CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203202Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

NDA # 203-202 (Division of Cardiovascular and Renal Products)
Date: 14-Aug-2013, Resubmission
Product Name: Northera™(droxidopa) Capsules
Company Name: Chelsea Therapeutics Inc.
Subject: Updated Drug Product Specification (Amendment 18-Dec-2013)

The applicant has provided the following updated sections of the NDA that include the approved proprietary drug product name "Northera":

3.2.P.1 Description and Composition of the Drug Product
3.2.P.4.1 Capsule specifications
3.2.P.5.1 Specifications

Specification for Release and Stability of Northera™ (droxidopa) capsules, 100 mg, 200 mg, and 300 mg

Test	Acceptance Criteria	Analytical Procedure
Appearance[a]	100 mg: Hard gelatin, size 3 capsule, with an opaque light blue cap and an opaque white body, printed with "Northera" on body and "100" on cap, filled with a white to light brown powder. 200 mg: Hard gelatin, size 2 capsule, with an opaque light yellow cap and an opaque white body, printed with "Northera" on body and "200" on cap, filled with a white to light brown powder. 300 mg: Hard gelatin, size 1 capsule, with an opaque light green cap and an opaque white body, printed with "Northera" on body and "300" on cap, filled with a white to light brown powder.	Visual
Identification: HPLC UV	 The retention time of sample conforms to that of the reference standard The UV spectrum of sample conforms to that of the reference standard	HPLC/UV CTMLP – 1727 (100 mg & 200 mg) CTMLP – 2056 (300 mg)
Assay[a]	(b) (4)	HPLC CTMLP – 1727 (100 mg & 200 mg) CTMLP – 2056 (300 mg)
Related Substances:[a] Individual Related Substances Total Related Substances	(b) (4)	HPLC CTMLP – 1727 (100 mg & 200 mg) CTMLP – 2056 (300 mg)
Content Uniformity	Meets USP <905> requirements	USP <905> CTMLP – 1727 (100 mg & 200 mg) CTMLP – 2056 (300 mg)

Test	Acceptance Criteria	Analytical Procedure
Dissolution[a]	Q = (b) (4) at 20 minutes	USP <711>, App I CTMLP – 1728 (100 mg & 200 mg) CTMLP – 2057 (300 mg)
Chiral Purity[a] (b) (4)	NMT (b) (4)	HPLC CTMLP – 1729 (100 mg & 200 mg) CTMLP – 2058 (300 mg)
(b) (4)	NMT (b) (4)	USP <921>, Method Ia
Microbial Limits:[a] Total Aerobic Microbial Count	NMT (b) (4)	USP <61> and <62>
Total Combined Yeasts and Molds Count	NMT (b) (4)	
E. coli	Absence/g	

[a] = Performed on stability.

Evaluation: Adequate. The updated sections of NDA incorporate the approved proprietary name "Northera".

Recommendation and Conclusion on Approvability

NDA 203-202 for Northera™ (droxidopa) Capsules, 100 mg, 200 mg and 300 mg, is recommended for APPROVAL from a Chemistry, Manufacturing and Controls standpoint. The drug substance DMF (b) (4) remains adequate. Based on the drug product stability data, the following expiration dating period is recommended only for Northera capsules manufactured using droxidopa synthesized by (b) (4) method at (b) (4) facility: 48 months for Northera™ (droxidopa) Capsules, 100 mg and 200 mg, packaged in 90 counts/90 cc HDPE bottles, 21 counts/60 cc bottles and 9 count/40 cc bottles. The 12 months expiration period for 300 mg capsules packaged in 120 cc HDPE bottles and 60 cc bottles is recommended. The expiration date of 36 months for 100 mg and 200 mg Northera capsules packaged in aluminum foil blister packs was granted previously, and remains as such. (b) (4) The Acceptable Overall OC recommendation for drug substance and drug product facilities is issued on 06-Feb-2014.

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/s/

LYUDMILA SOLDATOVA
02/10/2014

OLEN M STEPHENS
02/10/2014

NDA 203-202

Northera (TM) (droxidopa) Capsules

Chelsea Therapeutics, Inc.

Lyudmila N. Soldatova, Ph. D.
Office of New Drug Quality Assessment
for
Division of Cardiovascular and Renal Products

Review of Chemistry, Manufacturing, and Controls

Table of Contents

Chemistry Review Data Sheet

1. NDA 203-202

2. REVIEW #4

3. REVIEW DATE: February 7, 2014

4. REVIEWER: Lyudmila N. Soldatova

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
CMC Review #1	20-JAN-2012
CMC Review #2	22-MAR-2012
CMC Review #3	04-DEC-2013

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Resubmission (RTF)	03-JUL-2013
Resubmission	14-AUG-2013
Amendment	27-DEC-2013
Amendment	04-FEB-2014
Amendment	05-FEB-2014
Amendment	05-FEB-2014
Amendment	07-FEB-2014

7. NAME & ADDRESS OF APPLICANT:

Chemistry Review Data Sheet

Name:	Chelsea Therapeutics, Inc.
Address:	3530 Toringdon Way, Suite 200 Charlotte, NC 28277
Representative:	Loni da Silva, Regulatory Consultant
Telephone:	(b) (6)

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Northera
b) Non-Proprietary Name (USAN): Droxidopa
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Symptomatic Neurogenic Orthostatic Hypotension

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 100 mg, 200 mg, 300 mg

13. ROUTE OF ADMINISTRATION: Oral

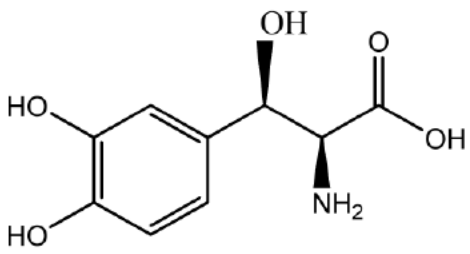
14. Rx/OTC DISPENSED: _x_Rx ___OTC

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:



(—)-threo-3-(3,4-Dihydroxyphenyl)-L-serine
Molecular weight: 213.19
Molecular formula: $C_9H_{11}NO_5$

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TY-PE	HOLDER	ITEM REFERENCED	CODE 1	STATUS 2	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Droxidopa	1	Adequate	Review #4 05-Nov-2013	Drug substance
(b) (4)	IV	(b) (4)		4	Adequate	N/A	Printing inks
	IV			4	Adequate	N/A	Gelatin capsules
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging

Chemistry Review Data Sheet

(b) (4)		(b) (4)				
	III		4	Adequate	N/A	Packaging
	III		4	Adequate	N/A	Packaging
	III		4	Adequate	N/A	Packaging
	III		4	Adequate	N/A	Packaging
	III		4	Adequate	N/A	Packaging
	III		4	Adequate	N/A	Packaging
	III		4	Adequate	N/A	Packaging
	III		4	Adequate	N/A	Packaging
	III		4	Adequate	N/A	Packaging
	III		4	Adequate	N/A	Packaging
	III		4	Adequate	N/A	Packaging

[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 77,248		

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	06-Feb-2014	OC Recommendation
Pharm/Tox	Approvable	03-Feb-2012	Donald Jensen, Ph.D.
Biopharm/ONDQA	Acceptable	13-Jan-2012	Tien Mien Chen, Ph.D.
DMEPA	No comments at this time	30-Jan-2014	Emily K. Baker, Ph. D.
Methods Validation	(b) (4)	29-Jan-2014	Division of Pharmaceutical Analysis, St. Louis, MO
EA	Categorical exclusion is granted as per Review #1	20-Jan-2012	Lyudmila N. Soldatova, Ph.D.

The Chemistry Review for NDA 203-202

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 203-202 for Northera™ (droxidopa) Capsules, 100 mg, 200 mg and 300 mg, is recommended for APPROVAL from a Chemistry, Manufacturing and Controls standpoint. The drug substance DMF (b) (4) remains adequate. Based on the drug product stability data, the following expiration dating period is recommended only for Northera capsules manufactured using droxidopa synthesized by (b) (4) method at (b) (4) facility: 48 months for Northera™ (droxidopa) Capsules, 100 mg and 200 mg, packaged in 90 counts/90 cc HDPE bottles, 21 counts/60 cc bottles and 9 count/40 cc bottles. The 12 months expiration period for 300 mg capsules packaged in 120 cc HDPE bottles and 60 cc bottles is recommended. The expiration date of 36 months for 100 mg and 200 mg Northera capsules packaged in aluminum foil blister packs was granted previously, and remains as such. (b) (4) . The Acceptable Overall OC recommendation for drug substance and drug product facilities is issued on 06-Feb-2014. The applicant will need to provide the updated drug product specification that includes the approved proprietary name Northera in the acceptance criteria for Appearance.

