CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203826Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM

TO: NDA 203-826

FROM: Wendy I. Wilson-Lee, Review Chemist, ONDQA Branch I

THROUGH: Kasturi Srinivasachar, Ph.D., CMC Lead, ONDQA Branch I

Ramesh Sood, Ph.D., Branch Chief, ONDQA Branch I

SUBJECT: Outcome of Facilities Inspections

DATE: 10/31/2012

CC: Quynh Nguyen, HFD 110 RPM; Teshara Bouie, ONDQA PM; Shari Targum, M.D, HFD 110 Medical Officer

Facilities Inspections

OC provided an overall recommendation of acceptable for all facilities listed for phenylephrine hydrochloride injection on 30-OCT-2012 (see Attachment I – EES Summary Report).

Overall Recommendation

Based on the outcome of the facilities inspections, we recommend phenylephrine hydrochloride injection for approval, from a CMC perspective.

Wendy I. Wilson

Wendy I. Wilson-Lee, Ph.D.
Review Chemist
ONDQA Branch I

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

WENDY I WILSON-LEE
10/31/2012

RAMESH K SOOD
10/31/2012

NDA 203-826
Quality Review #2

Phenylephrine Hydrochloride Injection
10 mg/mL

West-Ward Pharmaceutical Corp.

Wendy I. Wilson-Lee, Ph. D.
Office of New Drug Quality Assessment
For
Division of Cardio-Renal Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA: 203-826

2. REVIEW: **02**

3. REVIEW DATE: 10-OCT-2012

4. REVIEWER: Wendy I. Wilson-Lee, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Quality Review #1	05-SEP-2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	16-OCT-2012
Amendment	28-SEP-2012

7. NAME & ADDRESS OF APPLICANT:

Name:	West-Ward Pharmaceutical Corp.
Address:	2 Esterbrook Lane Cherry Hill, NJ 08003
Representative:	J. Barton Kalis, Director Regulatory Affairs
Telephone:	856-489-2247

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Phenylephrine Hydrochloride
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 7
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Treatment of acute hypotensive states

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 10 mg/mL

13. ROUTE OF ADMINISTRATION: Intravenous

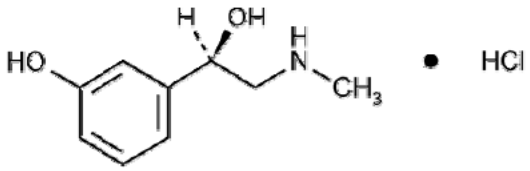
14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: (-)-*m*-Hydroxy-1-[(methylamino)methyl]benzyl alcohol hydrochloride
Mol. Formula: $C_9H_{13}NO_2 \cdot HCl$
Mol. Weight: 203.67



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF#	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	3	**Adequate**	24-DEC-2008	Reviewed for ND (b) (4)
(b) (4)	II	(b) (4)	(b) (4)	3	**Adequate**	20-AUG-2012	Reviewed for ANDA (b) (4)
(b) (4)	III	(b) (4)	(b) (4)	3	**Adequate**	24-FEB-2009	Reviewed for ANDA (b) (4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	109,977	Treatment of low blood pressure in shock and shock-like states and maintenance of blood pressure during spinal and anesthesia

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	-	-
EES	**Pending.**	**Pending.**	**Pending.**
Pharm/Tox	Approval. (b) (4)	30-MAY-2012	P. Gatti
Biopharm	No ONDQA Biopharm Review Needed.	08-MAR-2012	E. Chikale
LNC	N/A	-	-
Methods Validation	Method validation by FDA labs not needed.	05-SEP-2012	W. Wilson-Lee
DMEPA	Approval with PMC.	12-OCT-2012	I. Chan
EA	Categorical exclusion granted.	05-SEP-2012	W. Wilson-Lee
Microbiology	Approval.	18-MAY-2012	E. Pfeiler

