

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204308Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

**PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT, OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and Composition)
and/or Method of Use**

NDA NUMBER

204308

NAME OF APPLICANT/NDA HOLDER

Silvergate Pharmaceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

ENALAPED™ Powder for Oral Solution

ACTIVE INGREDIENT(S)

Enalapril maleate, USP

STRENGTH(S)

1 mg/mL

DOSAGE FORM

Powder for oral solution upon reconstitution

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
d. Name of Patent Owner	Address (of Patent Owner)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address (of agent or representative named in 1.e.)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?	<input type="checkbox"/> Yes	<input type="checkbox"/> No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
4.2 Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)	

5. No Relevant Patents

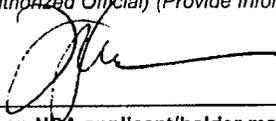
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	<input checked="" type="checkbox"/> Yes
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6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)



Date Signed

08/10/2012

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
Frank Seagrave

Address
5371 Gordon Way

City/State
Dublin, OH

ZIP Code
43017

Telephone Number
614-783-2497

FAX Number (if available)

E-Mail Address (if available)
frank.seagrave@silvergatepharma.com

The public reporting burden for this collection of information has been estimated to average 20 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
Office of Chief Information Officer
1350 Piccard Drive, Room 400
Rockville, MD 20850

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.

EXCLUSIVITY SUMMARY

NDA # 204308

SUPPL #

HFD #

Trade Name EPANED

Generic Name enalapril maleate

Applicant Name Silvergate Pharmaceuticals

Approval Date, If Known August 13, 2013

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The development program was designed to be able to bridge to the efficacy and safety findings of NDA 18-998. To that end, the applicant conducted three relative bioavailability studies.

The key findings were as follows:

- When administered in a fasted state, enalapril maleate pediatric oral solution 10 mL (1 mg/mL) was bioequivalent to Vasotec® 10 mg tablets.

- When enalapril maleate pediatric oral solution was administered in a fed state (after a high fat meal), C_{max}, AUC_{last}, and AUC_{inf} of enalapril and enalaprilat were lower compared to administration of the oral solution in the fasted state. C_{max} decreased by 46 and 36% for enalapril and enalaprilat, respectively. AUC_{last} and AUC_{inf} decreased by approximately 14 and 15% for enalapril and 23 and 20% for enalaprilat, respectively. The observed decrease in C_{max} and AUC is not expected to be clinically significant.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

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

7

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?

No

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# 018998

VASOTEC

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:

Name of person completing form: Michael Monteleone
Title: Regulatory Project Manager
Date: 2013-08-13

Name of Office/Division Director signing form: Norman Stockbridge, MD, PhD
Title: Director, Division of Cardiovascular and Renal Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

MICHAEL V MONTELEONE
08/13/2013

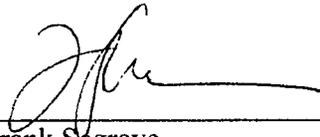
NORMAN L STOCKBRIDGE
08/13/2013

1.3.3 Debarment Certification

Silvergate Pharmaceuticals, Inc. (Silvergate), hereby certifies that it did not and will not use, in any capacity, the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act (the Act) in connection with this application.

Silvergate certifies that, during the previous 5 years, it has not sustained a conviction that is described in Sections 306(a) or (b) of the Act. In addition, no person affiliated with Silvergate, nor affiliated persons responsible for the development or submission of this application have been convicted of an offense described in Sections 306(a) or (b) of the Act.

Furthermore, Silvergate agrees to notify FDA of any changes in status of any employee with respect to Sections 306(a) or (b) of the Act.



Frank Segrave
Chief Executive Officer
Silvergate Pharmaceuticals, Inc.

August 10, 2012

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 204308 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: EPANED Established/Proper Name: enalapril maleate Dosage Form: powder for oral solution		Applicant: Silvergate Pharmaceuticals Agent for Applicant (if applicable): Beckloff Associates, Inc
RPM: Michael Monteleone		Division: Cardiovascular and Renal Products
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>	<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>VASOTEC NDA 018998</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>New dosage form</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input checked="" type="checkbox"/> This application relies on (explain) NDA 018998 (VASOTEC)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>	
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>August 14, 2013</u> 	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR	
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 	<input type="checkbox"/> None CR 2013-06-07	

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<p><input type="checkbox"/> Received</p>
<p>❖ Application Characteristics ³</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input checked="" type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDA: Subpart H BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42)</p> <p>Subpart I Subpart H <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Communication Plan <input type="checkbox"/> Submitted in response to a Pediatric Written Request <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required</p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<p><input type="checkbox"/> Yes, dates</p>
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> • Office of Executive Programs (OEP) liaison has been notified of action 	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> • Press Office notified of action (by OEP) 	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> • Indicate what types (if any) of information dissemination are anticipated 	<p><input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other</p>

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>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.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> 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. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input checked="" type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [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). 	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [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 section below (Summary Reviews)).</i> 	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input 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:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes 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)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) 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)?

