

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203826Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 203826

SUPPL #

HFD # 110

Trade Name None

Generic Name Phenylephrine HCl Injection

Applicant Name West-Ward Pharmaceutical Corp.

Approval Date, If Known 12-20-12

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) This NDA is based solely on the published literature.

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.

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?

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

YES NO

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

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

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

YES NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

Discontinued NDAs

NDA 8-306 for Phenergen VC with Codeine syrup (promethazine, phenylephrine and codeine combo

cough/cold syrup)

NDA 13-296 for Duo-Medihaler (isoproterenol/phenylephrine combo inhaler)

NDA 8604 for Phenergan VC syrup (promethazine/phenylephrine combo cough/cold syrup)

NDA 7953 for Prefrin-A ophth drops (phenylephrine/pyrilamine combo eye drops)

Marketed, OTC product

NDA 22565 for Advil Congestion Relief (ibuprofen and phenylephrine combo tablet)

2. Combination product.

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

YES NO

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new

clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

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

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

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

b) For each investigation identified as "essential to the approval", does the investigation

duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

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

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

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

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

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

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

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/

QUYNH M NGUYEN
12/20/2012

NORMAN L STOCKBRIDGE
12/20/2012

**DEBARMENT CERTIFICATION STATEMENT MADE PURSUANT TO THE
GENERIC DRUG ENFORCEMENT ACT OF 1992 (GDEA)**



On behalf of West-Ward Pharmaceutical Corp., the applicant, I hereby certifies, pursuant to Section 2(k) of the Generic Drug Enforcement Act of 1992 (GDEA), 21 U.S.C. § 335a(k), that drug product applicant has not used, is not using and will not, in the future, use in any capacity the services of any person who has been debarred pursuant to Section 2(a) and/or Section 2(b) of the Generic Drug Enforcement Act of 1992, 21 U.S.C. §§ 335a(a) and/or (b), in connection with this application.

Applicant further certifies that there have been no convictions of applicant for any of the types of crimes set forth in Section 2(a) and Section 2(b) of the Generic Drug Enforcement Act of 1992, 21 U.S.C. §§ 335a(a) and (b), within the five years prior to the date of this Certification, nor has any person affiliated with applicant, who is responsible in whole or in part for the development or submission of this application, been convicted of any crime of the types listed in Section 2(a) and Section (b) of the Generic Drug Enforcement Act of 1992, 21 U.S.C. §§ 335a(a) and (b), within the five years prior to the date of this Certification.

J. Barton Kalis

12/13/2012

J. Barton Kalis

Date

Director, Regulatory Affairs

West-Ward Pharmaceutical Corp.

West-Ward Pharmaceutical Corp.

2 Esterbrook Lane

Cherry Hill, NJ 08003

tel: 856-424-3700

fax: 856-424-8747

www.west-ward.com

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

TO: Sara Stradley, Chief, Project Management Staff
Division of Anesthesia, Analgesia, and Addiction Products

FROM: Edward Fromm, Chief, Project Management Staff
Division of Cardiovascular and Renal Products

SUBJECT: Application Transfer

APPLICATION: NDA 203826
Phenylephrine Injection

In the line with the OND policy of placing administrative responsibility of applications within the Division that reviews the principal clinical research activity of the drug, we are transferring the abovementioned application for your acceptance. If you do not concur, please include the reason as a signature comment. If you have any questions, please call me at 301-796-1072.

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
01/02/2013

SARA E STRADLEY
01/02/2013

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 203826 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Established/Proper Name: Phenylephrine HCl Injection Dosage Form: 10 mg/mL		Applicant: West-Ward Pharmaceutical Corp. Agent for Applicant (if applicable):
RPM: Quynh Nguyen, PharmD, RAC		Division: Cardiovascular and Renal Products
<p><u>NDAs 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>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input checked="" type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</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>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p> <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check: 12-20-12</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>December 20, 2012</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 on 11-9-12	

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>	<input type="checkbox"/> Received
<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 type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies</p> <p>BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies</p> <p>REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required</p> <p>Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request <input type="checkbox"/></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>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<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 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<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

