

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-276

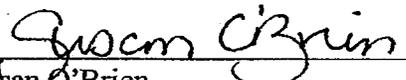
ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

1.3.5.2 Patent Certification

PARAGRAPH II CERTIFICATION

In accordance with the Federal Food, Drug, and Cosmetic Act, as amended September 24, 1984, and with the final regulations effective November 2, 1994, Patent Certification is hereby provided for our New Drug Application for Nicardipine Hydrochloride Injection.

Teva Parenteral Medicines, Inc. hereby certifies that in its opinion and to the best of its knowledge, U.S. Patent No. 4,880,823, listed for PDL Biopharma Inc.'s NDA 19-734 for Cardene® I.V. expired on November 14, 2006. This certification is made in accordance with Section 505(b)(2)(A)(ii) of Title 1 of the Federal Food, Drug, and Cosmetic Act, as amended September 24, 1984, and pursuant to 21 CFR § 314.50(i)(1)(i)(2).



Susan O'Brien
Director, Regulatory Affairs

9-28-07

Date

New Drug Application
Module 1: Regional- Administrative and Prescribing Information

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDERS

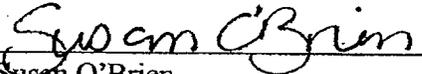
As required by Section 505(b)(3)(A) of the Federal Food, Drug, and Cosmetic Act and 21 CFR §314.94(a)(12)(i)(A)(4) and 21 CFR §314.95, Teva Parenteral Medicines, Inc., hereby states that Teva Parenteral Medicines, Inc., upon receipt from FDA of an acknowledgement letter stating that this NDA is sufficiently complete to permit a substantive review, will give notice required by Section 505(B)(3)(A) of the Federal Food, Drug, and Cosmetic Act and 21 CFR §314.95 to PDL Biopharma Inc., the holder of the approved application for Cardene® I.V., and the owner of the following U.S. Patent:

U.S. Patent No.
5,164,405

Patent Expiration
November 17, 2009

This notice to PDL Biopharma Inc, which will be sent by certified mail, return receipt requested, shall meet the requirements of 21 CFR §314.52(a) and 21 CFR §314.52(c).

Concurrently with sending the notice to PDL Biopharma Inc, Teva Parenteral Medicines, Inc. will, as required by 21 CFR §314.52(b), amend its Nicardipine Hydrochloride Injection NDA to include a certification that the notice has been provided to each person identified under 21 CFR §314.52(a) and that the notice met the content requirements of 21 CFR §314.52(c).


Susan O'Brien
Director, Regulatory Affairs

9-28-07
Date

PARAGRAPH IV CERTIFICATION

In accordance with the Federal Food, Drug, and Cosmetic Act, as amended September 24, 1984, and with the final regulations effective November 2, 1994, Patent Certification is hereby provided for our New Drug Application – 505(b)(2) for Nicardipine Hydrochloride Injection, 2.5 mg/mL.

Teva Parenteral Medicines, Inc. hereby certifies that in its opinion and to the best of its knowledge, the following U.S. Patents listed for PDL Biopharma Inc's NDA Number 19-734:

U.S. Patent No.
5,164,405

Patent Expiration
November 17, 2009

is invalid, unenforceable or will not be infringed upon by the manufacture, use, or sale by Teva Parenteral Medicines, Inc., for which this application is submitted. This certification is made in accordance with Section 505(b)(2)(A)(iv) of Title 1 of the Federal Food, Drug, and Cosmetic Act, as amended September 24, 1984, and pursuant to 21 CFR § 314.50(i)(1)(i)(4).

Susan O'Brien
Susan O'Brien
Director, Regulatory Affairs

9-28-07
Date

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 19-734

Cardene I.V.