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 the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) 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.

- (4) 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 section below (Summary Reviews).

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

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) 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).</p> <p><i>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 section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	YES
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) 2013-08-13; 2013-06-07
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	August 13, 2013
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	August 10, 2012
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. • Original applicant-proposed labeling • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	July 15, 2013
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	2013-03-01 – Not Acceptable 2013-06-07 – Acceptable 2013-07-05 – Acceptable
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA 2013-04-12 <input type="checkbox"/> DMPP/PLT (DRISK) <input checked="" type="checkbox"/> ODPD (DDMAC) 2013-05-15 <input checked="" type="checkbox"/> SEALD 2013-08-08 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	RPM Filing – 2012-10-02 <input type="checkbox"/> Not a (b)(2) 2013-05-14; 2013-07-08 <input type="checkbox"/> Not a (b)(2) 2013-08-13
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC _____ If PeRC review not necessary, explain: Firm received an orphan designation 2013-01-03 for pediatric hypertension; the product is appropriately labeled for use in all relevant pediatric populations. • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input type="checkbox"/> Included

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>)	YES
❖ Internal memoranda, telecons, etc.	NA
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• EOP2 meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	PIND 2010-10-07
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2013-06-06; 2013-08-13
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2013-06-05; 2013-08-13
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	NA
• Clinical review(s) (<i>indicate date for each review</i>)	2012-09-07 (Filing) 2012-12-05 (Review) 2013-05-31 (OODP Memo)
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See Clinical Review 2012-12-05 Page 12
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable

⁶ Filing reviews should be filed with the discipline reviews.

❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2012-09-12 (Filing)
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2012-09-11 (Filing) 2012-12-14 (Review)
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2012-09-07 (Filing)
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 2012-08-28 (Filing) 2012-08-31 (BioPharm) 2012-12-06 (Review) 2013-05-10 (Review) 2013-07-24 (Review)
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	See CMC Review 2012-12-06 Page 55
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷)</i>	Date completed: 2013-07-19 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/

MICHAEL V MONTELEONE
08/13/2013



NDA 204308

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Silvergate Pharmaceuticals, Inc
c/o Beckloff Associates, Inc.
7400 West 110th Street, Suite 300
Overland Park, KS 66210

ATTENTION: Wayne Vallee, RPh, RAC
Director, Managing Consultant
U.S. Agent for Silvergate Pharmaceuticals, Inc.

Dear Mr. Vallee:

Please refer to your Class 1 resubmission for your New Drug Application (NDA) dated and received June 14, 2012, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Enalapril Maleate Powder for Oral Solution, 1 mg/mL.

We also refer to your correspondence, dated and received June 21, 2013, requesting review of your proposed proprietary name, Epaned. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, Epaned, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your June 21, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Cheryle Milburn, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2084. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Michael Monteleone, at (301) 796-1952.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh

Director

Division of Medication Error Prevention and Analysis

Office of Medication Error Prevention and Risk Management

Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
07/05/2013



NDA 204308

**ACKNOWLEDGE --
CLASS 1 COMPLETE RESPONSE**

Silvergate Pharmaceuticals, Inc
Attention: Frank Segrave
Chief Executive Officer
6251 Greenwood Plaza Blvd.
Suite 101
Greenwood Village, CO, 80111

Dear Mr. Segrave:

We acknowledge receipt on June 14, 2013, of your June 14, 2013, resubmission to your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Epaned, (enalapril maleate) powder for oral solution, 1mg/mL.

We consider this a complete, class 1 response to our June 7, 2013, action letter. Therefore, the user fee goal date is August 14, 2013.

If you have any questions, please call Michael Monteleone, Regulatory Project Manager, at (301) 796-1952.

Sincerely,

{See appended electronic signature page}

Edward Fromm, RPh, RAC
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 J FROMM
06/27/2013



NDA 204308

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Silvergate Pharmaceuticals, Inc
c/o Beckloff Associates, Inc.
7400 West 110th Street, Suite 300
Overland Park, KS 66210

ATTENTION: Wayne Vallee, RPh, RAC
Director, Managing Consultant
U.S. Agent for Silvergate Pharmaceuticals, Inc.

