, 863 F.2d at 876.

C. No One Associated With The Prosecution of the '303 Patent Committed Inequitable Conduct During The Prosecution of the '303 Patent

74. Mylan has failed to prove by clear and convincing evidence that anyone associated with the prosecution of the '303 patent purposefully misrepresented or concealed material information with an intent to deceive the PTO.

75. Mylan contends that Dr. Wells misrepresented the results of the sticking test run by Mr. Davison. However, this test depended on comparisons of the rate of accumulation of amlodipine salts on tablet punches, not on absolute amounts of salt stuck to the punch press. The Court finds and rules that there was no misstatement or non-disclosure by the applicants of any material fact with regard to the stickiness data.

76. The '303 patent does not state that the amlodipine besylate does not stick at all. It simply states that amlodipine besylate is forty-one percent (41%) less sticky than amlodipine maleate.

77. Mylan contends that the patent applicants misrepresented the solubility and pH values reported in the patent. However, the evidence adduced at trial demonstrated that solubility and pH values may vary from one measurement to another based on differences in the purity of the salt from batch-to-batch and from variations in procedures used to measure solubility and pH.

78. The Court finds and rules that the difference between the different solubility values of amlodipine besylate was not material, as all reported values far exceeded the threshold value(s) needed for good bioavailability.

79. Moreover, the patent applicants did not assert that amlodipine besylate had solubility or pH values that made it superior to amlodipine maleate or the new amlodipine salts tested.

80. Mylan failed to prove by clear and convincing evidence that Dr. Wells' made any material misrepresentations or omissions to the PTO. In addition, Mylan failed to prove by clear and convincing evidence, either directly or inferentially, that Dr. Wells acted with an

intent to deceive the PTO. *See Semiconductor Energy Lab.*, 204 F.3d at 1373 ("inequitable conduct includes affirmative misrepresentation of material fact, failure to disclose material information, or submission of false material information, coupled with an intent to deceive.") (*quoting Molins*, 48 F.3d at 1178).

D. Conclusion Regarding Inequitable Conduct

81. Neither Dr. Wells, nor Mr. Davison, nor any person who substantively participated in the prosecution of the '303 patent made any misrepresentation of a material fact or failed to disclose a material fact to the PTO.

82. Neither Dr. Wells, nor Mr. Davison, nor any person who substantively participated in the prosecution of the '303 patent committed any acts during the prosecution of the '303 patent, or failed to take any action during the prosecution of the '303 patent, with an intent to deceive or mislead the PTO.

83. The Court finds and rules that Mylan has failed to prove by clear and convincing evidence any material misrepresentation or non-disclosure which would compel a finding of inequitable conduct.

84. Even if the Court had determined that Mylan had met its burdens of proof on the elements of materiality and intent for any of its arguments, the Court is vested with the discretion to balance the degree of materiality and degree of intent to make an equitable judgment as to whether the conduct was so culpable that the patent should be barred from enforcement. *Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1324 (Fed. Cir. 2000).

85. In this case, even if Mylan had proven the required elements, the degree of culpability of Pfizer's representatives would be ever so slight and thus not sufficient to convince this Court that the proper remedy would be to invalidate the '303 patent.

86. The totality of the evidence in this case demonstrates that Mylan has not proven by clear and convincing evidence that the '303 patent is unenforceable due to inequitable conduct on the part of the inventors or anyone at Pfizer.

IV. SUMMARY OF CONCLUSIONS

87. For the reasons hereinabove set forth, the Court find and rules that Mylan has failed to prove by clear and convincing evidence that claims 1, 2, and 3 of the '303 patent are invalid as obvious under 35 U.S.C. § 103. In the alternative, assuming arguendo, that the '303 patent claims are invalid based on *prima facie* obviousness, the Court finds and rules that Pfizer has established by clear and convincing evidence that amlodipine besylate exhibits an unexpectedly superior combination of formulation properties sufficient to overcome any case of *prima facie* obviousness.

88. Mylan has further failed to prove by clear and convincing evidence that the '303 patent is unenforceable for inequitable conduct.

89. Mylan has stipulated that if the '303 patent is valid and enforceable, then its actions constitute infringement. Therefore, Mylan's submission of its ANDA to the FDA is an act of infringement of claims 1, 2, and 3 the '303 patent. *24 U.S.C. § 271(e)(2)(A).*

90. Accordingly, the Court will enter Judgment in this matter in favor of Pfizer Inc. and an injunction will issue to prevent Mylan from making, using, selling, offering to sell, or

importing into the United States the Mylan Amlodipine Tablets described in ANDA No. 76-418 until after the expiration of the '303 patent term, as extended by the pediatric exclusivity period.

An appropriate Order and Judgment consistent with these Findings of Fact and Conclusions of Law will be filed contemporaneously herewith.

McVerry, J.

IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF PENNSYLVANIA

PFIZER INC.,	)	
	)	
Plaintiff and	)	
Counterclaim Defendant,	)	
	)	
v.	)	02: 02cv1628
	)	
MYLAN LABORATORIES, INC. and	)	
MYLAN PHARMACEUTICALS, INC.,	)	
	)	
Defendants and	)	
Counterclaim Plaintiffs.	)	

ORDER OF COURT

AND NOW, this 27th day of February, 2007, in accordance with the foregoing Findings of Fact and Conclusions of Law, is it **ORDERED**, **ADJUDGED, AND DECREED** that judgment in this action is hereby entered in favor of Pfizer Inc. and against Mylan Laboratories, Inc. and Mylan Pharmaceuticals, Inc.

Mylan Laboratories, Inc. and Mylan Pharmaceuticals, Inc., are hereby permanently enjoined from making, using, selling, offering to sell, or importing into the United States the Mylan Amlodipine Tablets described in ANDA No. 76-418 until after the expiration of Pfizer's '303 patent term, as extended by the pediatric exclusivity period.

BY THE COURT:

s/Terrence F. McVerry, Judge
United States District Court

cc: All Counsel of Record

Exhibit C

Plaintiffs' Emergency Application for a Temporary Restraining Order and/or Preliminary Injunction

IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF PENNSYLVANIA

PFIZER, INC.,	)	
	)	
Plaintiff and	)	
Counterclaim Defendant,	)	
	)	
v.	)	**02: 02cv1628**
MYLAN LABORATORIES, INC. and	)	
MYLAN PHARMACEUTICALS, INC.,	)	
	)	
	)	
Defendants and	)	
Counterclaim Plaintiffs.	)	

AMENDED JUDGMENT

AND NOW, this 16th day of March, 2007, it is **ORDERED, ADJUDGED AND DECREED** that, for the reasons set forth in the Court's findings of fact and conclusions of law, Judgment shall be entered in favor of Plaintiff Pfizer Inc. and against Defendants Mylan Laboratories, Inc. and Mylan Pharmaceuticals, Inc. (herein collectively "Mylan") on Pfizer's claims that Mylan has infringed claims 1-3 of United States Patent No. 4,879,303 (the "303 patent"); and it is further,

ORDERED, ADJUDGED AND DECREED that Judgment shall be entered in favor of Pfizer and against Mylan dismissing Mylan's counterclaims which alleged and sought declarations of noninfringement, invalidity, or unenforceability of the '303 patent; and it is further,

ORDERED, ADJUDGED AND DECREED that, pursuant to the provisions of 35 U.S.C. §271(e)(4)(A), the effective date of any approval of Mylan's Abbreviated New Drug Application No. 76-418, seeking FDA approval of amlodipine besylate tablets, 2.5, 5 and 10 mg

dosage strengths, shall be a date which is not earlier than the date of expiration of the '303 patent (March 25, 2007); and it is further,

ORDERED, ADJUDGED AND DECREED that, pursuant to the provisions of 35 U.S.C. §271(e)(4)(B), Mylan, its officers, agents, servants, employees and attorneys, and those persons in active concert or participation with Mylan are enjoined until the date of expiration of the '303 patent (March 25, 2007), from engaging in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of any product comprising the chemical compound amlodipine besylate covered by, or the sale or use of which is covered by claims 1-3 of the '303 patent.