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 (<u>No patent listed</u>) <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 checked="" type="checkbox"/> Verified (<u>No patent listed</u>) 21 CFR 314.50(i)(1) <input 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>	<input type="checkbox"/> Yes <input type="checkbox"/> No
---	--

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	12-20-12
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) AP 12-20-12 CR 11-9-12
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. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	Included
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	Included

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. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • 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 	10-23-12
<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>) • <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.</i> 	N/A
<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 10-12-12; 10-25-12 <input type="checkbox"/> DMPP/PLT (DRISK) <input checked="" type="checkbox"/> ODPD (DDMAC) 10-11-12 <input checked="" type="checkbox"/> SEALD 11-7-12 <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>) 	4-18-12
<ul style="list-style-type: none"> ❖ 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>) 	<input type="checkbox"/> Not a (b)(2) 10-15-12 <input type="checkbox"/> Not a (b)(2) 12-20-12
<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 <u>10-31-12 and 12-19-12</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ 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

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

❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>)	Included
❖ Internal memoranda, telecons, etc.	
❖ 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 type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 10-10-10
• 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>)	
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	9-13-12
• 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 12-20-12, 11-9-12
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 9-25-12
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None (2)
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	
• Clinical review(s) (<i>indicate date for each review</i>)	8-11-12; 12-10-12
• 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 checked="" type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Literature-based NDA; see 8-12-12 Clinical Review and 12-20-12 RPM Overview.
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None 12-10-12
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ 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
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested

⁶ Filing reviews should be filed with the discipline reviews.

Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input checked="" 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 8-10-12
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 8-15-12
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI 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 5-30-12
❖ 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
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI 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 type="checkbox"/> None 1-12-12
• Product quality review(s) including ONDQA biopharmaceutics reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 3-8-12; 9-5-12; 10-17-12; 10-31-12
❖ Microbiology Reviews <input checked="" 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 type="checkbox"/> Not needed 5-18-12
❖ 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</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	9-5-12
<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 checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷</i>)	Date completed: 10-30-12 <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</i>) (<i>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 type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" 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.

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

/s/

QUYNH M NGUYEN
12/20/2012



NDA 203826

**ACKNOWLEDGE --
CLASS 1 COMPLETE RESPONSE**

West-Ward Pharmaceutical Corp.
Attention: Mr. J. Barton Kalis
Director, Regulatory Affairs
2 Esterbrook Lane
Cherry Hill, NJ 08003

Dear Mr. Kalis:

We acknowledge receipt on November 29, 2012, of your November 28, 2012, resubmission of your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for for Phenylephrine Hydrochloride Injection, USP, 10 mg/mL.

We consider this a complete, class 1 response to our November 9, 2012 action letter. Therefore, the user fee goal date is January 29, 2013.

If you have any questions, please contact:

Quynh Nguyen, Pharm.D., RAC
Regulatory Health Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

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

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
12/17/2012



DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memo

NDA: 203826 phenylephrine hydrochloride to increase blood pressure in “acute hypotensive states”.

Sponsor: West-Ward Pharmaceuticals

Review date: 9 November 2012

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Distribution: NDA 203826

I previously (memo of 19 October) concluded that this application was approvable. An initial consensus was reached to waive requirements under PREA, and agreement with PERC was obtained. Subsequently, DAAAP altered its opinion regarding the need for data in children age 12 and up, and since the responsibility for this application devolves to them upon approval, it seemed appropriate to honor their request for a PREA study. Time did not permit negotiation of the details or timing with the sponsor, so a Complete Response letter will now be issued, naming the PMR as the sole barrier to approval.

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

/s/

NORMAN L STOCKBRIDGE
11/09/2012

**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 to: jkalis@west-ward.com

Attention: Mr. J. Barton Kalis

Subject: **Minutes of Guidance Telecons for
Phenylephrine HCl Injection PMC**

Date: November 9, 2012

Pages including this sheet: 6

From: **Quynh Nguyen, Pharm.D., RAC**
Phone: **301-796-0510**
Fax: **301-796-9838**
E-mail: **quynh.nguyen@fda.hhs.gov**