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

None as per this review.

II. Summary of Chemistry Assessments

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

Refer to the Review #2 dated 22-Mar-2012 for this NDA regarding the description of the Drug Product and Drug Substance, and refer to the Review #3 dated 04-Dec-2013 regarding the previous recommendation on the approvability of the NDA.

The updated information in this Review includes the following:

1. (b) (4) revised by the applicant in the resubmitted NDA is found unacceptable for regulatory purposes (refer to the Review by Michael Trehy, MVP Coordinator, dated 29-Jan-2014). As a result, the drug substance sourced from the (b) (4) can not be used in the manufacture of the drug product. The applicant has been informed on

this conclusion, and they will work with Division of Pharmaceutical Analysis, St. Louis to revise the method.

2. The applicant has provided additional information on 12-month shelf-life stability for 300 mg drug product batch of more than pilot scale size of (b) (4) capsules (HDPE bottles). Considering this new stability data and stability data previously provided in the original submission, and in the NDA resubmission, the conclusion was made to grant the 12-month expiration date for the 300 mg capsules packaged in 120 cc HDPE bottles and 60 cc bottles.
   Even though the stability studies did not comply with the ICH Guidance Q1A(R2) regarding the selection of the batch size of the primary stability batches, the decision on granting the expiration period for 300 mg droxidopa capsules was made based on the results of the stability studies that show the credible stability of the drug product, and utilizing the risk-based approach in solving the disputable regulatory issues.
3. The overall "Acceptable" OC recommendation for the manufacturing sites was made. The applicant has decided to withdraw the (b) (4) site from the list of the manufacturing facilities.
4. Since the proprietary name "Northera" was found acceptable by DMEPA (Review by Loretta Holmes BSN, PharmD, dated 23-Oct-2013), Chelsea should update the drug product specification to include the approved proprietary name Northera in the acceptance criteria for Appearance.

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

Northera™ (droxidopa) capsules, 100 mg, 200 mg and 300 mg were developed by Chelsea Therapeutics Inc. for the treatment of symptomatic neurogenic orthostatic hypotension (NOH) in patients with primary autonomic failure (Parkinson's Disease (PD), Multiple System Atrophy (MSA) and Pure Autonomic Failure (PAF)), Dopamine Beta Hydroxylase (DβH) Deficiency and Non-Diabetic Autonomic Neuropathy (NDAN).

Proposed Northera Administration

- 100 mg, administered three times per day (TID) orally. The dose may be increased in increments of 100 mg TID at the prescriber's discretion, up to a maximum dose of 600 mg TID. Patients should take NORTHERA consistently either with food or without food.
- Supine blood pressure should be monitored regularly and more frequently when changing dose.
- To reduce the potential for supine hypertension during sleep, the last dose should be taken at least 3-4 hours prior to bedtime.

C. Basis for Approvability or Not-Approval Recommendation

NDA 203-202 is recommended for APPROVAL from CMC standpoint. The NDA was recommended for Approval in the first cycle of NDA submission, and the similar but revised recommendation remains for resubmitted NDA. The drug substance DMF (b) (4) remains

Adequate. An overall Acceptable OC recommendation for drug substance and drug product facilities has been made.

III. Administrative

A. Reviewer's Signature

Lyudmila N. Soldatova

B. Endorsement Block

LSoldatova:	February 07, 2014
KSrinivasachar:	February 07, 2014
OStephens:	February 07, 2014

C. CC Block

YKnight
APark

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/s/

LYUDMILA SOLDATOVA
02/07/2014

OLEN M STEPHENS
02/07/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION REPORT SUMMARY

TO: Lyudmila Soldatova, CMC Reviewer
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: lyudmila.soldatova@fda.hhs.gov
Phone: (301) 796-1758
Fax: (301) 796-9747

FROM: FDA
Division of Pharmaceutical Analysis
Michael Trehy, MVP Coordinator
645 S Newstead Avenue
St. Louis, MO 63110
Phone: (314) 539-3815

Through: John Kauffman, Deputy Director
Phone: (314) 539-2168

SUBJECT: Methods Validation Report Summary

Application Number: 203202

Name of Product: Northera (droxidopa) Capsules, 100 mg, 200 mg, 300 mg

Applicant: Chelsea Therapeutics

Applicant's Contact Person: Loni de Silva, Regulatory Chemist

Address: 3530 Toringdon Way, Suite 200, Charlotte, NC 28277

Telephone (b) (6) Fax: (704) 752-1479

Date Methods Validation Consult Request Form Received by DPA: 11/6/2013

Date Methods Validation Package Received by DPA: 11/6/2013

Date Samples Received by DPA: 12/31/2013

Date Analytical Completed by DPA: 1/28/12014

Laboratory Classification: **1.** Methods are acceptable for control and regulatory purposes. ☐
2. Methods are acceptable with modifications (as stated in accompanying report). ☐
3. Methods are unacceptable for regulatory purposes. ☒

Comments: See attached memo for analyst's comments and link to work sheets and chromatograms

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
St. Louis, MO 63110
Tel. (314) 539-3866

Date: January 28, 2014

To: Lyudmila Soldatova, CMC Reviewer
Kasturi Srinivasachar, CMC Lead
Youbang Liu, ONDQA Methods Validation Project Manager

Through: John F. Kauffman, Deputy Director, Division of Pharmaceutical Analysis

From: Jamie D. Dunn, Chemist

Subject: Methods Validation for NDA 203202 (Re-submission)
Northera (Droxidopa) Drug Substance
Chelsea Therapeutics

The following method was evaluated and is unacceptable for quality control and regulatory purposes:

(b) (4)

The Division of Pharmaceutical Analysis (DPA) has the following comments pertaining to this method:

(b) (4)

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/s/

MICHAEL L TREHY
01/29/2014

JOHN F KAUFFMAN
01/29/2014

NDA 203-202

Northera (TM) (droxidopa) Capsules

Chelsea Therapeutics, Inc.

Lyudmila N. Soldatova, Ph. D.
Office of New Drug Quality Assessment
for
Division of Cardiovascular and Renal Products

Review of Chemistry, Manufacturing, and Controls

Table of Contents

Chemistry Review Data Sheet

1. NDA 203-202

2. REVIEW #3

3. REVIEW DATE: December 4, 2013

4. REVIEWER: Lyudmila N. Soldatova

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
CMC Review #1	20-JAN-2012
CMC Review #2	22-MAR-2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Resubmission (RTF)	03-JUL-2013
Resubmission	14-AUG-2013

7. NAME & ADDRESS OF APPLICANT:

Name:	Chelsea Therapeutics, Inc.
Address:	3530 Toringdon Way, Suite 200 Charlotte, NC 28277
Representative:	Loni da Silva, Regulatory Consultant
Telephone:	(b) (6)

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Northera
b) Non-Proprietary Name (USAN): Droxidopa
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Symptomatic Neurogenic Orthostatic Hypotension

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 100 mg, 200 mg, 300 mg

13. ROUTE OF ADMINISTRATION: Oral

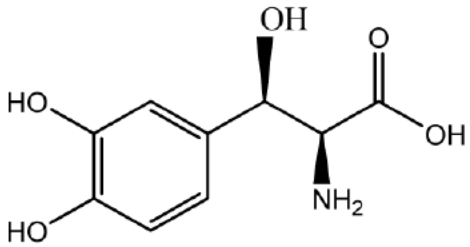
14. Rx/OTC DISPENSED: _x_Rx ___OTC

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:

(—)-threo-3-(3,4-Dihydroxyphenyl)-L-serine
Molecular weight: 213.19
Molecular formula: $C_9H_{11}NO_5$



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TY-PE	HOLDER	ITEM REFERENCED	CODE 1	STATUS 2	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Droxidopa	1	Adequate	Review #4 05-Nov-2013	Drug substance
(b) (4)	IV		(b) (4)	4	Adequate	N/A	Printing inks
	IV			4	Adequate	N/A	Gelatin capsules
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging

		(b) (4)				
(b) (4)	III		4	Adequate	N/A	Packaging
	III		4	Adequate	N/A	Packaging
	III		4	Adequate	N/A	Packaging
	III		4	Adequate	N/A	Packaging
	III		4	Adequate	N/A	Packaging
	III		4	Adequate	N/A	Packaging
	III		4	Adequate	N/A	Packaging

[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 77,248		

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
Pharm/Tox	Approvable	03-Feb-2012	Donald Jensen, Ph.D.
Biopharm/ONDQA	Acceptable	13-Jan-2012	Tien Mien Chen, Ph.D.
DMEPA	Pending		Forest Ford, Ph. D.
Methods Validation	(b) (4)	Requested on 28-Aug-2013	Division of Pharmaceutical Analysis, St. Louis, MO
EA	Categorical exclusion is granted as per Review #1	20-Jan-2012	Lyudmila. N. Soldatova, Ph.D.

