

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203202Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

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

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

NDA NUMBER

203202

NAME OF APPLICANT/NDA HOLDER

Chelsea Therapeutics, Inc.

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

TRADE NAME (OR PROPOSED TRADE NAME)

Northera

ACTIVE INGREDIENT(S)

L-threo-3,4-dihydroxyphenylserine

STRENGTH(S)

100mg  
200mg  
300mg

DOSAGE FORM

Oral

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

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

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

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

**1. GENERAL**

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

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

**2. Drug Substance (Active Ingredient)**

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

**3. Drug Product (Composition/Formulation)**

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

**4. Method of Use**

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

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

**5. No Relevant Patents**

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

**6. Declaration Certification**

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

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

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



Date Signed

05/25/2011

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

**Check applicable box and provide information below.**

NDA Applicant/Holder

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

Patent Owner

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

Name

Chelsea Therapeutics, Inc.

Address

3530 Toringdon Way, Suite 200

City/State

Charlotte, North Carolina

ZIP Code

28277

Telephone Number

704-341-1516

FAX Number (if available)

704-752-1479

E-Mail Address (if available)

hewitt@chelsearx.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services  
Food and Drug Administration  
Office of Chief Information Officer (HFA-710)  
5600 Fishers Lane  
Rockville, MD 20857

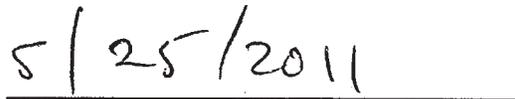
*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

***1.3.5.2 Patent Certification***

Pursuant to 21 U.S.C § 355(b)(2)(A) and 21 CFR § 314.50(i)(1)(ii), in the opinion and to the best knowledge of Chelsea Therapeutics, Inc. there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim use of such drug or drugs.



L. Arthur Hewitt, PhD  
Chief Scientific Officer



Date

## EXCLUSIVITY SUMMARY

NDA # **203202**

SUPPL #

HFD # **110**

Trade Name **Northera**

Generic Name **Droxidopa**

Applicant Name **Chelsea Therapeutics**

Approval Date, If Known **February 18, 2014**

### **PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

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

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

YES  NO

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

#### **505(b)(1)**

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

YES  NO

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

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

d) Did the applicant request exclusivity?

YES  NO

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

7

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

YES  NO

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

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

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

YES  NO

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

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES  NO

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES  NO

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

NDA#

NDA#

NDA#

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

IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If

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

YES  NO

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

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

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

YES  NO

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

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

YES  NO

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

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently

demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

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

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

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

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

Investigation #1 YES  NO

Investigation #2 YES  NO

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

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

Investigation #1 YES  NO



interest provided substantial support for the study?

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

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

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

YES  NO

If yes, explain:

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Name of person completing form: **Anna Park, R.Ph., RAC**  
Title: **Senior Regulatory Project Manager**  
Date: **February 18, 2014**

Name of Office/Division Director signing form: **Ellis F. Unger, M.D.**  
Title: **Director, Office of Drug Evaluation I**

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

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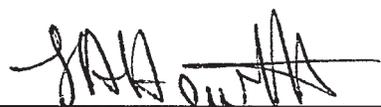
/s/  
-----

ANNA J PARK  
02/18/2014

NORMAN L STOCKBRIDGE  
02/18/2014

***1.3.5.3 Exclusivity Request***

Chelsea Therapeutics, Inc. was granted Orphan drug status on January 17, 2007 and is therefore requesting 7 years of market exclusivity in accordance with 21 CFR 316.34(b). No other exclusivity is requested.



L. Arthur Hewitt, PhD  
Chief Scientific Officer



Date

**PEDIATRIC PAGE**

**(Complete for all filed original applications and efficacy supplements)**

...JA #: 203202 Supplement Number: \_\_\_\_\_ NDA Supplement Type (e.g. SE5): \_\_\_\_\_

Division Name: DCRP PDUFA Goal Date: 3/28/12 Stamp Date: 9/28/2011

Proprietary Name: NORTHERA

Established/Generic Name: droxidopa

Dosage Form: capsule

Applicant/Sponsor: Chelsea Therapeutics, Inc.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) \_\_\_\_\_
- (2) \_\_\_\_\_
- (3) \_\_\_\_\_
- (4) \_\_\_\_\_

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1  
(Attach a completed Pediatric Page for each indication in current application.)

**Indication:** 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).

**Q1:** Is this application in response to a PREA PMR? Yes  Continue  
No  Please proceed to Question 2.

If Yes, NDA/BLA#: \_\_\_\_\_ Supplement #: \_\_\_\_\_ PMR #: \_\_\_\_\_

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
- No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

**Q2:** Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW  active ingredient(s) (includes new combination);  indication(s);  dosage form;  dosing regimen; or  route of administration?\*

(b)  No. PREA does not apply. **Skip to signature block.**

**\* Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

**Q3:** Does this indication have orphan designation?

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

**Q4:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
  - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - Deferred for some or all pediatric subpopulations (Complete Sections C)
  - Completed for some or all pediatric subpopulations (Complete Sections D)
  - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):  
 Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

# Not feasible:

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_

Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

pediatric patients in this/these pediatric subpopulation(s).

effective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

**Section C: Deferred Studies (for selected pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: \_\_\_\_\_

*Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)*

*If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
All Pediatric Subpopulations		0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

*If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.*

This page was completed by:

*{See appended electronic signature page}*

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Regulatory Project Manager

(Revised: 6/2008)

**NOTE: If you have no other indications for this application, you may delete the attachments from this document.**

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: \_\_\_\_\_

Q1: Does this indication have orphan designation?

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

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - Deferred for some or all pediatric subpopulations (Complete Sections C)
  - Completed for some or all pediatric subpopulations (Complete Sections D)
  - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**Reason(s) for full waiver: **(check, and attach a brief justification for the reason(s) selected)**

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

ack subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):  
 Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
		minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

**#** Not feasible:

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_

Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

**†** Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

**Δ** Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the eRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

**Section C: Deferred Studies (for some or all pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Population	minimum	maximum	Ready for Approval in Adults
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

**If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.**

**This page was completed by:**

{See appended electronic signature page}

**Regulatory Project Manager**

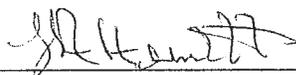
**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700**

(Revised: 6/2008)

***1.3.3 Debarment Certification***

**(FD&C Act 306(k)(1))**

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



L. Arthur Hewitt, PhD  
Chief Scientific Officer



Date

*1.3.3 Debarment Certification*

**(FD&C Act 306(k)(1))**

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



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L. Arthur Hewitt, PhD  
Chief Scientific Officer

5/4/2011

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Date

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # <b>203202</b> BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <b>Type 1</b>
Proprietary Name: <b>Northera</b> Established/Proper Name: <b>droxidopa</b> Dosage Form: <b>Oral Capsules</b>		Applicant: <b>Chelsea Therapeutics, Inc.</b> Agent for Applicant (if applicable):
RPM: <b>Anna Park</b>		Division: <b>Cardiovascular and Renal Drug Products</b>
<p><b><u>NDA and NDA Efficacy Supplements:</u></b></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1)    <input type="checkbox"/> 505(b)(2) Efficacy Supplement:    <input type="checkbox"/> 505(b)(1)    <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><b><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></b></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug.  <input type="checkbox"/> This application relies on literature.  <input type="checkbox"/> This application relies on a final OTC monograph.  <input type="checkbox"/> This application relies on (explain)</p> <p><b><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes    <input type="checkbox"/> Updated    Date of check:</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p>
❖ Actions		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <b>February 18, 2014</b></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input type="checkbox"/> None <b>CR March 28, 2012</b>

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

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

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics <sup>3</sup></p>	
<p>Review priority: <input type="checkbox"/> Standard <input type="checkbox"/> Priority <b>Class 2 Resubmission</b> Chemical classification (new NDAs only): <b>Type 1</b></p> <p> <input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input checked="" type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC  <input type="checkbox"/> Breakthrough Therapy designation         </p> <p>           NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510)  <input type="checkbox"/> Restricted distribution (21 CFR 314.520)            Subpart I <input type="checkbox"/> Approval based on animal studies         </p> <p> <input type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC  <input type="checkbox"/> Submitted in response to a Pediatric Written Request         </p> <p>           BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41)  <input type="checkbox"/> Restricted distribution (21 CFR 601.42)            Subpart H <input type="checkbox"/> Approval based on animal studies         </p> <p>           REMS: <input type="checkbox"/> MedGuide  <input type="checkbox"/> Communication Plan  <input type="checkbox"/> ETASU  <input checked="" type="checkbox"/> MedGuide w/o REMS – <b>deemed not necessary by FDA</b>  <input checked="" type="checkbox"/> REMS not required – <b>deemed not necessary by FDA</b> </p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Press Office notified of action (by OEP)</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

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

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

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

Yes       No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

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

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes       No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

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

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

Yes       No

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

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

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

Yes       No

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

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

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
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**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>4</sup>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) <b>CR 3/28/2012; AP 2/14/2014</b>
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	<b>February 18, 2014</b>
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<b>July 3, 2013</b>
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	<b>N/A</b>

<sup>4</sup> Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> <li>❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)</li> </ul>	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	<b>N/A – FDA deemed not necessary</b>
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<b>2/10/2012</b>
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	<b>N/A</b>
<ul style="list-style-type: none"> <li>❖ Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	<b>2/7/2014</b>
<ul style="list-style-type: none"> <li>❖ Proprietary Name             <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> <li>• Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</li> </ul> </li> </ul>	<b>10/28/2013</b> <b>10/23/2013</b>
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input checked="" type="checkbox"/> RPM 1/30/2014 <input type="checkbox"/> DMEPA <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 12/13/2013 <input checked="" type="checkbox"/> OPDP (DDMAC) 1/30/2014 <input checked="" type="checkbox"/> SEALD 1/23/2012 & 3/2/2012 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>5</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> </ul>	<b>N/A - resubmission</b>
<ul style="list-style-type: none"> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> </ul>	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input checked="" type="checkbox"/> Included 2/6/2014
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP             <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)             <ul style="list-style-type: none"> <li>• Date reviewed by PeRC _____ If PeRC review not necessary, explain: <b>Orphan</b></li> <li>• Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Included

<sup>5</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent ( <i>include certification</i> )	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications ( <i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i> )	included
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> N/A or no mtg 5/2/2012
• Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg 12/1/2010
• EOP2 meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg 8/21/2007
• Other milestone meetings (e.g., EOP2a, CMC pilots) ( <i>indicate dates of mtgs</i> )	
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	2/23/2012 & 1/14/2014
• 48-hour alert or minutes, if available ( <i>do not include transcript</i> )	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 2/14/2014
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 2/5/2014
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 2/5/2014
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input type="checkbox"/> None 1
<b>Clinical Information<sup>6</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	2/5/2014
• Clinical review(s) ( <i>indicate date for each review</i> )	12/5/2013
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	<b>Pages 1-2 from CDTL's 2/5/2014 review and page 14 from 12/5/2013 clinical review</b>
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input type="checkbox"/> Not applicable 3/2/2012
❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	<input type="checkbox"/> None 12/13/2013

<sup>6</sup> Filing reviews should be filed with the discipline reviews.

❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)	<input type="checkbox"/> None requested <b>please see Action Package</b>
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None <b>12/3/2013 &amp; 2/18/2014</b>
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None <b>12/3/2013 &amp; 2/18/2014</b>
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None <b>12/5/2013</b>
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None <b>12/5/2013</b>
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	<input type="checkbox"/> None <b>12/13/2013</b>
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> None <b>2/3/2012 &amp; 2/21/2012</b>
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None <b>2/3/2012</b>
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input type="checkbox"/> No carc <b>1/24/2012</b>
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None <b>1/10/2012</b> <b>Included in P/T review, page 97</b>
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	<input type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None <b>2/7/2014 &amp; 2/10/2014</b>
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	<input type="checkbox"/> None <b>CMC: 12/4/2013</b> <b>Biopharm: 12/24/13</b>
❖ Microbiology Reviews	<input checked="" type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (indicate date of each review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input checked="" type="checkbox"/> None

❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )		1/20/2012
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )		
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )		
❖ Facilities Review/Inspection		
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <b>NOT</b> include EER Detailed Report) ( <i>date completed must be within 2 years of action date</i> ) ( <i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>7</sup></i> )		Date completed: 2/6/2014 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER ( <i>date of most recent TB-EER must be within 30 days of action date</i> ) ( <i>original and supplemental BLAs</i> )		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation ( <i>check box only, do not include documents</i> )		<input checked="" type="checkbox"/> Completed <input checked="" type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

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

## Appendix to Action Package Checklist

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

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

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

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

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

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

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

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

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

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/s/  
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ANNA J PARK  
02/18/2014



NDA 203202

**GENERAL ADVICE**

Chelsea Therapeutics, Inc.  
Attention: Ms. Loni da Silva  
Regulatory Consultant  
3530 Torington Way, Suite 200  
Charlotte, NC 28277

Dear Ms. de Silva:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Northera™(droxidopa) Capsules.

We also refer to your August 14, 2013, resubmission.

We have reviewed the referenced material and have the following comments:

**Summary**



Figure 1. Standard Curve vs. Standard Addition

2 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page.

(b) (4)



If you have any questions, call Yvonne Knight, Regulatory Project Manager, at (301) 796-2133.

Sincerely,

*{See appended electronic signature page}*

Olen Stephens, Ph.D.  
Acting Branch Chief  
Branch I, Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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OLEN M STEPHENS  
02/07/2014



NDA 203202

**METHODS VALIDATION  
MATERIALS RECEIVED**

Chelsea Therapeutics  
Attention: Loni de Silva  
Regulatory Consultant  
3530 Toringdon Way  
Suite 200  
Charlotte, NC 28277  
FAX: (704) 752-1479

Dear Loni de Silva:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Northera (droxidopa) Capsules, 100 mg, 200 mg, 300 mg and to our December 2, 2013, letter requesting sample materials for methods validation testing.