Please note that you are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

Type A Meeting via Teleconference with Sponsor

Application: NDA 203826
Sponsor: West-Ward Pharmaceutical Corp.
Drug: Phenylephrine HCl Injection
Type of Meeting: Guidance
Classification: A
Meeting Date: October 18, 2012
Confirmation Date: October 17, 2012
Meeting Chair: Scott Dallas, R.Ph.
Recorder: Quynh Nguyen, Pharm.D., RAC

List of Attendees:

Food and Drug Administration

Office of New Drugs, Division of Cardiovascular and Renal Products

Shari Targum, M.D.	Clinical Team Leader
Edward Fromm, RPh, RAC	Chief, Project Management Staff
Quynh Nguyen, PharmD, RAC	Regulatory Health Project Manager

Office of Clinical Pharmacology, Division of Clinical Pharmacology I

Sudharshan Hariharan, Ph.D.	Clinical Pharmacologist
-----------------------------	-------------------------

Office of Drug Safety, Division of Medication Error Prevention and Analysis

Scott Dallas, R.Ph.	Associate Director
Irene Chan, Pharm.D., BCPS	Team Leader

West-Ward Pharmaceutical Corp.

J. Barton Kalis	Director, Regulatory Affairs
Sandra Bobila	Manager, Regulatory Affairs

BACKGROUND

The Division of Cardiovascular and Renal Products requested this teleconference to discuss the following Postmarketing Commitment (PMC) request for the sponsor's proposed Phenylephrine HCl Injection product under pending NDA 203826:

The proposed package insert provides dosing for intravenous bolus ranging from (b) (4) mcg to 250 mcg. However, you have proposed a single concentration of 10 mg/mL. In order to achieve doses as small as (b) (4) mcg to 250 mcg, one or more dilutions would need to be performed by a pharmacist or technician, which introduces opportunity for calculation and compounding confusion that can lead to dosing errors. For this reason, we request that you develop an appropriate ready-to-use concentration and packaging configuration (i.e. 100 mcg/mL multiple dose vial) to administer the approved intravenous bolus doses. A ready-to-use concentration and packaging configuration will help mitigate the risks of calculation and compounding errors as well as unsafe sterile technique and injection practices.

A teleconference was held on October 18, 2012 to discuss the PMC request. A follow-up teleconference was subsequently held on November 1, 2012 to clarify the PMC request following receipt of the sponsor's PMC submission dated October 26, 2012.

DISCUSSION DURING TELECONFERENCE

During the October 18, 2012 teleconference, the sponsor discussed their concerns regarding the PMC request, specifically a change in concentration and the impact on current clinical practice. The sponsor noted that historically, the existing 10 mg/mL concentration has been used by clinicians and anesthesiologists successfully. In addition, the sponsor expressed concerns regarding the manufacturing of a new ready-to-use formulation, which would involve considerable research and development. Mr. Dallas acknowledged the sponsor's concerns, but stated that the sponsor should develop a concentration that the clinicians can readily use. He suggested that the sponsor perform a risk assessment to study potential issues with medication errors, ideal dosing, and best clinical practices. Mr. Dallas emphasized that the risk assessment should involve the expertise of anesthesiologists, other clinicians, as well as personnel who are familiar with conducting risk assessments. A risk assessment would help guide their development of a ready-to-use packaging configuration and concentration for administration of bolus doses. Per the Guidance, the sponsor should submit their proposal for the PMC with milestone dates for the Division's review.

The sponsor subsequently submitted their proposed PMC in a submission dated October 26, 2012. The Division provided the following response in an email dated October 31, 2012:

We acknowledge receipt of your correspondence dated October 26, 2012 concerning the Postmarketing Commitment for Phenylephrine Hydrochloride injection, USP. The Agency had originally forwarded a Postmarketing Commitment (PMC) request that read:

"The proposed package insert provides dosing for intravenous bolus ranging from (b) (4) mcg to 250 mcg. However, you have proposed a single concentration of 10 mg/mL. In order to achieve doses as small as (b) (4) mcg to 250 mcg, one or more dilutions would need to be performed by a pharmacist or technician, which introduces opportunity for calculation and compounding confusion that can lead to dosing errors. For this reason, we request that you develop an appropriate ready-to-use concentration and packaging configuration (i.e. 100 mcg/mL multiple dose vial) to administer the approved intravenous bolus doses. A ready-to-use concentration and packaging configuration will help mitigate the risks of calculation and compounding errors as well as unsafe sterile technique and injection practices."