Dear Mr. Vallee:

Please refer to your New Drug Application (NDA) dated August 9, 2012, received August 10, 2012, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Enalapril Maleate Powder for Oral Solution, 1 mg/mL.

We also refer to your correspondence, dated and received March 13, 2013, requesting review of your proposed proprietary name, Epaned. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, Epaned, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you. If **any** of the proposed product characteristics as stated in your March 13, 2013 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Cheryle Milburn, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2084. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Michael Monteleone, at (301) 796-1952.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
06/07/2013

Duggan, Leora

From: Duggan, Leora
Sent: Friday, April 12, 2013 10:43 AM
To: 'WVallee@beckloff.com'
Cc: McKnight, Rebecca
Subject: RE: NDA 204308 Contact e-mail

Dear Dr. Vallee,

In your March 18th amendment you proposed the following changes to the preservative specifications: methylparaben from [REDACTED] (b) (4), propylparaben from [REDACTED] (b) (4) and potassium sorbate from [REDACTED] (b) (4). Please provide justification for the proposed specification of Methylparaben, Propylparaben and Potassium sorbate (e.g., preservative effectiveness at the proposed levels). Please respond via email to me and as a formal amendment to the application by COB Friday, 4/19/2013.

Best Regards,

Leora Duggan, MBA, PMP
Regulatory Project Manager
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
CDER, FDA
Phone (240) 402 – 3777
Fax: (301) 796 – 9749

From: Vallee, Wayne [<mailto:WVallee@beckloff.com>]
Sent: Friday, April 12, 2013 10:11 AM
To: Duggan, Leora
Subject: NDA 204308 Contact e-mail

Hi Leora,

Sorry you had to contact me to obtain my e-mail. It's provided below.

Best regards,

Wayne

Wayne F. Vallee, R.Ph., RAC
Director, Managing Consultant

Scientific and Regulatory Consulting (Beckloff Associates)

Cardinal Health Specialty Solutions.

Commerce Plaza II, Suite 300

7400 West 110th St.,

Overland Park, KS 66210

913.661.3813 (direct)

913.451.3846 (facsimile)

e-mail: wvallee@beckloff.com

Beckloff Associates, Inc. web-site: www.beckloff.com

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/s/

LEORA F DUGGAN
05/10/2013



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 204308

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Silvergate Pharmaceuticals, Inc.
c/o Beckloff Associates, Inc.
7400 West 110th Street Suite 300
Overland Park, KS 66210

ATTENTION: Wayne Vallee, RPh, RAC
Director, Managing Consultant

Dear Mr. Vallee;

Please refer to your New Drug Application (NDA) dated August 9, 2012, received August 10, 2012, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Enalapril Maleate Powder for Oral Solution, 1 mg/mL.

We also refer to your correspondence, dated and received January 15, 2013, requesting review of your proposed proprietary name, (b) (4). We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:



We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”).

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Cheryle Milburn, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2084. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Michael Monteleone, at (301) 796-1952.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
03/01/2013



NDA 204308

INFORMATION REQUEST

Silvergate Pharmaceuticals, Inc.
c/o Beckloff Associates, Inc., a Cardinal Health Company
Attention: Wayne F. Vallee, R.Ph., RAC
7400 West 110th Street, Suite 300
Overland Park, KS 66210

Dear Mr. Vallee:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Enalapril Maleate, Powder for Oral Solution, 1mg/mL.

We are reviewing the Quality 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. You indicate that releasing the drug substance will be based on review of [REDACTED] (b) (4) and “an identification test”. We request that you commit to release testing the drug substance for identification by HPLC and IR as per the USP monograph.
2. The UV method used is not an acceptable method to evaluate the content uniformity in the drug product based on your results showing interference from the impurities. Moreover, we also notice that the studies were done by spiking impurities at levels much lower than the specification. Therefore, we recommend that you commit to testing the content uniformity in future batches of the drug product by HPLC

If you have any questions, contact Teshara G. Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

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

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/s/

RAMESH K SOOD
02/08/2013



NDA 204308

INFORMATION REQUEST

Silvergate Pharmaceuticals, Inc.
c/o Beckloff Associates, Inc., a Cardinal Health Company
Attention: Wayne F. Vallee, R.Ph., RAC
7400 West 110th Street, Suite 300
Overland Park, KS 66210

Dear Mr. Vallee:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Enalapril Maleate, Powder for Oral Solution, 1mg/mL.