We acknowledge receipt on December 31, 2013, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email ([Michael.Trehy@fda.hhs.gov](mailto:Michael.Trehy@fda.hhs.gov)).

Sincerely,

*{See appended electronic signature page}*

Michael L. Trehy  
MVP Coordinator  
Division of Pharmaceutical Analysis  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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/s/  
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MICHAEL L TREHY  
12/31/2013



NDA 203202

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Chelsea Therapeutics, Inc.  
3530 Torington Way  
Suite 200  
Charlotte, NC 28277

ATTENTION: Loni de Silva  
Regulatory Consultant

Dear Ms. de Silva:

Please refer to your New Drug Application (NDA), dated September 23, 2011, received September 28, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Droxidopa Capsules, 100 mg, 200 mg, and 300 mg.

We also refer to your August 13, 2013, resubmission, received August 14, 2013, which included a request for review of your proposed proprietary name, Northera. We have completed our review of the proposed proprietary name, Northera, and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your August 14, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Cheryle Milburn, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2084. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Anna Park, at (301) 796-1129.

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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CAROL A HOLQUIST  
10/28/2013



NDA 203202

**ACKNOWLEDGE –  
CLASS 2 RESPONSE**

Chelsea Therapeutics, Inc.  
Attention: Ms. Loni da Silva  
Regulatory Consultant  
3530 Toringdon Way, Suite 200  
Charlotte, NC 28277

Dear Ms. da Silva:

We acknowledge receipt on August 14, 2013, of your August 13, 2013, resubmission of your new drug application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Northera (droxidopa) Capsules, 100 mg, 200 mg, and 300 mg.

We consider this a complete, class 2 response to our March 28, 2012, action letter. Therefore, the user fee goal date is February 14, 2014.

If you have any questions, please contact:

Anna Park, R.Ph., RAC  
Regulatory Health Project Manager  
(301) 796- 1129

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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EDWARD J FROMM  
09/04/2013



NDA 203202

**ACKNOWLEDGE INCOMPLETE RESPONSE**

Chelsea Therapeutics Inc.  
Attention: Loni da Silva  
Regulatory Consultant  
3530 Toringdon Way, Suite 200  
Charlotte, NC 28277

Dear Ms. da Silva:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for droxidopa 100 mg, 200 mg, and 300 mg capsules.

We also refer to our letter dated July 15, 2013 in which we identified your July 3, 2013 submission as a complete, class 2 response to our March 28, 2012 action letter.

Upon further review of your submission, we do not consider this a complete response to our action letter. Therefore, we will not start the review clock until we receive a complete response. The following deficiencies from our action letter still need to be addressed:

Statistical

1. The definition file for the raw datasets in Study 306B missed the following 12 raw datasets: baseline.xpt, cglo.xpt, fall.xpt, fallseterm\_axio.xpt, format.xpt, kit.xpt, mds.xpt, medic.xpt, ohq.xpt, pdq39.xpt, pglo.xpt, titrate.xpt. These include the raw datasets used to derive primary and secondary endpoints.
2. A number of variables in the definition file cannot be located in the analyses datasets. Among them, over 20 variables cannot be located in adohq.xpt, which is the dataset used for analyzing the primary endpoint. Every analysis dataset in Study 306B also has some undefined variables starting with name "VARX".
3. Dataset adohsa1impbocf.xpt and adohsa1imp.xpt in Study 306B had the same imputation method for OHS A item 1, which is not mentioned in CSR or SAP. The referenced Excel file has a Chelsea local path and cannot be located in the submission. The derivation note for the imputation method also needs to be clarified.
4. The SAS macro called by the SAS programs are not submitted in any SAS programs. This includes %mancova and %mancova2, which were used for the primary and secondary analyses in Study 306B.
5. The analysis datasets in Study 306A do not have a definition file.
6. SAP version 2 for Study 306B is missing.
7. Study 306B datasets do not have information on last contact date.

Clinical

1. We acknowledge our agreement that you could provide summaries in a tabular format of AEs leading to discontinuation. However, please provide CRFs of all patients in 306A and 306B who discontinued, regardless of reason.
2. In the synopsis of the study 306B report, it states that there were 80 study centers in the United States. However, section 16.1.4.1 (List of Investigators and Sites) lists 62 sites, and the dataset dm.xpt lists only 57 sites. Please clarify this apparent discrepancy.

If you have any questions, please call Anna Park, Regulatory Project Manager, at (301) 796-1129.

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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NORMAN L STOCKBRIDGE  
07/29/2013

July 26, 2013

On July 3, 2013, Chelsea Therapeutics, Inc. resubmitted their NDA application (Supporting Document [SD] 45). This letter acknowledged SD 45 as a Class 2 resubmission. However, upon further review by the Division, several issues were identified. It was determined that this resubmission did not constitute a complete response to the Complete Response Letter that was issued on March 28, 2012. A decision was made to reclassify SD 45 as "resubmission/incomplete," reclassify this Acknowledgement Letter as an Advice Letter, and issue an Acknowledge Incomplete Response letter.



NDA 203202

**ACKNOWLEDGE INCOMPLETE RESPONSE**

Chelsea Therapeutics Inc.  
Attention: Loni da Silva  
Regulatory Consultant  
3530 Toringdon Way, Suite 200  
Charlotte, NC 28277

Dear Ms. da Silva:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for droxidopa 100 mg, 200 mg, and 300 mg capsules.

We also refer to our letter dated July 15, 2013 in which we identified your July 3, 2013 submission as a complete, class 2 response to our March 28, 2012 action letter.

Upon further review of your submission, we do not consider this a complete response to our action letter. Therefore, we will not start the review clock until we receive a complete response. The following deficiencies from our action letter still need to be addressed:

Statistical

1. The definition file for the raw datasets in Study 306B missed the following 12 raw datasets: baseline.xpt, cglo.xpt, fall.xpt, fallseterm\_axio.xpt, format.xpt, kit.xpt, mds.xpt, medic.xpt, ohq.xpt, pdq39.xpt, pglo.xpt, titrate.xpt. These include the raw datasets used to derive primary and secondary endpoints.
2. A number of variables in the definition file cannot be located in the analyses datasets. Among them, over 20 variables cannot be located in adohq.xpt, which is the dataset used for analyzing the primary endpoint. Every analysis dataset in Study 306B also has some undefined variables starting with name "VARX".
3. Dataset adohsa1impbocf.xpt and adohsa1imp.xpt in Study 306B had the same imputation method for OHS A item 1, which is not mentioned in CSR or SAP. The referenced Excel file has a Chelsea local path and cannot be located in the submission. The derivation note for the imputation method also needs to be clarified.
4. The SAS macro called by the SAS programs are not submitted in any SAS programs. This includes %mancova and %mancova2, which were used for the primary and secondary analyses in Study 306B.
5. The analysis datasets in Study 306A do not have a definition file.
6. SAP version 2 for Study 306B is missing.
7. Study 306B datasets do not have information on last contact date.

Clinical

1. In the study report for 306B, we are unable to find narratives for subjects who discontinued due to adverse events.
2. In the synopsis of the study 306B report, it states that there were 80 study centers in the United States. However, section 16.1.4.1 (List of Investigators and Sites) lists 62 sites, and the dataset dm.xpt lists only 57 sites. Please clarify this apparent discrepancy.

If you have any questions, please call Anna Park, Regulatory Project Manager, at (301) 796-1129.

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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NORMAN L STOCKBRIDGE  
07/25/2013

**REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW  
CONSULTATION**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

**\*\*Please send immediately following the Filing/Planning meeting\*\***

TO: <b>CDER-DDMAC-RPM</b>	FROM: (Name/Title, Office/Division/Phone number of requestor) <b>Anna Park/OND1/DCRP/796-1129</b>
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REQUEST DATE <b>7/18/13</b>	IND NO.	NDA/BLA NO. <b>203202</b>	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
--------------------------------	---------	------------------------------	---

NAME OF DRUG <b>droxidopa</b>	PRIORITY CONSIDERATION <b>Priority</b>	CLASSIFICATION OF DRUG <b>NME</b>	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) <b>October 31, 2013</b>
----------------------------------	---	--------------------------------------	---

NAME OF FIRM:	PDUFA Date:
---------------	-------------

**TYPE OF LABEL TO REVIEW**

<b>TYPE OF LABELING:</b> (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)	<b>TYPE OF APPLICATION/SUBMISSION</b> <input checked="" type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	<b>REASON FOR LABELING CONSULT</b> <input checked="" type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION
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**EDR link to submission: \\CDSESUB1\evsprod\NDA203202\0044**

**Please Note:** There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:  
  
 Mid-Cycle Meeting: 9/23/13  
 Labeling Meetings: 10/16, 11/18, 12/4/13  
 Wrap-Up Meeting: 12/5/13

SIGNATURE OF REQUESTER: **Anna Park**

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check all that apply) <input type="checkbox"/> eMAIL <input checked="" type="checkbox"/> DARRTS <input type="checkbox"/> HAND
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06/18/2013

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/s/  
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ANNA J PARK  
07/18/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR PATIENT LABELING REVIEW CONSULTATION</b>	
TO: <b>CDER-DMPP-PatientLabelingTeam</b>		FROM: (Name/Title, Office/Division/Phone number of requestor) LCDR Anna Park, RPM, OND1/DCRP/ (301)796-1129	
REQUEST DATE 7/17/13	NDA/BLA NO. 203202	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)	
NAME OF DRUG droxidopa	PRIORITY CONSIDERATION Priority	CLASSIFICATION OF DRUG NME	DESIRED COMPLETION DATE (Generally 2 Weeks after receiving substantially complete labeling) October 31, 2013
Sponsor: Chelsea Therapeutics, Inc.		PDUFA Date: January 3, 2014	
<b>TYPE OF LABEL TO REVIEW</b>			
TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)		TYPE OF APPLICATION/SUBMISSION <input checked="" type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	
REASON FOR LABELING CONSULT <input checked="" type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION			
EDR link to submission: <a href="\\CDSESUB1\evsprod\NDA203202\203202.enx">\\CDSESUB1\evsprod\NDA203202\203202.enx</a>			
Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.			
COMMENTS/SPECIAL INSTRUCTIONS: Filing/Planning Meeting: 7/22/13 Mid-Cycle Meeting: 9/23/13 Labeling Meetings: 10/16, 11/18, 12/4/13 Wrap-Up Meeting: 12/5/13			
SIGNATURE OF REQUESTER Anna Park			
SIGNATURE OF RECEIVER		METHOD OF DELIVERY (Check one) <input type="checkbox"/> eMAIL (BLAs Only) <input checked="" type="checkbox"/> DARRTS	

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ANNA J PARK  
07/17/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): <b>Mail: OSE</b>		FROM: Anna Park/OND1/DCRP/796-1129		
DATE July 15, 2013	IND NO.	NDA NO. 203202	TYPE OF DOCUMENT electronic	DATE OF DOCUMENT July 3, 2013
NAME OF DRUG droxidopa	PRIORITY CONSIDERATION Priority	CLASSIFICATION OF DRUG NME	DESIRED COMPLETION DATE October 31, 2013	
NAME OF FIRM:				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY	<input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input checked="" type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> CONTROL SUPPLEMENT		<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: Please review the PI and label. EDR Location: <a href="#">\\CDSESUB1\evsprod\NDA203202\0044</a>				
SIGNATURE OF REQUESTER Anna Park		METHOD OF DELIVERY (Check all that apply) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> DARRTS <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		



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ANNA J PARK  
07/15/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): <b>Mail: OSE</b>		FROM: Anna Park/OND1/DCRP/796-1129		
DATE July 15, 2013	IND NO.	NDA NO. 203202	TYPE OF DOCUMENT electronic	DATE OF DOCUMENT July 3, 2013
NAME OF DRUG droxidopa	PRIORITY CONSIDERATION Priority	CLASSIFICATION OF DRUG NME	DESIRED COMPLETION DATE October 31, 2013	
NAME OF FIRM:				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY	<input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input checked="" type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> CONTROL SUPPLEMENT		<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: This NDA was submitted with a Medication Guide. Please review the appropriate documents. EDR Location: <a href="#">\\CDSESUB1\evsprod\NDA203202\0044</a>				
SIGNATURE OF REQUESTER Anna Park		METHOD OF DELIVERY (Check all that apply) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> DARRTS <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		



06/18/2013

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/s/  
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ANNA J PARK  
07/15/2013



NDA 203202

**ACKNOWLEDGE –  
CLASS 2 RESPONSE**

Chelsea Therapeutics, Inc.  
Attention: Ms. Loni da Silva  
Regulatory Consultant  
3530 Toringdon Way, Suite 200  
Charlotte, NC 28277

Dear Ms. Silva:

We acknowledge your July 3, 2013 resubmission of your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Northera (droxidopa) Capsules, 100 mg, 200 mg, and 300 mg.

We consider this a complete, class 2 response to our March 28, 2012, action letter. Therefore, the user fee goal date is January 3, 2014.

If you have any questions, please contact:

Anna Park, R.Ph., RAC  
Regulatory Health Project Manager  
(301) 796-1129

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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EDWARD J FROMM  
07/15/2013



NDA 203202

**MEETING MINUTES**

Chelsea Therapeutics Inc.  
Attention: Loni da Silva  
Regulatory Consultant  
3530 Toringdon Way, Suite 200  
Charlotte, NC 28277

Dear Ms. da Silva:

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

We also refer to the meeting between representatives of your firm and the FDA on March 20, 2013. The purpose of the meeting was to discuss your plans for resubmission and the next droxidopa clinical trial.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Anna Park, Regulatory Project Manager at (301) 796-1129.