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical

investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # YES ! NO
! Explain:

Investigation #2 !
IND # YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES
Explain:

!
! NO
! Explain:

Investigation #2

YES
Explain:

!
! NO
! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Alisea Crowley
Title: Regulatory Health Project Manager
Date: 07/25/2008

Name of Office/Division Director signing form: Norman Stockbridge, M.D., Ph.D.
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Alisea R. Crowley
7/25/2008 10:03:35 AM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA # : 22-276 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: 28Sep07 PDUFA Goal Date: 1Aug07

HFD-110 Trade and generic names/dosage form: Nicardipine Hydrochloride Injection

Applicant: Teva Parenteral Pharmaceuticals, Inc. Therapeutic Class: Calcium Channel Blocker

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- Yes. Please proceed to the next question.
- No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): _____

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): _____

Indication #1: _____

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: ___ Partial Waiver ___ Deferred ___ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

NDA 22-276

Page 3

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH
STAFF at 301-796-0700**

(Revised: 10/10/2006)

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

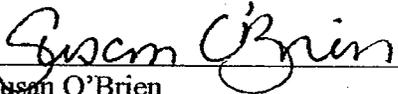
Denise Hinton
11/13/2007 04:25:29 PM

1.3.3 Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other

Debarment Certification

As required by the Generic Drug Enforcement Act of 1992, Teva Parenteral Medicines, Inc. certifies that we have not nor will we use in any capacity the services of any person debarred under subsections (a) or (b) [section 306 (a) or (b)] of the Act, in connection with our application for Nicardipine Hydrochloride Injection, 2.5 mg/mL.

There have been no convictions of crimes (as specified in section 306 (a) and (b) of the Act) within the previous five years of any Teva Parenteral Medicines, Inc. employees or affiliated company, or employees of the affiliated companies responsible for the development or submission of this application for Nicardipine Hydrochloride Injection, 2.5 mg/mL.



Susan O'Brien
Director, Regulatory Affairs

9-28-07

Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Teva Parenteral Medicines, Inc.	DATE OF SUBMISSION 12/11/2007
TELEPHONE NO. (Include Area Code) 949-455-4724	FACSIMILE (FAX) Number (Include Area Code) 949-583-7351
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 19 Hughes Irvine, CA 92618	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE N/A

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) N/A	
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Nicardipine Hydrochloride Injection	PROPRIETARY NAME (trade name) IF ANY N/A
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) See Continuation Sheet	CODE NAME (if any) N/A
DOSAGE FORM: Injectable	STRENGTHS: 2.5 mg/mL
	ROUTE OF ADMINISTRATION: Intravenous
(PROPOSED) INDICATION(S) FOR USE: For the short-term treatment of hypertension when oral therapy is not feasible or not desirable.	

APPLICATION DESCRIPTION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (CDA, 21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b)(1) <input checked="" type="checkbox"/> 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: Cardene® I.V. Holder of Approved Application: PDL BioPharma, Inc.
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input checked="" type="checkbox"/> AMENDMENT TO PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)
REASON FOR SUBMISSION Patent Amendment - Paragraph Certification Notice for U. S. Patent 5,164,405 sent to PDL BioPharma, Inc.

PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED N/A THIS APPLICATION IS <input type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input checked="" type="checkbox"/> 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.

See Continuation Sheet

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

_____ b(4)

This application contains the following items: (Check all that apply)	
<input type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(f); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input checked="" type="checkbox"/>	20. OTHER (Specify) Patent Amendment - Paragraph Certification Notice for U. S. Patent 5,164,405 sent to PDL BioPharma, Inc.

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

Susan O'Brien

TYPED NAME AND TITLE

Susan O'Brien, Director, Regulatory Affairs

DATE:

12/11/2007

ADDRESS (Street, City, State, and ZIP Code)