We are reviewing the Quality 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 the full specification that you will use to release drug substance batches.
2. Provide tests and acceptance criteria used to accept Ora-Sweet[®] SF from the manufacturer.
3. Provide details of process parameters for the blending operation [REDACTED] (b)(4) and the data to support the proposed process parameters.
4. Content uniformity for the drug product is accomplished by UV; however, it is not clear if the impurities contribute to the assay at the prescribed wavelength. Please clarify
5. The known impurities in the drug substance and drug product should be reported in weight percent and not area percent.
6. The proposed acceptance criterion for [REDACTED] (b)(4) in the drug product specification is "calculate results". This is not acceptable. Propose acceptance criteria that are based on data generated from batches of the drug product manufactured by the proposed commercial process and on the available stability data.
7. As per ICH Q3B(R), the proposed acceptance criterion for the individual unidentified related substance in the drug product is above the identification threshold and therefore not acceptable. Revise the acceptance criterion for the individual unidentified related substance in the drug product to NMT [REDACTED] (b)(4)%.
8. The acceptance criterion for the reconstitution time in the drug product specification is overly broad. Revise this specification to be consistent with the reconstitution instruction on the label.
9. Evaluate the limit for water content in the drug product and propose a limit based on your available data.
10. The assay data for the reconstituted drug product demonstrates a decreasing trend over time. It is not clear if product that is reconstituted from Powder for Oral Solution with an

assay closer to (b)(4)% will remain within the specification for the proposed in-use shelf life. Propose an assay release specification for the drug product that will accommodate a loss of (b)(4)% in the reconstituted solution.

11. Provide updated stability data for the Powder for Oral Solution.
12. Provide updated in-use stability data for the aged drug (i.e. stored at least 12 months).
13. Revise the stability protocol to include in-use stability testing at the last timepoint.
14. Update the post-approval stability commitment to include storage under accelerated conditions for the first three commercial batches as per ICH Q1A (R2).
15. Ora-Sweet® SF will have an expiry assigned by the manufacture. The Powder for Oral Solution will have an expiry assigned based on the available stability data. Please clearly delineate how the differences in these expiration dates will be addressed.
16. The molecular weight for Enalapril Maleate listed in the description section of the package insert is (b)(4). The molecular weight for Enalapril Maleate as indicated in the USP is 492.52. Update the package insert to be reflective and consistent with the information in the USP.
17. Revise the storage statement and the “How Supplied Section” to include a statement that is specific for the powder and a statement that is specific for the oral solution (b)(4) Do not freeze.” (b)(4)
18. The following statement in the How Supplied section of the package insert is misleading and should be changed or deleted: (b)(4)
19. Update the Description section of the package insert to include the components of the diluent, Ora-Sweet® SF.
20. The proposed change in the comparability protocol is not acceptable. In addition to the photostability data, you should commit to full testing of the Powder for Oral Solution and for the reconstituted drug product. At the time of submission, you should include a minimum of 3 months of accelerated data for the Powder for Oral Solution and 12 weeks for reconstituted drug product stored in the new container closure system for 3 batches manufactured with the proposed container/closure system together with the appropriate DMF references and corresponding letters of authorization. This information should be submitted to the agency in the form of a CBE-30 supplement.
21. “Report Results” is not an acceptable acceptance criterion for the preservative content in the reconstituted drug product. Propose acceptance criteria for methyparaben, propylparaben and potassium sorbate based on the available data.

If you have any questions, contact Teshara G. Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of New Drug Quality Assessment I

Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

KASTURI SRINIVASACHAR
12/03/2012

**DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS
FOOD AND DRUG ADMINISTRATION**

WHITE OAK COMPLEX
10903 NEW HAMPSHIRE AVE
BLDG. 22
SILVER SPRING, MD 20993



US Mail 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

This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to:

FDA/CDER/DCaRP 5901-B Ammendale Rd. Beltsville, MD 20705-1266

Transmitted via Email:

[Redacted] (b) (4)

Attention:

Company Name:

EnalaPed, LLC [Redacted] (b) (4)

Phone:

[Redacted] (b) (4)

Subject:

Meeting Minutes

Date:

October 07, 2010

Pages including this sheet:

8

From:

Mike Monteleone

Phone:

301.796.1952

Fax:

301.796.9841

PIND Meeting Minutes

Application: PIND 109473
Sponsor: Enalaped, LLC
Drug: enalapril
Type of Meeting: Pre-IND
Classification: B