Sincerely,

*{See appended electronic signature page}*

Ellis F. Unger, M.D.  
Director  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** A  
**Meeting Category:** Guidance

**Meeting Date and Time:** March 20, 2013 4:00 PM – 5:00 PM, EST  
**Meeting Location:** Bldg 22 Room 1313  
**Application Number:** NDA 203202  
**Product Name:** droxidopa capsules  
**Indication:** Treatment of symptomatic neurogenic orthostatic hypotension (NOH) in patients with primary autonomic failure, dopamine- $\beta$ -hydroxylase deficiency or non-diabetic autonomic neuropathy  
**Applicant Name:** Chelsea Therapeutics, Inc.

**Meeting Chair:** Ellis F. Unger, M.D.  
**Meeting Recorder:** Anna Park, R.Ph., RAC

**FDA ATTENDEES**

Office of Drug Evaluation I

Ellis Unger, M.D. Director

Office of Drug Evaluation I, Division of Cardiovascular and Renal Products

Norman Stockbridge, M.D., Ph.D. Director  
Stephen Grant, M.D. Deputy Director  
Shari Targum, M.D. Clinical Team Leader  
Melanie Blank, M.D. Clinical Reviewer  
Fred Senatore, M.D. Clinical Reviewer  
Edward Fromm, R.Ph., RAC Chief, Project Management Staff  
Anna Park, R.Ph., RAC Regulatory Project Manager

Office of Clinical Pharmacology, Division of Clinical Pharmacology I

Sabarinath Sreedharan, Ph.D. Clinical Pharmacology Reviewer

Office of Biostatistics, Division of Biometrics I

Jialu Zhang, Ph.D. Statistician

Office of New Drug Quality Assessment, Division of Drug Quality Assessment I

Kasturi Srinivasachar, Ph.D. Pharmaceutical Assessment Lead  
Lyudmila Soldatova, Ph.D. Product Quality Reviewer

Office of New Drug Quality Assessment, Biopharmaceutics Team

Tien-Mien Chen, Ph.D. Biopharmaceutics Reviewer

**CHELSEA THERAPEUTICS ATTENDEES**

L. Arthur Hewitt, Ph.D.	Chief Scientific Officer
Jeff Nelson	Director of Strategic Planning
Joseph Oliveto	Interim President and Chief Executive Officer
William Schwieterman, M.D.	Chief Medical Officer
Michael Weiser, M.D., Ph.D.	Chairman of the Board
Loni da Silva	Regulatory Consultant

## 1.0 BACKGROUND

Chelsea Therapeutics, Inc. submitted a New Drug Application (NDA) for droxidopa for the treatment of neurogenic orthostatic hypotension (NOH) on September 23, 2011.

### Summary of Key Regulatory Milestones:

January 2007	Orphan drug designation granted for the NOH indication
February 2008	Agreement on a Special Protocol Assessment for study 301
August 2008	Fast Track designation granted
November 2009	Type C Meeting – discussion of sponsor’s planned modifications of study 301. The Division noted that study 302 could not be used as one of two studies to support efficacy because it failed on its primary endpoint
January 2010	Correspondence to sponsor – FDA agreed to a change in the primary endpoint of study 301 from the Orthostatic Hypotension Symptoms Assessment (OHSA) Item 1 to the Orthostatic Hypotension Questionnaire (OHQ)
December 2010	Pre-NDA meeting – FDA reminded Chelsea that one trial is not usually sufficient for approval. FDA requested validation data for the PRO instruments used in the studies, as well as support for the view that the observed effect size in study 301 is clinically meaningful
September 2011	NDA submitted
February 2012	NDA presented at the Cardiovascular and Renal Drugs Advisory Committee Meeting
March 28, 2012	Complete Response Letter issued
May 31, 2012	Study 306B submitted as an additional pivotal, confirmatory efficacy study required for approval
Jun 29, 2012	Correspondence to sponsor – The sponsor amended their analytic plan after substantial information was accumulated in the trial and therefore, the Agency could not be confident that information from the trial did not influence the redesign of the statistical analytic plan. Moreover, due to concerns the randomization code was available to a number of individuals, the Agency could not ascertain that interim results did not somehow influence decisions to change the primary efficacy endpoint of study 306

December 12, 2012	Formal Dispute Resolution Request submitted for approval or full approval with a post-marketing requirement for a clinical trial
January 10, 2013	Type A Meeting – Discuss Formal Dispute Resolution Request
February 8, 2013	Formal Dispute Resolution Request Denied
March 1, 2013	Type A Meeting submitted to discuss plans for resubmission and next droxidopa clinical trial

Preliminary responses were not provided to the sponsor prior to the meeting. FDA requested that the sponsor present their topline results of Study 306B.

## 2. DISCUSSION

After brief introductions, the sponsor presented their topline results of Study 306B. The sponsor's slide presentation attached below.

**Extension:** *We hereby formally request an extension of time to resubmit the NDA.*

**Discussion:** The Agency stated it would grant Chelsea's request.

**Clinical/Statistical:** *The agency indicated "an additional positive study will be needed to support efficacy." The Agency further suggested such a study demonstrate durability of effect.*

*In Dr Jenkins' response (dated February 8th, 2013) to Chelsea's formal appeal letter, the letter stated "...data strongly demonstrating a short-term clinical benefit... of droxidopa in patients with NOH would be adequate to support approval...." Chelsea intends to rely upon Study 306B as an additional supportive positive study for the short-term endpoint of OHS A Item #1 (dizziness/lightheadedness) at Week 1 of treatment. Chelsea intends to show that, in combination with Study 301 as previously filed, Study 306B constitutes a second pivotal trial ( $p < 0.05$ ) to demonstrate effectiveness. Study 306B demonstrated statistically significant improvements for patients treated with Northera compared to placebo in dizziness/lightheadedness at Week 1 ( $p = 0.018$ ), the primary endpoint, and an increase in standing systolic blood pressure at Week 1 ( $p = 0.032$ ), an important secondary endpoint.*

*Chelsea intends to show evidence of durability of effect in Study 306B, and proposes to verify durable clinical benefits via a post approval study. We request that a portion of the meeting be allotted to feedback and discussion regarding key study design considerations, such as the efficacy measures, primary and secondary endpoints, enrichment techniques and treatment duration. Chelsea plans to proceed with development of this study in parallel with the NDA resubmission. We would incorporate feedback from initial discussions of key study parameters into a protocol that would be submitted to the Agency for review around the second quarter 2013. Agency feedback would be incorporated into the final protocol, and we would initiate study conduct with a goal to start enrolling patients in the second half of 2013.*

**Discussion:** The Agency acknowledged Chelsea's plan to conduct a post-approval trial to demonstrate durability of droxidopa's clinical benefit. The Agency noted that longer-term efficacy and safety data would be crucial towards gaining an understanding the clinical utility of droxidopa, given that the condition being treated is chronic. Depending on the data submitted in the NDA, the Agency could consider full approval for treatment up to 1 week, as well as accelerated approval with a 1-week treatment effect serving as a surrogate for a longer-term effect. With respect to a 1-week treatment effect serving as a surrogate for longer-term effectiveness, however, the observation that effectiveness appeared to diminish over time in Studies 302 and 303 was discussed as an impediment.

**Labeling:** *FDA Comments from the complete response letter are provided below.*

*We have provided draft recommendations to several sections of the labeling, but reserve comment on the remaining sections until the application is otherwise adequate. Please submit*

*draft labeling that incorporates revisions to the attached labeling. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.*

*To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations that support any proposed changes.*

*Add the following bolded statement or appropriate alternative to the carton and container labels per 21 CFR 208.24(d): "**ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide.**"*

*Chelsea will revise the labeling in accordance with the Agency's recommendations as well as OHS A Item #1 as the primary measure of clinical benefit, including revised safety and efficacy information based on new data from Study 306 and the long term extension Study 304.*

**Discussion:** No additional discussion.

**Risk Evaluation and Mitigation Strategy Requirements:** *FDA Comments from the complete response letter are below:*

*We acknowledge receipt of your submission dated September 28, 2011 of a proposed risk evaluation and mitigation strategy (REMS). We have determined that, at this time, a REMS is not necessary for droxidopa to ensure that its benefits outweigh its risks. Once the complete response (CR) is submitted, we will notify you if we become aware of new safety information and make a determination that a REMS is necessary.*

*Chelsea will not submit a REMS based on your recommendation.*

Discussion: No additional discussion.

**Product Quality:** *FDA Comments from the complete response letter are below:*

*Since the primary drug product stability batches did not meet the recommended batch size criteria as per ICH Q1A (R2), include available stability data for batches manufactured at pilot or commercial scale representing the commercial process and container/closure system for all three strengths.*

*Stability update and data will be included in sections 3.2P8.1 and 8.3, respectively. It will include additional data generated since the original NDA. The updates do not represent new stability studies, only updates to the previously submitted studies. The stability studies comply with ICH Q1A (R2). Regarding the commercial batch size/scale, the typical batch formulation will be updated to reflect the batch size for commercial batches per FDA communication dated 31 August 2012. The batch size will be (b) (4) for all three capsule strengths.*

Discussion: The Agency responded to Chelsea's proposal for reduced commercial batch sizes on 31 August 2012 stating that the "Agency accepts Chelsea's proposal to reduce the batch size to (b) (4) and the Agency will assign the expiration date for Northera (droxidopa) capsules, 100 mg and 200 mg only based on the provided data." Chelsea agreed to conduct stability studies including dissolution studies on the new reduced size batches.

Post-Meeting Comments: The Agency recommends that the sponsor provide a side by side comparison table describing the pre- and post-manufacturing changes to equipment, processes, etc., associated with the batch size reduction. Based on this information the "Level" for each one of the corresponding manufacturing changes will be determined, as well as the documentation that would be needed to support those changes.

The new bio-batch(es) to be used in the proposed new Phase 3 and BE studies should represent at least 1/10 of the newly proposed full-production batch size.

**Clinical Pharmacology:** *FDA Comments from the complete response letter are below:*

*The Office of Scientific Investigations (OSI) performed clinical and bioanalytical site inspections for pivotal bioequivalence (BE) study 101 and concluded that the bioanalytical part of the pivotal BE evaluation between 3 x 100 mg capsules (phase III formulation) and 1 x 300 mg capsules (proposed new formulation) is not reliable. Therefore, the BE results from this study are not acceptable. You will need another BE study, preferably comparing 1 x 300 mg capsules (proposed new strength) and 1 x 100 mg + 1 x 200 mg capsules (as used in the Phase III program), if you wish to pursue the approval of 300 mg formulation.*

*Chelsea is finalizing the BE study protocol to support introduction of Northera (droxidopa) capsules, 300 mg in the NDA for approval and future commercialization. As noted above, the original BE study utilized three 100 mg capsules compared to one 300 mg capsule. Based on the Agency recommendation, one 100 mg and one 200 mg Northera capsule will be compared to one 300 mg capsule in the new BE study.*

*The planned BE study will be conducted according to the original protocol design with changes only to the subject capsules used in the study. Specifically, A Randomized, Open-Label, Bioequivalence Study in Healthy Subjects will be conducted. Each subject will receive a single, oral dose of one 100 mg and one 200 mg capsule of droxidopa with 240 mL of water in the fasted state (Treatment A) and a single, oral dose of one 300 mg capsule of droxidopa with 240 mL of water in the fasted state (Treatment B) on Days 1 and 4. Subjects will be discharged from the research clinic on Day 5 after completing all post-treatment follow-up assessments.*

*Chelsea is requesting that FDA confirm that it is acceptable to conduct the BE study using the original protocol design and comparing one 300 mg capsule with one 100 mg and one 200 mg capsule to pursue the approval of 300 mg capsule and not repeat the previously submitted BE study comparing three 100 mg capsules with one 300 mg capsule. Reference is made to the attachment 2 for additional details concerning the planned BE study. Does the agency agree?*

Discussion: The Agency stated Chelsea's proposed study design was acceptable. Under PDUFA V, however, an application is expected to be complete when submitted. When asked if marketing only the 100 mg and 200 mg capsules might have negative consequences, such as causing drug shortages, Chelsea stated there may be some difficulties for patients receiving higher doses because of pill burden. Chelsea indicated that if they need to include the results of the study in the re-submission, it would delay re-submission by one to two months to revalidate methods and write the reports. The Agency indicated that Chelsea must choose whether to delay re-submission in order to complete the necessary BE studies or submit to market only the 100-mg and 200-mg capsules. If they choose the latter, then they can submit the BE studies in a Prior Approval Supplement (which will have a 4-month review timeline).

*Due to scheduling the study at the CRO, the BE study may take longer than the planned resubmission work. Chelsea is proposing the BE study report to be filed up to 60 days after the resubmission date, without resetting or impacting the PDUFA date on the resubmission. Will the agency agree to this?*

Discussion: The Agency asserted that the BE study needs to be completed at the time of NDA submission or submitted as a supplement to their approved NDA, but not as a late submission to their pending NDA, with a 4-month PDUFA clock.

Safety Update: *The following items will be addressed in a revised ISS submitted in the resubmission. Specific questions are addressed below:*

- *Describe in detail any significant changes or findings in the safety profile.*
- *When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:*
- *Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.*
- *Present tabulations of the new safety data combined with the original NDA data.*

- *Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.*
- *For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.*
- *Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.*
- *Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.*

*Previously in the NDA, Chelsea provided tabulated summaries, as in Appendix 4 [Section 11.4] of the ISS. There would be over 100 written narrative summaries for these AEs. Does the agency prefer a tabulated format as previously provided or written text narratives in the ISS for AEs leading to discontinuation?*

Discussion: The Agency requested submission of the narrative summaries in a tabular format. In addition, Chelsea agreed to submit CRFs of all patients who discontinued, as well as CRFs for any patient requested by the Division.

- *Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.*
6. *Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).*
  7. *Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.*

*Chelsea intends to include the summary of worldwide safety experience as an appendix to the ISS. Does the agency agree this is acceptable?*

Discussion: The Agency agreed with Chelsea's proposal.