On October 18, 2012, West-Ward Pharmaceutical Corp. and the Agency discussed the Postmarketing Commitment request via a teleconference. Based upon your revised proposal it appears that you have misinterpreted our intent for completing a risk assessment. The intent for completing a risk assessment is to help guide you to the ultimate goal, which is to design an appropriate ready-to use phenylephrine hydrochloride injection product for intravenous bolus administration. There are many attributes that must be researched when designing a product. Based upon the dosage a 100 mcg/mL appears to be an appropriate concentration. However, many other attributes need to be evaluated such as the exact total drug content (volume) and package configuration (vial, or prefilled syringe), and formulation (with or without preservative). As well as designing a product that promotes safe injection practices by practitioners and decreases the risk of medication errors. Thus, in the telecon we recommended that you complete a risk assessment to help guide your development to an appropriate ready to use product that can be safely used by practitioners to administer an appropriate intravenous bolus dose. However, if you believe another method(s) is equally effective to guide the design of an appropriate ready to use product for intravenous bolus administration, then it would be acceptable not to complete a formal risk assessment and instead use your preferred methodology.

We would like to outline the goal and milestones of the PMC:

PMC Goal:

Develop a ready to use phenylephrine hydrochloride injection product for intravenous bolus administration.

PMC Scheduled Milestones:

PMC Report Completion Date: 9 months from approval
(The report should include your methodology, research and conclusions used to design an appropriate ready to use phenylephrine hydrochloride injection product.)
Supplement Submission Date: ?
(A supplement should be submitted to request approval of your ready to use phenylephrine hydrochloride injection product)

A November 1, 2012 teleconference was subsequently held to clarify the above comments. The following participated in the teleconference:

Food and Drug Administration

Office of New Drugs, Division of Cardiovascular and Renal Products

Mary Ross Southworth, Pharm.D.	Deputy Director for Safety
Shari Targum, M.D.	Clinical Team Leader
Edward Fromm, RPh, RAC	Chief, Project Management Staff
Quynh Nguyen, PharmD, RAC	Regulatory Health Project Manager

Office of Drug Safety, Division of Medication Error Prevention and Analysis

Scott Dallas, R.Ph.	Associate Director
---------------------	--------------------

West-Ward Pharmaceutical Corp.

J. Barton Kalis	Director, Regulatory Affairs
-----------------	------------------------------

During the teleconference, the sponsor confirmed that they agree to conduct the PMC to develop a ready-to-use formulation. The sponsor also understood that the risk assessment could be used to guide them in the design of an appropriate ready-to-use product for intravenous bolus administration and that the risk assessment was not intended to be performed in lieu of developing a ready-to-use formulation. The sponsor described their risk assessment proposal as submitted in their October 26, 2012 submission and Mr. Dallas stated that the sponsor's proposed risk assessment was acceptable. Mr. Dallas also added that the sponsor could use another methodology besides a risk assessment as part of their research to develop an appropriate ready-to-use product.

Regarding the sponsor's proposed milestone dates, Mr. Dallas suggested that the sponsor propose shorter milestone dates. He stated, for example, that the sponsor's proposed final report submission date of October 31, 2014 was too long and that a date of nine months from approval seemed more reasonable. In addition, the sponsor should propose a milestone for the date that they intend to submit a supplement for the new ready-to-use formulation, which would be based on consultation with their product development experts. The sponsor agreed to submit an updated PMC submission with shorter milestone dates, including a supplement submission date. The PMC submission will also include a statement that they agree to conduct the PMC to develop a ready-to-use formulation.

Mr. Dallas added that with development of an appropriate ready-to-use formulation, the sponsor had a considerable opportunity to promote the safe use of the product by practitioners and mitigate the risk of medication errors, and the sponsor acknowledged this.

CONCLUSION

Based on the discussions, the sponsor confirmed that they agree to conduct the PMC to develop a ready-to-use formulation and they will submit an updated PMC submission with revised milestone dates for the Division's review.