The Chemistry Review for NDA 203-202

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 203-202 for Northera™ (droxidopa) Capsules, 100 mg and 200 mg , is recommended for APPROVAL from a Chemistry, Manufacturing and Controls standpoint pending the overall OC recommendation. The drug substance DMF (b) (4) remains adequate. Based on the drug product stability data, the following expiration dating period is recommended only for Northera capsules manufactured using droxidopa synthesized by (b) (4) method at (b) (4) facility: 48 months for Northera™ (droxidopa) Capsules, 100 mg and 200 mg, packaged in 90 counts/90 cc HDPE bottles, 21 counts/60 cc bottles and 9 count/40 cc bottles. The expiration date of 36 months for 100 mg and 200 mg Northera capsules packaged in aluminum foil blister packs was granted previously, and remains as such. The expiration period for 300 mg capsules packaged in 120 cc HDPE bottles, 21 counts/60 cc bottles and 9 count/40 cc bottles, (b) (4) is not granted due to the insufficient amount of stability data (regarding the size of these batches) for granting expiry. The overall OC recommendation for drug substance and drug product facilities is currently pending.

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

None as per this review.

II. Summary of Chemistry Assessments

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

Refer to the Review #2 dated 22-Mar-2012 for this NDA regarding the description of the Drug Product and Drug Substance.
The size of the primary stability batches was an issue in the original NDA submission, and resulted in granting potential expiry only for two strengths of the droxidopa capsules, 100 mg and 200 mg. In response to the CMC comment in the IR Letter (28-Mar-2012) requesting additional stability data for batches manufactured at pilot or commercial scale, Chelsea has (b) (4) As a result, the commercial batch size for capsules each of the three dosage strengths (b) (4) to comply with the requirements for size of the primary stability batches for granting the drug product expiry. However, the primary stability batches for 300 mg capsules still do not meet the recommended batch size criteria as per ICH Q1A (R2). (b) (4)

(b) (4) The updated stability data for 100 mg and 200 mg Northera capsules packaged in HDPE bottles of all configurations support extension of the expiry from (b) (4) to 48 months.

The applicant has provided description of the modified manufacturing process (b) (4) For in-process tests, the applicant refers to respective section of the original submission; this information was found acceptable in the Review #2 dated 22-Mar-2013. The equipment used in the manufacture of clinical/stability batches is comparable to that to be used in the manufacture of the proposed commercial batches. Additional batch release data are provided for 300 mg capsules that include two batches of (b) (4) capsules used in the clinical and bulk stability studies; these data comply with the proposed specifications.

The referenced DMF (b) (4) for drug substance manufactured at (b) (4) was found adequate on 22-Mar-2012; the subsequent amendments were reviewed, and the DMF continues to be adequate (Review #4 dated 05-Nov-2013).

(b) (4) Therefore, the approval of the NDA could be done only for Northera capsules manufactured using droxidopa synthesized by (b) (4) method at (b) (4) facility.

The overall OC recommendation for the manufacturing sites is currently pending.

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

Northera™ (droxidopa) capsules, 100 mg, 200 mg and 300 mg were developed by Chelsea Therapeutics Inc. for the treatment of symptomatic neurogenic orthostatic hypotension (NOH) in patients with primary autonomic failure (Parkinson's Disease (PD), Multiple System Atrophy (MSA) and Pure Autonomic Failure (PAF)), Dopamine Beta Hydroxylase (DβH) Deficiency and Non-Diabetic Autonomic Neuropathy (NDAN).

Proposed Northera Administration

- 100 mg, administered three times per day (TID) orally. The dose may be increased in increments of 100 mg TID at the prescriber's discretion, up to a maximum dose of 600 mg TID. Patients should take NORTHERA consistently either with food or without food.
- Supine blood pressure should be monitored regularly and more frequently when changing dose.
- To reduce the potential for supine hypertension during sleep, the last dose should be taken at least 3-4 hours prior to bedtime.

C. Basis for Approvability or Not-Approval Recommendation

NDA 203-202 is recommended for APPROVAL from CMC standpoint with pending overall OC recommendation. The NDA was recommended for Approval in the first cycle of NDA submission, and the similar but revised recommendation remains for resubmitted NDA. The drug substance DMF (b) (4) remains to be Adequate. An overall acceptable OC recommendation for drug substance and drug product facilities is currently pending.

III. Administrative

A. Reviewer's Signature

Lyudmila N. Soldatova

B. Endorsement Block

LSoldatova:	December 04, 2013
KSrinivasachar:	December 04, 2013
OStephens:	December 04, 2013

C. CC Block

YKnight
APark

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/s/

LYUDMILA SOLDATOVA
12/04/2013

OLEN M STEPHENS
12/04/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION CONSULT REQUEST FORM

TO: **FDA**
Division of Pharmaceutical Analysis
Attn: Michael Trehy
Suite 1002
1114 Market Street
St. Louis, MO 63101

FROM: Lyudmila Soldatova, CMC Reviewer
Kasturi Srinivasachar, CMC Lead
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: lyudmila.soldatova@fda.hhs.gov
Phone: (301)-796-1758
Fax.: (301)- 796-9747

Through: Ramesh Sood, Branch Chief, Acting Division Director DPAI
Phone: (301)- 796-1466
and
Youbang Liu, ONDQA Methods Validation Project Manager
Phone: (301)- 796-1926

SUBJECT: Methods Validation Request

Application Number: NDA 203202

Name of Product: Northera (droxidopa) Capsules, 100 mg, 200 mg, 300 mg

Applicant: Chelsea Therapeutics

Applicant's Contact Person: Loni de Silva, Regulatory Cosultant

Address: 3530 Toringdon Way, Suite 200, Charlotte, NC 28277
Telephone: (b) (6) Fax: 704-752 1479

Date NDA Received by CDER: **8/14/2013 (Re-submission)**

Date of Amendment(s) containing the MVP: **8/14/2013**

DATE of Request: **8/26/2013**

Requested Completion Date: **10/25/2013**

PDUFA User Fee Goal Date: **2/14/2014**

Submission Classification/Chemical Class: NME

Special Handling Required: No

DEA Class: N/A

Format of Methods Validation Package (MVP)

☐ Paper X Electronic ☐ Mixed

We request suitability evaluation of the proposed manufacturing controls/analytical methods as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request*. Upon receipt of the samples, perform the tests indicated in Item 3 of the attached *Methods Validation Request* as described in the NDA. We request your report to be submitted in DARRTS promptly upon completion, but no later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager of the date that the validation process begins. If the requested completion date cannot be met, please promptly notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying *Methods Validation Report Summary*). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by the director via DARRTS. The ONDQA CMC Reviewer, ONDQA Methods Validation Project Manager, and ONDQA CMC Lead/Branch Chief should be included as cc: recipients for this document.

All information relative to this application is to be held confidential as required by 21 CFR 314.430.

ATTACHMENT(S): *Methods Validation Request Sheet*, NDA Methods Validation Package (if not available in the EDR).

MVP Reference #	**METHODS VALIDATION REQUEST**	NDA #

⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT

ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION
(b) (4) Droxidopa Drug Substance	Not specified	None

⇒ ITEM 2: **Contents of Attached Methods Validation Package**	Volume/Page Number(s)
Specifications/Methods for New Drug Substance(s)	3.2.S.4.2 (b) (4)
Other:	

⇒ ITEM 3: **REQUESTED DETERMINATIONS**
Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.

Method ID	Method Title	Volume/Page	MV Request Category (see attached)	Comments
Drug Substance, (b) (4)	(b) (4)	3.2.S.4.2	**0**	Potential mutagen Method Validation Report in 3.2.S.4.3

Additional Comments: The analytical procedure for [redacted] (b) (4) has been updated as compared to the method in the original NDA submission.