Date of Meeting: October 1, 2010

List of FDA Meeting Participants:

Norman Stockbridge, MD, PhD	Director, Division of Cardio-Renal Products
Thomas Marciniak, MD	Clinical Team Leader
Khin U, MD	Clinical Reviewer
Divya Menon-Andersen, PhD	Clinical Pharmacology
Henry Startzman, MD	Office of Orphan Products Development
Linda Ulrich, MD	Office of Orphan Products Development
Denise Pica-Branco, PhD	Pediatric and Maternal Health Team
Ed Fromm, RPh, RAC	Chief, Project Management
Russell Fortney	Regulatory Project Manager
Michael Monteleone, MS	Regulatory Project Manager

List of Sponsor Meeting Participants:

(b) (4)



Background

The Sponsor, EnalaPed, LLC, is seeking guidance on the development of a formulation of (b) (4) % enalapril maleate powder for oral solution for treatment of pediatric hypertension. The sponsor seeks agreement with the agency regarding their development plan leading up to the submission of a 505(b)(2) NDA referencing Vasotec tablets (NDA 018998 held by Biovail Labs, International). The sponsor is also seeking guidance regarding the possibility of an orphan drug designation. The Division provided the sponsor with preliminary responses on September 23, 2010, and met with the sponsor via TCON on October 1, 2010, the minutes of that meeting follow.

The following questions were addressed:

Question 1:

The specifications for related substances in the drug substance are based on ICH limits with regard to dose of enalapril maleate (5 mg per day [max] in pediatric patients). Details of the drug substance manufacturing and the controls associated are provided in Section 10.1.1.4 of this meeting information package. The proposed NDA specification will comply with ICH Q3A.

Does the Agency agree that the current drug substance specification is appropriate for the NDA?

FDA preliminary response: The test attributes are appropriate, however, the suitability of the proposed acceptance criteria will be determined during NDA review. You should follow ICH Q3A thresholds for reporting, identification and qualification of impurities.

Discussion during the meeting: None

Question 2:

The specifications for related substances in the drug product are based on ICH limits with regard to dose of enalapril maleate (5 mg per day [max] in pediatric patients). Details of the drug product manufacturing and the controls associated are provided in Section 10.1.2.6 of this meeting information package. The proposed NDA specification will comply with ICH Q3B.

Does the Agency agree that the current drug product specification is appropriate for the NDA?

FDA preliminary response: No. Identification by HPLC retention time alone is not considered specific – see ICH Q6A. Propose an additional test or combine the HPLC test with (b) (4) (b) (4) The Content Uniformity test in accordance with USP <905>, appearance of the reconstituted oral liquid and reconstitution time should be included in the specification. You should follow ICH Q3B thresholds for reporting, identification and qualification of degradation products. No comments are provided for the proposed acceptance criteria, since this is based on review of your data.

Discussion during the meeting: None

Question 3:

The current plan is to submit the NDA with 3 months accelerated and room-temperature stability data on three registration batches, supplementing the stability data during the review process.

Does the Agency agree that this plan is acceptable?

FDA preliminary response: You should have 6 months of accelerated and 12 months of room temperature data at the mid-point of the review cycle, i.e. 5 months for a standard review application. The “microbial limit” tests should be performed on the stability lots of the drug product and on the reconstituted solution since it not known if the preservatives in Ora Sweet SF will be effective for this formulation over the intended duration of use. For stability testing of the reconstituted solution, you are expected to propose acceptance criteria for assay, degradation products and pH and perform the testing on the primary stability batches at initial and final time points as recommended in ICH Q1A (R2)

Discussion during the meeting: None

Question 4:

EnalaPed plans to make reference to the nonclinical section of the Vasotec label (the reference listed drug) to fulfill the nonclinical requirements for the 505(b)(2) NDA. In addition, a literature search will be conducted to identify new pediatric information. Any significant findings will be included in the NDA.

Please confirm that the nonclinical plan is acceptable and will meet the nonclinical requirements of the NDA.

FDA preliminary response: Please refer to the response to Q8 for the answer to this question.

Discussion during the meeting: None

Question 5:

EnalaPed plans to conduct a three-way study in normal, healthy adult males and females comparing the bioavailability of a 20 mg dose of the 1 mg/mL enalapril solution to a 20 mg Vasotec tablet under fasted conditions and a 20 mg dose of the 1 mg/mL enalapril solution under fed conditions. The primary end points of the study are to demonstrate comparable bioavailability, not necessarily bioequivalence, between the formulations and to determine if there is a food effect for the 1 mg/mL enalapril solution.

