WATSON Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

April 4, 2007

Food and Drug Administration
Office of Generic Drugs, HFD-600
Attention: Gary J. Buehler, Director
7519 Standish Place
Rockville, MD 20855

RE: Amlodipine Besylate (Norvasc®)
ANDA #77-073

Dear Dr. Buehler:

This correspondence responds to your March 29, 2007 request for comments relating to regulatory issues stemming from the Federal Circuit's recent decision in *Pfizer Inc. v. Apotex, Inc.*, relating to amlodipine besylate (Norvasc®) tablets.

Question 1. What date controls FDA's giving effect to the *Pfizer v. Apotex* Federal Circuit decision holding U.S. Patent No. 4,879,303 invalid? That is, can FDA treat the '303 patent as invalid as of March 22, 2007 or must FDA await issuance of the Federal Circuit mandate? Is the answer the same for all purposes, that is, for determining the applicability of pediatric exclusivity, the triggering of 180-day exclusivity, and the eligibility of other ANDA applicants for final approval?

U.S. Patent No. 4,879,303 ("the '303 patent") should be considered invalid of March 22, 2007, the date of the *Pfizer v. Apotex* decision, wherein the Court of Appeals for the Federal Circuit ("CAFC") held that the '303 patent is invalid. For ANDAs containing a paragraph IV certification to the '303 patent, approval shall be made effective on the date on which the court of appeals decides that the patent is invalid or not infringed. *See* § 355j(5)(B)(iii)(II)(AA).

March 22, 2007 is also the date that the 180-day exclusivity should be considered to have been triggered. (*See* 21 U.S.C. § 355(j)(5)(B)(iv) (A subsequent-filer's ANDA shall be given final approval no earlier than 180 days after a triggering event, which is the first commercial marketing of the ANDA product or "the date of a decision of a court" holding the patent invalid or not infringed, whichever is earlier)).[1]

[1] This provision was amended by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA), Pub. L. No. 108-173, tit. XI, § 1102(a)(2)(D)(i)(I)(bb)(CC), (a)(2)(D)(ii), 117 Stat. 2066, 2457-59 (Dec. 8, 2003) (codified at 21 U.S.C. §355(j)(5)(D)(i)(I)(bb)(CC), (j)(5)(D)(ii) (2003)). The Federal Circuit and lower decisions in the *Pfizer* case were made pursuant to the Hatch Waxman Amendments as interpreted before implementation of the MMA. The MMA was not made retroactive, § 1102(b)(1), 117 Stat. at 2460. Therefore, amendments made by the MMA do not affect the issues under consideration in this letter.

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As discussed in the answer to question 4 below, March 22, 2007 is also the date for determining the applicability of pediatric exclusivity for ANDAs containing a paragraph IV certification to the '303 patent.

Accordingly, since the '303 patent was held invalid by the CAFC on March 22, 2007, FDA need not await issuance of the mandate to determine the applicability of pediatric exclusivity to ANDAs containing paragraph IV certifications to the '303 patent, the triggering of 180-day exclusivity and the eligibility of other ANDA applicants for final approval.

Question 2. If FDA must await issuance of the mandate, does pediatric exclusivity bar approval of all unapproved ANDAs in the meantime?

For ANDAs containing a paragraph IV certification to the '303 patent, the approval shall be made effective on the date on which the court of appeals decides that the patent is invalid or not infringed. *See* § 355j(5)(B)(iii)(II)(AA). Therefore, as of March 22, 2007, pediatric exclusivity should not bar approval of all unapproved ANDAs containing a paragraph IV certification to the '303 patent.

Question 4. If and when the *Apotex* decision is implemented and the patent is treated as invalid, does pediatric exclusivity attach to the '303 patent with respect to any unapproved ANDAs? Does it matter whether the ANDA applicant filed a paragraph III or IV certification before patent expiration?

Pediatric exclusivity should not attach to patents that have been found by a court to be invalid. According to 21 U.S.C. § 355a(c)(2)(B):

> if the drug is the subject of a listed patent for which a certification has been submitted under subsection (b)(2)(A)(iv) or (j)(2)(A)(vii)(IV) of section 355 of this title, 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 application may not be approved under section 355 (c)(3) of this title or section 355 (j)(5)(B) of this title shall be extended by a period of six months after the date the patent expires (including any patent extensions).

(Emphasis added).

Regardless of whether an applicant filed a paragraph III or a paragraph IV certification against a patent that is found to be invalid, the NDA holder should not be

allowed to extend the term of that invalid patent via pediatric exclusivity. Therefore, once the '303 patent is treated as invalid, pediatric exclusivity should not attach to the '303 patent with respect to any unapproved ANDAs.