19 Hughes, Irvine, CA 92618-1902

Telephone Number

949-455-4724

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 22-276	Efficacy Supplement Type N/A	Supplement Number N/A
Drug: Nicardipine Hydrochloride Injection 2.5mg/mL		Applicant: Teva Parenteral Medicines, Inc.
RPM: Alisea Cowley, Pharm.D.		HFD- 110 Phone # (301) 796-1144
<p>Application Type: () 505(b)(1) (X) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p>(X) Confirmed and/or corrected</p>		<p>Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): NDA 19-734, Cardene I.V.</p>
❖ Application Classifications:		
Review priority		(X) Standard () Priority
Chem class (NDAs only)		
Other (e.g., orphan, OTC)		
❖ User Fee Goal Dates		
		August 2, 2008
❖ Special programs (indicate all that apply)		
		(X) None Subpart H () 21 CFR 314.510 (accelerated approval) () 21 CFR 314.520 (restricted distribution) () Fast Track () Rolling Review () CMA Pilot 1 () CMA Pilot 2
User Fee Information		
User Fee		(X) Paid UF ID number
User Fee waiver		() Small business () Public health () Barrier-to-Innovation () Other
User Fee exception		() Orphan designation () No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) (X) Other (specify) <u> Sponsor did not submit clinical data for review and relied on the RLD for all indications.</u>
❖ Application Integrity Policy (AIP)		

Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
This application is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Exception for review (Center Director's memo).	
OC clearance for approval	
Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	<input checked="" type="checkbox"/> Verified
❖ Patent	
Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified
Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	Patent 1 Certification 21 CFR 314.50(i)(1)(i)(A) (Verified) 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
[505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
[505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).</i>	<input type="checkbox"/> N/A (no paragraph IV certification) <input checked="" type="checkbox"/> Verified
[505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.	
Answer the following questions for each paragraph IV certification:	
Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).	
<i>If "Yes," skip to question (4) below. If "No," continue with question (2).</i>	
Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?	<input type="checkbox"/> Yes <input type="checkbox"/> No
<i>If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).</i>	
<i>If "No," continue with question (3).</i>	
Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	<input type="checkbox"/> Yes <input type="checkbox"/> No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
Exclusivity summary Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	No
Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.	<input type="radio"/> Yes, Application # _____ <input checked="" type="radio"/> No
Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	July 25, 2008

General Information	
❖ Actions	
Proposed action	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA
Previous actions (specify type and date for each action taken)	
Status of advertising (approvals only)	<input type="checkbox"/> Materials requested in AP letter <input type="checkbox"/> Reviewed for Subpart H
❖ Public communications	
Press Office notified of action (approval only)	<input type="checkbox"/> Yes <input type="checkbox"/> Not applicable
Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> Press Release <input type="checkbox"/> Talk Paper <input type="checkbox"/> Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
Division's proposed labeling (only if generated after latest applicant submission of labeling)	
Most recent applicant-proposed labeling	July 23, 2008
Original applicant-proposed labeling	September 28, 2007
<ul style="list-style-type: none"> Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings) 	DMETS: n/a DDMAC: 07/08/2008
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling) 	
❖ Labels (immediate container & carton labels)	
<ul style="list-style-type: none"> Division proposed (only if generated after latest applicant submission) 	
Applicant proposed	September 28, 2007
Reviews	See CMC reviews
Post-marketing commitments	N/A
Agency request for post-marketing commitments	
Documentation of discussions and/or agreements relating to post-marketing commitments	
Outgoing correspondence (i.e., letters, E-mails, faxes)	ACK Letter- 10/18/2007 Filling Letter- 11/29/2007 Information Request Ltr- 04/25/2008, 05/28/2008
Memoranda and Telecons	N/A
Minutes of Meetings	N/A
EOP2 meeting (indicate date)	N/A
Pre-NDA meeting (indicate date)	N/A
Pre-Approval Safety Conference (indicate date; approvals only)	N/A
Other-	
Advisory Committee Meeting	N/A
Date of Meeting	
48-hour alert	
Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	Div. Director- 06/16/08
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	N/A
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
Safety Update review(s) (indicate date or location if incorporated in another review)	N/A
Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	N/A
Pediatric Page(separate page for each indication addressing status of all age groups)	N/A
Demographic Worksheet (NME approvals only)	N/A
❖ Statistical review(s) (indicate date for each review)	N/A
❖ Biopharmaceutical review(s) (indicate date for each review)	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
Clinical studies	N/A
Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) (indicate date for each review)	05/06/2008 & 06/04/2008
Environmental Assessment	Refer to CMC review
Categorical Exclusion (indicate review date)	Refer to CMC review
Review & FONSI (indicate date of review)	N/A
Review & Environmental Impact Statement (indicate date of each review)	Refer to CMC Review
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	03/31/2008
❖ Facilities inspection (provide EER report)	Date completed: N/A () Acceptable () Withhold recommendation
Methods validation	(X) Completed () Requested () Not yet requested
Nonclinical Pharmacology Information	
Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	03/31/2008
Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	
❖ CAC/ECAC report	