Please confirm this type of study should provide suitable bioavailability information for review for approval and that no additional studies would be required if the bioavailability results are comparable.

FDA preliminary response: As proposed in the synopsis, the study design in healthy adult male and female subjects appears to be adequate to assess bioavailability. Please note that

demonstrating bioequivalence to Vasotec would be ideal. If the pharmacokinetic time course of the pediatric formulation differs significantly from that of Vasotec in the peak to trough (inter-dosing interval) ratio or if the C_{min} of your product is less than that of Vasotec, then you will have to establish effectiveness similar to Vasotec.

Discussion during the meeting: None

Question 6:

A literature search will be conducted to identify new clinical pediatric information. Any significant findings will be included in the NDA.

Please confirm that the clinical plan is acceptable and will meet the clinical requirements of the NDA.

FDA preliminary response: Please refer to the answer to Q8 for advice pertaining to reliance on literature.

Discussion during the meeting: None

Question 7:

Because the planned study will not exceed the maximum single or total daily dose specified in the approved Vasotec labeling, the planned bioavailability study would not meet the requirements for an IND under 21 CFR 320.31—Applicability of requirements regarding an “Investigational New Drug Application”.

Please confirm that an Investigational New Drug application would not be needed to conduct the proposed bioavailability study.

FDA preliminary response: While the planned bioavailability study will not exceed the maximum single or total daily dose specified in the approved Vasotec labeling, for this planned bioavailability study be conducted without an IND, it must satisfy the conditions described in 21 CFR 320.31 (d) (1) and (2), and must be conducted in compliance with the requirements of 21 CFR 50 and 21 CFR 56.

Discussion during the meeting: None

Question 8:

The application is planned as a 505(b)(2) NDA, referencing Vasotec 20 mg tablets, the reference listed drug.

Please confirm the acceptability of the proposed application as a 505(b)(2) NDA.

FDA preliminary response: We agree. Consult the Agency’s regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry “Applications Covered by Section 505(b)(2)” available at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/01p-0323-pdn0001-voll.pdf>)).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that the regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies. Please note that if the published literature relied upon to support approval describe a specific listed drug(s), you should identify that specific listed drug(s), that is described in the literature, in accordance with the Agency's regulations at 21 CFR 314.54, if you have not already identified that listed drug as one on which you intend to rely on the Agency's finding of safety and/or effectiveness. As noted above, the regulatory requirements for 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

Discussion during the meeting: None

Question 9:

The proposed draft labeling will be almost identical to the approved labeling for Vasotec tablets. Differences will be the inclusion of the bioavailability study results, deletion of directions for the preparation of a suspension using tablets, and revisions to the "How Supplied" section and manufacturing and distribution contact information.

Please confirm that the proposed draft labeling will be acceptable for review in the 505(b)(2) application.

FDA preliminary response: The labeling approach appears reasonable.

Discussion during the meeting: None

Question 10:

Information will be provided regarding the prevalence of pediatric hypertension. However, the potential patient population for enalapril solution will be a subset of pediatric patients with hypertension because enalapril is only one of many drugs used for treatment. Of those pediatric patients prescribed enalapril, those 10–14 years of age and under will be candidates for the enalapril solution because older children usually prefer tablets. It is, therefore, believed that the potential pediatric population for enalapril solution is significantly less than the 200,000 patients required for designation as an orphan drug. Information will be provided to support this position in the briefing document. A formal Orphan Drug Designation request will be made.

Does the Agency agree that enalapril solution will only be used in a subset of pediatric hypertension patients, which will be documented to be below 200,000, and that upon review of the Orphan Drug Designation request enalapril solution could be designated as an Orphan Drug?

FDA preliminary response: The Office of Orphan Products Development (OOPD) designates products for the treatment, diagnosis, or prevention of a rare disease or condition. OOPD recognizes the pediatric population (ages 16 years and younger) as a medically unique population for purposes of designation. In this case, it appears that the disease or condition being treated by enalapril is Pediatric Hypertension.

For purposes of orphan product designation, the prevalence of Pediatric Hypertension will need to be established as being less than 200,000 in the United States. If the prevalence of pediatric hypertension exceeds 200,000, in order to qualify as a medically plausible subset, there must be some intrinsic characteristic of the drug that precludes its use in patients not in the subset. User preference is not considered a basis for establishing a medically plausible subset.