Question 5. Does 180-day exclusivity triggered before a patent expires continue to bar approvals of other ANDAs after the patent expires, even if other ANDA applicants change their certifications to paragraph II or withdraw their certifications altogether?

When the '303 patent expired on March 25, 2007, the first ANDA-filer's 180-day period of generic exclusivity simultaneously terminated. (*See Ranbaxy v. Leavitt*, 469 F.3d 120, 126 (D.C. Cir. 2006) (noting that Ranbaxy and Teva acknowledged that the first generic applicant no longer retains exclusivity when the patent has expired); *see also* 21 U.S.C. §°355(j)(5)(B)(i) and *Dr. Reddy's Labs.*, 302 F. Supp. 2d at 354-55.

An Orange Book patent is active until the end of the natural term of the patent or any 180-day period of generic exclusivity, whichever occurs first. 59 Fed. Reg. 50,338, 50,348 (Oct. 3, 1994); *see also Dr. Reddy's Labs., Inc.*, 302 F. Supp. 2d at 352. FDA confirmed this interpretation in the preamble to its 1999 proposed regulations, expressly stating that 180-day exclusivity does not survive patent expiration:

> The agency is clarifying that once the patent for which the first applicant filed a paragraph IV certification expires, the first applicant is no longer eligible for exclusivity. When the first applicant is no longer eligible for exclusivity, FDA may approve all otherwise eligible ANDAs. FDA regulations at § 314.94(a)(12)(viii) currently provide that exclusivity cannot extend beyond the term of a patent.

64 Fed. Reg. 42,873, 42,877 (Aug. 6, 1999).

FDA has also applied this statutory interpretation in administrative rulings involving at least cisplatin and omeprazole. First, FDA's September 2, 1999 ruling on cisplatin stated that "because exclusivity cannot extend beyond the expiration of a patent, [the first-filer] lost its eligibility for exclusivity when the '515 patent expired before either of the events described in 505(j)(5)(B)(iv)(I) and (II) occurred." (9/2/99 Admin. Ruling in Docket No. 99P-1271).

Similarly, in connection with exclusivity relating to omeprazole, FDA concluded that patent expiration extinguishes any unused generic exclusivity:

> A 180-day exclusivity period cannot extend beyond the expiration date of a patent (21 C.F.R § 314.94(a)(12)(viii)).

(FDA 11/16/01 Admin. Ruling at 1).

FDA reiterated this position in a second letter relating to omeprazole, stating "[U]nder the statute and FDA's regulations, eligibility for exclusivity – or eligibility itself – expires with the patent." (FDA 3/28/02 Admin. Ruling at 5).

The *Dr. Reddy's* court confirmed FDA's interpretation, holding that awarding 180-day exclusivity based only upon paragraph IV certifications to unexpired patents "makes sense in terms of the basic statutory objective of encouraging ANDA applicants to challenge listed patents that prevent final ANDA approval." 302 F. Supp. 2d at 354. Consequently, the court upheld FDA's decision that generic exclusivity expires with the patent.

Should you have further questions concerning our response to FDA's questions, please contact the undersigned.

Very truly yours,

Watson Laboratories, Inc.

By: _____
Ernest Lengle, Ph.D.
Executive Director, Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0430
Expiration Date: April 30, 2009
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Watson Laboratories, Inc.	April 4, 2007
TELEPHONE NO *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(951) 493-5446	(951) 493-4581
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S License number if previously issued)*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
311 Bonnie Circle, Corona, CA 92880	Not Applicable

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* **ANDA #77-073**

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Amlodipine Besylate Tablets	

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
(R,S) 3-ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulphonate

CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	2.5 mg, 5 mg, and 10 mg (base)	Oral

(PROPOSED) INDICATION(S) FOR USE:

1. Indicated for the treatment of hypertension, alone or in combination with other antihypertensive agents.
2. Indicated for the treatment of chronic stable angina, used alone or in combination with other antianginal agents.
3. Indicated for the treatment of confirmed or suspected vasospastic angina (Prinzmetal's or Variant Angina), used as monotherapy or in combination with other antianginal drugs.

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)*
☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Norvasc® Holder of Approved Application Pfizer

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Response to FDA Letter dated March 29, 2007

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 Archival, 1 Review THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Refer to the original ANDA dated February 25, 2004 for primary manufacturing & testing sites and contract manufacturing facilities. Added secondary packaging site (for secondary labeling only): Watson Laboratories, Inc., 311 Bonnie Circle, CA 92880.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

Refer to the original ANDA

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☒ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19 Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* Response to FDA Letter dated March 29, 2007

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Ernest Lengle, Ph.D.	Ernest Lengle, Ph.D., Executive Director, Regulatory Affairs	April 4, 2007

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
311 Bonnie Circle, Corona, CA 92880	(951) 493-5446

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