BY THE COURT:

s/ Terrence F. McVerry
United States District Court Judge

cc: All Counsel of Record

Exhibit D

Plaintiffs' Emergency Application for a Temporary Restraining Order and/or Preliminary Injunction

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

717 MADISON PLACE, N.W.
WASHINGTON, D.C. 20439

JAN HORBALY
CLERK

TELEPHONE: (202) 633-6550
FAX: (202) 633-9623

FAX MATERIAL COVER SHEET

TO: DAVID J. HARTH

FROM: CLERK'S OFFICE

This is page 1 of 3 pages being transmitted.

Day sent: MARCH 23, 2007

Message/Instructions:

****

FOR QUESTIONS, CALL (202) 633-6550
FOR RETURN FAX, DIAL (202) 633-9623

****

NOTE: This order is nonprecedential.

United States Court of Appeals for the Federal Circuit

2007-1194

PFIZER INC.,

Plaintiff-Appellee,

v.

MYLAN LABORATORIES, INC. and MYLAN PHARMACEUTICALS, INC.,

Defendants-Appellants.

ON MOTION

Before PROST, Circuit Judge.

ORDER

Mylan Laboratories, Inc. and Mylan Pharmaceuticals, Inc. (Mylan) move for a stay, pending appeal, of the amended judgment of the United States District Court for the Western District of Pennsylvania that ordered that the effective date of any approval of Mylan's abbreviated new drug application "shall be a date which is not earlier than the date of expiration of the '303 patent" and that prohibited Mylan from making, using or selling the concerned drug. Pfizer Inc. opposes. Mylan replies. Mylan also moves for leave to "append" to its motion certain news articles that are not part of the district court record. Mylan submits a supplement to its motion to make arguments concerning this court's recent decision in Pfizer Inc. v. Apotex, Inc., --- F.3d ---, no. 2006-1261 (Fed. Cir. March 22, 2007), invalidating the asserted claims of the patent in this case. Pfizer responds.

Upon consideration thereof,

IT IS ORDERED THAT:

(1) Pfizer and Mylan are each are directed to respond, no later than 10 a.m. on Monday, March 26, 2007, concerning how the invalidity determination affects the pediatric exclusivity period and the ANDA approval. Inter alia, the parties should address when and how the FDA will likely respond to the court's decision in no. 2006-1261. Each response should not exceed 15 pages.

(2) Mylan's motion for a stay, pending appeal, is held in abeyance pending receipt of the parties' responses to this order and the court's consideration of the papers submitted.

(3) The district court's order is temporarily stayed, pending this court's further consideration of the papers submitted.

MAR 23 2007
Date

Sharon Prost
Circuit Judge

cc: Richard G. Greco, Esq.
David J. Harth, Esq.

s8

Exhibit E

Plaintiffs' Emergency Application for a Temporary Restraining Order and/or Preliminary Injunction

Guidance for Industry

Court Decisions, ANDA Approvals, and 180-Day Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Procedural

March 2000

Guidance for Industry

Court Decisions, ANDA Approvals, and 180-Day Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act

Comments and suggestions regarding this document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the guidance. All comments should be identified with the docket number provided at the beginning of the notice. Submit comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

After the comment period closes, comments should be provided in writing to the Center for Drug Evaluation and Research (CDER), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

Additional copies of this Guidance are available from:

Office of Training and Communications
Division of Communications Management
Drug Information Branch, HFD-210
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, Rockville, MD 20857
(Phone 301-827-4573)
Internet: http://www.fda.gov/cder/guidance/index.htm.

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Guidance for Industry[1]

Court Decisions, ANDA Approvals, and 180-Day Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act

I. WHY IS FDA ISSUING THIS GUIDANCE?

This guidance is being issued in response to recent litigation and is intended to provide guidance to the pharmaceutical industry regarding (1) the timing of approval of abbreviated new drug applications (ANDAs) following an unsuccessful patent infringement action by the patent owner or new drug application (NDA) holder and (2) the start of 180 days of generic drug exclusivity.

FDA's interpretation of two provisions of the Federal Food, Drug, and Cosmetic Act (the Act) have been affected by recent court decisions interpreting the phrase "decision of a court" or "court decision." Section 505(j)(5)(B)(iii) of the Act governs the approval of ANDAs when the patent owner or NDA holder has brought a timely patent infringement action in response to the ANDA applicant's notice of filing of a paragraph IV certification to a listed patent. Section 505(j)(5)(B)(iv) of the Act governs the eligibility for and timing of 180-day exclusivity. The regulations implementing these statutory provisions are found at 21 CFR 314.107. Certain aspects of these regulations have been successfully challenged in *TorPharm, Inc. v. Shalala* and *Mylan Pharmaceuticals, Inc. v. Shalala*.[2] This guidance describes the Agency's response to those court decisions.

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[1]This guidance has been prepared by the Office of Generic Drugs in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance represents the Agency=s current thinking on sections 505(j)(5)(B)(iii)(I) and (iv) of the Act. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both.

[2] *TorPharm, Inc. v. Shalala*, No. 97-1925, 1997 U.S. Dist. LEXIS 21983 (D.D.C. Sep. 15, 1997), *appeal withdrawn and remanded,* 1998 U.S. App. LEXIS 4681 (D.C. Cir. Feb. 5, 1998); *vacated* No. 97-1925 (D.D.C. Apr. 9, 1998); *Mylan Pharmaceuticals, Inc. v. Shalala*, No. 99-2995, slip op. (D.D.C. Jan. 4, 2000).

II. STATUTORY AND REGULATORY BACKGROUND

A. ANDA Approvals and Court Decision

The concept of a court decision is used in two important places in section 505(j) of the Act — in the provision governing the timing of ANDA approvals and in the 180-day exclusivity provision. There is a 30-month statutory bar to approval of an ANDA that is the subject of patent infringement litigation except if "before the expiration of such period the court decides that such patent is invalid or not infringed, the approval will be made effective on the date of the ***court decision***" (section 505(j)(5)(B)(iii)(I) (emphasis added)). In implementing this provision, FDA interpreted *court* to mean "the court that enters final judgment from which no appeal can be or has been taken" (21 CFR 314.107(e)(1) (1999)). The Agency's reasons for adopting this interpretation are discussed in the preambles to the proposed and final rules implementing the 1984 Drug Price Competition and Patent Term Restoration Act.[3]

B. 180-Day Exclusivity and Decision of a Court

Certain court decisions are also important for 180-day generic drug exclusivity. FDA's interpretation of *court* in the court decision described in Section 505(j)(5)(B)(iii)(I) was influenced by the role such a decision plays in 180-day exclusivity. The 180-day period of exclusivity can begin on either (1) the date of first commercial marketing or (2) Athe date of *a* ***decision of a court*** ... holding the patent which is the subject of the [paragraph IV] certification to be invalid, or not infringed, whichever is earlier@ (section 505(j)(5)(B)(iv) (emphasis added)). As described in the preambles to the implementing regulations, FDA believed that for the 180-day exclusivity to have real meaning for the eligible ANDA applicant, the court decision triggering the exclusivity must be the one that finally resolves the patent infringement litigation related to the ANDA.[4] Therefore, for purposes of section 505(j)(5)(B)(iv), FDA determined that *court* means "the court that enters final judgment from which no appeal can be or has been taken" (21 CFR 314.107(e)(1) (1999)).

III. LITIGATION, CURRENT ISSUES, AND AGENCY POSITION

FDA=s interpretation of the term *court* has been successfully challenged in the context of both the timing of ANDA approvals and the commencement of 180-day exclusivity. In *TorPharm v. Shalala*, the D.C. District Court found the FDA=s interpretation not supported by the statute and directed FDA to approve an ANDA upon a decision of the district court finding a patent invalid, unenforceable, or not infringed. When the case became moot, FDA's appeal of that decision was withdrawn, and the district

[3] 54 FR 28872, 28893-95 (July 10, 1989); 59 FR 50338, 50352-54 (October 3, 1994).