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/s/

Alisea R. Crowley
7/25/2008 11:14:21 AM

Crowley, Alisea

From: Soldatova, Lyudmila
Sent: Friday, June 06, 2008 2:51 PM
To: Crowley, Alisea
Cc: Srinivasachar, Kasturi; Sood, Ramesh
Subject: FW: Please review
Attachments: Nicardipine Label post SEALDS review.doc

Hi Alisea,

I have reviewed the draft of the Package Insert and concluded that it includes all changes I wanted; I also made one revision in the Dosage and Administration Section, 2.2 Preparations (see the change in the same file).

Please revise the CMC comment in the Action Letter to the following:

"Based on the provided stability data, 9-month expiry is granted for the Nicardipine Hydrochloride Injections drug product".

Thank you.

Lyudmila

From: Crowley, Alisea
Sent: Friday, June 06, 2008 10:26 AM
To: Soldatova, Lyudmila
Subject: Please review

Hi Lyudmila,

Please review this label to make sure that the label includes the changes you wanted.

Thank you!

Alisea

6/6/2008



NDA 22-276

INFORMATION REQUEST LETTER

Teva Parenteral Medicines, Inc.
Attention: Susan O'Brien
Director, Regulatory Affairs
19 Hughes
Irvine, CA 92618-1902

Dear Ms. O'Brien:

Please refer to your September 28, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nicardipine Hydrochloride Injection 2.5 mg/mL solution.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1.

b(4)

2.

If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality, at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Ramesh Sood
5/28/2008 11:23:18 AM



NDA 22-276

INFORMATION REQUEST LETTER

Teva Parenteral Medicines, Inc.
Attention: Susan O'Brien
Director, Regulatory Affairs
19 Hughes
Irvine, CA 92618-1902

Dear Ms. O'Brien:

Please refer to your September 28, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nicardipine Hydrochloride Injection 2.5 mg/mL solution.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide information on the containers for diluents that were utilized in the Admixture study, and confirm that the same containers will be recommended for dilution of the commercial product. Provide information on the light sensitivity of the drug product diluted with different diluents. In addition, provide information on any potency loss of the admixture solutions after passing through the administration set (tubings, etc.).
2. Tighten the specification limit _____ derivative and for the total impurities in the drug product specification based on the levels observed over the shelf life. **b(4)**
3. Confirm that the 6-months stability studies at the accelerated conditions in addition to the long-term stability studies for the first three commercial lots, is included into the Stability Commitment for Nicardipine Hydrochloride Injection marketed product. Confirm that Commercial Stability Protocol _____ is the same as Stability Protocol _____ used to support stability program for Nicardipine Hydrochloride Injection. **b(4)**
4. The submitted 3-month stability data for Nicardipine Hydrochloride Injection, 2.5 mg/ml, at long term and accelerated conditions do not support the _____ of the requested expiry. Please provide additional stability data to support the requested expiry according to the recommendations provided in the ICH Guidance Q1A(R2) and ICH Guidance Q1E. **b(4)**
5. Provide stability data at the intermediate storage condition (30°C/65% RH) since the primary stability batches failed the proposed acceptance limit of NMT _____ under the accelerated conditions.

6. Provide clarification on the container and on the light protection method used for the Control Formulation of the drug product in the ICH Stressed Light Study (refer to the Module 3, Section 3.2.P.2.2.3, p. 12).