Chemistry Review for NDA 203-826

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

We recommend approval of 10 mg/mL Phenylephrine Hydrochloride Injection packaged in the commercial package and stored as recommended, from a CMC perspective, pending labeling and final OC facilities recommendation.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no quality Phase IV commitments, agreements, risk management steps required.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Phenylephrine hydrochloride, USP is an odorless, white, (b) (4) crystalline powder that is very soluble in water, freely soluble in ethanol and not soluble in chloroform and ethyl ether. Phenylephrine hydrochloride is light sensitive (b) (4) supplies the sponsor with drug substance that complies with the current USP monograph for phenylephrine hydrochloride. West-Ward's regulatory drug substance specification controls appearance; identification (IR, HPLC, chloride test); melting range; specific rotation; loss on drying; residue on ignition; sulfate; limit of ketones; chloride content; assay (HPLC); related compounds (HPLC); chromatographic purity (TLC); residual solvents (GC); bacterial endotoxins; and bioburden. All drug substance analytical methods are appropriate and validated for their intended use. The drug substance supplier assigns a (b) (4) retest period to the drug substance. West-Ward internally assigns a 12 month expiry for phenylephrine hydrochloride upon release with the option for extension of the expiry by up to (b) (4) but not to exceed the supplier's retest date.

The Phenylephrine hydrochloride 10 mg/mL formulation contains sodium chloride, USP; sodium citrate dihydrate, USP; citric acid monohydrate, USP; sodium metabisulfite, USP; and water for injection, USP. If pH adjustment is needed, the formulation may also contain sodium hydroxide, NF or hydrochloric acid, NF. The drug product does (b) (4) (b) (4) duct is during that are (b) (4), packaged, and released for distribution. In-process controls monitor the critical process parameters final pH after (b) (4)

The regulatory drug product specification controls appearance; identification (TLC, HPLC); pH, volume in container, sodium metabisulfite content (titration); assay (HPLC); related compounds (HPLC); particulate matter; residual solvents; sterility; and bacterial endotoxins. All drug product analytical methods are appropriate and v (b) (4) eir intended use. The sponsor proposes one packaging configuration for market – a (b) (4) glass, (b) (4) vials with (b) (4) aluminum seal, (b) (4) gray liner, (b) (4) white flip-off closures. West-Ward proposes a 24 month drug product expiry when stored in the commercial container closure at 25ºC (77ºF); excursions permitted to

15-30ºC (59-86ºF) [USP controlled room temperature]. Based on the stability data provided in the submission and in accordance with ICH Q1E, we concur with the proposed drug product expiry and storage condition.

B. Description of How the Drug Product is Intended to be Used

Phenylephrine hydrochloride is an α-1 adrenergic receptor agonist. The proposed indication is as an agent to increase blood pressure in acute hypotensive states, namely endotoxin shock and perioperative hypotension following intravenous administration. Each vial provides a single dose. The proposed dosing regimen titrates to a normotensive state based on the level of hypotension.

Proposed Indication	Proposed Routes of Administration	Proposed Doses
Acute Perioperative Hypotension	I.V. bolus	50 µg – 250 µg
	Continuous I.V. infusion	0.5 µg/kg/min – 1.4 µg/kg/min
	I.V. bolus followed by continuous I.V. infusion	40 µg bolus followed by 0.5 µg/kg/min infusion
Acute Hypotension in Patients with Septic Shock	Continuous I.V. infusion	(b) (4) µg/kg/min (b) (4) g/kg/min (b) (4)
Acute Hypotension in Children	Continuous I.V. infusion	

C. Basis for Approvability or Not-Approval Recommendation

We recommend approval of 10 mg/mL Phenylephrine Hydrochloride Injection packaged in the commercial packaging and stored as recommended, from a CMC perspective, pending labeling and final establishment inspection. The sponsor adequately responded to our information requests. There are no outstanding quality deficiencies. The Office of Compliance has not issued a final recommendation for the manufacturing facilities associated with this application.

III. Administrative

A. Reviewer's Signature

Wendy I. Wilson-Lee

B. Endorsement Block

WWilson-Lee 16-OCT-2012
KSrinivasachr 16-OCT-2012
RSood 16-OCT-2012

C. CC Block

TBouie
NQuygen
STargum

10 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

WENDY I WILSON-LEE
10/17/2012

KASTURI SRINIVASACHAR
10/17/2012

NDA 203-826

Phenylephrine Hydrochloride Injection, USP
10 mg/mL

West-Ward Pharmaceutical Corp.