[4] 54 FR 28893-95 (July 10, 1989); 59 FR 50352-54 (October 3, 1994).

court opinion was vacated. In the period since the *TorPharm* decision, FDA has continued to apply the definition of *court* set out at 314.107(e).[5]

Recently, in *Mylan Pharmaceuticals, Inc. v. Shalala.*, the D.C. District Court found FDA=s interpretation of *court* as used in the 180-day exclusivity context inconsistent with the statute=s plain meaning. However, the court also determined that the applicant who relied in good faith on FDA=s interpretation of the 180-day exclusivity provision should not be punished by losing its exclusivity. The court therefore refused to order FDA to begin the running of 180-day exclusivity upon the decision of the district court in the patent litigation at issue.

These recent decisions add considerable uncertainty to FDA=s implementation of the ANDA approval and 180-day generic drug exclusivity programs. These regulatory programs already have been disrupted by the changes in eligibility for 180-day exclusivity necessitated by *Mova Pharmaceutical Corp. v. Shalala* and *Granutec, Inc. v. Shalala*.[6] Therefore, in determining its response to the *TorPharm* and *Mylan* decisions, a primary concern for the Agency has been to identify an approach that will minimize further disruption and provide the regulated industry with reasonable guidance for making future business decisions.

The government has decided not to appeal the *Mylan* decision and will follow that court=s interpretation of the statute in approving ANDAs and calculating the commencement of 180 days of exclusivity. Although the Agency believes that the statutory provisions at issue may properly be interpreted as FDA sets out in § 314.107(e), the Agency nonetheless has determined that it is in the interest of the regulated industry and the Agency to accept the interpretation of the *TorPharm* and *Mylan* courts. Therefore, the Agency will not apply the definition of the *court* found at § 314.107(e) (1) and (2) (i)-(iii).[7] The Agency intends to formally remove the relevant sections of § 314.107(e), and will incorporate the *TorPharm* and *Mylan* courts= interpretation of the statute into the final rule implementing the changes in 180-day exclusivity.[8] As described in section IV, FDA will implement the new interpretation of the term "court" prospectively, in a manner consistent with the court=s approach in *Mylan*.

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[5] Guidance for industry *180-Day Generic Drug Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act*, June 1998, p. 2, n. 3.

[6] *Mova Pharmaceutical Corp. v. Shalala*, 140 F.3d 1060 (D.C.Cir. 1998); *Granutec, Inc. v. Shalala*, 46 U.S.P.Q.2d 1398 (4th Cir. 1998).

[7] Applicants will still be required to submit a copy of the relevant order or judgment to the Office of Generic Drugs under § 314.107(e)(2)(iv).

[8] 64 FR 42873 (August 6, 1999).

IV. EFFECT ON ANDA APPROVALS AND 180-DAY EXCLUSIVITY

A. New Definition of *Court*

FDA will interpret the term *court* as found in section 505(j)(5)(B)(iii)(I) and 505(j)(5)(B)(iv) to mean the first court that renders a decision finding the patent at issue invalid, unenforceable, or not infringed. When it is the district court that renders such a decision, FDA may approve the ANDA as of the date the district court enters its decision. For eligible applicants, 180-day exclusivity will also begin to run on that date, unless it has already begun with commercial marketing. If the district court finds the patent is infringed, but that decision is reversed on appeal, the Agency may approve the ANDA on the date the district court issues a judgment that the patent is invalid, unenforceable, or not infringed pursuant to a mandate issued by a court of appeals.[9]

Neither a stay nor a reversal of a district court decision finding the patent invalid, unenforceable, or not infringed will have an effect on the approval of the ANDA or on the beginning, or continued running, of exclusivity. Should the NDA holder or patent owner wish to prevent an applicant with an approved ANDA from marketing its product during the course of an appeal, it must obtain an injunction from the court. If there is an injunction barring marketing of an approved drug, the ANDA applicant and NDA holder are asked to notify FDA, and the Agency will move the drug to the discontinued section of *Approved Drug Products with Therapeutic Equivalence Evaluations* (the *Orange Book*), so as to minimize confusion in the marketplace. Once the injunction is lifted or expires and if the ANDA applicant notifies the Agency it has begun marketing its product, the drug will be moved back to the active section of the *Orange Book*. The 180-day exclusivity period will continue to run during the pendency of a stay or injunction.

B. Implementation of New Definition of *Court*

The new definition of *court* will apply to certain ANDAs submitted after the publication of this guidance. Specifically, the new definition will be used for approval and exclusivity determinations for ANDAs containing a paragraph IV certification where the ANDA cites a reference listed drug for which no other ANDA containing a paragraph IV certification has been submitted.

This new interpretation of the statute may substantially change the value of the 180-day exclusivity. As Judge Roberts recognizes in the *Mylan* opinion, applicants who have made certain business decisions in good faith reliance upon an FDA regulation should not be penalized for their actions. For example, the potential change in the value of exclusivity may have considerable effect upon an ANDA applicant=s willingness to file a paragraph IV certification to a patent and to undertake the effort and expense of litigating a patent infringement suit. This may be particularly true for patent challenges that are seen as risky, but for which the possible award of a full exclusivity was an adequate incentive. Judge Roberts also noted that based upon FDA=s interpretation of the statute, ANDA applicants have held products off the market even after a victory in the district court.

[9] This is the same process as described in current § 314.107(e)(2)(iii).

The Agency believes that an implementation plan for the new definition of *court* that recognizes the industry=s reliance on the previous definition and establishes a *bright line* for ANDAs affected by the new definition will minimize the disruption to the ANDA approval and 180-day exclusivity programs. Moreover, the Agency believes that this approach will lessen the likelihood that ANDA applicants will sue the Agency alleging that they, like Geneva in the *Mylan* case, relied in good faith on the Agency=s regulation and would be irreparably injured by application of the new interpretation to pending ANDAs.

Exhibit F

Plaintiffs' Emergency Application for a Temporary Restraining Order and/or Preliminary Injunction

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUN 22 2004

NDA 19-813
ANDA 76-258

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Dear Messrs. Figg and Safir:

This letter responds to letters sent to the Food and Drug Administration (FDA) on behalf of Mylan Technologies, Inc. (Mylan) dated March 26, 2004, April 2, 2004, and April 12, 2004, as well as those sent on behalf of ALZA Corporation (ALZA) dated March 31, 2004 and April 8, 2004. In those letters, Mylan asks FDA to confirm that Mylan is not subject to ALZA's pediatric exclusivity for fentanyl. ALZA, on the other hand, asks FDA to confirm that pediatric exclusivity applies as to Mylan's generic fentanyl transdermal system. For the reasons described below, we find that effective approval of Mylan's ANDA will be subject to ALZA's pediatric exclusivity.

Background

ALZA obtained approval for its fentanyl transdermal system (trade name: Duragesic) on August 7, 1990. As required by section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (the Act), ALZA submitted with its new drug application (NDA) a list of any patents that claimed its drug and/or its approved uses. The last of these to expire was U.S. Patent Number 4,588,580 (the '580 patent), which is due to expire July 23, 2004. FDA listed these patents in *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book).[1]

On July 15, 1999, FDA issued a letter requesting pediatric studies (written request) to ALZA under section 505A of the Act, 21 U.S.C. 355a(c).[2] Specifically, the written request asked ALZA to evaluate the use of its fentanyl transdermal system in opioid-tolerant pediatric patients with chronic pain. ALZA submitted the requested studies on November 26, 2002. On January

[1] Two other patents listed for Duragesic have already expired - U.S. Patent No. 4,144,317 expired September 9, 1992 and U.S. Patent No. 4,060,084 expired June 29, 1994.
[2] The written request was subsequently amended on November 30, 1999 and on February 22, 2001.