Methods Validation Request Criteria

MV Request Category	Description
0	New Molecular Entity (NME) application, New Dosage Form or New Delivery System
1	Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)
2	Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms)
3	Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)
4	Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)
5	Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method

6	Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation)
7	Methods that are subject to a “for cause” reason

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/s/

LYUDMILA SOLDATOVA
08/26/2013

RAMESH K SOOD
08/27/2013

YOUBANG LIU
08/27/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION REPORT SUMMARY

TO: Lyudmila Soldatova, CMC Reviewer
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: Lyudmila.soldatova@fda.hhs.gov
Phone: (301) 796-1758
Fax: (301) 796-9747

FROM: FDA
Division of Pharmaceutical Analysis
Michael Trehy, MVP Coordinator
Suite 1002
1114 Market Street
St. Louis, MO 63101
Phone: (314) 539-3815

Through: Benjamin J. Westenberger, Deputy Director
Phone: (314) 539-3869

SUBJECT: Methods Validation Report Summary

Application Number: 203202

Name of Product: Northera (droxidopa) Capsules, 100 mg, 200 mg, 300 mg

Applicant: Chelsea Therapeutics

Applicant's Contact Person: Rex Horton, Director, Regulatory Affairs

Address: 3530 Torington Way, Suite 200, Charlotte, NC 28277

Telephone: (704) 341-1516 Fax: (704) 752-1479

Date Methods Validation Consult Request Form Received by DPA: 11/28/2011

Date Methods Validation Package Received by DPA: 11/28/2011

Date Samples Received by DPA: 1/25/2012

Date Analytical Completed by DPA: 5/4/2012

Laboratory Classification: **1.** Methods are acceptable for control and regulatory purposes. ☐
2. Methods are acceptable with modifications (as stated in accompanying report). ☐
3. Methods are unacceptable for regulatory purposes. ☒

Comments: Cover memo and summary of results are attached.

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
St. Louis, MO 63101
Tel. (314) 539-3866

Date: May 4, 2012

To: Lyudmila Soldatova, CMC Reviewer
Kasturi Srinivasachar, CMC Lead

Through: B. J. Westenberger, Deputy Director, Division of Pharmaceutical Analysis, (HFD-920)

From: Jamie D. Dunn, Chemist (HFD-920)

Subject: Methods Validation for NDA 203202
Northera (Droxidopa) 300 mg and 100 mg Capsules
Chelsea Therapeutics, Inc.

The following method is unacceptable for quality control and regulatory purposes because it can not detect (b) (4) at the specification concentration:

1. (b) (4)

The following methods were evaluated and are acceptable for quality control and regulatory purposes:

2. (b) (4)
3.

The Division of Pharmaceutical Analysis (DPA) has the following comments on why the method is unacceptable.

1. (b) (4)

The Division of Pharmaceutical Analysis (DPA) has the following comments on the methods that should be addressed:.

1. (b) (4)

4 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

MICHAEL L TREHY
05/04/2012

BENJAMIN J WESTENBERGER
05/04/2012

Northera
(droxidopa) Capsules
NDA 203-202

Summary Basis for Recommended Action
From Chemistry, Manufacturing, and Controls

Applicant: Chelsea Therapeutics, Inc.,
3530 Toringdon Way, Suite 200, Charlotte, NC 28277

Indication: Indicated for the treatment of symptomatic neurogenic orthostatic hypotension.

Presentation: Droxidopa capsules, 100 mg and 200 mg, packaged in 90-count/90 cc HDPE bottles, 21-count/ 60 cc bottles, 9-count/40 cc bottles, and 9-count blister packs.

EER Status: Pending

Consults:
Methods Validation – Revalidation by Agency not completed yet. This has no impact on the approvability of the application.
EA – Categorical exclusion granted under 21 CFR §25.31(c).

Post-Approval Agreements: None

II. Summary of Chemistry Assessments

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

Drug Substance:
The active ingredient, droxidopa [chemical name (–)-threo-3-(3,4-Dihydroxyphenyl)-L-serine] is a small molecule with molecular formula $C_9H_{11}NO_5$ and molecular weight 213.19. Droxidopa, a synthetic amino acid precursor of norepinephrine, is white to off-white crystalline powder with two asymmetric centers. The drug substance is synthesized (b) (4) It is manufactured by two suppliers. Information regarding the manufacture, characterization, and control of droxidopa from one supplier, (b) (4) is incorporated by cross-reference to DSP's DMF (b) (4). The second droxidopa supplier is (b) (4) All information related to the manufacture and control of the drug substance from both sources was reviewed and found to be acceptable to support the approval of this NDA.

Conclusion: A**cceptable.**

Drug product:

The proposed dosage form is immediate release capsules containing 100 mg, 200 mg and 300 mg. All excipients used in the manufacturing of the drug product are compendial except the hard gelatin capsule shells. The manufacturing process involves (b) (4) The manufacturing process has standard in-process controls used in the manufacturing of capsules. The control strategy further includes end product testing that ensures identity, strength, quality, purity, potency and bioavailability of the drug product.

All analytical procedures used for the analysis are appropriately validated to support their intended use.

Overall conclusion: The application is being recommended for approval pending an overall acceptable recommendation from the Office of Compliance.

Additional Items: None

Ramesh Sood, Ph.D.
Branch Chief/DPA1/Branch 1/ONDQA

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
03/22/2012

NDA 203-202

Northera (TM) (droxidopa) Capsules

Chelsea Therapeutics, Inc.

Lyudmila N. Soldatova, Ph. D.
Office of New Drug Quality Assessment
for
Division of Cardiovascular and Renal Products

Review of Chemistry, Manufacturing, and Controls

Table of Contents

Chemistry Review Data Sheet

1. NDA 203-202

2. REVIEW #2:

3. REVIEW DATE: January 31, 2012

4. REVIEWER: Lyudmila N. Soldatova

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	23-SEP-2011
Amendment	08-DEC-2011
Amendment	19-DEC-2011
Amendment	09-JAN-2012
Review #1	20-JAN-2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	31-Jan-2012
Amendment	30-Jan-2012
Amendment	10-Feb-2012
Amendment	14-Feb-2012
Amendment	08-Mar-2012
Amendment (email communication)	16-Mar-2012

7. NAME & ADDRESS OF APPLICANT:

Name: Chelsia Therapeutics, Inc.

Chemistry Review Data Sheet

Address:	3530 Toringdon Way, Suite 200 Charlotte, NC 28277
Representative:	Rex Horton, Director, Regulatory Affairs
Telephone:	704-973-4248

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Northera
b) Non-Proprietary Name (USAN): Droxidopa
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Symptomatic Neurogenic Orthostatic Hypotension

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 100 mg, 200 mg, 300 mg

13. ROUTE OF ADMINISTRATION: Oral

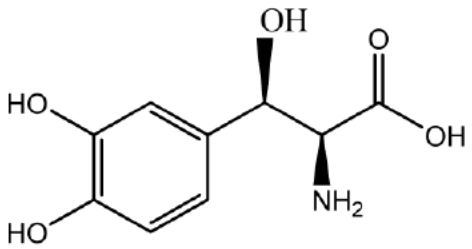
14. Rx/OTC DISPENSED: _x__Rx ___OTC

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:

(—)-threo-3-(3,4-Dihydroxyphenyl)-L-serine
Molecular weight: 213.19
Molecular formula: $C_9H_{11}NO_5$



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Droxidopa	1	Adequate	22-Mar-2012	Drug substance
(b) (4)	IV		(b) (4)	4	Adequate	N/A	Printing inks
	IV			4	Adequate	N/A	Gelatin capsules
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging

(b) (4)	III	(b) (4)	4	Adequate	N/A	Packaging
	III		4	Adequate	N/A	Packaging
	III		4	Adequate	N/A	Packaging
	III		4	Adequate	N/A	Packaging

[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 related 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 77,248		

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		Office of Compliance
Pharm/Tox	Approvable	03-Feb-2012	Donald Jensen, Ph.D.
Biopharm/ONDQA	Acceptable	13-Jan-2012	Tien Mien Chen, Ph.D.
DMEPA	Deficiencies were found	23-Jan-2012	Forest Ford, Ph. D.
Methods Validation	(b) (4)	Requested 22-Nov-2011	Division of Pharmaceutical Analysis, St. Louis, MO

Chemistry Review Data Sheet

	(b) (4)		
EA	Categorical exclusion is granted as per this Review	03-Jan-2012	Lyudmila. N. Soldatova, Ph.D.