8. *Provide English translations of current approved foreign labeling not previously submitted.*

*The following are sections of the NDA that will be provided in the resubmission:*

**Module 1**

*Forms 356h, 3674 and cover letter*

*1.3.1.4 Transfer of Obligations*

*1.3.4 Financial disclosure information for study 306*

*1.4 New DMF authorization letter for [REDACTED] (b) (4) will be submitted due to addition of DUNS numbers to 3.2.S.2.1 and allow reference to the current DMF.*

*1.6 Additional meeting information since the NDA*

*1.14 Revised labeling*

**Discussion:** [REDACTED] (b) (4)

If resubmitted to DCaRP, it will have a six-month clock. It is likely to be discussed again by the Cardiovascular and Renal Drug Advisory Committee. If so, the unusual results from sites 507 and 505 of study 301 will be presented for discussion. Chelsea agreed that presentation of the results from 507 and 505 was appropriate.

### **Module 2**

*2.3; Chelsea intends to revise Sections 2.3 that have been updated in module 3, Information in module 2 will match module 3 in summary form and no new information will be included in module 2 (See Module 3 information to be updated).*

*2.5; Chelsea intends to resubmit the Clinical Overview containing revised efficacy, safety, and risk benefit conclusions including study 306.*

*2.7.3 and 2.7.4; Chelsea proposes not to revise Sections 2.7.3, and 2.7.4, instead relying on Section 2.5 to provide the summary of changes to conclusions and risk benefit. Does the agency agree?*

**Discussion:** The Agency agreed with Chelsea's proposal as long as it is included in both the ISE and CSR.

*Due to the time frame to a final BE study report, Chelsea proposes to not revise the pharmacokinetics and pharmacodynamics sections of Module 2 or Module 5 with that study. Does the agency agree?*

**Discussion:** The Agency agreed with Chelsea's proposal.

### **Module 3**

#### **Drug Substance:**

- (i) 3.2.S.2.1: Updates to reflect new company name, (b) (4) will be provided. The name change does not reflect new manufacturing site or ownership.
- (ii) Updates for drug substance suppliers, (b) (4) DUNS numbers for each site manufacturing and/or testing drug substance will be provided.
- (iii) 3.2.S.4.2, 3.2.S.4.3: (b) (4) Per FDA request in correspondence dated 31 August 2012, concerning (b) (4) drug substance, updates to the test method and validation will be provided. As requested by the FDA, the test method has been updated and the validation performed accordingly.
- (iv) 3.2.S.4.4: Updates to batch analysis table representing new (b) (4) drug substance lots.
- (v) 3.2.S.7.1, 3.2.S.7.3: Updates to (b) (4) stability studies will be provided to allow extension of the retest date.

**Discussion:** The Agency advised Chelsea that they will need to provide stability data on the reduced batch size.

#### **Drug Product:**

- 3.2.P.3.1: Updates to manufacturing, testing, and packaging sites to include DUNS numbers will be provided.
- 3.2.P.3.2: The typical batch formulation will be updated to reflect the batch size for commercial batches per FDA communication dated 31 August 2012. The batch size will be (b) (4) for all capsule strengths.
- 3.2.P.3.3: The manufacturing process will be updated to reflect equipment and scale changes based on the new batch size of (b) (4)
- 3.2.P.5.4: The batch analysis table will be updated to reflect additional batches and the agreed upon specifications.
- 3.2.P.8.1, 3.2.P.8.3: The stability section will be submitted for additional data generated since the original NDA. The stability studies comply with ICH Q1A (R2) recommendations and agreement reached concerning the proposed commercial batch size and supporting stability studies (31 August 2012 FDA communication).

### **Module 4**

No new information

### **Module 5**

- 5.3.1.2 Bioequivalence Study (to be submitted up to 60 days after the resubmission, as outlined in letter)
- 5.3.5.1 Final CSR for Study 306B, the analysis set of patients after the interim analysis in Study 306 – This CSR will serve as the key component of the resubmission. It will be an extensive CSR, containing not only pre-specified analyses from the SAP, but a number of sensitivity analyses on data imputation, references to the interim analysis and blinding issues with relevant post-hoc analyses, a review of potential clinical site effects, discussion on the

*robustness of the data, and discussion on the secondary endpoint of falls and fall related injuries.*

*Study 306B analyses were based on a modified Intent to Treat (mITT) population as pre-specified in the SAP v 1.0 (IND 77,248 amendment SN095 11/19/10, 2.0 (IND 77,248 amendment SN107 submitted 5/13/2011 [http://us-mg6.mail.yahoo.com/neo/launch?.rand=79vqqvo231a4k\\_-\\_msocom\\_1](http://us-mg6.mail.yahoo.com/neo/launch?.rand=79vqqvo231a4k_-_msocom_1)) and 3.0 (IND 77,248 amendment SN137 submitted 11/05/2012). There were more dropouts during titration in the droxidopa than placebo arm of the study, and data for the primary endpoint OHSA Item #1 were not collected during titration. Data and analyses regarding dropouts and sensitivity analyses similar to those proposed in IND 77,248 FDA letter 1/19/2011 will be included in the CSR for Study 306B.*

*CSR for Study 306A, the analysis set of patients prior to the interim analysis in Study 306 – this CSR will be submitted primarily for informational purposes and not as a key element for approval.*

*5.3.5.2 Final CSR for Study 304, the long term safety extension*

*5.3.5.3 ISE and ISS*

*Integrated Summary of Effectiveness (ISE) – As Study 306 had a fundamentally different design from previous studies (double blind titration, long term double blind treatment, Parkinson's patients only) Chelsea intends to do only minimal integration of Study 306. The resubmitted ISE will primarily present analyses of 306 A and B datasets combined, along with some minimal integration of key efficacy endpoints in Study 301 and 306. Due to the lack of differences across subgroups in 301/302 and 306B, the ISE will not contain new analyses of efficacy by subgroups.*

*Integrated Summary of Safety (ISS) - As Study 306 had a fundamentally different design from previous studies (double blind titration, long term double blind treatment, Parkinson's patients only) Chelsea intends to do only minimal integration of Study 306. The resubmitted ISS will contain safety data from 306 A and B datasets combined, and exposure data across all studies. Data from 306 will be presented along with other study safety data as requested in the complete response letter for the purposes of comparison, but the datasets will not be integrated. Due to the lack of signal in previous studies and 306B, the ISS will not contain new analysis of safety by concomitant medication subgroups. The resubmitted ISS will also contain updated long term safety sections, with final data from Study 304. The ISS will also contain safety information from studies in indications other than NOH.*

**Additional Questions:**

*Chelsea proposes to not submit full patient line listings in the CSR for 306 (A or B) and Study 304, instead providing the data as SAS datasets. Does the agency agree with this?*

**Discussion:** The Agency agreed with Chelsea's proposal.

*Chelsea intends to rely on the NDA amendment, sequence 036, submitted 5/31/12, regarding the interim analysis and blinding of study 306B as the primary means of addressing this issue with the study. Is there additional information that agency wants submitted regarding the interim analysis in Study 306?*

Discussion: The Agency recommended submitting all data that would be useful to evaluate dropouts, and should include treatment stop dates, follow-up stop dates, whether dropouts were preceded by an AE, dates of titration, and any other information that would be helpful.

*Does the agency agree that the attached information in the table of contents and analysis etc. as outlined is sufficient for a complete resubmission of the NDA?*

Discussion: No additional discussion occurred at the meeting on the contents of the resubmission.

Post-meeting comments: We do not have any additional requests for submission beyond those requested at the meeting.

**Attachment 2**

**Request for Comment and Follow-up to March 28, 2012 Communication from FDA  
Concerning Bioequivalence Study for Northera™ Capsules, 300 mg**

*In the Complete Response letter dated March 28, 2012, FDA provided the following comment under the Clinical Pharmacology section:*

*“The Office of Scientific Investigations (OSI) performed clinical and bioanalytical site inspections for pivotal bioequivalence (BE) study 101 and concluded that the bioanalytical part of the pivotal BE evaluation between 3 x 100 mg capsules (phase III formulation) and 1 x 300 mg capsules (proposed new formulation) is not reliable. Therefore, the BE results from this study are not acceptable. You will need another BE study, preferably comparing 1 x 300 mg capsules (proposed new strength) and 1 x 100 mg + 1 x 200 mg capsules (as used in the Phase III program), if you wish to pursue the approval of 300 mg formulation.”*

*In response to the request for a new bioequivalence (BE) study, Chelsea is in the process of finalizing the BE study protocol to support introduction of Northera™ (droxidopa) capsules, 300 mg in the NDA for approval and future commercialization. The 300 mg capsule was not the subject of clinical efficacy studies, but introduced into the NDA using a BE study per agreement with the Agency as stated in August 4, 2009 correspondence. A BE study was required for introduction of the 300 mg in the NDA* (b) (4)

*The difference was considered a SUPAC IR Level 3 change; therefore requiring a BE study. Reference is made to Table 1 for information supporting the formulations.*

*As noted above, the original BE study utilized three 100 mg capsules compared to one 300 mg capsule. Based on the Agency recommendation, one 100 mg and one 200 mg Northera capsule will be compared to one 300 mg capsule in the new BE study. Northera capsules, 100 mg and 200 mg batches selected for the BE study are representative of material used in the Phase III clinical program and represent the proposed commercial formulation, manufacturing process, and site of commercial manufacture. The selected 300 mg capsule batch is also representative of the proposed commercial formulation, manufacturing process, and site of commercial manufacture.*

*The planned BE study will be conducted according to the original protocol design with changes only to the subject capsules used in the study. Specifically, A Randomized, Open-Label, Bioequivalence Study in Healthy Subjects will be conducted. Each subject will receive a single, oral dose of one 100 mg and one 200 mg capsule of droxidopa with 240 mL of water in the fasted state (Treatment A) and a single, oral dose of one 300 mg capsule of droxidopa with 240 mL of water in the fasted state (Treatment B) on Days 1 and 4. Subjects will be discharged from the research clinic on Day 5 after completing all post-treatment follow-up assessments.*

*Question:*

Can the FDA confirm that it is acceptable to conduct the BE study using the original protocol design and comparing one 300 mg capsule with one 100 mg and one 200 mg capsule to pursue the approval of 300 mg capsule and not repeat the previously submitted BE study comparing three 100 mg capsules with one 300 mg capsule?

**FDA Response:** This matter was discussed previously.

**Table 1: Description and Composition of the Drug Product [Northera™ (droxidopa) capsules] (Previously submitted in Original NDA)**

<b>Components of Northera™ (droxidopa) capsules, 100, 200, and 300 mg</b>								
<b>Ingredient</b>	<b>Function</b>	<b>100 mg Capsule</b>		<b>200 mg Capsule</b>		<b>300 mg Capsule</b>		
		<b>mg/Capsule</b>	<b>Percent w/w</b>	<b>mg/Capsule</b>	<b>Percent w/w</b>	<b>mg/Capsule</b>	<b>Percent w/w</b>	
Droxidopa	Active	100	(b) (4)	200	(b) (4)	300	(b) (4)	
Mannitol, USP/Ph. Eur.								(b) (4)
Corn starch, NF/Ph. Eur./JP								
Magnesium Stearate, NF/Ph. Eur.								
<b>Total Weight</b>		270 mg	100.0	370 mg	100.0	480 mg	100.0	
Empty Capsule <sup>a</sup>	Encapsulation	Size 3		Size 2		Size 1		
<sup>a</sup> = Size 3 capsules are light blue/white opaque, Size 2 capsules are light yellow/white opaque and, Size 1 are light green/white opaque. The capsules will be imprinted with (b) (4) or (b) (4) black ink.								

<i>Components of Capsules Shells Size 1, 2, and 3</i>			
	<i>100 mg: Size 3</i>	<i>200 mg: Size 2</i>	<i>300 mg: Size 1</i>
(b) (4)			
<i>Titanium Dioxide</i>			
<i>Gelatin</i>			
(b) (4)			
<i>FD&amp;C Blue #1</i>			
<i>FD&amp;C Blue #2</i>			
(b) (4) <i>Black Iron Oxide</i>			
(b) (4) <i>Red Iron Oxide</i>			
(b) (4) <i>Yellow Iron Oxide</i>			
<i>FD&amp;C Yellow #5</i>			
<i>FD&amp;C Red #40</i>			
(b) (4)			

*Northera (droxidopa) capsules will be packaged in high density polyethylene bottles* (b) (4)

Discussion: (b) (4)

The Agency indicated to Chelsea that if accelerated approval is granted and post-marketing studies fail to verify the clinical benefit, droxidopa must be removed from the market. The Agency stated Chelsea should include in the proposal for post-approval studies under subpart H, a mechanism for automatically withdrawing the drug if the studies fail.

**3.0 PREA REQUIREMENTS**

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting occurred prior to November 6, 2012 or an EOP2 meeting will not occur, then:

- if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).
- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP, including a PSP Template, please refer to:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email [pdit@fda.hhs.gov](mailto:pdit@fda.hhs.gov).