29, 2003, FDA determined that ALZA's pediatric studies were timely submitted, fairly responded to the written request, were conducted in accordance with good scientific principles, and were reported in accordance with FDA's requirement for filing. Accordingly, FDA granted pediatric exclusivity to ALZA for fentanyl at that time. On May 20, 2003, FDA approved the labeling supplement that ALZA had submitted in response to the written request. Duragesic's labeling was amended to include important information about pediatric use.

Mylan submitted its abbreviated new drug application (ANDA) for fentanyl transdermal system on October 15, 2001. Mylan's ANDA contained a paragraph IV certification to the '580 patent. Mylan sent the required notice of this certification to ALZA. ALZA received that notice on December 10, 2001. ALZA filed suit for patent infringement against Mylan in the United States District Court for the District of Vermont (Vermont District Court) on January 25, 2002, one day after the end of the statutory 45-day period for suit.[3] Because suit was filed outside of the 45-day period prescribed in section 505(j)(5)(B)(iii), there was no 30-month stay of approval on Mylan's ANDA for fentanyl transdermal system. Thus, the pending patent litigation did not present a barrier to ANDA approval. FDA approved Mylan's ANDA on November 21, 2003.

Approximately four months after FDA approved Mylan's ANDA, on March 25, 2004, the Vermont District Court found the '580 patent to be valid and infringed by Mylan's generic fentanyl transdermal system. The court enjoined Mylan from "making, using, offering to sell, selling within the United States or importing into the United States" the fentanyl transdermal system described in its ANDA and ordered that, although Mylan had previously received a final, effective approval from FDA, "the effective date of any approval of Mylan's ANDA product shall be no earlier than the date of expiration" of the '580 patent. Thus, the question arises whether Mylan's previously approved but infringing product is subject to ALZA's pediatric exclusivity.

Statutory and Regulatory Framework

Under the Act, a pharmaceutical company seeking to market a "pioneer" or innovator drug must first obtain FDA approval of an NDA by filing "full reports" that demonstrate the safety and effectiveness of the proposed drug product under the conditions of use described in the label. 21 U.S.C. § 355(a), (b). An NDA applicant must also submit information on any patent that claims the drug or a method of using the drug, and for which a claim of patent infringement could reasonably be asserted against an unauthorized party. 21 U.S.C. 355(b)(1), (c)(2). FDA publishes the patent information it receives in the Orange Book. *Id.; see also* 21 C.F.R. § 314.53(e).

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments), codified at 21 U.S.C. 355, 360cc, and 35 U.S.C. § § 156, 271, 282, permits the submission of ANDAs for approval of generic versions of approved drug products. 21 U.S.C. § 355(j). The ANDA process shortens the time and reduces the quantity of information required for approval. If an ANDA applicant establishes that its proposed drug product has the same active ingredient, strength, dosage form, route of administration, labeling, and conditions of use

[3] The 45-day period begins on the day after notice is received. 21 U.S.C. 505(j)(5)(B)(iii).

as a drug described in an NDA (the listed drug), and that it is bioequivalent[4] to that drug, the applicant can rely on FDA's previous finding that the listed drug is safe and effective to obtain approval. 21 U.S.C. 355(j).

Tentative and Final ANDA Approval

Once FDA concludes that an ANDA has met the technical requirements for approval, FDA has two options: it can issue a full effective approval or it can issue a tentative approval. The rights and obligations that stem from each of these options differ. If FDA reviews an ANDA and concludes that the drug described in the ANDA is safe and effective under the conditions of use described in the labeling, and that there are no patent or exclusivity barriers to approval, the ANDA will get a full, effective approval. An applicant who gets a full effective approval will receive an approval letter that permits marketing. 21 C.F.R. 314.105(a). The approval of the application becomes effective on the date the approval letter is issued. *Id.* An application with full effective approval has no continuing obligation to update its patent certifications. See 21 C.F.R. 314.94(a)(12)(viii)(C) (obligation to amend certification applies before effective date of approval).

However, if FDA reviews an ANDA and concludes that the drug described in the ANDA is safe and effective for the conditions of use described in the labeling but patent protection or other marketing exclusivities prevent the approval from becoming effective immediately, FDA will issue a tentative approval. A tentative approval indicates that the technical requirements for approval have been met as of a particular date but that approval cannot be made effective (and marketing is not permitted) until after some future event (such as expiration of a 30-month stay, a patent, or a period of marketing exclusivity). *See* 21 C.F.R. 314.105(d). Under FDA's regulations and longstanding practice, an approval with a delayed effective date is a tentative approval and does not become final before the effective date. A new drug that has received an approval with a delayed effective date or tentative approval "may not be introduced or delivered for introduction into interstate commerce until approval of the [ANDA] is effective." 21 C.F.R. 314.105(a), (d). Moreover, a tentative approval cannot become effective without a final approval letter from the agency resulting in a final effective approval. 21 C.F.R. 314.107(b)(3)(v); *see also*, 59 Fed. Reg. 50338, 50352 (October 3, 1994) (a tentative approval becomes "final and, therefore, effective only when the agency sends an approval letter to the applicant"); *Barr Labs., Inc. v. Thompson,* 238 F. Supp. 2d 236, 245-50 (D.D.C. 2002) (affirming FDA's decision that an approval with a delayed effective date is tentative and does not give applicants the right to enter the market on a date certain without further action from FDA).

In contrast to the holder of a fully approved ANDA, the holder of a tentatively approved ANDA must amend its application to reflect any material changes in circumstances, such as expiration of the patent or withdrawal of a patent challenge. See 21 C.F.R. 314.94(a)(12)(viii)(C)(1). That regulation provides that "an applicant shall amend a submitted certification if, at any time before the effective date of the approval of the application, the applicant learns that the submitted certification is no longer accurate." *Id. See also* 21 U.S.C. § 355(j)(4)(K) (barring approval of an application containing an untrue statement of material fact).

[4] Two drugs are considered bioequivalent if, in general, the rate and extent of absorption of the proposed drug is not significantly different from the rate and extent of absorption of the listed drug. 21 U.S.C. § 355(j)(8)(B).

Once all patent and exclusivity barriers to approval have been removed, a tentatively approved ANDA may be eligible for final approval. Before issuing a final approval letter to a tentatively approved application, FDA "will examine the application to determine whether there have been any changes in the conditions under which the application was tentatively approved." 59 Fed. Reg. 50338 at 50352. Even when an applicant has a tentative approval, final approval is neither inexorable nor automatic; the applicant with the tentative approval enjoys no vested right to market on a particular date. *See Barr Labs., Inc.*, 238 F. Supp. 2d at 245-50 (affirming FDA's decision that tentatively approved ANDAs do not have vested right to immediate approval upon patent expiry); *Ranbaxy Labs. Ltd. v. FDA*, 307 F. Supp. 2d. 15, 19, 21 (D.D.C. 2004) (upholding FDA's position that an applicant with a tentative approval has "no vested right to enter the market until the FDA gives its final formal approval.") *aff'd per curiam*, Civ. Action 04-5079 2004 U.S. App. LEXIS 8311 (D.C. Cir. Apr. 26, 2004). Instead, FDA must have time and the opportunity to reexamine an application to determine that the approval requirements continue to be met. Only after that examination has been completed will FDA issue a final approval letter. *Id.*

Patent Certifications and Timing of Approval

As noted above, the timing of an ANDA's approval depends in part on patent protections for the listed drug the ANDA references. A pending ANDA must contain one of four specified certifications for each patent that "claims the listed drug" or "a use for such drug for which the applicant is seeking approval." 21 U.S.C. § 355(j)(2)(A)(vii). The certification must state one of the following:

(I) that the required patent information relating to the patent has not been filed;
(II) that such patent has expired;
(III) that such patent will expire on a particular date; or
(IV) that such patent is invalid or will not be infringed by the drug for which approval is sought.