Wendy I. Wilson-Lee, Ph. D.
Office of New Drug Quality Assessment
For
Division of Cardio-Renal Drug Products

Table of Contents

CHEMISTRY REVIEW

Executive Summary Section

Chemistry Review Data Sheet

1. NDA: 203-826

2. REVIEW: 01

3. REVIEW DATE: 05-SEP-2012

4. REVIEWER: Wendy I. Wilson-Lee, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None.	N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	18-JUL-2012
Amendment	27-APR-2012
Amendment	24-APR-2012
Amendment	01-MAR-2012
Original	22-DEC-2011

7. NAME & ADDRESS OF APPLICANT:

Name:	West-Ward Pharmaceutical Corp.
Address:	2 Esterbrook Lane Cherry Hill, NJ 08003
Representative:	J. Barton Kalis, Director Regulatory Affairs
Telephone:	856-489-2247

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	N/A
b) Non-Proprietary Name (USAN):	Phenylephrine Hydrochloride
c) Code Name/# (ONDQA only):	N/A
d) Chem. Type/Submission Priority (ONDQA only):	
• Chem. Type:	7
• Submission Priority:	S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Treatment of acute hypotensive states

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 10 mg/mL

13. ROUTE OF ADMINISTRATION: Intravenous

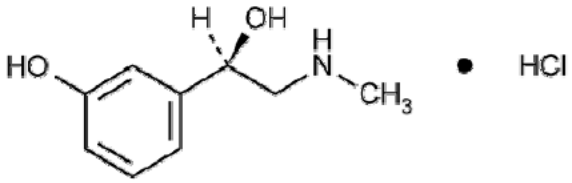
14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: (-)-*m*-Hydroxy-1-[(methylamino)methyl]benzyl alcohol hydrochloride
Mol. Formula: $C_9H_{13}NO_2 \cdot HCl$
Mol. Weight: 203.67



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF#	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	3	**Adequate**	24-DEC-2008	(b) (4)
(b) (4)	II	(b) (4)	(b) (4)	3	**Adequate**	20-AUG-2012	Reviewed for ANDA (b) (4)
(b) (4)	III	(b) (4)	(b) (4)	3	**Adequate**	24-FEB-2009	Reviewed for ANDA (b) (4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	109,977	Treatment of low blood pressure in shock and shock-like states and maintenance of blood pressure during spinal and anesthesia

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	-	-
EES	Pending.	Pending.	Pending.
Pharm/Tox	Approval (b) (4)	30-MAY-2012	P. Gatti
Biopharm	No ONDQA Biopharm Review Needed.	08-MAR-2012	E. Chikale
LNC	N/A	-	-
Methods Validation	Method validation by FDA labs not needed.	05-SEP-2012	W. Wilson-Lee
DMEPA	Pending.	Pending.	Pending.
EA	Categorical exclusion granted.	05-SEP-2012	W. Wilson-Lee
Microbiology	Approval.	18-MAY-2012	E. Pfeiler

Chemistry Review for NDA 203-826

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

We recommend a complete response action for 10 mg/mL Phenylephrine Hydrochloride Injection, USP, from a CMC perspective. The sponsor has not responded to date to our 14-JUN-2012 information request. Several CMC deficiencies are outstanding. In addition, the Office of Compliance has not issued a final recommendation regarding manufacturing facilities associated with this application.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no quality Phase IV commitments, agreements, risk management steps required.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Phenylephrine hydrochloride, USP is an odorless, white, (b) (4) crystalline powder that is very soluble in water, freely soluble in ethanol and not soluble and ethyl ether. Phenylephrine hydrochloride is light sensitive. (b) (4) supplies the sponsor with drug substance that complies with the current USP monograph for phenylephrine hydrochloride. West-Ward's regulatory drug substance specification controls appearance; identification (IR, HPLC, chloride test); melting range; specific rotation; loss on drying; residue on ignition; sulfate; limit of ketones; chloride content; assay (HPLC); related compounds (HPLC); chromatographic purity (TLC); residual solvents (GC); bacterial endotoxins; and bioburden. All drug substance analytical methods are appropriate and validated for their intended use. The drug substance supplier assigns a (b) (4) retest period to the drug substance. West-Ward internally assigns a 12 month expiry for phenylephrine hydrochloride upon release with the option for extension of the expiry by up to (b) (4) but not to exceed the supplier's retest date.