#### **4.0 ISSUES REQUIRING FURTHER DISCUSSION**

**None.**

#### **5.0 ACTION ITEMS**

**None.**

#### **6.0 ATTACHMENTS AND HANDOUTS**

Sponsor's presentation provided below.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ANNA J PARK  
04/03/2013

ELLIS F UNGER  
04/03/2013



NDA 203202

**DISPUTE APPEAL – DENIED**

Chelsea Therapeutics  
Attention: Joseph Oliveto  
President & Interim CEO  
3530 Toringdon Way  
Charlotte, NC 28277

Dear Mr. Oliveto:

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

Chelsea Therapeutics submitted a request for formal dispute resolution (FDRR) to the Office of New Drugs (OND) on December 12, 2012, concerning the complete response (CR) letter issued on March 28, 2012, by Dr. Ellis Unger, Acting Director of the Office of Drug Evaluation I (ODE I).<sup>1</sup> Specifically, you appealed Dr. Unger's conclusion that the application for droxidopa could not be approved for the treatment of neurogenic orthostatic hypotension (NOH) and that at least one additional adequate and well-controlled clinical trial would be needed to demonstrate efficacy prior to approval. In your appeal, you request that FDA reconsider the available clinical data, which in your view support the safety and efficacy of droxidopa, and grant accelerated approval with a requirement for a post-approval clinical trial to confirm clinical benefit in patients with NOH. As part of my review of your appeal, I, along with other FDA staff, met with Chelsea on January 10, 2013. In that meeting the issues raised in your request for formal dispute resolution were discussed in detail. I also acknowledge your submission of additional information, which was received on January 17, 2013, submitted in response to questions I posed to Chelsea after our meeting.

I have carefully reviewed the materials you submitted in support of your appeal, the reviews, meeting minutes, and decision memoranda prepared by FDA staff, the CR letter, and other pertinent material (e.g. material and transcripts from the February 23, 2012, Cardiovascular and Renal Drugs Advisory Committee (CRDAC) meeting). I have also consulted with staff in the Division of Cardiovascular and Renal Products (DCRP), Office of Drug Evaluation I (ODE I), Office of Regulatory Policy, Office of Biostatistics (OB), Dr. Lisa LaVange, Director, OB, and Robert Temple, M.D., Deputy Center Director for Clinical Science.

I have completed my review of your request for formal dispute resolution and deny your appeal. I summarize the basis for my conclusions below. I have organized my response according to the three broad themes articulated in your appeal; fairness, regulatory flexibility, and whether the totality of the available data support approval of droxidopa for NOH. I also provide my thoughts on a possible path forward in support of a resubmission of the NDA in response to the CR letter.

**Fairness**

You argue in your appeal that Chelsea has been treated unfairly by FDA because midodrine, the only other drug approved by FDA for treatment of orthostatic hypotension, was approved under the accelerated approval provisions in 1996 based on improvement in standing systolic blood pressure (SSBP), a surrogate endpoint that at that time the Agency considered reasonably likely to predict clinical benefit in patients with orthostatic

<sup>1</sup> Dr. Unger subsequently became the Director of ODE I.

hypotension. You state that, in contrast, starting at the pre-IND meeting held on March 30, 2007, FDA has consistently advised Chelsea that a demonstration of clinical benefit (e.g., improvement in patient symptoms or ability to function), not an increase in SSBP, would be required to support approval. You argue, and provide legal citations in support of your argument, that FDA must treat similarly situated entities similarly and, therefore, must approve droxidopa under the accelerated approval provisions based on an improvement in SSBP, which you argue has been demonstrated in trials conducted by Chelsea and others. You also argue that ODE I has failed to provide an adequate explanation to justify its disparate treatment of midodrine and droxidopa.

I agree that the FDA has an obligation to treat similarly situated parties similarly. However, I disagree with your assertion that FDA has neglected that obligation in this case or that midodrine and droxidopa are similarly situated.

At the time of the approval of midodrine in 1996 the Agency concluded that an increase in SSBP was reasonably likely to predict clinical benefit (e.g., improvement in patient symptoms or ability to function) in patients with orthostatic hypotension. The Agency's conclusion was reasonable given the scientific information available at that time. Although we remain hopeful that ongoing clinical trials will verify midodrine's clinical benefit, based on the accumulated scientific information we now have reason to doubt our 1996 conclusion about SSBP as a predictor of clinical benefit in patients with orthostatic hypotension. In your appeal you correctly note that "In the 16 years since its accelerated approval, there has not been a single positive clinical study demonstrating the clinical symptomatic benefit of midodrine."<sup>2</sup>

Since the approval of midodrine, the Agency's thinking has changed concerning the merit of SSBP as a surrogate endpoint for accelerated approval in patients with orthostatic hypotension. Specifically, we no longer believe a change in SSBP meets the statutory and regulatory standard as "reasonably likely to predict clinical benefit" based on the scientific evidence available today. We further note that you have not submitted evidence indicating that an increase in SSBP of a given magnitude is reasonably likely to predict clinical benefit.

Based on the new scientific information from the multiple clinical trials of midodrine that failed to demonstrate clinical benefit, the Agency advised Chelsea, beginning in 2007, to design the development program for droxidopa to show an improvement in a clinical endpoint, such as an improvement in symptoms or ability to function, and not changes in SSBP. My review of the record shows no evidence that Chelsea objected to this advice from the Agency at that time. Chelsea was first given this advice about the proposed clinical development program for droxidopa during the March 30, 2007, pre-IND meeting. Less than 6 months later, on September 20, 2007, Chelsea met with the Agency for an end-of-phase 2 meeting. By that time Chelsea had fully incorporated the Agency's advice into the development plan for droxidopa; i.e., Chelsea proposed the Orthostatic Hypotension Symptom Assessment (OHSA) as the primary endpoint to measure symptomatic benefit of droxidopa in its Phase 3 clinical trials to support approval.

I believe that Chelsea clearly understood the Agency's position that SSBP could not be used as a surrogate endpoint to support accelerated approval, and that conclusion is supported by statements made by Dr. William Schwieterman, Chelsea's Chief Medical Officer, during the CRDAC meeting on February 23, 2012. At that meeting, Dr. Schwieterman said "...because of the weak correlation of symptoms to blood pressure, blood pressure alone cannot be used as a primary judge of droxidopa's, or any drug's, effect on clinical benefit in NOH."<sup>3</sup> In a later exchange in response to a committee member's question about the poor correlation between blood pressure and patient symptoms, Dr. Schwieterman stated "The difficulty in this disease – and I think it's a difficulty that has plagued this field, actually, for many, many years; certainly the FDA called it to our attention at the very beginning of the development program when they mandated that we study symptoms alone as a primary endpoint for this disease, and not blood pressure."<sup>4</sup> I interpret Dr. Schwieterman's comments at the Advisory Committee meeting as clear evidence that he, and Chelsea, understood that the Agency's advice on

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<sup>2</sup> Chelsea FDRR background package, December 12, 2012, page 14.

<sup>3</sup> Transcript of February 23, 2012, Cardiovascular and Renal Drugs Advisory Committee, page 49.

<sup>4</sup> Transcript of February 23, 2012, Cardiovascular and Renal Drugs Advisory Committee, page 273.

clinical endpoints for the droxidopa program was based on accumulated scientific information about the poor correlation between changes in SSBP and symptoms in patients with NOH.

The challenge the Agency faces anytime it makes a new scientific determination regarding the requirements for approval for a specific indication is how to apply the new requirements to future marketing applications from sponsors whose development programs were ongoing at that time, as well as the impact of the new requirements on drugs that were approved previously. The Agency appropriately advised Chelsea of its expectations regarding the data necessary to support approval of droxidopa for patients with NOH from the initial meeting in 2007 to discuss the development program, well before the design and initiation of the Phase 3 clinical trials for droxidopa. Chelsea clearly understood and applied the Agency's advice to the design of its Phase 3 clinical trials. Chelsea confirmed the accuracy of its understanding of the Agency's advice by submitting Study 301 for Agency review under a Special Protocol Assessment (SPA). Only after the Agency concluded that the clinical program conducted by Chelsea did not support approval did Chelsea raise the issue of fairness. I find that the facts in this case support a conclusion that the Agency made a sound, science-based decision to no longer accept SSBP as a surrogate for clinical benefit for accelerated approval for a drug intended to treat NOH. The passage of time and the availability of new scientific information support a conclusion that the facts surrounding the Agency's 1996 approval of midodrine and its 2012 review and non-approval of droxidopa are not "similar" and that the Agency has treated Chelsea fairly.

The Agency's policy is that it must apply the most current thinking and science as it makes decisions on individual applications. To do otherwise would prevent the Agency from incorporating new science into its decision making and perpetuate past practices that in some cases may have proven to be flawed or outdated. The Agency has generally not revisited all past decisions once our policy on a given issue changes. The Agency may, however, revisit past decisions if it has concerns that the approved drug may be ineffective or unsafe for its intended use. With regard to midodrine, the Agency has revisited its approval decision and initiated appropriate regulatory actions.

On August 16, 2010, the Agency issued a Notice of Opportunity for a Hearing (NOOH) to the holders of approved NDAs and ANDAs for midodrine proposing to withdraw approval because of the applicants' failure to conduct postmarketing clinical trials that verify and describe the clinical benefit of midodrine. Although the action was based on the failure of the applicants to provide the evidence required under accelerated approval, the repeated failure of trials attempting to show an effect on symptoms constituted the new scientific information that led the Agency to advise Chelsea to use improvement in patient symptoms or ability to function as primary endpoints in its development program for droxidopa. The NOOH process is being held in abeyance following an agreement between Shire, the NDA application holder, and FDA on a timeline for the conduct of two new controlled clinical trials to demonstrate clinical benefit of midodrine in patients with orthostatic hypotension. The Agency has made clear, however, and Shire has agreed, that if the two new clinical trials are not completed according to the timeline specified in the agreement, or if the trials fail to demonstrate clinical benefit, the approval of midodrine will be withdrawn without an opportunity for a hearing. I believe the Agency has taken the proper steps to apply the appropriate legal and regulatory procedures to new drugs under development for NOH and midodrine, the only drug currently approved by FDA to treat orthostatic hypotension.

### **Regulatory flexibility**

In your appeal you argue that FDA should exercise regulatory flexibility in reviewing the data submitted in support of droxidopa since it is intended to treat a serious rare disease where there is an unmet medical need. You cite examples of other drugs for rare diseases where, in your opinion, the FDA exercised a greater degree of regulatory flexibility than has been applied during the review of droxidopa. You also suggest that accelerated approval, with a requirement to confirm clinical benefit after approval, would be an appropriate pathway for droxidopa for treatment of patients with NOH.

I agree that FDA can apply regulatory flexibility in its review and decision making, particularly for drugs intended to treat serious diseases with an unmet medical need. The Agency has a long history of applying such

regulatory flexibility to drugs for the treatment of rare diseases. Regulatory flexibility, however, cannot overcome failure of a drug's sponsor to submit data that meet the substantial evidence standard under the Food, Drug, and Cosmetic Act for demonstration of effectiveness of a drug for its intended use. The substantial evidence standard applies to all drugs, including orphan drugs and drugs being considered for accelerated approval. Although the Agency can, and does, apply regulatory flexibility in determining the type and quantity of data required to demonstrate effectiveness, in all cases we must conclude that the submitted data meet the substantial evidence standard. FDA has issued guidance on demonstration of effectiveness, and that guidance describes in clear terms how the Agency interprets the statutory standard, and applies regulatory flexibility in its decisions on whether the data submitted in a particular application meet the statutory standard.<sup>5</sup> Based on my review of the data for droxidopa, I believe that ODE I properly concluded that substantial evidence of effectiveness has not been demonstrated for droxidopa in the treatment of NOH.

### **Totality of the data**

In your appeal you argue that the totality of the data support accelerated approval of droxidopa for the treatment of NOH. I summarize below my review of the available data and why I concur with ODE I that the statutory standard for substantial evidence of effectiveness has not been met.<sup>6</sup>

Chelsea's development program for droxidopa included three Phase 3 controlled clinical trials, Studies 301, 302, and 303. Study 302 was conducted first. This was a randomized withdrawal study in which patients were titrated to a maximally effective and/or tolerated dose of droxidopa during an open label phase. Those patients who appeared to respond to and/or tolerate droxidopa (e.g., an enriched population) were randomized to either continuation of droxidopa or to placebo for two weeks. The pre-specified primary endpoint for this trial was OHSA Item 1 (i.e., dizziness, lightheadedness, feeling faint, or feeling like you may black out), which reflects a clinically relevant patient-reported outcome for this disease. The trial results showed no difference between droxidopa and placebo on OHSA Item 1 after two weeks of randomized treatment (p=0.509). This failed trial, in a population enriched for responders, does not provide support for a demonstration of substantial evidence of effectiveness of droxidopa in NOH.

A post hoc analysis of the Orthostatic Hypotension Questionnaire (OHQ), a composite patient-reported outcome that includes the OHSA and the Orthostatic Hypotension Daily Activity Scale (OHDAS), found nominal statistical significance (p=0.042) and was used as the justification to change the primary endpoint for Study 301 to OHQ. This post hoc analysis, which was derived from a trial that failed on its pre-specified primary endpoint, is useful for hypothesis generation, but does not provide support for a demonstration of substantial evidence of effectiveness of droxidopa in patients with NOH.

Study 301 also included an open-label phase in which patients were titrated to a maximally effective and/or tolerated dose of droxidopa. Those patients who appeared to respond to and tolerate droxidopa (again an enriched population) underwent a one-week washout period in which they received no droxidopa. After the wash out, patients were randomized to either droxidopa (at the dose they were titrated to in the open-label phase of the trial) or placebo for one week. Based on the results of Study 302, the primary efficacy endpoint for Study 301 was changed during the study from OHSA Item 1 to OHQ. The results of the study showed a placebo-subtracted mean change from baseline in OHQ score of 0.9 favoring droxidopa, p=0.003. Analyses of various secondary endpoints, including OHSA Item 1 and SSBP were also positive favoring droxidopa. Thus, Study 301 appeared to be a strongly positive study supporting the effectiveness of droxidopa in treatment of patients with NOH (albeit with questions regarding the clinical importance of the 0.9 change on the OHQ scale).

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<sup>5</sup> FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products ("effectiveness guidance") (May 1998) at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078749.pdf>.

<sup>6</sup> In your appeal you base many of your arguments on a proposal for accelerated approval based on SSBP as a surrogate endpoint. The Agency no longer considers SSBP a surrogate endpoint reasonably likely to predict clinical benefit in patients with NOH and SSBP was not the pre-specified primary endpoint of Studies 301, 302, and 303. Therefore, my analysis focused on study endpoints related to improvement in patient symptoms or ability to function.