Since enalapril (the active moiety) is already approved for pediatric hypertension, you will need to present a plausible hypothesis that your enalapril solution is an improved formulation which is clinically superior to the approved tablets in order to be eligible for orphan drug designation (21 CFR 316.20(a)). This will need to be included in a formal request for orphan drug designation. For additional information, please refer to the Office of Orphan Product Development website, www.fda.gov/orphan.

Please note that orphan designation for the product must be obtained **prior** to your submission of the NDA in order to qualify for a waiver of the user fee for the application.

Discussion during the meeting: The sponsor provided a background and rationale for why their proposed formulation of enalapril is clinically superior. The sponsor outlined issues with respect to pill splitting and subsequent accuracy in dosing, compliance, the need for refrigeration in the currently available therapy, as well as recent studies by Dr. Dan Benjamin raising efficacy concerns with the use of pill splitting strategies vs. liquid formulations. Mr. Fromm asked how long the sponsor's formulation would be stable once reconstituted at the pharmacy. The sponsor responded they expect stability to be about eight weeks.

The sponsor also provided a rationale for how they intend to define the target population for orphan designation purposes. The sponsor outlined the difficulties in assigning a population number to 'hypertension', including differences in definition, documentation and classification.

The sponsor described their plan to stratify incidence by age group and referenced recent studies by the National Institutes for Child Health and Development (NICHD). The sponsor outlined that their research has indicated that the number of children <17 diagnosed with primary hypertension is below 200,000. From that population, those taking a liquid formulation are generally under the age of 11, further depressing their intended population.

There was some discussion over how best to define the pediatric hypertension population in the absence of outcome data – most classification schemes are arbitrary at best.

Dr. Stockbridge asked if there were any thoughts on how best to draw a line around the intended population. Dr. Startzman commented that the sponsor's rationale seems to make sense, but that they should formally submit their proposal to the Office of Orphan Products for review.

There was clarification to the Division's preliminary comment on orphan designation. The timing and sequence of submissions is critical; a request for designation must be received prior to the marketing application, and, if not yet granted, a fee must be paid upon submission. However, a refund can be requested within 180 days of submission, and if/when orphan designation is granted the fee will be refunded. For information on user fees you are advised to contact Mike Jones in the FDA, Office of Regulatory Policy, 301-796-3602 (michael.jones@fda.hhs.gov).

Signature, Meeting Chair: *{See appended electronic signature page}*
Norman Stockbridge, M.D., Ph.D.

Reviewed:

MMonteleone	01 OCT 2010 (Drafted)
RFortney	01 OCT 2010
LUlrich	04 OCT 2010
HStartzman	05 OCT 2010
EFromm	05 OCT 2010
KU	05 OCT 2010
TMarciniak	05 OCT 2010
NStockbridge	07 OCT 2010
MMonteleone	07 OCT 2010 (Finalized)

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/s/

NORMAN L STOCKBRIDGE
10/07/2010



NDA 204308

FILING COMMUNICATION

Silvergate Pharma
Attention: Frank Segrave
Chief Executive Officer
5371 Gordon Way
Dublin, OH 43017

Dear Mr. Segrave:

We have received your New Drug Application (NDA) submitted August 10, 2012 pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for (b)(4), (enalapril maleate) powder for oral solution, 1mg/mL.

We also refer to your amendments dated August 13 and September 13, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is June 10, 2013.

We acknowledge your request for a Priority review based on the following:

- ensured standardized amount of enalapril in a standardized volume and ease of constituting the oral solution, and
- ease of patient use because the (b)(4) oral solution can be kept without refrigeration, and does not require shaking the bottle before consumption.

However, we have determined a Priority review is not appropriate because the above properties of this drug product do not fulfill the criteria for Priority review, which require that the drug product, if approved, has the potential to provide, in the treatment, prevention, or diagnosis of a disease, one of the following:

- (1) safe and effective therapy where no satisfactory alternative therapy exists (unmet medical need); or
- (2) a significant improvement compared to marketed products (approved, if approval is required), including nondrug products or therapies. Significant improvement is illustrated by the following examples:
 - (a) evidence of increased effectiveness in treatment, prevention, or diagnosis of disease;
 - (b) elimination or substantial reduction of a treatment-limiting drug reaction;
 - (c) documented enhancement of patient compliance; or

(d) evidence of safety and effectiveness in a new subpopulation.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by May 13, 2013.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment: *Headers should be removed from Prescribing Information*