The 1% Phenylephrine hydrochloride, USP formulation contains sodium chloride, USP; sodium citrate dihydrate, USP; citric acid monohydrate, USP; sodium metabisulfite, USP; and water for injection, USP. If pH adjustment is needed, the formulation may also contain sodium hydroxide, NF or hydrochloric acid, NF. The drug product does (b) (4) duct is (b) (4) during that are (b) (4) packaged, and released for distribution. In-process controls monitor the critical process parameters final pH after (b) (4)

The regulatory drug product specification controls appearance; identification (TLC, HPLC); pH, volume in container, sodium metabisulfite content (titration); assay (HPLC); related compounds (HPLC); particulate matter; residual solvents; sterility; and bacterial endotoxins. All drug product analytical methods are appropriate and validated for their intended use except the HPLC method used for identification, assay, and related substances. The sponsor proposes one packaging configuration for market – a (b) (4) glass, (b) (4) vials with (b) (4), aluminum seal, (b) (4)

gray liner, (b) (4) white flip-off closures. West-Ward proposes a 24 month drug product expiry when stored in the commercial container closure at 25ºC (77ºF); excursions permitted to 15-30ºC (59-86ºF) [USP controlled room temperature]. We cannot provide a final determination of drug product expiry until the sponsor responds to our information request.

B. Description of How the Drug Product is Intended to be Used

Phenylephrine hydrochloride is an α-1 adrenergic receptor agonist. The proposed indication is as an agent to increase blood pressure in acute hypotensive states, namely endotoxin shock and perioperative hypotension following intravenous administration. Each vial provides a single dose. The proposed dosing regimen titrates to a normotensive state based on the level of hypotension experienced by the patient.

Proposed Indication	Proposed Routes of Administration	Proposed Doses
Acute Perioperative Hypotension	I.V. bolus	50 µg – 250 µg
	Continuous I.V. infusion	0.5 µg/kg/min – 1.4 µg/kg/min
	I.V. bolus followed by continuous I.V. infusion	40 µg bolus followed by 0.5 µg/kg/min [illegible]usion
Acute Hypotension in Patients with Septic Shock	Continuous I.V. infusion	(b) (4) µg/kg/min (b) (4) g/kg/min
Acute Hypotension in Children	Continuous I.V. infusion	(b) (4)

C. Basis for Approvability or Not-Approval Recommendation

We recommend a complete response action for 10 mg/mL Phenylephrine Hydrochloride Injection, USP, from a CMC perspective. We sent an information request to the sponsor on 14-JUN-2012 listing several deficiencies in CMC information. The sponsor has not responded to date. In addition, the Office of Compliance has not issued a final recommendation regarding the adequacy of the manufacturing facilities associated with this application.

III. Administrative

A. Reviewer's Signature

Wendy I. Wilson-Lee

B. Endorsement Block

WWilson-Lee 05-SEP-2012
KSrinivasachr 05-SEP-2012
RSood 05-SEP-2012

C. CC Block

TBouie
NQuygen
STargum

43 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

WENDY I WILSON-LEE
09/05/2012

RAMESH K SOOD
09/05/2012

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

Initial Quality Assessment
Branch I
Division of New Drug Quality Assessment I

OND Division:	Division of Cardiovascular and Renal Products
NDA:	203826
Applicant:	West-Ward Pharmaceutical Corp.
Letter Date:	22 Dec 2011
Stamp Date:	28 Dec 2011
PDUFA Date:	28 Oct 2012
Trade name:	Phenylephrine Hydrochloride Injection, USP, 10 mg/mL
Established Name:	Phenylephrine Hydrochloride
Dosage Form:	Sterile Solution
Route of Administration:	Bolus or Intravenous Injection
Indication:	Treatment of Hypotension
Assessed by:	Shastri Bhamidipati
ONDQA Fileability:	Yes

Summary
West Ward Pharmaceuticals submitted this NDA in eCTD format for Phenylephrine Hydrochloride Injection for treatment of acute hypotensive states such as shock and peri-operative hypotension. Phenylephrine Hydrochloride is a selective α1-adrenergic receptor agonist and vasoconstrictor. It is commonly used for temporary relief of nasal congestion and there are several phenylehrine containing combination drugs including ophthalmic solutions. Phenylephrine Hydrochloride Injection is an unapproved drug product marketed by Baxter HealthCare. A commercial IND 109977 was filed by Baxter and the firm met with the clinical division in November 2010 to discuss the possible approval of an NDA under 505 (b) (2) for this indication with the existing formulation of 1% Phenylephrine Hydrochloride Injection, USP based on literature data. There were neither CMC relevant questions nor discussion at this meeting.