Following discussion of the droxidopa NDA at the February 23, 2012, CRDAC meeting (at which the majority of advisors voted in favor of approval), FDA staff performed additional analyses of the positive responders seen for droxidopa on the cumulative distribution curve presented by Chelsea at the AC meeting. These analyses were conducted to better understand the characteristics of the patients who experienced 4-point or greater reductions in OHQ score during the randomized treatment phase of the trial. These “super responders” were of great interest to members of the AC who voted in favor of approval, and analysis of the characteristics of these patients was considered potentially useful in selecting patients for treatment if droxidopa were to be approved.

FDA reviewers were surprised to find that 6 out of the 15 “super responders” to droxidopa (i.e, patients experiencing a 4-point or greater reduction in OHQ score) were enrolled at a single site, Site 507, in the Ukraine. Further examination of the data from Site 507, the highest enrolling site in Study 301, showed remarkably homogeneous change from baseline scores in both the droxidopa and placebo groups for the OHQ primary endpoint as well as for secondary endpoints such as OHSa Item 1 and SSBP. That is, patients in the droxidopa group showed consistently large improvement in all three outcomes, whereas patients in the placebo group showed consistently negligible improvement or worsening. The treatment effect observed for OHQ at Site 507 alone was highly statistically significant even though the analysis included only 16 patients. When Site 507 was removed from the intent-to-treat (ITT) population of Study 301, the study was no longer positive for the OHQ primary endpoint ( $p=0.082$ ). The FDA statistical reviewer performed a simulation of 10,000 runs to randomly remove 16 subjects (9 droxidopa, 7 placebo) from the Study 301 dataset. She found that the probability of observing a p-value of 0.082 or greater by randomly removing 16 subjects from the ITT population was less than 0.0001.

Study 303 was also a randomized withdrawal design in which all patients were treated with droxidopa in an open-label manner for three months before being randomized to receive droxidopa (at the dose the patient was receiving in the open-label phase) or placebo for 14 days. There was no significant difference in change in OHQ, the pre-specified primary endpoint, between the droxidopa and placebo groups during the randomized treatment period ( $p=0.44$ ). This failed trial, in a population enriched for responders, does not provide support for a demonstration of substantial evidence of effectiveness of droxidopa in NOH.

In your appeal you argue Studies 302 and 303, the randomized withdrawal trials, likely failed on their primary endpoints because of a carryover effect of drug such that differences between drug and placebo could not be observed in a period of two weeks. This is an interesting hypothesis; however, you have not provided convincing evidence of such a carryover effect of the drug.

During our meeting on January 10, 2013, you presented analyses of Studies 301, 302, and 303, which you argue demonstrate the carryover effect of droxidopa.<sup>7</sup> These analyses compared the change in SSBP from baseline to randomization (Study 301) or from baseline to end-of-study visit (Studies 302 and 303) in patients who were titrated to a maximum effective and/or tolerable dose of droxidopa and then withdrawn from the drug for 1-2 weeks. I do not find these analyses convincing of a carryover effect for several reasons. First, the patients included in the analyses at the time of randomization (Study 301) or end-of-study visit (Studies 302 and 303) were only a subset of the patients included in the baseline group because of the trial procedures that dropped patients who did not respond to or tolerate droxidopa during the titration phase. The increase in SSBP that you attribute to a persistent effect of droxidopa after withdrawal of treatment may simply be related to the selection of a subset of patients with higher SSBP unrelated to an effect of the drug. Second, the analyses do not include a control group and do not isolate the effect, if any, of droxidopa. Third, these analyses do not account for other factors that may have resulted in higher SSBP in patients enrolled in the trial, such as improved attention to volume status and use of compression stockings. Finally, your analyses ignore the fact that the SSBP after drug withdrawal in Study 303 was higher in the placebo group than in the droxidopa group. This paradoxical effect is directly opposite to what should have been observed if there is a carryover effect of droxidopa. Additional

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<sup>7</sup> Chelsea slides 34-38 from the January 10, 2013, meeting.

adequately designed controlled clinical trials would be necessary to support your hypothesis of a carryover effect of droxidopa.

In summary, two of the Phase 3 trials (302 and 303) conducted by Chelsea to support approval of droxidopa were negative and results from the single positive trial (301) were largely due to the extremely positive and unusually homogeneous results at a single site (Site 507).<sup>8</sup> During our meeting on January 10, 2013, you reported that you had carefully audited Site 507 on two occasions, including once during the conduct of the trial, and found no evidence of fraud. You also noted that FDA inspected this site during the NDA review and also found no evidence of fraud. You argue that the absence of evidence of fraud from three inspections suggests that the data from this site are reliable and should not be excluded from the overall analysis of Study 301. During the meeting you also provided possible explanations for the extreme results observed at Site 507 (e.g., there was a record heat wave in the Ukraine during the time the trial was being conducted); however, these are simply hypotheses and do not provide actual evidence to explain the extreme results. Moreover, they explain neither the remarkable homogeneity of responses in droxidopa-treated patients nor the observation of no significant variation in SSBP in any placebo patient on measures taken a week apart.

In considering the weight of evidence supplied by the results of Study 301 it is not necessary for the FDA to conclude that the data from Site 507 were fraudulent in order for us to be concerned about the observation that the extreme results at this site were largely responsible for the overall results of the single positive Phase 3 trial. As described in detail in the FDA effectiveness guidance, FDA has generally interpreted the substantial evidence standard in the statute to require "...at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness." In section 115(a) of the FDA Modernization Act of 1997, Congress amended section 505(d) of the Act to make it clear that the Agency may consider "data from one adequate and well-controlled clinical investigation and confirmatory evidence" to constitute substantial evidence if FDA determines that such data and evidence are sufficient to establish effectiveness. Section II.C.3 of the effectiveness guidance outlines the criteria the Agency considers when evaluating an application in which a single study is proposed to provide the necessary data to provide substantial evidence of effectiveness. I have carefully considered those criteria as they relate to the droxidopa NDA.

Although Study 301 has some of the features described in the effectiveness guidance that could support reliance on a single adequate and well-controlled trial to support demonstration of effectiveness, the guidance makes clear that if a single site is largely responsible for the overall effect seen in a multicenter trial, the credibility of the trial as the sole support for effectiveness is diminished. As noted above, the positive results from Study 301 are largely due to the highly favorable and extremely homogeneous results observed at Site 507. This observation raises serious questions about the generalizability of the results seen in Study 301 to the patients who are likely to receive in the drug in the US. Moreover, the finding that two other controlled trials, each enriched for responders, showed no effect on the pre-specified primary endpoint further weakens the support of effectiveness provided by Study 301. Based on these findings, I concur with Dr. Unger's conclusion that the data submitted in the NDA do not constitute substantial evidence of effectiveness of droxidopa in the treatment of patients with NOH.

### **Potential path forward**

In the CR letter Dr. Unger advised that "...an additional positive study will be needed to support efficacy" and also noted that evidence to support durability of the effect of droxidopa in treatment of NOH would be needed. He recommended that an additional trial be conducted to show durability of effect over a 2- to 3-month treatment period.

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<sup>8</sup> On further review FDA staff noted similar extreme results and homogeneity at a second site (Site 505), which was also located in the Ukraine. This was the second largest enrolling site (11 subjects) and was also nominally statistically significant ( $p=0.007$ ) when analyzed alone.

I concur with Dr. Unger that at least one additional strongly positive adequate and well-controlled trial is necessary to support a demonstration of effectiveness of droxidopa in NOH. I also agree with Dr. Unger that ideally there should be evidence of the durability of the effectiveness of droxidopa since NOH is a chronic condition and it can be expected that patients will take droxidopa long-term. I note, however, that in the agreement reached between Shire and FDA on the additional trials needed to support continued marketing of midodrine the Agency agreed to accept data demonstrating a short-term benefit of midodrine as adequate evidence to support continued approval. Therefore, I believe that data strongly demonstrating a short-term clinical benefit (e.g., improvement in symptoms or ability to function) of droxidopa in patients with NOH would be adequate to support approval, with a possible requirement to verify durable clinical benefit postapproval.

During the post-action meeting between Chelsea and DCRP/ODE I held on May 2, 2012, Chelsea proposed that the results of Study 306B, which was ongoing at that time, be accepted as an adequate and well-controlled trial in support of approval of droxidopa. Study 306B was a randomized, 8-week, placebo-controlled trial of droxidopa in patients with Parkinson's disease and symptomatic orthostatic hypotension. Chelsea also proposed to change the primary endpoint of the ongoing trial from reduction in the rate of falls to OHSA Item 1.

DCRP and ODE I expressed significant reservations regarding the usefulness of Study 306B as an adequate and well-controlled trial to support effectiveness. Their reservations were based on concerns related to the unblinded interim analysis of Study 306A, the first half of Study 306, and the possibility that scientific staff from Chelsea who were responsible for decisions to continue Study 306B and to change the primary endpoint may have had inappropriate contact with the unblinded statisticians at the contract research organization (CRO) who conducted the interim analysis of Study 306A and who had access to randomization codes for the full trial. DCRP and ODE I were concerned that Chelsea staff may have had inappropriate access to the results for patients enrolled in Study 306B and made decisions, therefore, regarding the conduct and analysis of the trial based on knowledge of the ongoing trial data.

Chelsea provided extensive documentation to support the assertion that all Chelsea staff remained blinded to the data from (then) ongoing Study 306B and that all decisions related to the conduct and analysis of Study 306B were made based on the unblinded data for the patients included in Study 306A, which will not be included in the analysis of Study 306B. DCRP and ODE I carefully reviewed the information submitted and remained concerned about the integrity of the conduct and analysis of Study 306B. In a letter dated June 29, 2012, Dr. Unger amended prior advice provided by DCRP and ODE I, which stated that "Study NOH306B will not be useful as an efficacy trial regardless of the results," and advised that "If an analysis of all subjects enrolled in study 306 after you amended the analytic plan demonstrated a statistically significant benefit on the primary endpoint, we might regard this as a positive trial; however, we believe that such an outcome is highly unlikely." Thus, DCRP and ODE I continued to have significant reservations about the usefulness of Study 306B to support a demonstration of effectiveness.

While not a part of your request for dispute resolution, as part of my review of your appeal I asked staff in the Office of Scientific Investigations (OSI) and Dr. Lisa LaVange, Director of OB, to review the circumstances related to the unblinded interim analysis of Study 306A and the interactions between Chelsea staff and the unblinded CRO statisticians. OSI staff and Dr. LaVange have extensive experience in evaluating the integrity of the conduct of clinical trials and I thought it was important to understand their assessment of the potential impact of the events on the Agency's ability to rely on the data from Study 306B to support the effectiveness of droxidopa in patients with NOH. Based on the documentation submitted to the Agency concerning the timeline and procedures for unblinding Study 306A and maintaining the blind of study teams at both the CRO and the sponsor for Study 306B, OSI staff and Dr. LaVange concluded that the data from Study 306B may be acceptable for Agency review.

Because Study 306B is a relatively large trial in patients with NOH, I believe that it has the potential to serve as the basis for a resubmission of the NDA in response to the CR letter's request for at least one additional adequate and well-controlled trial. In your appeal you argue that FDA should consider the totality of the data in

making its decision, and I agree. The Agency has not had a chance to review the data from Study 306B since the study data were only recently unblinded and preliminary results reported.

I suggest that Chelsea carefully evaluate whether the results of Study 306B can address the deficiencies in demonstration of effectiveness noted in the CR letter and in my denial of your appeal. In making this assessment, Chelsea should carefully consider the strengths and weaknesses of the trial design and conduct, the robustness of the reported positive results of the trial on OHSA Item 1 as well as findings on important secondary endpoints of clinical benefit. Given the significant limitations of the data from Study 301, as described above, to support a finding of substantial evidence of effectiveness, it will be important that the results of Study 306B be strongly positive; i.e., the trial should closely adhere to the criteria specified in the Agency's effectiveness guidance for a single trial. If your evaluation of Study 306B is favorable I recommend that you request a meeting with DCRP/ODE I to discuss submission of a complete response to the CR letter to include full data sets and analysis of Study 306B. I must stress that a decision on the approvability of the resubmitted application will be made by DCRP and ODE I following a complete review of the data, which may include audits of the conduct and results of Study 306B (e.g., clinical site inspections, inspection of Chelsea and the CROs). In other words, while the Agency is willing to review the results of Study 306B as part of a complete response to the CR letter, the outcome of that review will be based on the strength of the new trial and its ability to provide substantial evidence of effectiveness to support approval.

If Chelsea does not believe that the results of Study 306B meet the Agency's expectations to support approval, I suggest that you request a meeting with DCRP and ODE I to discuss the design of a new adequate and well-controlled trial(s) to provide substantial evidence of effectiveness of droxidopa in NOH.<sup>9</sup>

Any questions regarding next steps as described in this letter should be directed to Anna Park, Senior Regulatory Health Project Manager, DCRP, at (301) 796-1129.

If you wish to appeal this decision to the next level, your appeal should be directed to Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research. The appeal should be sent to the NDA administrative file as an amendment, and a copy should be sent to the Center's Formal Dispute Resolution Project Manager, Amy Bertha. Any questions concerning your appeal should be addressed to Ms. Bertha at (301) 796-1647.

Sincerely,

*{See appended electronic signature page}*

John Jenkins, M.D.  
Director  
Office of New Drugs  
Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JOHN K JENKINS  
02/08/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 203202

**MEETING MINUTES**

Chelsea Therapeutics  
Attention: Joseph Oliveto  
President & Interim CEO  
3530 Toringdon Way  
Charlotte, NC 28277

Dear Mr. Oliveto:

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

We also refer to the meeting between representatives of your firm and the FDA on January 10, 2013. The purpose of the meeting was to discuss the issues raised in your request for formal dispute resolution dated December 12, 2012.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1270.