See id. If a certification is made under paragraphs I or II (indicating that patent information has not been filed or that the patent has expired), the patent, in itself, will not delay the approval of an ANDA.[5] 21 U.S.C. § 355(j)(5)(B)(i). A certification under paragraph III indicates that the ANDA applicant does not intend to market the drug until after the applicable patent has expired, and FDA will not issue a final effective approval for the ANDA until after patent expiration. 21 U.S.C. § 355(j)(5)(B)(ii).

If an ANDA applicant wishes to challenge the validity of a listed patent, or to claim that the patent will not be infringed by the product proposed in the ANDA, the applicant must submit a paragraph IV certification. The applicant must provide notice of its paragraph IV certification to the NDA holder and the patent owner. The applicant must also describe the factual and legal basis for its opinion that the patent is invalid or is not infringed. 21 U.S.C. 355(j)(2)(B). The filing of a paragraph IV certification "for a drug claimed in a patent or the use of which is

[5] Of course approval may still be delayed due to other patents or marketing exclusivity or because the application is otherwise not ready for approval.

claimed in a patent" is an act of infringement. 35 U.S.C. 271(e)(2)(A). This provision enables the NDA holder to suc the ANDA applicant before the ANDA has been approved.

If the patent owner or NDA holder does not bring suit within 45 days after it has received notice of the paragraph IV certification, FDA may approve the ANDA despite the unexpired patent. FDA may do so as long as there are no other patent or exclusivity barriers to approval and the other conditions of approval are met. 21 U.S.C. 355(j)(5)(B)(iii); 21 C.F.R. 314.107(f)(2). FDA may also do so even if patent litigation was commenced outside the 45-day period and is ongoing as of the time the requirements for approval have been met.

If the patent owner or NDA holder brings a patent infringement suit against the ANDA applicant *within* 45 days, there will be an automatic stay of FDA approval for 30 months from the date that the patent owner or NDA holder received notice of the paragraph IV certification (30-month stay). (That is, unless a court decision has been reached earlier in the patent case or the patent court otherwise orders a longer or shorter stay period). 21 U.S.C. 355(j)(5)(B)(iii). If at the end of 30 months (or such shorter or longer period that the court orders) the litigation is ongoing, the 30-month stay will be lifted. If the ANDA is otherwise ready for approval, FDA will approve the ANDA in spite of the ongoing litigation and unexpired patent. Similarly, if the ANDA applicant were to win in the district court and the district court decision were appealed, the 30-month stay would be lifted after the district court decision. In these circumstances, if the ANDA is otherwise ready for approval, FDA can approve the ANDA in spite of the pending appeal -- unless the court otherwise imposes a stay of approval while the appeal is pending.

Delaying the Effective Date under 271(e)(4)

The Hatch-Waxman amendments also amended the patent code to specify the consequences that follow when the NDA holder or patent owner sues the ANDA applicant, and the court hearing the patent infringement litigation finds the patent valid and infringed. In these circumstances, 35 U.S.C. 271(e)(4)(A) provides that "the court shall order the effective date of any approval of the drug . . . involved in the infringement to be a date which is not earlier than the date of the expiration of the patent which has been infringed." 35 U.S.C. 271(e)(4)(A). As the unqualified plain meaning of the statute reflects, this mandated delay of the effective date of approval takes place regardless of whether the ANDA remains pending or has obtained a final effective approval.[6]

The legislative history explicitly recognized that this requirement would affect previously approved as well as unapproved applications:

> If the infringing party has not begun commercial marketing of the drug, injunctive relief may be granted to prevent any

[6] As noted above, if an applicant meets the requirements for final approval, final effective approval may be issued while patent litigation is ongoing under 3 different circumstances: (1) the ANDA applicant was sued outside of the 45 days so no 30-month stay of approval was imposed; (2) the applicant was sued within the 45 days but the 30-month stay expired while the litigation was ongoing; or (3) the ANDA applicant was sued within the 45 days, won at the lower court level, and the decision lifted the 30-month stay and permitted approval, but that decision was appealed.

> commercial activity with the drug and FDA would be mandated to make the effective date not earlier than the expiration date of the infringed patent . . . **In the case where an ANDA had been approved, the order would mandate a change in effective date.**

H.R. Rep. No. 98-857, pt. 1, at 46 (1984) (emphasis added).

The language of the provision regarding a delay in the effective date under 271(e)(4)(A) parallels the language of the provisions regarding 30-month stays, 5-year exclusivity, 3-year exclusivity and 180-day exclusivity that were enacted at the same time as part of the Hatch-Waxman amendments. Section 271(e)(4)(A), like the provisions regarding 30-month stays, 5-year exclusivity, 3-year exclusivity, and 180-day exclusivity, speaks not in terms of delays in FDA approvals but in terms of delays in the dates such approvals can be made effective. See 21 U.S.C. 505(j)(5)(B)(iii) ("approval shall be made effective upon the expiration of the thirty month period"); 21 U.S.C. 505(j)(5)(B)(iv) ("application shall be made effective not earlier than one hundred eighty days after . . ."); 21 U.S.C. 505(j)(5)(D)(ii) ("approval of such an application shall be made effective in accordance with subsection (b)"); 21 U.S.C. 505(j)(5)(D)(iii) ("Secretary may not make the approval of an application submitted under this subsection for the conditions of approval of such drug in the subsection (b) application effective before the expiration of three years . . . .").

If an ANDA has met the technical requirements for approval and a delay in effective dates is required due to a 30-month stay, 5-year exclusivity, 3-year exclusivity or 180-day exclusivity, FDA issues a tentative approval. 21 C.F.R. 314.105, 314.107. ANDA applicants with tentative approvals that are subject to delays due to 30-month stays, 5-year, 3-year or 180-day exclusivity are not entitled to go to market immediately when the barrier to approval expires; after the applicable stay or exclusivity expires, applicants must still wait until FDA issues an approval letter. FDA will not issue a letter to make the approval of the tentatively approved application effective until after FDA has reexamined the application to determine whether the requirements for approval continue to be met.

Similarly, where patent litigation between an ANDA applicant and NDA holder or patent owner results in a court order under 271(e)(4)(A) stating that the effective date of ANDA approval shall be no earlier than the date the patent expires, FDA will not issue a final effective approval until after the date in the order has passed. If, in the interim between the court's order and the date the approval can be made effective, FDA determines that the applicant meets the technical requirements for approval, a tentative approval will be issued. FDA will not issue a letter to make the approval of the tentatively approved application effective until after the period stated in the court order has run and FDA has reexamined the application to determine whether the requirements for approval continue to be met.

The same result obtains where an ANDA has already received a full effective approval and a court finding patent validity and infringement issues an order under 271(e)(4)(A) stating that the approval of the ANDA not be made effective until after the date the patent expires -- that is, the ANDA reverts to tentative approval status. As the legislative history of the Hatch-Waxman

amendments confirms, Congress contemplated that, in these circumstances, the approval would no longer remain effective and the date of effective approval should be delayed to a date in the future. See H.R. Rep. No. 98-857, pt. 1, at 46 (1984) ("In the case where an ANDA had been approved, the order would mandate a change in effective date"). Like other applications with approvals with delayed effective dates, such an approval is tentative and does not give the applicant a vested right to go to market on a date certain. Applicants with tentative approvals cannot go to market until they have received an approval letter. As noted above, FDA will not issue an approval letter until after the barrier to approval has expired (i.e., the period stated in the court order has run) and FDA has reexamined the application to determine whether the requirements for approval continue to be met.