2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Comment: *Highlights is over one-half page.*

3. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment: *Capitalize “Full Prescribing Information”*

4. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment: *Statement needs to be included in Clinical Trials Experience subsection of Adverse Reactions.*

We request that you resubmit labeling that addresses these issues by 10/23/2012. The resubmitted labeling will be used for further labeling discussions.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We note that you have not addressed how you plan to fulfill this requirement for pediatric patients 12 years of age and older. Within 30 days of the date of this letter, please submit a partial waiver request for the pediatric group not covered or revise your plan to cover the full pediatric age range. A description of how you would use information from patients above and below this age range to interpolate for children 12-18 years of age should suffice. All waiver requests must include supporting information and documentation.

If you have any questions, please call Michael Monteleone, Regulatory Project Manager, at (301) 796-1952.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Cc: Beckloff Associates, Inc
Attention: Wayne Vallee, RPh, RAC
US Agent for Silvergate Pharma
Director, Managing Consultant
A Cardinal Health Company
7400 West 110th Street, Suite 300
Overland Park, KS 66210

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/s/

NORMAN L STOCKBRIDGE
10/02/2012



NDA 204308

NDA ACKNOWLEDGMENT

Silvergate Pharma
Attention: Frank Segrave
Chief Executive Officer
5371 Gordon Way
Dublin, OH 43017

Dear Mr. Segrave:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: (b) (4) (enalapril maleate)
Powder for oral solution, 1 mg/mL (after reconstitution)

Date of Application: August 10, 2012

Date of Receipt: August 10, 2012

Our Reference Number: NDA 204308

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 October 9, 2012, 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/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. 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 conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should 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/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please call Michael Monteleone, Regulatory Project Manager, at (301) 796-1952.

Sincerely,

{See appended electronic signature page}

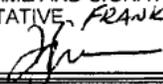
Edward Fromm, RPh, RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Cc: Beckloff Associates, Inc
Attention: Wayne Vallee, RPh, RAC
US Agent for Silvergate Pharma
Director, Managing Consultant
A Cardinal Health Company
7400 West 110th Street, Suite 300
Overland Park, KS 66210

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

/s/

EDWARD J FROMM
08/29/2012

Form Approved: OMB No. 0910 - 0297 Expiration Date: January 31, 2013. See instructions for OMB Statement, below.					
DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	PRESCRIPTION DRUG USER FEE COVERSHEET				
A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on FDA's website: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm					
1. APPLICANT'S NAME AND ADDRESS SILVERGATE PHARMACEUTICALS INC Wayne Vallee 5371 Gordon Way Dublin OH 43017 US	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 204-308				
2. NAME AND TELEPHONE NUMBER OF REPRESENTATIVE 913-661-3813	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: 018998				
3. PRODUCT NAME (b) (4) Powder for Oral Solution (Enalapril Maleate, USP)	6. USER FEE I.D. NUMBER PD3012512				
7. ARE YOU REDEEMING A PRIORITY REVIEW VOUCHER FOR THE TREATMENT OF TROPICAL DISEASES? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO PRIORITY REVIEW VOUCHER NUMBER:					
8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION. <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY					
9. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO If a waiver has been granted, include a copy of the official FDA notification with your submission.					
OMB Statement: Public reporting burden for this collection of information is estimated to average 30 minutes 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: <table style="width:100%; border: none;"> <tr> <td style="width: 33%; vertical-align: top;"> Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research Office of Information Management (HFA-710) 1350 Piccard Drive, 4th Floor Rockville, MD 20850 </td> <td style="width: 33%; vertical-align: top;"> Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research Office of Information Management (HFA-710) 1350 Piccard Drive, 4th Floor Rockville, MD 20850 </td> <td style="width: 33%; vertical-align: top;"> 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. </td> </tr> </table>			Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research Office of Information Management (HFA-710) 1350 Piccard Drive, 4th Floor Rockville, MD 20850	Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research Office of Information Management (HFA-710) 1350 Piccard Drive, 4th Floor Rockville, MD 20850	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.
Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research Office of Information Management (HFA-710) 1350 Piccard Drive, 4th Floor Rockville, MD 20850	Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research Office of Information Management (HFA-710) 1350 Piccard Drive, 4th Floor Rockville, MD 20850	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.			
PRINTED NAME AND SIGNATURE OF AUTHORIZED REPRESENTATIVE, FRANK SEGRAVE 	TITLE CEO	DATE 7/31/2012			
9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION \$920,750.00					
Form FDA 3397 (01/10)					