The Chemistry Review for NDA 203-202

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 203-202 for Northera™ (droxidopa) Capsules, 100 mg and 200 mg , is recommended for APPROVAL from a Chemistry, Manufacturing and Controls standpoint with pending overall OC recommendation. The drug substance DMF (b) (4) deficiencies, and NDA deficiencies have been resolved; the droxidopa DMF (b) (4) is found adequate. Based on the drug product stability data, the following expiration dating period is recommended: 36 months for Northera™ (droxidopa) Capsules, 100 mg and 200 mg, (b) (4) and in 9-count blister packs. The expiration period for 300 mg capsules packaged in 120 cc HDPE bottles, 21 counts/60 cc bottles and 9 count/40 cc bottles, and in blisters is not granted since this dosage strength is not approved by Clin/Pharm reviewer. The overall OC recommendation for drug substance and drug product facilities is currently pending.

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

None as per this review.

II. Summary of Chemistry Assessments

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

The proposed dosage form for NDA 203-202 for Northera™ (droxidopa) Capsules, 100 mg, 200 mg and 300 mg is immediate release capsule containing 100mg , 200 mg and 300 mg of droxidopa. The capsules are hard gelatin capsules of three different sizes (size 3 for 100 mg capsules, size 2 for 200 mg capsules, and size 1 for 300 mg capsules). The three different strengths are differentiated by the color of capsule caps (opaque light blue cap for 100 mg , opaque light yellow cap for 200 mg, and opaque light green cap for 300 mg), and by imprinted "100", "200" or "300" on the caps; (b) (4) is printed on opaque white body of each capsule of three strengths. All capsule excipients are of compendial grade except for the empty hard gelatine capsules and black inks used for printing on the capsules. The compendial excipients, mannitol, corn starch and magnesium stearate are commonly used for manufacture of solid oral dosage forms. The components/colorants of the gelatin capsules are approved for use in drugs according to 21CFR Part 73 and Part 74, and all components of the (b) (4) and (b) (4) black inks were used in the approved drug products. (b) (4) The droxidopa capsules are manufactured (b) (4) No critical process parameters have been identified for

manufacturing process. The standard in-process controls for a solid oral dosage form as capsulated product are provided, (b) (4) Droxidopa capsules will be packaged in 9-count and 21-count (physician samples) and 90-count (90 cc and 120 cc; commercial packaging) HDPE (b) (4) bottles (b) (4) and in (b) (4) unit dose blister packs. (b) (4) Droxidopa capsules will be manufactured at the (b) (4) Standard specifications for solid oral dosage forms have been proposed; dissolution method was found acceptable by ONDQA biopharm reviewer, however, the dissolution specification has been revised by Chelsea from Q = (b) (4) to Q = (b) (4) at 20 minutes as a result of the biopharm reviewer's request. The NDA stability package includes the 36-month long term stability data for the batches of 100 mg and 200 mg capsules, and 24-month long term data for 300 mg capsules manufactured with droxidopa produced by (b) (4) process. The 18-month long term stability data for the batches of 100 mg, 200 mg and 300 mg capsules manufactured with droxidopa produced by (b) (4) processes is provided. The bracketing design of the stability studies was utilized for drug product batches, 100 mg and 200 mg, packaged in the HDPE bottles. Chelsea has not followed recommendations of ICH Q1A(R2) in selecting batches for primary stability studies; the stability data are not sufficient for granting the expiration period for drug product of 100 mg, 200 mg and 300 mg in all packaging configurations. In the response to IR Letter dated 13-Jan-2012, Chelsea has provided additional data and justification in support of granting the drug product expiry. As a result, even though the stability batches were not manufactured at pilot scale, the expiration period of 36 months could be granted for 100 mg and 200 mg droxidopa capsules packaged in (b) (4) 9-unit blisters, based on the results of the stability studies that show the credible stability of the drug product (refer to the Section P.8 of the Review #1 dated 20-Jan-2012), and utilizing the risk-based approach in solving the disputable regulatory issues (refer to the Conclusion in the Evaluation of Chelsea's response to the Question #8 for Drug Product of this Review). The expiration period for 300 mg capsules packaged in 120 cc HDPE bottles, 21 counts/60 cc bottles and 9 count/40 cc bottles, (b) (4) is not granted since this dosage strength is not approved by Clin/Pharm reviewer.
The deficiencies listed in the IR Letter dated 02-Mar-2012 are resolved. The drug substance DMF # (b) (4) is found to be Adequate.
The drug product is stored at 20-25°C (68-77°F). Excursions permitted to 15-30ºC (59-86ºF).

The active ingredient, droxidopa [chemical name (–)-threo-3-(3,4-Dihydroxyphenyl)-L-serine] is a small molecule with molecular formula $C_9H_{11}NO_5$ and molecular weight 213.19. Droxidopa is a synthetic amino acid precursor of norepinephrine. Droxidopa is white to off-white crystalline powder; it does not have definite melting point since it starts to melt with decomposition at ~ 200º C. (b) (4) Droxidopa is slightly soluble in water (1.92 mg/ml), and practically insoluble in methanol, ethanol, acetone, acetonitrile, and dimethylsulfoxide; it is freely soluble in dilute hydrochloric acid (14.1 mg/ml). (b) (4) . The drug substance is manufactured by two

suppliers. Information regarding the manufacture, characterization, and control of droxidopa from one supplier, [redacted] is incorporated by cross-reference to [redacted] DMF [redacted] This DMF contains CMC information for the original [redacted] method, and for the new [redacted] process. Droxidopa manufactured only by [redacted] process will be used in the commercial drug product while the drug substance produced by [redacted] method was used in the clinical trials and in the primary stability studies. The DMF holder (DMF [redacted]) has provided acceptable response to the Deficiency Letters dated 16-Dec-2011 and 27-Feb-2012. As a result, the DMF is found to be Adequate. A second droxidopa supplier, [redacted] is utilizing the [redacted] synthetic process which is identical to that of [redacted] process except for the use of [redacted] The issues raised in the second NDA IR Letter (dated 02-Mar-2012) concerning the [redacted] process has been resolved.

A categorical exclusion from the preparation of an environmental assessment is claimed by the firm, as provided under 21 CFR 25.31(b).

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

The subject of the NDA is Northera™ (droxidopa) capsules, 100 mg, 200 mg and 300 mg, being developed by Chelsea Therapeutics Inc. for the treatment of symptomatic neurogenic orthostatic hypotension (NOH) in patients with primary autonomic failure (Parkinson's Disease (PD), Multiple System Atrophy (MSA) and Pure Autonomic Failure (PAF)), Dopamine Beta Hydroxylase (DβH) Deficiency and Non-Diabetic Autonomic Neuropathy (NDAN).

Proposed Northera Administration

- 100 mg, administered three times per day (TID) orally. The dose may be increased in increments of 100 mg TID at the prescriber's discretion, up to a maximum dose of 600 mg TID. Patients should take NORTHERA consistently either with food or without food.
- Supine blood pressure should be monitored regularly and more frequently when changing dose.
- To reduce the potential for supine hypertension during sleep, the last dose should be taken at least 3-4 hours prior to bedtime.

C. Basis for Approvability or Not-Approval Recommendation

NDA 203-202 is recommended for APPROVAL from CMC standpoint with pending overall OC recommendation. The drug substance DMF [redacted] deficiencies have been resolved , and this DMF is found to be Adequate. The NDA deficiencies have been resolved in the firm's responses to issues raised in the IR Letters dated 13-Jan-2012, 02-Mar-2012 and email communication dated 16-Mar-2012. The results of Method Validation Consult is pending but validation of the analytical methods was found acceptable by this reviewer. An overall acceptable OC recommendation for drug substance and drug product facilities is currently pending.

III. Administrative

A. Reviewer's Signature

Lyudmila N. Soldatova

B. Endorsement Block

LSoldatova:	March 20, 2012
KSrinivasachar:	March 20, 2012
RSood:	March 20, 2012

C. CC Block

DHenry/TBouie
APark

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/s/

LYUDMILA SOLDATOVA
03/21/2012

RAMESH K SOOD
03/22/2012

NDA 203-202

Northera (TM) (droxidopa) Capsules

Chelsea Therapeutics, Inc.