Pediatric Exclusivity

In 1997, as part of the Food and Drug Administration Modernization Act ("FDAMA"), Congress amended the Act to provide an economic incentive for drug manufacturers to invest the resources necessary to conduct and submit studies of the safety and effectiveness of drugs in pediatric populations. Recognizing that pediatric populations are "therapeutic orphans," and that pediatric studies "pose ethical and moral issues," carry the risk of product liability, and are hard to attract patients for and conduct, Congress created the pediatric exclusivity incentive to ensure that more drugs were studied and adequately labeled for the pediatric patients who use them. S. Rep. No. 105-43 at 51 (1997). Under these provisions, codified at 21 U.S.C. 355a[7], FDA can issue a written request to ask a sponsor to conduct and submit studies on the use of a drug in the pediatric population. If FDA issues a written request for pediatric studies, and the company submits pediatric studies that "fairly respond" to the written request in accordance with FDA's requirements for filing, and conducts the studies in accordance with good scientific principles and protocols, the company is entitled to six months of additional exclusivity (pediatric exclusivity) that attaches to existing patent and exclusivity protection for the moiety. This exclusivity results in an additional six-month delay of approval for ANDAs that are blocked from approval by existing patent or exclusivity rights. By giving NDA sponsors an additional six-month period without generic competition, Congress elevated the goal of obtaining pediatric labeling information over the goal of approving generic copies of brand name drugs at the earliest possible time.[8]

In fact, even if an ANDA is on the verge of being given an effective approval, the submission of pediatric studies in response to a written request allows FDA to delay the effective date while FDA determines whether the studies qualify for a pediatric exclusivity award. 21 U.S.C. § 355a(e) ("if the approval of an [ANDA] . . . may occur after submission of reports of pediatric studies . . . but before the Secretary has determined whether the requirements of subsection (d)

[7] Congress reauthorized and amended the pediatric exclusivity provisions in the Best Pharmaceuticals for Children Act, Pub. L. No. 107-109 (2001) and made additional amendments in the Pediatric Research Equity Act of 2003, Pub. L. No. 108-155 (2003).

[8] *See, e.g.* S. Rep No. 107-79, at 11 (2001) ("By granting drug manufacturers a 6-month extension of market exclusivity for a drug upon satisfactory completion of requested pediatric studies of the product and delaying the availability of lower cost generics alternatives, the bill will make those prescription drugs . . . more expensive . . . There would also be cost savings . . . by, for example, the reduced need for hospitalization of children and reduced error in medicating children.").

have been satisfied, the Secretary shall delay the . . . approval . . . until the determination under subsection (d) is made, but any such delay shall not exceed 90 days").

The prospect of an additional six months of delay in ANDA approvals has been a valuable incentive for NDA holders. Whereas previous attempts to obtain pediatric information from sponsors had largely failed, the pediatric exclusivity provision has proven highly effective. *See* The Pediatric Exclusivity Provision, January 2001 Status Report to Congress, at 3-5, 12 ("In general, the pediatric exclusivity provision has done more to generate clinical studies and useful prescribing information for the pediatric population than any other regulatory or legislative process to date")(available at http://www.fda.gov/cder/pediatric/reportcong01.pdf). Since the pediatric exclusivity provisions took effect in November 1997, FDA has issued 288 requests for pediatric studies, has made 108 pediatric exclusivity determinations, and has granted pediatric exclusivity for 98 drugs for indications ranging from hypertension to HIV. *See* http://www.fda.gov/cder/pediatric/exgrant.htm.

The statute governing which ANDAs are blocked by pediatric exclusivity provides in relevant part:

> (c) MARKET EXCLUSIVITY FOR ALREADY MARKETED DRUGS. If the Secretary determines that information relating to the use of an approved drug in the pediatric population may produce health benefits in that population and makes a request to the holder of the approved [NDA] for pediatric studies (which shall include a timeframe for completing such studies), the holder agrees to the request, the studies are completed within any such timeframe, and the reports are submitted in accordance with subsection (d)(2) of this section or accepted in accordance with subsection (d)(3) of this section -
>
> * * *
>
> (2)(A) if the drug is the subject of–
>
> (i) a listed patent for which a [paragraph II] certification has been submitted . . . and for which pediatric studies were submitted prior to the expiration of the patent (including any patent extensions); or
>
> (ii) a listed patent for which a [paragraph III] certification has been submitted . . . ,
>
> the period during which an [ANDA] . . . may not be approved . . . shall be extended by a period of six months after the date the patent expires (including any patent extensions); or

> (B) if the drug is the subject of a listed patent for which a [paragraph IV] certification has been submitted under subsection . . . (j)(2)(A)(vii)(IV) of section 505, and in the patent infringement litigation resulting from the certification the court determines that the patent is valid and would be infringed, the period during which an ANDA may not be approved under . . . section 505(j)(5)(B) shall be extended by a period of six months after the date the patent expires (including any patent extensions).

21 U.S.C. 355a(c).

Here, there is no dispute that ALZA conducted pediatric studies fairly responding to a written request issued by FDA. ALZA conducted the studies in accordance with good scientific principles and protocols, and submitted them in a supplement appropriate for filing. At issue in this dispute are which statutory provisions govern whether ALZA's pediatric exclusivity delays the approval of Mylan's ANDA beyond the date the '580 patent expires, as well as how those provisions apply to the facts presented.

Mylan's Argument

Mylan contends that it is not subject to ALZA's pediatric exclusivity. Mylan argues that because its application was submitted with a paragraph IV certification, section 355a(c)(2)(B) (relating to paragraph IV certifications) determines whether pediatric exclusivity will attach.[9] Under 355a(c)(2)(B), if the NDA holder satisfies the prerequisites for pediatric exclusivity by completing the requested studies in the requested timeframe, and in the lawsuit resulting from the paragraph IV certification the patent is found valid and infringed, "the period during which an ANDA may not be approved under . . . section [505(j)(5)(B)] shall be extended by six months after the date the patent expires." Mylan notes that the statute's provisions regarding paragraph IV certifications at 355a(c)(2)(B) provide for an extension of the "period in which an application may not be approved under 505(j)(5)(B)." Mylan argues that the only period during which an application may not be approved under 505(j)(5)(B) is the 30-month stay provided for in that section. Because Mylan was sued outside of the 45-day period, it contends that no 30-month stay attached, there is no "period" to extend, and the terms of 355a(c)(2)(B) do not require a delay of Mylan's approval.

Moreover, although the court reset the effective date of Mylan's ANDA under 271(e)(4)(A) to a date that is not earlier than the date the '580 patent expires, in Mylan's view, the court order did not create a "period during which [Mylan's ANDA] may not be approved." Mylan maintains that its application remains approved and such approval can only be withdrawn in accordance with the withdrawal provisions of section 505(e) of the Act, 21 U.S.C. 355(e), which require, among other things, notice and opportunity for hearing before withdrawal can occur. Similarly, in Mylan's view, the court's order does not and cannot convert (or require FDA to convert) its final approval to a tentative approval.

[9] Mylan argues that because it has appealed the district court order of validity and infringement, in the interim, its paragraph IV certification (indicating it is challenging the validity or infringement of the patent) remains valid.

On the contrary, Mylan argues that although a tentatively approved application is subject to further FDA review before an approval letter will issue and the approval becomes effective, Mylan's application has a different status that does not necessitate such review. In Mylan's view, the court's order does not require FDA to act on Mylan's application before Mylan can begin marketing under it. The court order merely creates a new date certain when the approval will be made effective by operation of law (i.e., the date the patent expires). Under this theory, when the patent expires on July 23, 2004, Mylan's ANDA will once again have a final effective approval without any further action by Mylan or FDA.

Under Mylan's theory, even if new patents have been listed, or ALZA supplements its NDA with a material change in formulation or labeling, or Mylan's application otherwise falls out of compliance with applicable statutes and regulations before July 23, 2004, the approval of Mylan's ANDA would nevertheless "become effective" -- and it may begin marketing -- the moment the patent expires. Moreover, because its application will regain a final effective approval at the moment the patent expires, and because applications with final effective approval have no further obligation to update their patent certifications post approval, Mylan argues that it will not be required to amend its application to change to a paragraph II certification when the patent expires. Mylan thus argues that 355a(c)(2)(A)(i) (which prohibits FDA's approval of ANDAs with paragraph II certifications for six months after the patent expires) will never apply to delay approval of Mylan's ANDA.