Labeling & Package Insert

7. _____

b(4)

8. _____

b(4)

If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality, at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Ramesh Sood

4/25/2008 12:06:52 PM



TEVA PARENTERAL MEDICINES

December 11, 2007

Norman Stockbridge, M.D., Ph.D
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Food and Drug Administration
Attention: Documentation Center
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: Nicardipine Hydrochloride Injection
25 mg/Vial, 2.5 mg/mL
NDA: 22-276

PATENT AMENDMENT

Dear Dr. Stockbridge:

Reference is made to Teva Parenteral Medicines, Inc.'s (Teva) new drug application for Nicardipine Hydrochloride Injection, 25 mg/vial, submitted to the Agency on September 29, 2007.

In accordance with Section 505(j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.95(d), we hereby amend this application to include this certification that the notice has been provided to PDL BioPharma, Inc., the holder of the approved application for Cardene® I.V. (NDA 19-734), and the owner of U.S. Patent No. 5,164,405, at the same time this amendment was submitted to the application. The notice met the content requirements of 21 CFR 314.95(c) and was sent by FedEx. Clearance to send the notice by FedEx was given to Teva by Ms. Denise Hinton, OND, DCRP, FDA.

We trust you will find the information in this application satisfactory for your review and approval. If there are any questions concerning this application, please do not hesitate in contacting me at (949) 455-4724. I can also be contacted by facsimile at (949) 583-7351.

Sincerely,

Susan O'Brien
Director, Regulatory Affairs



FILING COMMUNICATION

NDA 22-276

Teva Parenteral Medicines, Inc.
Attention: Ms. Susan O'Brien
19 Hughes
Irvine, CA 92618-1902

Dear Ms. O'Brien:

Please refer to your new drug application (NDA) dated September 28, 2007, received October 1, 2007, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Nicardipine Hydrochloride 2.5 mg/mL Injection.

We also refer to your submissions dated October 30 and November 15, 2007.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is Standard. Therefore, the user fee goal date is August 1, 2008.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application; however we are recommending a deferral of pediatric studies for this application for pre-school children (age 2- 6 years, school age children (age 6 –Tanner Stage 3), and adolescent children (Tanner Stage 3 – 16 years).

If you have any questions, please call Denise Hinton, Regulatory Project Manager, at (301) 796-1090.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.

Director

Division of Cardiovascular and Renal Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

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/s/

Norman Stockbridge
11/29/2007 05:01:35 PM

Crowley, Alisea

From: Addy, Rosemary
Sent: Sunday, November 18, 2007 3:33 PM
To: Hinton, Denise
Subject: RE: NDA 22-276 Peds full waiver request/Module 1.pdf

Denise,

After looking at this, PREA doesn't apply, so no waiver or deferral is necessary. In the AP letter, you may want to indicate something to the effect of "Because this application does not represent a new indication, new active ingredient, new dosage form, new route of administration, or new dosing regimen, PREA does not apply. Therefore, no waiver from pediatric studies is required."

Rosemary

From: Hinton, Denise
Sent: Tuesday, November 13, 2007 2:44 PM
To: Addy, Rosemary
Subject: NDA 22-276 Peds full waiver request/Module 1.pdf

Hi Rosemary,

Attached is the Peds Full Request for Nicardipine Hydrochloride Injection. It can be located in Section 1.9. From the Division's perspective, a full waiver can be granted. A Peds Written Request has been issued for the RLD NDA 19-734.

<< File: Module 1.pdf >>

Thank you,

Denise



NDA 22-276

NDA ACKNOWLEDGMENT

Teva Parenteral Medicines, Inc.
Attention: Susan O'Brien
Director, Regulatory Affairs
19 Hughes
Irvine, CA 92618-1902

Dear Ms. O'Brien:

We have received your new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Nicardipine Hydrochloride Injection

Date of Application: September 28, 2007

Date of Receipt: October 1, 2007

Our Reference Number: NDA 22-276

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 30, 2007 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must be in the Prescribing Information (physician labeling rule) format.

The NDA number provided above shown above be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, please contact:

Ms. Denise Hinton
Regulatory Project Manager
(301) 796 1090

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Edward Fromm
10/18/2007 10:54:45 AM