Lyudmila N. Soldatova, Ph. D.
Office of New Drug Quality Assessment
for
Division of Cardiovascular and Renal Products

Review of Chemistry, Manufacturing, and Controls

Table of Contents

Chemistry Review Data Sheet

1. NDA 203-202

2. REVIEW #1:

3. REVIEW DATE: January 5, 2012

4. REVIEWER: Lyudmila N. Soldatova

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 77,248	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	23-SEP-2011
Amendment	08-DEC-2011
Amendment	19-DEC-2011
Amendment	09-JAN-2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Chelsia Therapeutics, Inc.
Address:	3530 Toringdon Way, Suite 200 Charlotte, NC 28277
Representative:	Rex Horton, Director, Regulatory Affairs
Telephone:	704-973-4248

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Northera
b) Non-Proprietary Name (USAN): Droxidopa
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Symptomatic Neurogenic Orthostatic Hypotension

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 100 mg, 200 mg, 300 mg

13. ROUTE OF ADMINISTRATION: Oral

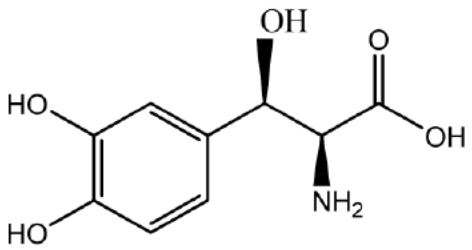
14. Rx/OTC DISPENSED: _x__Rx ___OTC

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:

(—)-threo-3-(3,4-Dihydroxyphenyl)-L-serine
Molecular weight: 213.19
Molecular formula: $C_9H_{11}NO_5$



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Droxidopa	1	Inadequate	09-Dec-2011	Drug substance
(b) (4)	IV	(b) (4)		4	Adequate	N/A	Printing inks
	IV			4	Adequate	N/A	Gelatin capsules
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging

(b) (4)			(b) (4)			
	III		4	Adequate	N/A	Packaging
	III		4	Adequate	N/A	Packaging
	III		4	Adequate	N/A	Packaging
	III		4	Adequate	N/A	Packaging

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
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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 77,248		

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		Office of Compliance
Pharm/Tox	Pending		Donald Jensen, Ph.D.
Biopharm/ONDQA	Acceptable	13-Jan-2012	Tien Mien Chen, Ph.D.
DMEPA	Pending		
Methods Validation	(b) (4)	Requested 22-Nov-2011	Division of Pharmaceutical Analysis, St. Louis, MO

Chemistry Review Data Sheet

	(b) (4)		
EA	Categorical exclusion is granted as per this Review	03-Jan-2012	Lyudmila. N. Soldatova, Ph.D.

The Chemistry Review for NDA 203-202

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 203-202 for Northera™ (droxidopa) Capsules, 100 mg, 200 mg and 300 mg, cannot be approved in this current form from CMC standpoint. The approval is contingent upon satisfactory resolution of the drug substance DMF (b) (4) deficiencies, drug substance and drug product deficiencies summarized in the IR Letter dated 13-January-2012, and overall acceptable OC recommendation for drug substance and drug product facilities.

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

None as per this review.

II. Summary of Chemistry Assessments

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

The proposed dosage form for NDA 203-202 for Northera™ (droxidopa) Capsules, 100 mg, 200 mg and 300 mg is immediate release capsule containing 100mg , 200 mg and 300 mg of droxidopa. The capsules are hard gelatin capsules of three different sizes (size 3 for 100 mg capsules, size 2 for 200 mg capsules, and size 1 for 300 mg capsules). The three different strengths are differentiated by the color of capsule caps (opaque light blue cap for 100 mg , opaque light yellow cap for 200 mg, and opaque light green cap for 300 mg), and by imprinted "100", "200" or "300" on the caps; (b) (4) is printed on opaque white body of each capsule of three strengths. All capsule excipients are of compendial grade except for the empty hard gelatine capsules and black inks used for printing on the capsules. The compendial excipients, mannitol, corn starch and magnesium stearate are commonly used for manufacture of solid oral dosage forms. The components/colorants of the gelatin capsules are approved for use in drugs according to 21CFR Part 73 and Part 74, and all components of the (b) (4) and (b) (4) black inks were used in the approved drug products. (b) (4) The droxidopa capsules are manufactured in (b) (4) No critical process parameters have been identified for manufacturing process. The standard in-process controls for a solid oral dosage form as capsulated product are provided, (b) (4) Droxidopa capsules will be packaged in 9-count and 21-count (physician samples) and 90-count (90 cc and 120 cc; commercial packaging) HDPE (b) (4) bottles (b) (4)

[redacted] and in [redacted] unit dose blister packs. Chelsea informed that [redacted] Droxidopa capsules will be manufactured at the [redacted] Standard specifications for solid oral dosage forms have been proposed; dissolution method was found acceptable by ONDQA biopharm reviewer, however, the dissolution specification has been revised by Chelsea from Q = [redacted] to Q = [redacted] at 20 minutes as a result of the biopharm reviewer's request. The NDA stability package includes the 36-month long term stability data for the batches of 100 mg and 200 mg capsules, and 24-month long term data for 300 mg capsules manufactured with droxidopa produced by [redacted] process. The 18-month long term stability data for the batches of 100 mg, 200 mg and 300 mg capsules manufactured with droxidopa produced by [redacted] and [redacted] processes. The bracketing design of the stability studies was utilized for drug product batches, 100 mg and 200 mg, packaged in the HDPE bottles. Chelsea has not followed recommendations of ICH Q1A(R2) in selecting batches for primary stability studies; the stability data are not sufficient for granting the expiration period for drug product of 100 mg, 200 mg and 300 mg in all packaging configurations. As a result, the recommendation on the expiration dating period for drug product in all packaging configurations is currently pending upon resolution of the issue with the proper selection of the primary stability batches, and upon resolution of the drug substance and drug product deficiencies listed in the IR Letter dated 13-Jan-2012.
The drug product is stored at 20-25°C (68-77°F). Excursions permitted to 15-30ºC (59-86ºF).

The active ingredient, droxidopa [chemical name (–)-*threo*-3-(3,4-Dihydroxyphenyl)-L-serine] is a small molecule with molecular formula $C_9H_{11}NO_5$ and molecular weight 213.19. Droxidopa is a synthetic amino acid precursor of norepinephrine. Droxidopa is white to off-white crystalline powder; it does not have definite melting point since it starts to melt with decomposition at ~ 200º C. [redacted]. Droxidopa is slightly soluble in water (1.92 mg/ml), and practically insoluble in methanol, ethanol, acetone, acetonitrile, and dimethylsulfoxide; it is freely soluble in dilute hydrochloric acid (14.1 mg/ml). [redacted] The drug substance is manufactured by two suppliers. Information regarding the manufacture, characterization, and control of droxidopa from one supplier, [redacted] is incorporated by cross-reference to [redacted] DMF [redacted] This DMF contains CMC information for the original [redacted] method, and for the new [redacted] process. Droxidopa manufactured only by [redacted] process will be used in the commercial drug product while the drug substance produced by [redacted] method was used in the clinical trials and in the primary stability studies. The DMF [redacted] is currently Inadequate pending the [redacted] response to the Deficiency Letter dated 16-Dec-2011. The process flow chart, specification, and batch analysis data are included in the NDA. A second droxidopa supplier, [redacted] is utilizing the [redacted] synthetic process which is identical to that of [redacted] process except for the use of [redacted] The CMC information for [redacted] process is included in NDA.

A categorical exclusion from the preparation of an environmental assessment is claimed by the firm, as provided under 21 CFR 25.31(b).

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

The subject of the NDA is Northera™ (droxidopa) capsules, 100 mg, 200 mg and 300 mg, being developed by Chelsea Therapeutics Inc. for the treatment of symptomatic neurogenic orthostatic hypotension (NOH) in patients with primary autonomic failure (Parkinson's Disease (PD), Multiple System Atrophy (MSA) and Pure Autonomic Failure (PAF)), Dopamine Beta Hydroxylase (DβH) Deficiency and Non-Diabetic Autonomic Neuropathy (NDAN).

Proposed Northera Administration

- 100 mg, administered three times per day (TID) orally. The dose may be increased in increments of 100 mg TID at the prescriber's discretion, up to a maximum dose of 600 mg TID. Patients should take NORTHERA consistently either with food or without food.
- Supine blood pressure should be monitored regularly and more frequently when changing dose.
- To reduce the potential for supine hypertension during sleep, the last dose should be taken at least 3-4 hours prior to bedtime.

C. Basis for Approvability or Not-Approval Recommendation

NDA 203-202 cannot be approved as submitted from the CMC standpoint. The outstanding issues that need to be resolved include deficiencies in the DMF (b) (4) identification by structural alert and computational toxicology assessment of several potentially genotoxic impurities in the drug substance, and Chelsea's action on this issue. In addition, Chelsea should address the issue with the proper selection of the primary stability batches for drug product stability studies to be eligible for granting the expiration dating period. An overall acceptable OC recommendation for drug substance and drug product facilities is required as well. In addition, the results of a pharm/tox consult regarding the levels of several residual solvents is pending, and results of Method Validation Consult is also pending.