ALZA's Argument

ALZA, on the other hand, argues that its pediatric exclusivity delays final effective approval of Mylan's fentanyl transdermal system ANDA until no earlier than 6 months after the date the '580 patent expires. ALZA argues that where an application has been approved and a court subsequently holds the patent valid and infringed, FDA properly responds to a court order delaying the effective date of approval by converting the full approval to a tentative approval. ALZA notes that, under FDA's regulations, where FDA issues an approval with a delayed effective date, that approval is tentative and does not become final until (1) patent and exclusivity barriers to approval expire, (2) FDA determines that the approval requirements continue to be met, and (3) FDA issues an approval letter. ALZA contends that, under *Barr Labs. Inc. v. Thompson,* when FDA issues an approval with a delayed effective date, the ANDA applicant has no vested right to obtain a final effective approval on a particular date. ALZA argues that the same result necessarily applies when the delay in effective date has been ordered by the court under 271(e)(4)(A). Although in this case the patent is due to expire shortly after the court order resetting the ANDA effective date, ALZA notes that, under Mylan's theory, the same result would apply even if the patent were due to expire 10 or more years in the future.

Moreover, ALZA argues that, once Mylan's effective approval has been converted to a tentative approval, the statutory language, regulations, and policy underlying pediatric exclusivity, require that Mylan be subject to ALZA's pediatric exclusivity. ALZA argues that, under FDA's regulations at 21 C.F.R. 314.94(a)(12)(i)(C), Mylan should have converted its certification to a paragraph III certification after it lost its patent suit. However, ALZA notes that, regardless of whether Mylan's ANDA should now contain a paragraph III or a paragraph IV certification, upon patent expiration, Mylan's ANDA must contain a paragraph II certification to be accurate.

ALZA notes that, under the rule of *Ranbaxy*, the only relevant certification for determining pediatric exclusivity is the one in place at the time of final approval. *Ranbaxy Labs. Ltd.*, 307 F. Supp. 2d at 19, 21. Accordingly, because Mylan cannot receive final effective approval until after the patent has expired and patent expiration will require Mylan to submit a paragraph II certification, ALZA argues that 355a(c)(2)(A)(i) (relating to paragraph II certifications), not 355(c)(2)(B) (relating to paragraph IV certifications) determines whether pediatric exclusivity will attach. Under 355(a)(c)(2)(A)(i), pediatric studies were submitted before expiration of the patent so the period during which Mylan's ANDA cannot be approved is "extended six months after the date the patent expires."

FDA's Determination

FDA finds that ALZA's pediatric exclusivity for fentanyl will attach, and thus delay effective approval of Mylan's ANDA. Unless Mylan were to win its patent case on appeal, Mylan's ANDA would be eligible for final effective approval no earlier than six months after the '580 patent expires on July 23, 2004.

The Vermont District Court found that Mylan infringed ALZA's valid patent. As noted above, pursuant to 35 U.S.C. 271(e)(4)(A), the district court hearing the patent infringement case enjoined Mylan from "making, using, offering to sell [and] selling within the United States or importing into the United States" its fentanyl transdermal system and ordered that the effective date of Mylan's ANDA "shall be no earlier than the date of expiration of U.S. Patent No. 4,588,480."

Under the FDA's regulations, as upheld in *Barr Labs. Inc. v. Thompson* , an approval with a delayed effective date is a tentative approval that cannot be made effective until FDA issues a letter granting final effective approval. 21 C.F.R. 314.107(b)(3)(v); see also *Barr Labs,* 238 F.Supp at 245-50. This is the case regardless of whether approval has been blocked by a 30-month stay, 5-year exclusivity, 3-year exclusivity, 180-day exclusivity or, as in this case, because the court has issued an order prohibiting approval from being made effective until after the patent expires. In each of these cases, the Hatch-Waxman amendments bar FDA's issuance of a final effective approval. See 21 U.S.C. 505(j)(5)(B)(iii); 21 U.S.C. 505(j)(5)(B)(iv); 21 U.S.C. 505(j)(5)(D)(ii); 21 U.S.C. 505(j)(5)(D)(iii); 35 U.S.C. 271(e)(4)(A).

Just as applicants barred from final approval due to 5-year or other Hatch-Waxman exclusivity need FDA to act to issue an approval letter before they are permitted to have a final effective approval, so too, does the Vermont District Court's order require FDA to act before Mylan's effective approval can be restored. Under the court's order, approval of Mylan's ANDA cannot be made effective until after the '580 patent has expired. An approval with a delayed effective date (including a previously effective approval that has had its effective date delayed by court

order) is tentative.[10] It does not give Mylan an unqualified right to obtain final effective approval without further action by Mylan or FDA on the date the patent expires. Although tentatively approved status embodies FDA's determination that the requirements for approval have been met as of a particular date, FDA must review a tentatively approved application to determine whether the standards for approval continue to be met before it will issue a final approval letter. Among other requirements, Mylan's ANDA, like all applications with tentative approvals, must maintain accurate patent certifications. 21 C.F.R. 314.94(a)(12)(viii)(C)(i).

Once the patent expires, Mylan's paragraph IV certification (indicating that the patent is invalid or not infringed) will no longer remain accurate. See *Ranbaxy*, 307 F. Supp. 2d at 19, 21. A change in certification (in this case to a paragraph II certification indicating that the patent has expired) is required when an applicant whose application does not have final, effective approval learns that its existing certification is no longer proper. See 21 C.F.R. 314.94(a)(12)(viii)(C)(i) ("an applicant shall amend a submitted certification if, at any time before the effective date of the approval of the application, the applicant learns that the submitted certification is no longer accurate."); see also 21 U.S.C. 355(j)(4)(K) (an ANDA that contains an untrue statement of material fact cannot be approved). If Mylan refuses to amend its application to change its certification after the patent expires, FDA can treat that certification as automatically amended to contain a paragraph II certification (because there is no other proper certification upon patent expiry). See *Ranbaxy*, 307 F. Supp. 2d at 19, 21. Alternatively, FDA can refuse to issue a final approval letter on the ground that the application contains an untrue statement of material fact. In either case, Mylan cannot obtain final approval until its application actually contains or is deemed to contain a paragraph II certification. See *id.*

Once Mylan's certification has changed - *de facto* or *de jure* - to a paragraph II certification, pediatric exclusivity attaches under 355a(c)(2)(A)(i). See *Ranbaxy*, 307 F. Supp. 2d at 20, 21. Under 355a(c)(2)(A)(i), if an application contains a paragraph II certification and the pediatric studies qualifying for exclusivity were submitted before the patent expires, "the period during which an [ANDA] may not be approved . . . shall be extended by a period of six months after the date the patent expires." This provision gives ALZA pediatric exclusivity as to Mylan and further delays the effective date of Mylan's approval for 6 months after the patent expires. If, at the end of this additional 6 months, FDA were to determine that Mylan's ANDA continues to meet the approval requirements and there are no remaining patent or exclusivity barrier to approval, FDA will issue a new letter granting Mylan a final effective approval.

[10] Although, in essence, the court's order withdraws Mylan's full effective approval, contrary to Mylan's arguments FDA was not required to comply with the withdrawal provisions of 505(e). Under 505(e), FDA can withdraw approval of an approved application after notice and opportunity for hearing under certain narrowly defined circumstances. However, 505(c) does not state the only circumstances in which withdrawal of effective approval is possible. Instead, 35 U.S.C. 271(e)(4)(A) speaks more specifically to the circumstances at issue. This provision mandates a withdrawal of effective approval where, as here, an ANDA applicant has received a final effective approval and subsequently loses its patent lawsuit with a finding that the patent is valid and infringed. Once that effective approval is withdrawn, the status of Mylan's ANDA is the same as that of other ANDAs blocked from final approval by patent or exclusivity rights - tentatively approved.

This approach properly rewards ALZA for conducting and submitting its pediatric studies and preserves the necessary incentive to conduct such studies.[11] It is consistent with *Barr* and *Ranbaxy* as well as with the structure and purpose of 21 U.S.C. 355a. For all of these reasons, FDA concludes that effective approval of Mylan's ANDA for fentanyl transdermal systems will be subject to ALZA's pediatric exclusivity.