Sincerely,

*{See appended electronic signature page}*

Khushboo Sharma, M.B.A, R.A.C  
Senior Regulatory Project Manager  
Office of New Drugs  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Date and Time:** January 10, 2013 4:00-5:30 pm EST  
**Meeting Location:** White Oak Campus, Building 22, Rm 1415

**Application Number:** NDA 203202  
**Product Name:** Northera (droxidopa) Capsules  
**Sponsor/Applicant Name:** Chelsea Therapeutics

**Meeting Chair:** John Jenkins, M.D.  
**Meeting Recorder:** Khushboo Sharma, M.B.A, RAC

**FDA ATTENDEES**

**Office of New Drugs**

John Jenkins, M.D.	Office Director
Amy Bertha	Formal Dispute Regulatory Project Manager
Khushboo Sharma, M.B.A, RAC	Sr. Regulatory Health Project Manager

**Office of New Drugs/Office of Drug Evaluation I (ODE I)**

Ellis Unger, M.D.	Director, ODE I
Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardiovascular and Renal Products (DCRP)
Stephen Grant, M.D.	Deputy Director, DCRP
Shari Targum, M.D.	Clinical Team Leader, DCRP
Anna Park, R.Ph.	Regulatory Health Project Manager, DCRP

**Office of Translational Sciences/ Office of Biostatistics**

Lisa LaVange, Ph.D.	Director
James Hung, Ph.D.	Director, Division of Biometrics I
Jialu Zhang, Ph.D.	Statistician, Division of Biometrics I
Steven Thomson, Ph.D.	Statistician, Division of Biometrics VI

**Office of Regulatory Policy**

David Joy	Senior Regulatory Counsel
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**Office of Chief Counsel**

Abigail Brandel	General Attorney
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**Office of Scientific Investigations**

Ann Meeker – O’Connell	Acting Division Director
Susan Leibenhaut	Acting Team Leader

**Center for Drug Evaluation and Research**

Robert Temple, M.D.

Deputy Center Director for Clinical Sciences

**SPONSOR ATTENDEES**

Loni Da Silva

L. Arthur Hewitt, Ph.D.

(b) (4)

Nicole Devirgilis

(b) (4)

Jeff Nelson

Joseph Oliveto

Gerry Rowse, Ph.D.

William Schwieterman, M.D.

Michael Weiser, M.D., Ph.D.

Cameron Szakacs, Ph.D.

Regulatory Consultant

Chief Scientific Officer

(b) (4)

Director of Quality Assurance

(b) (4)

Director of Strategic Planning

Interim President & Chief Executive Officer

Sr. Director Pharmaceutical Science &

Preclinical Studies

Chief Medical Officer

Chairman of the Board of Directors

Senior Director, Drug Development

**BACKGROUND**

Chelsea Therapeutics submitted a request for formal dispute resolution to the Office of New Drugs (OND) on December 12, 2012, concerning the complete response (CR) action taken on March 28, 2012, specifically the deficiency to conduct at least one additional positive study to support efficacy. Chelsea Therapeutics requests that FDA grant droxidopa accelerated approval on the basis of clinical evidence that has been submitted in the New Drug Application (NDA) and application of consistent regulatory standards for the approval of orphan drugs to treat neurogenic orthostatic hypotension (NOH). Dr. John Jenkins, Director, OND is the deciding authority. Dr. Jenkins requested a meeting with Chelsea Therapeutics before he renders his decision on the matter. Chelsea agreed to a meeting, and it was held on January 10, 2013.

**MEETING OBJECTIVES**

The objective of this meeting was to discuss the issues surrounding the appeal.

**DISCUSSION**

- On January 3, 2013, FDA emailed Chelsea a list of topics that Dr. Jenkins requested the sponsor to focus on at the meeting:
  - Data for droxidopa in the context of the provisions in the evidence guidance for when FDA can rely on a single trial with supportive data. Specifically, addressing the concerns related to Site 507 and the expectations stated in the guidance related to the qualities of a single trial that support approval.
  - Data for the randomized withdrawal trials that were conducted (study 302 and 303) and why Chelsea believed those highly enriched trials failed to show benefit on the pre-specified primary endpoint.
- Chelsea Therapeutics presented several slides to open the meeting and addressed the two points requested by Dr. Jenkins (presentation attached).
- Chelsea Therapeutics made the argument that midodrine was granted accelerated approval based on standing systolic blood pressure (SSBP) as a surrogate endpoint

reasonably likely to predict clinical benefit; hence, the same accelerated approval standards should be applied to droxidopa. Since the approval of midodrine, new scientific data from controlled clinical trials have led FDA to have serious doubts regarding the merit of SSBP as a surrogate endpoint reasonably likely to predict clinical benefit in patients with NOH. In several controlled clinical trials, midodrine has not shown clinical benefit.

- FDA stated that the statutory standard for approval for orphan drugs are the same as for non-orphan drugs and that substantial evidence of effectiveness is needed for both. In addition, FDA cited the Guidance for Industry, “Providing Evidence of Effectiveness for Human Drug and Biological Products,” highlighting that when relying on a single adequate and well-controlled clinical trial to support approval, if single site in the clinical trial is largely responsible for the beneficial effect the strength of the trial is diminished.
- There was in-depth discussion regarding the quality of the data at Site 507 in Study 301. The company discussed several potential factors (i.e. referral center with access to patients from a wide region, a record heat wave in that region during the conduct of the trial, enrollment of younger patients who were naïve to treatment) that may have affected the site results. One of FDA’s concerns was the lack of variability in the placebo and droxidopa-treated patients at that site. Chelsea Therapeutics reported that they conducted several audits of Site 507, and the results indicated no concerns.
- Chelsea Therapeutics clarified the chronology of events related to the unblinding of Study 306B and the interim analysis of the data. This chronology included the conversation between the Clinical Research Organization (CRO) and the Sponsor to discuss the interim analysis data for the 51 patients. According to Chelsea Therapeutics, the firewalls placed to protect the blinding of Study 306B were not compromised.

**DECISION (AGREEMENTS) REACHED:**

This meeting was not conducted with the expectation that decisions would be made or agreements would be reached at the meeting. The issues discussed will be taken into consideration when reaching a decision regarding the formal dispute resolution request, which will be made within 30 days from the meeting date.

**ATTACHMENTS/HANDOUTS:**

Slides from Chelsea Therapeutics presentation

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KHUSHBOO SHARMA  
02/08/2013



NDA 203202

**ACKNOWLEDGE DISPUTE APPEAL  
AND MEETING REQUESTED**

Chelsea Therapeutics  
Attention: Joseph Oliveto  
President & Interim CEO  
3530 Toringdon Way  
Charlotte, NC 28277

Dear Mr. Oliveto:

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

We acknowledge receipt on December 12, 2012, of your December 12, 2012, request for formal dispute resolution, concerning the deficiency in the complete response (CR) letter dated March 28, 2012 to conduct an additional clinical trial for approval. You are requesting accelerated approval or full approval with a post-marketing requirement for a clinical trial.

Your appeal has been forwarded for review to Dr. John Jenkins, Director, Office of New Drug (OND), Center for Drug Evaluation and Research. We have reviewed your appeal and conclude that additional input is needed to reach a decision. Therefore, we have scheduled the following meeting with you to clarify the issues.

**Date:** January 10, 2013  
**Time:** 4:00-5:30 pm EST  
**Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1415  
Silver Spring, Maryland 20903

**CDER participants (Invited):**

**Office of New Drugs**

John Jenkins, M.D.  
RADM Sandra L. Kweder, M.D.  
Amy Bertha  
Khushboo Sharma, M.B.A.

Office Director  
Deputy Office Director  
Team Lead, Regulatory Affairs Team  
Sr. Regulatory Health Project Manager, Regulatory  
Affairs Team

**Office of New Drugs/Office of Drug Evaluation I (ODE I)**

Ellis Unger, M.D.	Director, ODE I
Colleen Locicero	Associate Director for Regulatory Affairs, ODE I
Norman Strockbridge, M.D., Ph.D.	Director, Division of Cardiovascular and Renal Products (DCRP)
Stephen Grant, M.D.	Deputy Director, DCRP
Shari Targum, M.D.	Clinical Team Leader, DCRP
Melanie Blank, M.D.	Medical Officer, DCRP
Anna Park, R.Ph.	Regulatory Health Project Manager, DCRP

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Lisa LaVange, M.D.	Director, Office of Biostatistics
James Hung, Ph.d.	Director, Division of Biometrics I
Jialu Zhang, Ph.D.	Statistician, Division of Biometrics I
Steven Thomson, Ph.D.	Statistician, Division of Biometrics VI

**Office of Regulatory Policy**

Denise Esposito	Deputy Associate Director for Policy
David Joy	Senior Regulatory Counsel

**Center for Drug Evaluation and Research**

Janet Woodcock, M.D.	Center Director (non-decisional capacity)
Robert Temple, M.D.	Deputy Center Director for Clinical Sciences (non-decisional capacity)

Please e-mail your attendees to Khushboo Sharma, at [Khushboo.sharma@fda.hhs.gov](mailto:Khushboo.sharma@fda.hhs.gov), at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

A few days before the meeting, you may receive an email with a barcode generated by FDA's Lobbyguard system. If you receive this email, bring it with you to expedite your group's admission to the building. Ensure that the barcode is printed at 100% resolution to avoid potential barcode reading errors.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Khushboo Sharma (301) 796-1270 or Charmaine Johnson at the OND Immediate Office main number (301) 796-0700.

Subsequent to the meeting, we will respond to the formal dispute request within 30 days of the meeting (February 9, 2013). We will contact you should we have any questions or require additional information.

If you have any questions please contact Khushboo Sharma or call me at (301) 796-1647.

Sincerely,

*{See appended electronic signature page}*

Amy Bertha  
Team Leader, Regulatory Affairs Team  
Office of New Drugs  
Center for Drug Evaluation and Research

ENCLOSURE: Foreign Visitor Data Request Form

## FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

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/s/  
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AMY E BERTHA  
12/20/2012



NDA 203202

**GENERAL ADVICE**

Chelsea Therapeutics, Inc.  
Attention: Mr. Rex Horton  
Director of Regulatory Affairs  
3530 Toringdon Way, Suite 200  
Charlotte, NC 28277

Dear Mr. Horton:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NORTHERA (droxidopa) 100 mg, 200 mg, and 300 mg Capsules. We also refer to your May 31, 2012 submission, containing a revised protocol summary for Study 306B and supporting documents. We have reviewed the referenced material and have the following comments and recommendations.

As we have previously discussed, the results of study 301 were predominantly driven by the data generated at site 507, and the results at site 507 are highly irregular. If the data from site 507 are excluded from the analysis of the primary endpoint, the results are not statistically significant. Hence the support provided by study 301 is weak. We would, however, view study 301 as supportive if you were to submit the results of an additional adequate and well-controlled study with the characteristics outlined in FDA guidance.<sup>1</sup> Such a study should be quite strong; there should be no important issues regarding its veracity and/or interpretability. As presently planned, however, we do not believe that study 306 will provide this level of evidence.

We routinely inform sponsors that if they amend their analytic plan after substantial information has accumulated in the trial, we cannot be confident that information from the trial did not influence the redesign of the statistical analytic plan. We believe that at least 80 subjects had completed the trial and at least an additional 80 subjects had been enrolled (out of the 200 total proposed) prior to your amending the analytic plan for study 306. We reviewed the information you provided to support your assertion that you were unaware of any results from study 306 at the time of amending the analytic plan. It appears to us that some individuals external to the DMC may have been inappropriately unblinded. And whereas you have described the communications that took place between Chelsea, PPD, and the unblinded DMC statistical team, it is not possible for us to be confident that you are aware of every verbal (i.e., non-electronic) communication regarding the results. Given the availability of the randomization code to a number of individuals, it is really not possible to know with certainty that interim results did not somehow influence decisions to change the primary efficacy endpoint of study 306.

If an analysis of all subjects enrolled in study 306 after you amended the analytic plan demonstrated a statistically significant benefit on the primary endpoint, we might regard this as a

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<sup>1</sup> FDA Guidance for Industry: Providing Evidence of Effectiveness for Human Drug and Biological Products, 1998.

positive trial; however, we believe that such an outcome is highly unlikely. Hence we recommend that you design and conduct an additional trial to demonstrate that droxidopa has a significant and persistent effect on symptoms of orthostatic hypotension. We have suggested that a withdrawal trial in patients who appear to have responded to chronic administration of droxidopa (perhaps recruited from the many patients now taking droxidopa in your expanded access program) would be acceptable. There are many other designs that would be acceptable as well.

Given the important need of these patients for a safe and effective therapy, we are anxious to work with you in designing a new trial.

If you have any questions, please call Anna Park, Regulatory Project Manager, at (301) 796-1129.

Sincerely,

*{See appended electronic signature page}*

Ellis F. Unger, M.D.  
Director (acting)  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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ELLIS F UNGER  
06/29/2012



NDA 203202

**MEETING MINUTES**

Chelsea Therapeutics, Inc.  
Attention: Rex Horton  
Director of Regulatory Affairs  
3530 Toringdon Way, Suite 200  
Charlotte, NC 28277

Dear Mr. Horton:

Please refer to your New Drug Application (NDA) dated September 23, 2011, received September 28, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for NORTHERA (droxidopa) 100 mg, 200 mg and 300 mg Capsules.

We also refer to the meeting between representatives of your firm and the FDA on May 2, 2012. The purpose of the meeting was to reach an agreement on the additional data and information required to resolve all outstanding items and deficiencies as outlined in the Complete Response Letter issued by FDA on March 28, 2012.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Anna Park, Regulatory Project Manager at (301) 796-1129.