III. Administrative

A. Reviewer's Signature

Lyudmila N. Soldatova

B. Endorsement Block

LSoldatova:	January 4, 2012
KSrinivasachar:	January 4, 2012
RSood:	January 4, 2012

C. CC Block

DHenry
APark

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/s/

LYUDMILA SOLDATOVA
01/19/2012

RAMESH K SOOD
01/20/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION CONSULT REQUEST FORM

TO: **FDA**
Division of Pharmaceutical Analysis
Attn: Benjamin (Nick) Westenberger
Suite 1002
1114 Market Street
St. Louis, MO 63101

FROM: Lyudmila Soldatova, CMC Reviewer
Kasturi Srinivasachar, CMC Lead
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: lyudmila.soldatova@fda.hhs.gov
Phone: (301)-796 1758
Fax.: (301)-796 9747

Through: Ramesh Sood
Phone: (301)-796 1466
and
Jeannie David, ONDQA Methods Validation Project Manager
Phone: 301-796-4247

SUBJECT: Methods Validation Request

Application Number: NDA 203202

Name of Product: Northera (droxidopa) Capsules, 100 mg, 200 mg, 300 mg

Applicant: Chelsea Therapeutics

Applicant's Contact Person: Rex Horton, Director, Regulary Affairs

Address: 3530 Toringdon Way, Suite 200, Charlotte, NC 28277

Telephone: 704-341 1516 Fax: 704-752 1479

Date NDA Received by CDER: **9/28/2011**

Date of Amendment(s) containing the MVP: **9/28/2011**

DATE of Request: **November 22, 2011**

Requested Completion Date: **1/15/2012**

PDUFA User Fee Goal Date: **3/28/2011**

Submission Classification/Chemical Class: NME

Special Handling Required: No

DEA Class: N/A

Format of Methods Validation Package (MVP)

☐ Paper ☒ Electronic ☐ Mixed

We request suitability evaluation of the proposed manufacturing controls/analytical methods as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request*. Upon receipt of the samples, perform the tests indicated in Item 3 of the attached *Methods Validation Request* as described in the NDA. We request your report to be submitted in DARRTS promptly upon completion, but no later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager of the date that the validation process begins. If the requested completion date cannot be met, please promptly notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying *Methods Validation Report Summary*). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by the director via DARRTS. The ONDQA CMC Reviewer, ONDQA Methods Validation Project Manager, and ONDQA CMC Lead/Branch Chief should be included as cc: recipients for this document.

ATTACHMENT(S): *Methods Validation Request Sheet*, NDA Methods Validation Package (if not available in the EDR).

MVP Reference #	**METHODS VALIDATION REQUEST**	NDA # 203202

⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT

ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION
(b) (4) Droxidopa Drug Substance Drug Product Capsules, 100, 200 and 300 mg	Not specified	None

⇒ ITEM 2: **Contents of Attached Methods Validation Package**	Volume/Page Number(s)
Statement of Composition of Finished Dosage Form(s)	3.2.P.1
Specifications/Methods for New Drug Substance(s)	3.2.S.4.1-1 (b) (4)
Specifications/Methods for Finished Dosage Form(s)	3.2.P.5.1-1
Supporting Data for Accuracy, Specificity, etc.	See Item. 3
Applicant's Test Results on NDS and Dosage Forms	3.2.S.4.4 (b) (4) 3.2.P.5.4 (Dosage Form)
Other: MVP	3.2.R.2

⇒ ITEM 3: **REQUESTED DETERMINATIONS**
Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.

Method ID	Method Title	Volume/Page	MV Request Category (see attached)	Comments
Drug Substance, (b) (4)	(b) (4)	3.2.S.4.2.11	**0**	Potential mutagen Method Validation Report in 3.2.S.4.3
Drug Product CTMLP-1729 and CTMLP-2058	Chiral Purity	3.2.P.5.2.6	**0**	CTMLP-1729 is for 100 and 200mg capsules. CTMLP-2058 is for 300 mg capsules. Method Validation Report in 3.2.P.5.3

Additional Comments:

Methods Validation Request Criteria

MV Request Category	Description
0	New Molecular Entity (NME) application, New Dosage Form or New Delivery System
1	Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)
2	Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms)
3	Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)
4	Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)
5	Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method

6	Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation)
7	Methods that are subject to a "for cause" reason

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/s/

KASTURI SRINIVASACHAR
11/22/2011

RAMESH K SOOD
11/25/2011

JEANNIE C DAVID
11/28/2011
ONDQA Methods Validation Project Manager

Initial Quality Assessment
Branch I

OND Division:	Division of Cardiovascular and Renal Products
NDA:	203-202
Applicant:	Chelsea Therapeutics
Letter Date:	Sep 23, 2011
Stamp Date:	Sep 28, 2011
PDUFA Date:	Mar 28, 2012
Tradename:	Northera
Established Name:	Droxidopa
Dosage Form:	Capsules, 100, 200 and 300 mg
Route of Administration:	Oral
Indication:	Treatment of symptomatic neurogenic orthostatic hypotension
Assessed by:	Kasturi Srinivasachar
ONDQA Fileability:	Yes

(b) (4)

Summary

This is an e-CTD 505(b)(1) NME NDA application for droxidopa capsules. Clinical development of this drug was carried out under IND 77,248. Droxidopa is a synthetic amino acid precursor of norepinephrine. This NDA is based on 6 clinical studies to assess the safety and efficacy of the product. The tradename Northera was accepted by DMEPA in Dec 2008 but will be reviewed again and a final recommendation given before an action on the NDA is taken. Northera has received orphan drug designation.

After IND submission there was only one CMC specific meeting with the Applicant on Aug 10, 2009. Most of the discussion revolved around drug substance issues, specifically (b) (4)

(b) (4) As far back as 2007, the Applicant had been informed that the levels of (b) (4) in drug substance batches used for clinical trials were well above (b) (4) which would be the permissible limit based on the 1.5µg/day exposure limit for genotoxic impurities using an anticipated maximum drug dose of (b) (4) They had been informed that they could either (b) (4) the drug substance to meet the (b) (4) or come up with a (b) (4) In response, two new routes of synthesis were developed, one by (b) (4) and the other by (b) (4) Since these processes could result in residual amounts of (b) (4) and (b) (4) in the drug substance, the Applicant sought agency concurrence on their proposed limits of (b) (4) The (b) (4) limit was found acceptable for (b) (4) since this would produce a lower daily exposure than from a typical diet. Concerning (b) (4) the Applicant was recommended to submit toxicology data and validate the sensitivity of the method for routine monitoring of this compound in drug substance batches. It was agreed that primary stability data for the drug substance could be from the (b) (4) method if supplemented with stability data from the other two processes. Regarding drug product, since a 300 mg capsule is proposed to be marketed but was not used in clinical trials, Chelsea therapeutics was informed that a bioequivalence study would be needed for this strength (b) (4)

Drug Substance

Droxidopa is a white to off-white crystalline compound with no definite melting point since it starts to melt with decomposition around 200˚C. (b) (4) It is slightly soluble in aqueous buffers, pH 3.0 to 6.8 but sparingly soluble in 0.1 mol/L HCl. It is practically insoluble in most organic solvents. One of the suppliers of the droxidopa, (b) (4) has a DMF (b) (4) which contains CMC information for the original (b) (4) method as well as the new (b) (4) process. Commercial drug product will only utilize droxidopa manufactured by the (b) (4) process, however, since clinical trials were carried out using drug substance made by the (b) (4) process, CMC information on the latter is still relevant. The DMF has not been reviewed since it was opened in May 2007 and several amendments have been submitted since then. Some CMC information on (b) (4) droxidopa e.g. process flow chart, specifications, batch analysis data etc. has also been submitted to the NDA. The batch analysis data covers batches manufactured by the (b) (4) method as well as the (b) (4) method. In general, impurity levels across all batches are low and well below the ICH identification threshold. A retest date for droxidopa is not given in the NDA but is presumably provided in (b) (4) DMF.
All CMC information on droxidopa from the second supplier, (b) (4) is in the NDA and no DMF has been established for this source. The reaction sequence is identical to that of (b) (4) except for the use of (b) (4) The specifications provided for (b) (4) droxidopa are quite similar to the (b) (4) specification with the same acceptance criteria for most attributes. As expected, the

residual solvents are different and residual [redacted] is specified instead of [redacted] Batch analysis data are provided for 3 batches manufactured at one tenth the planned commercial scale. 18 months long term and 6 months accelerated data have been submitted for these 3 batches and a retest period of [redacted] is proposed.