Drug Substance
The drug substance, Phenylephrine Hydrochloride is a well established vasoconstrictor commonly used for temporary relief of nasal congestion and pressure. Phenylephrine Hydrochloride, USP, is an odorless, white crystalline powder. It is very soluble in water, freely soluble in ethanol. The drug substance is manufactured by (b) (4) and the sponsor referenced to type II DMF (b) (4) by providing a letter of authorization for all CMC information. The drug substance is tested by the drug product manufacturer (the sponsor) and certificates of analysis were provided for DS lots used in generating primary stability data for the drug product.

Drug Product
Phenylephrine Hydrochloride Injection, USP, is a clear, colorless sterile parenteral solution intended for intravenous injection and the unit composition consists of Phenylephrine Hydrochloride 10 mg; Sodium Chloride 3.5 mg; Sodium Citrate Dihydrate 4 mg; Citric Acid Monohydrate 1 mg; Sodium Metabisulfite 2 mg; in 1 mL Water for Injection. The pH of the solution is adjusted with Hydrochloric acid/ Sodium hydroxide as necessary to be in the pH range of 3.0-6.5. The drug product is packaged as a 1 mL (b) (4) single dose glass vial and stoppered with (b) (4) aluminum button seal closure with (b) (4) gray (b) (4) Liner. The drug product is manufactured by (b) (4) in to vials and (b) (4) by (b) (4) process. The pharmaceutical development section consists of several reports detailing the formulation, manufacturing process, temperature cycling and in-use stability studies with different diluents.

The drug product vials are secondary packaged in cartons (25 count) for protection from light and stored at 20°C-25°C (68°-77°F) per USP controlled room temperature conditions. The drug product for the primary stability batches (registration batches) was manufactured at (b) (4) scale (b) (4) and the proposed commercial scale batches will be manufactured at (b) (4) scale at the same location by West-ward Pharmaceuticals. The sponsor submitted stability data for three registration batches up to 6 months at 25°C/60% RH and 40°C/75% RH and requesting a 24 month expiration dating for the drug product.

Critical Review Issues

Drug substance

• DMF for the drug substance is currently in inadequate status as it was recently reviewed by OGD and the response from DMF holder to the deficiency letter is pending evaluation.

Drug Product

• This is a sterile solution for bolus or intravenous injection and thus the major critical issue is sterility assurance of the product after manufacture and maintenance of sterility over the shelf-life. These aspects are expected to be covered by the microbiology reviewer.

• Sodium metabisulfite is included in the drug product formulation (b) (4) A justification as to its content and its intended effect throughout the shelf-life should be considered.

• Labeling of the drug product should be verified for (b) (4)

• The proposed limits of (b) (4) for active content during stability is considered (b) (4)

• The sponsor is requesting a shelf-life of 24 months for the drug product whereas the primary stability data submitted are limited to 6 months. The sponsor should be informed in 74-day letter to submit additional stability data in support of the proposed shelf-life no later than mid-cycle of NDA review period.

Comments and Recommendations

It was noted that majority of the CMC information for the drug product submitted in this NDA was generated (b) (4) and the sponsor, West-Ward Pharmaceuticals, appears to have recently acquired the manufacturing facility and thus rights to the data in the NDA, though there was no explicit statement by the sponsor to that effect. The application is suitable for filing in the current format from CMC perspective. Manufacturing, testing and packaging facilities are entered into EES and the reviewer should verify the accuracy and completeness of the entries. A microbiology review consult was requested for this NDA. A single CMC reviewer is recommended for this application.

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

NDA Number: 203-826	**Supplement Number and Type: Original**	**Established/Proper Name: Phenylephrine Hydrochloride Injection, USP**
Applicant: West-Ward Pharmaceutical Corp.	**Letter Date:22-DEC-2011**	**Stamp Date: 28-DEC-2011**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			Not Applicable

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	X		

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	X		Referred to DMF through a letter of Authorization
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		Very limited stability data submitted
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	X		Microbiology Review Consult requested

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not Applicable
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	X		The sponsor is recommended to submit additional stability data prior to mid-cycle of NDA review period.

{See appended electronic signature page}

Shastri Bhamidipati
CMC Reviewer
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Ramesh Sood
Branch Chief
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment

Date

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

/s/

SHASTRI P BHAMIDIPATI
01/12/2012

RAMESH K SOOD
01/12/2012