Minutes preparation: Quynh Nguyen, Pharm.D., RAC

Concurrence, Chair: *{See appended electronic signature page}*
Scott Dallas, R.Ph.

Rd:

S Dallas	11-7-12
I Chan	11-5-12
MR Southworth	11-5-12
E Fromm	11-5-12

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

/s/

SCOTT M DALLAS
11/09/2012



NDA 203826

INFORMATION REQUEST

West-Ward Pharmaceutical Corp.
Attention: Sandra P. Bobila, Manager, Regulatory Affairs
2 Esterbrook Lane
Cherry Hill, NJ 08003-4099

Dear Ms. Bobila:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Phenylephrine Hydrochloride injection.

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

1. Revise the proposed drug substance regulatory specification to include USP <231> testing for heavy metals.
2. Per ICH Q2B, specificity is usually demonstrated using samples stored under relevant stress conditions instead of expired drug substance (ICH Q2B Section II B.2). Provide updated method validation results for specificity for the proposed regulatory assay, identification, and related substances HPLC method used for both the drug substance and the drug product. Identify any differences in sample preparation for the proposed regulatory assay, identification, and related substances HPLC method (Method TM D145) when testing the drug substance versus the drug product.
3. Provide the results for extractable and leachables characterization of the container closure system. Identify any functional tests conducted on the container closure system and provide a summary of the results.
4. Provide the impurity profiles of each of the samples studied as part of the diluent compatibility study, comparing the results observed at time zero and after 24 hours.
5. Provide the rationale for incorporating a (b) (4) into the manufacturing process.
6. Identify the manufacturing steps used to (b) (4) a batch. Identify the tests and criteria used to evaluate (b) (4) batch.
7. We recommend revising your proposed drug product regulatory specification to include all test attributes identified currently in your release specification and to use the proposed shelf-life acceptance criteria as the regulatory specification acceptance criteria for those tests with both a proposed release limit and a proposed shelf-life limit. Your acceptance criterion for individual,

unknown impurities should comply with ICH Q3B. You may use your former proposed release drug product regulatory specification for internal release of drug product as part of your in-house control.

8. USP <788> does not provide for tiered testing of sub-visible particulate matter but rather provides alternative methods for analysis based on the physiochemical properties of the drug product. Revise the proposed drug product regulatory specification to include one set of acceptance criterion based on the analytical method and the corresponding limits most appropriate for your drug product.
9. We recommend removing the verification sample test and acceptance criterion from the regulatory specification. An internal standard operating procedure or the batch record may be more appropriate locations for this information.
10. Update Section 3.2.P.3.5 of your submission to list all proposed regulatory drug product analytical procedures. Provide a description for each method or where appropriate, provide the compendial method reference.
11. Your approach for (b) (4) testing of the drug product based on the cumulative (b) (4) (b) (4) of the drug product components is acceptable. However, since this test is listed as a release test, report the results for this test instead of N/A.
12. We do not agree that a control for sodium metabisulfite content is not needed as part of the stability protocol. It is important to the overall quality of the drug product to ensure that the amount of sodium metabisulfite remaining in the drug product over its shelf-life is sufficient to provide the necessary (b) (4). Revise your stability protocol to include testing for sodium metabisulfite.
13. Information provided in Sections 2.3.P.7, 3.2.P.7.1, and 3.2.P.7.2 of the submission lists the flip-off cap as a (b) (4) flip-off. However, information provided in Sections 3.2.P.7.3, 3.2.P.7.5, and 3.2.P.7.7 of the submission lists the flip-off cap as a (b) (4) flip-off cap. Clarify which flip-off cap will be used for the to-be-mark (b) (4) ntify the material of construction for the shelf pack secondary packaging.
14. The stability conditions used for the drug product registration stability batches and proposed for the post-approval stability protocol do not comply with ICH Q1A(R2) in terms of the relative humidity proposed. The guidance recommends a relative humidity of 60% for long-term conditions and 75% for accelerated conditions. Revise the post-approval stability protocol to include testing under these relative humidities or provide justification for testing at ambient humidity for the registration drug product batches and post-approval.
15. Update your methods validation package to identify the samples to be submitted. Include the lot number, identity, package type and size, date of manufacture, special storage or handling instructions, and quantity of samples for each sample listed. Provide the regulatory specification and a description of all analytical procedures listed in the specification or include cross-references to the appropriate sections of your submission.
16. Revise your claim of categorical exclusion to include the language required by 21 CFR 25.15(a), that to the applicant's knowledge, no extraordinary circumstances exist (21 CFR 25.15(d)). Refer to our *Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications* for additional information.