Drug Product

Northera capsules have been formulated into 3 strengths, 100, 200 and 300 mg. The different strengths are differentiated by capsule cap color and capsule size. In addition to the drug substance, the capsules contain the [redacted] mannitol and corn starch and the [redacted] magnesium stearate. All excipients are compendial grade except for the empty hard gelatin capsules (sizes 1, 2 and 3) and the black inks used for printing on the capsules. [redacted] The 100 and 200 mg capsules were used in the Phase 3 trials but the 300 mg strength was not used. The firm has conducted a Phase 1 bioequivalence study comparing 3 capsules of the 100 mg strength with one 300 mg capsule in healthy volunteers. The proposed commercial formulations are identical to the Phase 3 formulation for the 100 and 200 mg strengths and the Phase 1 (bioequivalence) formulation for the 300 mg strength.

The manufacturing process is straightforward and consists of [redacted] The capsules are [redacted] packaged in different bottle configurations and blisters. The proposed commercial batch sizes are [redacted] capsules for the 100 mg strength, [redacted] for the 200 mg strength and [redacted] for the 300 mg strength. Registration batches were manufactured at $1/10^{th}$ or somewhat larger scales for each of the strengths. It is stated that the same process and in-process controls will be used for scale-up to commercial batch sizes. [redacted]

Customary specifications have been proposed for the finished product and include microbial limits testing in accordance with USP <61> and <62>. Chiral purity is also tested with a limit of NMT [redacted] Dissolution testing is carried out with USP Apparatus I at 100 rpm using 900 mL 0.1N HCl as the medium and an HPLC analytical procedure. Batch analysis data for several lots of each strength used in developmental, clinical and stability studies have been submitted.

Stability data have been generated on registration batches packaged in 40 mL, 60 mL and 90 mL HDPE bottles and [redacted] Foil blister packs. For each strength 3 batches packaged in blisters were placed on stability. For the HDPE bottles, a bracketing plan which was previously discussed with and agreed to by the Agency, was employed. These drug product batches were manufactured using droxidopa drug substance synthesized by the [redacted] processes. Long term stability data up to 36 months are available for the 100 and 200 mg strengths. For the 300 mg strength 24 months' long term data have been submitted. Accelerated data at 40˚C/ 75% RH up to 6 months are available for all strengths. It is stated that the batches represent the commercial process and were manufactured at the intended commercial

site, [redacted]. A 36 month expiration dating period is proposed for [redacted] blisters stored at controlled room temperature.

Critical Review Issues

Drug Substance

- DMF [redacted] and its amendments should be critically evaluated since [redacted] will be one of the commercial suppliers of droxidropa drug substance. The [redacted] process should also be reviewed since clinical trials as well as some of the primary stability studies used drug product manufactured with drug substance synthesized by the [redacted] process.
- Regarding specifications for droxidopa manufactured by [redacted]
  - Only [redacted] is specified – is this acceptable? Has adequate justification been provided for not including other solvents and reagents [redacted]
  - Is there a need to test for potential genotoxic impurities [redacted] in the drug substance?
  - Is a particle size specification unnecessary as claimed?
- Regarding [redacted] droxidopa:
  - Is the manufacturing process described in adequate detail?
  - Are the specifications for intermediates and in-process controls acceptable?
  - Is it sufficient to test for specific [redacted] be included in its specification?
  - Is there any discussion of potential genotoxic impurities and their control strategy?
  - What justification has been provided for the [redacted] limit for [redacted] and [redacted]
  - Why is the limit for the [redacted] of droxidopa [redacted] the level specified for [redacted] droxidopa?
  - Is the analytical procedure for quantifying residual [redacted] suitably validated? Is the proposed limit of [redacted] acceptable to the pharm/tox reviewer?
  - Is a particle size specification needed?
- Has the Applicant established equivalence of droxidopa manufactured by the three processes [redacted] with respect to physical properties and impurity profiles?
- The utility of combining droxidropa specifications from the two suppliers into one set of regulatory specifications to be used by the applicant should be considered. Suitable notation can be used to denote tests (e.g. specific residual solvents) that are applicable to only one source of the drug substance.

Drug Product

- Has the compatibility of the excipients with the drug substance been adequately established?
- The dissolution method development report and the proposed specifications should be evaluated by the Biopharmaceutics reviewer.
- It is stated that particle size of the drug substance is not a CQA and that it has no impact on dissolution. Have satisfactory data been generated to support this statement?
- Is the drug product manufacturing process described in sufficient detail? Are the proposed in-process controls and associated acceptance criteria, (b) (4) acceptable?
- Is there a hold time between the (b) (4) operations? Has it been demonstrated that no (b) (4) occurs?
- Is the information provided on non-compendial inactive components (capsule shells and black ink) sufficient and satisfactory?
- Since the product has only been manufactured at pilot scale so far, are there any concerns about scale-up of the process to full production scale?
- Regarding finished product specifications:
    - Is the limit of (b) (4) for total related substances justified based on batch release and stability data?
    - Why is the acceptance criterion for the (b) (4) (chiral purity) (b) (4) in the drug product than in the drug substance?
    - Have the identification and qualification thresholds been correctly calculated for this product with a maximum daily dose of (b) (4)
- The proposed marketing package configurations listed in 2.3.P.7 do not match the draft container labels or the How Supplied section of the PI. These discrepancies should be reconciled.
- Have the stability studies, including bracketing, been carried out as agreed to in the correspondence of May 30, 2008?
- Were there any stability differences in the product manufactured using drug substance from any of 3 processes?
- Can a (b) (4) expiration dating period be granted for the 300 mg capsules (b) (4)?
- Generally, the protocol for the commitment batches (first 3 commercial scale batches) should be the same as for the registration batches. Is this what is proposed? Should accelerated testing be required for these batches in addition to long term testing?

Comments and Recommendations

The application is fileable -- see attached Filing Check List. Facilities have been entered into EES and the overall recommendation is currently "Pending"; the reviewer should confirm the completeness and accuracy of the entries. A categorical exclusion from environmental assessment has been requested. A Methods Validation request will be initiated shortly; two analytical procedures will be submitted: 1) the residual (b) (4) content in droxidopa drug substance by LC-MS and 2) the chiral purity determination in the drug product by HPLC. This does not preclude the reviewer from identifying other analytical procedures for validation later in the review timeframe. A single CMC reviewer is recommended since the drug product section is not very extensive or complex.

Kasturi Srinivasachar — Nov. 2, 2011
Pharmaceutical Assessment Lead — Date

Ramesh Sood — Nov. 2, 2011
Branch Chief — Date

PRODUCT QUALITY -- CMC and BIOPHARMACEUTICS
FILING REVIEW FOR NDA

NDA Number:	**NDA Type:**	**Established/Proper Name:**
203-202	**Original NDA, N-000**	**Droxidopa**
		GRMP Goal:
Applicant:	**Letter Date: September 23, 2011**	**Jan. 30, 2012 (Primary) and**
Chelsea Therapeutics	**Stamp Date: September 28, 2011**	**Feb. 04, 2012 (Secondary)**
		PDUFA Goal: March 28, 2012

CMC Reviewer: Lyudmila Soldatova, Ph.D.

Biopharmaceutics Reviewer: Tien-Mien Chen, Ph.D.

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.**			NA
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		

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.

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

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		
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		Some QbD elements in DMF (b) (4)
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

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 Comparability Protocols 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		
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	

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?			NA

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		DMF (b) (4) for drug substance

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		

J. BIOPHARMACEUTICS				
	Parameter	**Yes**	**No**	**Comment**
34.	Does the application contain dissolution data?	X		
35.	Is the dissolution test part of the DP specifications?	X		
36.	Does the application contain the dissolution method development report?	X		
37.	Is there a validation package for the analytical method and dissolution methodology?	X		
38.	Does the application include a biowaiver request?		X	To be requested for the 200 mg tablet since only a BE study conducted to link the 300 mg to the 100 mg cap.

39.	Does the application include a IVIVC model?		X	
40.	Is information such as BCS classification mentioned, and supportive data provided?		X	
41.	Is there any in *vivo* BA or BE information in the submission?	X		A BE study conducted to link the 300 mg cap to the 100 mg cap and to be reviewed by Clinpharm.

K. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
42.	**IS THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	X		
43.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			NA
44.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			NA
45.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	X		A biowaiver request for the proposed 200 mg cap is needed from the Biopharmaceutics perspective. Clarification of discrepancies between packaging configurations proposed for marketing in 3.2.P.7 and those listed in the How Supplied section of PI

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/s/

KASTURI SRINIVASACHAR
11/02/2011

RAMESH K SOOD
11/04/2011