Sincerely,

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

[11] Although Mylan argues that its approach (which prevents ANDAs from being subject to pediatric exclusivity if they obtain approval and the effective date of approval is reset by a court) properly punishes NDA holders for failing to sue within the statutory 45-day period, the logic of Mylan's argument applies to any application that has a final effective approval that is reset after a finding of validity and infringement; it is not limited to applications that received approval because the NDA holder or patent owner missed the deadline for suit. Specifically, Mylan's argument would also apply where the NDA holder sued the ANDA applicant within the 45-day period and the ANDA was approved after 30 months while the litigation was ongoing. In that case, if the court subsequently found the patent valid and infringed and reset the effective date of approval, under Mylan's theory this approval would become effective on the date of patent expiry regardless of whether the NDA holder had earned pediatric exclusivity because there is no remaining "period" under 505(j)(5)(B) to extend. Similarly, if the ANDA applicant won its patent litigation at the district court level, obtained final, effective approval after that victory, and subsequently lost on appeal with an order resetting the ANDA approval effective date, approval of that application would also become effective on the date of patent expiration, regardless of whether the NDA holder had earned pediatric exclusivity. This outcome makes little sense, and would substantially diminish the incentives for innovator firms to undertake the studies requested by FDA to earn a pediatric exclusivity which was so tenuous and easily evaded.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

MYLAN LABORATORIES INC. and MYLAN PHARMACUETICALS INC. Plaintiffs, v. MICHAEL O. LEAVITT, in his official capacity as SECRETARY OF HEALTH AND HUMAN SERVICES, and ANDREW C. VON ESCHENBACH, M.D., in his official capacity as COMMISSIONER OF FOOD AND DRUGS, and UNITED STATES FOOD AND DRUG ADMINISTRATION, Defendants.	)	Civil Action No.

DECLARATION OF BRIAN S. ROMAN IN SUPPORT OF MYLAN'S EMERGENCY APPLICATION FOR A TEMPORARY RESTRAINING ORDER

I, Brian S. Roman, declare as follows:

1. I currently am the Vice President and General Counsel of Mylan Pharmaceuticals Inc. ("Mylan Pharmaceuticals"), a Plaintiff in this action. Prior to being appointed to this position, from April 2003, I was responsible for overseeing and directing all litigation involving Mylan Pharmaceuticals' parent corporation, Mylan Laboratories Inc. ("Mylan Laboratories").

The latter included all litigation including, but not limited to, Mylan Pharmaceuticals.

2. I submit this declaration in support of the Emergency Application for a Temporary Restraining Order filed in this Court by Mylan Pharmaceuticals and Mylan Laboratories (collectively "Mylan"). All statements contained herein as to Mylan are based upon my personal knowledge, including those relating to the organization and operation of both Mylan Pharmaceuticals and Mylan Laboratories. All statements contained herein as to persons other than Mylan, and matters unrelated to Mylan, such as the sales and marketing activities of both brand and generic pharmaceuticals, are based upon my knowledge, information and belief.

3. Mylan Pharmaceuticals is a wholly owned subsidiary of Mylan Laboratories, which is a publicly traded company. Mylan Pharmaceuticals develops, manufactures and sells generic pharmaceuticals in the United States. This case involves Mylan Pharmaceuticals' Abbreviated New Drug Application ("ANDA") No. 76-418, for amlodipine besylate tablets, 2.5 mg (base), 5 mg (base) and 10 mg (base) ("Mylan's ANDA"). Mylan Pharmaceuticals has expended tremendous resources toward the development and approval of its amlodipine products, including millions of dollars on materials, studies, overhead and litigation. .

4. The Food and Drug Administration ("FDA") issued Final Approval for Mylan's ANDA on October 3, 2005. The 180-day exclusivity period granted to Mylan currently prevents the FDA from issuing Final Approval to any generic companies other than Mylan Pharmaceuticals, which means that Mylan Pharmaceuticals enjoys a six-month head start over its generic competitors.

5. I am aware that FDA is considering issuing final approval to other ANDAs for amlodipine besylate as early as Monday, March 26, 2007. At least one other ANDA filer has publicly announced its view that no company has exclusivity and that it expects to launch the product in the very near future. See Apotex 3/21/07 Press Release attached hereto.

6. Any approval of additional amlodipine besylate ANDAs prior to expiration of Mylan's exclusivity would not only destroy the 180-day exclusivity rights that FDA already granted to Mylan, but it would also fundamentally undermine the value of Mylan's enormous investments aimed at capitalizing on its 180-day exclusivity. Any FDA approval of other ANDAs would deprive Mylan of its first entrant, leadership position in the market for generic amlodipine besylate. Mylan would lose a portion of the amlodipine market and associated sales that are forecasted to reach the hundreds of millions of dollars, harms for which there is no legal redress. Mylan has forecasted that its revenues would reach several million dollars per day. Being the first to launch into the generic marketplace also permits Mylan to secure distribution channels, favorable positioning in customer supply programs and access to additional customers, thereby obtaining and retaining a greater market share in the long term.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on March 23, 2007.

Brian S. Roman

APOTEX CORP.

NEWS

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FOR IMMEDIATE RELEASE

Apotex Invalidates Norvasc® Patent

Company to Launch In Near Future

Weston, Fl (March 21, 2007) – Apotex Corp. announced today the Federal Circuit Court of Appeals in the case of Pfizer, Inc. v. Apotex, Inc. reversed a trial court's ruling and found that Pfizer's U.S. Patent 4,879,303 (the '303 patent) covering the Pfizer product Norvasc® was invalid. The '303 patent covers amlodipine besylate the active ingredient in Norvasc® as well as tablets made from amlodipine besylate. Because the limiting patent expires in two days, no company will have exclusivity over the product. Apotex expects to launch the product in the very near future.

The Federal Circuit found that Apotex had proven that the '303 patent was invalid because it was obvious. In other words, the patent should never had been issued because someone skilled in the art would have known to make amlodipine besylate from materials, called prior art, that were publicly available. The Federal Circuit cited as some of the prior art an earlier Pfizer patent that taught amlodipine maleate as well as amlodipine with other pharmaceutically acceptable salts. The earlier Pfizer patent did not specifically mention besylate but the Court found that it was sufficient that besylate salt was discussed in other pieces of prior art.

By finding the Pfizer '303 patent invalid and not infringed by Apotex's ANDA, the Court is allowing Apotex to obtain final approval for its generic amlodipine besylate product. By finding Pfizer'303 patent invalid the Court also causes Pfizer to loose the additional six months of pediatric exclusivity that they had obtained.

"Our pursuit of this case after losing at the District Court level was rooted in Apotex's belief that the right thing to do for consumers and customers is to never, ever stop fighting to bring generics to market at the earliest possible time," said Apotex CEO Barry Sherman. "There was no guarantee when we appealed the case that we would be able to enter the market if we won. The odds, in fact, were against us achieving that outcome. But we believed we have an obligation to consumers to keep fighting, and are extremely pleased that our victory in the courts will bring significant savings in short order to the US health care system."

"It goes without saying that we will continue to press on all fronts for changes in the US legislative and regulatory framework that will better serve consumers . The commitment to the consumer that guided our actions in this case will continue to guide our efforts in Washington, DC, for instance, to work with policymakers to put an end to anti-competitive patents settlements that delay consumer access to affordable, quality generic medicines," Sherman added.

"Today's decision also has implications for the outcome of the clopidogrel case as some of the same legal principles are at stake in that trial. As today's ruling underscores, consumers can be sure we will do everything in our power to prevail in that case as well," Sherman added.

The Apotex Group manufactures more than 200 different high-quality generic pharmaceuticals, used by millions of patients worldwide. Its product line includes oral solids, liquids, injectables, nasal sprays, opthalmics, and inhalation solutions.