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

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

/s/

RAMESH K SOOD
06/14/2012



NDA 203826

FILING COMMUNICATION

West-Ward Pharmaceutical Corp.
Attention: Mr. J. Barton Kalis
Director, Regulatory Affairs
2 Esterbrook Lane
Cherry Hill, NJ 08003

Dear Mr. Kalis:

Please refer to your New Drug Application (NDA) dated December 28, 2011, received January 12, 2012 (user fee receipt date), submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Phenylephrine Hydrochloride Injection, USP, 10 mg/mL.

We also refer to your amendment dated March 1, 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 November 12, 2012.

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 October 12, 2012.

During our filing review of your application, we identified the following potential review issue:

None of the published literature you submitted regarding use in pediatric patients come from prospective, randomized, controlled, blinded trials that we would normally require and therefore the information may not be adequate to meet the pediatric study requirements. See "**REQUIRED PEDIATRIC ASSESSMENTS**" below.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

MICROBIOLOGY

1. Please clarify whether there are circumstances in which you intend to (b) (4) the final drug product by (b) (4). If you do plan to (b) (4), please provide (b) (4) during this process, as well as a demonstration that the container closure system will maintain its integrity under these conditions.
2. The specifications for this product list endotoxin limits as NMT (b) (4) of drug product, and the maximum human dose of the drug product listed for the purposes of endotoxin limit calculations is (b) (4). However, your label indications for acute hypotension with septic shock and pediatric acute hypotension list doses of (b) (4). These doses would exceed the endotoxin limit for parenteral drugs of NMT (b) (4). We recommend that you decrease the endotoxin specification for the drug product to NMT (b) (4) so as to not exceed the limit of (b) (4) in the highest hourly dose.
3. Your application states that the production (b) (4) used to sterilize the final drug product (b) (4) undergo annual requalification with (b) (4) studies, however the most recent (b) (4) studies in your application are from 1997. Please provide your most recent (b) (4) studies for both (b) (4).

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

Format Comments:

1. Place the Highlights (HL) section in portrait, not landscape, orientation. HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
2. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g., end of each bullet). Include references in the HL for the Indications and Usage, Dosage and Administration, and Dosage Forms and Strengths sections and subsections.
3. A horizontal line must separate HL and Table of Contents (TOC) and a horizontal line must separate TOC from the FPI.
4. Use UPPER CASE lettering for the name of the drug product in the HL Limitation Statement.
5. Product title in HL must be bolded (b) (4)
6. Propose an initial U.S. Approval Date in HL.
7. In HL, delete the (b) (4) as it applies only to supplements.
8. In HL, since there is more than one contraindication, add a bullet for each contraindication.

9. White space must be present before each major heading in HL. Add white space before the ADVERSE REACTIONS heading.
10. In HL, list the most common adverse reactions on one line.
11. Patient Counseling Information Statement in HL must include the following bolded verbatim statement: “See 17 for PATIENT COUNSELING INFORMATION.”
12. Place the FULL PRESCRIBING INFORMATION: Contents* section in portrait, (b) (4)
13. All subsection headings in the FULL PRESCRIBING INFORMATION: Contents* section must be indented.
14. The preferred presentation for cross-references in the FPI is the section heading (b) (4) followed by the numerical identifier in italics, e.g., “[see *Warnings and Precautions (5.1)*].” Correct the presentation for cross-references in subsections (b) (4)
15. Remove the (b) (4) following the number in the section titles in the FPI, e.g., correct to “5 WARNINGS AND PRECAUTIONS” instead of (b) (4), in the section titles.
16. In the Clinical Studies section in the FPI, do not include (b) (4) only include two number identifiers (e.g., 14.2).

Additional Non-Format Comments:

1. Although hypotensive patients treated with phenylephrine may not understand instructions, information in the Patient Counseling Information section is required. We recommend that the family of patients treated with phenylephrine injection be counseled about most important safety risks with this drug.
2. Your proposed Warnings and Precautions section is not consistent with the 2011 *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products - Content and Format* Guidance. The titles of the Warnings and Precautions should reflect the adverse reaction; they should not state (b) (4).
Revise this section to be consistent with this guidance. For more information see this guidance at:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075096.pdf>
3. Your proposed Drug Interactions section is not consistent with the 2012 *Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations* Guidance because it does not contain clear practical instructions for preventing or managing the drug interactions. Revise this section to be consistent with this guidance. See this guidance at:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>
4. Your proposed Clinical Studies section is not consistent with the 2006 *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products - Content and Format* Guidance because many of the studies included are not adequate and well-controlled. Revise this section to

be consistent with this guidance. See this guidance at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075059.pdf>

5. Only references to an "authoritative scientific body, or on a standardized methodology, scale, or technique" should be included in Section 15. See 21 CFR 201.57(c)(16).

We request that you resubmit labeling that addresses these issues by April 26, 2012. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

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 note that you have submitted pediatric studies with this application, and you have not requested a partial waiver or deferral for any additional studies. Once the review of this application is complete, we will notify you whether you have fulfilled the pediatric study requirement for this application.

If you have any questions, please contact:

Quynh Nguyen, Pharm.D., RAC
Regulatory Health Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

NORMAN L STOCKBRIDGE
03/21/2012



NDA 203826

**NDA ACKNOWLEDGEMENT
USER FEES RECEIVED**

West-Ward Pharmaceutical Corp.
Attention: Mr. J. Barton Kalis
Director, Regulatory Affairs
2 Esterbrook Lane
Cherry Hill, NJ 08003

Dear Mr. Kalis:

Please refer to your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug and Cosmetic Act for Phenylephrine Hydrochloride Injection, USP, 10 mg/mL.

You were notified in our letter dated January 11, 2012 that your application was not accepted for filing due to non-payment of fees. This is to inform you that the Agency has received all required fees and your application has been accepted as of January 12, 2012.

Unless we notify you within 60 days of the above date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on March 12, 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 cited above should be included 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

If you have any questions, please contact:

Quynh Nguyen, Pharm.D., RAC
Regulatory Health Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

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

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
01/17/2012



NDA 203826

UNACCEPTABLE FOR FILING

West-Ward Pharmaceutical Corp.
Attention: Mr. J. Barton Kalis
Director, Regulatory Affairs
2 Esterbrook Lane
Cherry Hill, NJ 08003

Dear Mr. Kalis:

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

Name of Drug Product: Phenylephrine Hydrochloride Injection, USP, 10 mg/mL
Date of Application: December 28, 2011
Date of Receipt: December 28, 2011
Our Reference Number: NDA 203826

We have not received the appropriate user fee for this application. An application is considered incomplete and cannot be accepted for filing until all fees owed have been paid. Therefore, this application is not accepted for filing. We will not begin a review of this application's adequacy for filing until FDA has been notified that the appropriate fee has been paid. Payment should be submitted to the following address:

Food and Drug Administration
P.O. Box 979107
St. Louis, MO 63197-9000

Checks sent by courier should be addressed to:

U.S. Bank
Attention: Government Lockbox 979107
1005 Convention Plaza
St. Louis, MO 63101

When submitting payment for an application fee, include the User Fee I.D. Number, the Application number, and a copy of the user fee coversheet (Form 3397) with your application fee payment. When submitting payment for previously unpaid product and establishment fees, please include the Invoice Number(s) for the unpaid fees and the summary portion of the invoice(s) with

your payment. The FDA P.O. Box number (P.O. Box 979107) should be included on any check you submit.

The receipt date for this submission (which begins the review for filability) will be the date the review division is notified that payment has been received by the bank.

Please cite the NDA number listed above 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

If you wish to send payment by wire transfer, or if you have any other user fee questions, please call Bev Friedman or Mike Jones at 301-796-3602.

If you have any questions, please contact:

Quynh Nguyen, Pharm.D., RAC
Regulatory Health Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

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

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
01/11/2012