Sincerely,

*{See appended electronic signature page}*

Ellis F. Unger, M.D.  
Acting Director, Office of Drug Evaluation I  
Center for Drug Evaluation and Research

ENCLOSURE:  
Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** A  
**Meeting Category:** End of Review Conference

**Meeting Date and Time:** May 2, 2012 3:00 PM – 4:30 PM  
**Meeting Location:** Bldg 22 Room 1311

**Application Number:** NDA 203202  
**Product Name:** NORTHERA (droxidopa)  
**Indication:** 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 (DBH) Deficiency and Non-Diabetic Autonomic Neuropathy (NDAN)

**Sponsor/Applicant Name:** Chelsea Therapeutics, Inc.

**Meeting Chair:** Ellis F. Unger, M.D.  
**Meeting Recorder:** Anna Park

**FDA ATTENDEES**

Office of Drug Evaluation I

Ellis Unger, M.D. Acting Director

Division of Cardiovascular and Renal Products

Norman Stockbridge, M.D., Ph.D.	Director
Stephen Grant, M.D.	Deputy Director
Shari Targum, M.D.	Clinical Team Leader
Donald Jensen, DVM., M.S.	Pharmacology Reviewer
Edward Fromm, R.Ph., RAC	Chief, Project Management Staff
Anna Park, R.Ph.	Regulatory Project Manager

Office of New Drugs, Study Endpoints and Labeling Development Team

Elektra Papadopoulos, M.D. Study Endpoints Reviewer

Office of Clinical Pharmacology

Rajnikanth Madabushi, Ph.D.	Team Leader
Sreedharan Sabarinath, Ph.D.	Clinical Pharmacology Reviewer

Office of Biostatistics, Division of Biometrics I

James Hung, Ph.D.	Director
Jialu Zhang, Ph.D.	Statistician

Office of New Drug Assessment and Quality Assurance

Kasturi Srinivasachar, Ph.D.	Pharmaceutical Assessment Lead
Lyudmila Soldatova, Ph.D.	Product Quality Reviewer

Office of Scientific Investigations

Sharon Gershon, Pharm.D.	Reviewer
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**SPONSOR ATTENDEES**

Chelsea Therapeutics, Inc.

Bill Schwieterman, M.D.	Chief Medical Officer
Art Hewitt, Ph.D.	Chief Scientific Officer
Rex Horton	Director, Regulatory Affairs
Joe Oliveto, M.B.A.	Vice President, Operations
Simon Pedder, Ph.D.	President and Chief Executive Officer
Gerry Rowse, Ph.D.	Senior Director, Pharmaceutical Science and Pre-clinical Programs
Christopher Cioffi, Ph.D.	Associate Director, Drug Development
Cameron Szakacs, Ph.D.	Senior Director, Drug Development

External Consultants



## 1. BACKGROUND

Chelsea Therapeutics, Inc. submitted their New Drug Application for Droxidopa on September 23, 2011. Droxidopa is a new molecular entity, currently approved in Japan for the treatment of neurogenic orthostatic hypotension.

### Summary of Key Regulatory Milestones:

January 2007	Orphan drug designation granted for the NOH indication
February 2008	Agreement on a Special Protocol Assessment for study 301
August 2008	Fast Track designation granted
November 2009	Type C Meeting – discussion of sponsor’s planned modifications of study 301. The Division noted that study 302 could not be used as one of two studies to support efficacy because it failed on its primary endpoint
January 2010	Correspondence to sponsor – FDA agreed upon a change in the primary endpoint of study 301 from the Orthostatic Hypotension Symptoms Assessment (OHSA) Item 1 to the Orthostatic Hypotension Questionnaire (OHQ)
December 2010	Pre-NDA meeting – FDA reminded Chelsea that one trial is not usually sufficient for approval. FDA requested validation data for the PRO instruments used in the studies, as well as support for the view that the observed effect size in study 301 is clinically meaningful
September 2011	NDA submitted
February 2012	NDA presented at the Cardiovascular and Renal Drugs Advisory Committee Meeting
March 28, 2012	Complete Response Letter issued

Preliminary responses to the submitted questions were provided to the sponsor, and are copied below, followed by any additional discussions that took place during the meeting.

## 2. DISCUSSION

### 2.1. Accelerated Approval

**Question 1a:** Does the Agency agree that submission of results from Study 306B followed by an adequate and well-designed post-approval study to confirm durability of effect (as proposed above) will provide sufficient data for accelerated approval for droxidopa for the proposed indication?

**Question 1b):** Does the Agency agree that Study 306B would no longer be considered an exploratory study and would be considered supportive of efficacy and included in labeling under accelerated approval?

**Preliminary FDA Response:** In our correspondence of 4/11/2011 we explained to you that “Study NOH306B will not be useful as an efficacy trial regardless of the results.” Our position on this issue has not changed.

In your submission, dated April 23, 2012, you proposed the endpoint for Study 306B be changed to OHSA Item 1. You also proposed that study 306B be considered as one of two efficacy trials for an accelerated approval. However, because study 306B has included an unblinded interim analysis and subsequent changes to both the primary efficacy endpoint and sample size, it is not possible to consider this trial as a pivotal efficacy trial. Therefore, you will need to conduct an additional adequate and well-controlled trial in order to have droxidopa considered for approval.

## 2.2. *Clinical and Statistical*

**Question 2:** Does the Agency agree with the proposal that, *in lieu* of a Black Box Warning, specific language may be added to the product labeling (b) (4)

**Preliminary FDA Response:** A Box Warning will likely be used to convey the importance of the 30-degree elevation.

## 2.3. *Clinical Pharmacology/Bioequivalence*

**Question 3:** Can the Agency clarify the issue and confirm that the responses to the 483 observations were adequate?

**Preliminary FDA Response:** The records at (b) (4) lacked complete data for the preparation of the droxidopa solutions, and we have therefore concluded that the bioanalytical data in the bioequivalence part of Study 101 are not reliable. This study will need to be re-done.

## 2.4. *Chemistry, Manufacturing and Controls/ Product Quality*

**Question 4:** Does the Agency agree that the stability data proposed (including the proposed stability matrix for additional batches) is sufficient for approval of the commercial batch size? (b) (4)

**Preliminary FDA Response:** The proposed stability plan for all three dosage strengths of drug product is acceptable with respect to the selection of the batch size and number of batches. However, for stability studies for additional batches of all three strengths, we recommend that you apply the same stability protocol as used for previous primary stability batches. This way, we will be able to compare directly the new stability data with the previous data. In addition, since you are proposing to place the additional batches of commercial scale on stability, you will be able to use the data from these commercial batches as a part of post-approval stability commitment.

**Question 5:** Does the Agency agree that 6 months data from additional stability batches proposed at the time of resubmission is sufficient?

**Preliminary FDA Response:** You may be able to submit less data at the time of resubmission; however, the long-term data for additional stability batches should cover a minimum 12-month testing period by the mid-point of the resubmission review cycle. You may be able to submit these additional data prior to the mid-cycle of the review cycle.

## 2.5. *Additional Regulatory Considerations*

**Question 6:** Does the Agency Agree with the proposal for expedited review of the resubmission?

**Preliminary FDA Response:** If you plan is to submit new efficacy studies (not including Study 306) for the NOH indication, it is likely that the NDA review would be considered to be a class 2 resubmission with a 6-month goal date. If the indication substantially changes, the new submission would be considered to be a new NDA (with a 6- or 10-month goal date depending on the indication).

**Question 7:** Can the Agency confirm that there are no additional items other than the issues and deficiencies outlined in the Complete Response letter that are required for approval?

**Preliminary FDA Response:** No additional issues have been identified to date. If additional issues arise, they will be reported promptly to you.

### **Meeting**

**After brief introductions, the sponsor presented a brief PowerPoint presentation.**

### **Discussion**

### **Study 301, Site 507**

**In the March 28, 2012 Complete Response Letter, the Agency noted two key deficiencies that precluded the approval of droxidopa:**

1. *“The disproportionate contribution of Site 507 to the overall results of study 301 diminishes the persuasiveness of the study, providing an even stronger reason for not accepting study 301, the sole positive study, as adequate evidence of effectiveness”*
2. *“Inconsistencies in the overall findings, therefore, constitute a reasonable basis for not accepting study 301 alone as adequate evidence of effectiveness”*

Dr. Unger explained that, near the end of the review cycle and after the advisory committee meeting, the Division focused on the fact that the results at site 507 were disproportionately responsible for the overall effect on the primary endpoint, the orthostatic hypotension questionnaire (OHQ). Importantly, beyond the impressive effect size at site 507, the within-group variances for OHQ were exceedingly small, such that the p-value at that site was astonishingly small (many leading zeros). Moreover, site 507 data were similar with respect to variances and p-values for important secondary endpoints, notably systolic blood pressure, and clinical global impressions-improvement (CGI-I). (Chelsea then showed a slide illustrating remarkable separation of the systolic blood pressure data from site 507, versus the rest of the study.) In light of these unusual findings, most on the review team thought the site 507 data were “too good to be true.” FDA noted that if the site 507 data were not trustworthy, the results of Study 301 would not be statistically significant, and the study would not be deemed positive.

Chelsea explained that they had also noted the striking treatment effect at site 507 and, in fact, had audited the site on two occasions. Having found no evidence of wrongdoing, the company stated that they believed the veracity of the site 507 data, and attributed the marked treatment effect to selection of younger patients, predominantly with pure autonomic failure (PAF), with robust activity of droxidopa in that population.

Dr. Unger went on to explain the ease with which the investigational product could be unblinded, which could have facilitated fraud (the contents of placebo and active capsules, although both white in color, are easily distinguishable; everyone associated with the study was aware that all subjects initially received active drug). Chelsea representatives explained they had not been aware of this problem.

Dr. Unger also noted that, despite the rarity of PAF, site 507 enrolled numerous patients with PAF within a span of only a few days. FDA questioned whether site 507 might have enrolled “professional patients.” Chelsea explained that site 507 is a major referral center with a large catchment area, such that rapid enrollment of these patients would have been feasible. FDA questioned whether there were source data to establish that the enrolled subjects carried their stated diagnoses. Chelsea stated they would check on this.

Chelsea went on to present various sensitivity analyses of the efficacy data for study 301, in particular showing the favorable trend for efficacy at US sites. They cited examples of recent drug approvals with disparate treatment effects in the US and the rest of the world.

Chelsea also outlined the favorable data for the secondary endpoints in study 302, as well as positive blood pressure data in study 305.

Dr. Unger noted that, aside from the unusual results in Ukraine, the review team takes no issue with the sponsor's assertions. The review team agrees that study 301, without the site 507 data, trends favorably, but is not statistically significantly positive. FDA reiterated that, depending on the final conclusions regarding site 507 data, study 301 might not be deemed to be positive.

Chelsea agreed to submit all information pertaining to the investigation of site 507, to include any re-interview of patients and/or re-review of medical records. The Agency agreed to review the data upon receipt.

### **Study 306B**

To address the deficiencies outlined in the CR Letter, Chelsea proposed to submit data from an additional 10-week placebo-controlled randomized study of droxidopa for the treatment of symptomatic NOH in patients with Parkinson's disease (PD). The primary endpoint for study 306B will be modified from cumulative reduction in the rate of falls to a primary endpoint of reduction in dizziness/lightheadedness at Visit 4 (one week at stable blinded dosing after up to 2 weeks of blinded titration). There would be two main secondary endpoints, reduction in dizziness/ lightheadedness at the End of Study and reduction in the rate of falls from Visit 2 (baseline) through the End of Study. Ultimately, Study 306 would characterize the drug's acute and chronic effect over time and confirm efficacy of study 301 through one week.

Dr. Targum explained that falls may not be generalizable from patients with PD to all patients with NOH because the effect in PD may be related to a freezing phenomenon rather than orthostatic hypotension. (b) (4)

Chelsea explained that there are currently 160 blinded subjects enrolled. For item 1 (dizziness), the sponsor proposed to unblind the first 160 subjects for their week 1 and 3 data to support its acute effects, while the long-term data for these subjects remains blinded. The enrollment would continue up to a total of 400 subjects, including the first 160 subjects to ensure power for analysis at 8 weeks. The sponsor believed that if the study provided evidence of short-term efficacy likely to predict durable clinical benefit, this could provide the basis for an accelerated approval.

(b) (4)  
Drs. Targum and Unger also stated their preference for longer-term efficacy data (and longer-term placebo-controlled safety data), expressing the belief that one week was insufficient for the primary endpoint. FDA recommended something longer, ideally 8 weeks. The sponsor noted that, with a one-week endpoint, some subjects would actually have been taking the drug for as long as 21 days, given the leading titration period, and they noted difficulties in extending the trial because of dropouts and recall difficulties, which would increase over time. FDA noted that longer

is better, and urged that the primary endpoint be assessed at some time point beyond one week.

Dr. Unger noted that, in terms of changing the analytic plan, some of the details for study 306B were difficult to understand from the background package and suggested that Chelsea provide specific information on times of subject enrollment, details on changes in the primary endpoint, and a full explanation of how the blind has been maintained. Specifically, this would include an explanation of how one could be certain that, for all patients to be included in the analysis of the primary endpoint, information regarding their responses on particular variables was shielded from individuals who made decisions regarding selection of the primary endpoint.

In light of the difficulties with 306, Dr. Grant suggested the sponsor consider a randomized withdrawal study of patients currently taking open label droxidopa with the endpoint of time-to-failure, avoiding OHQ altogether. The definition of “failure” would need to be carefully thought out and pre-specified, but generally meant to capture the point in time when patients feel that recurrence of symptoms requires re-institution of therapy. This design allows for institution, or re-institution, of therapy as soon as patients believe they believe they require it, and would reduce the impact of dropouts. Chelsea noted a number of challenges with this approach but would consider it.

Chelsea noted that in practice, many patients would use droxidopa on an intermittent basis. Accordingly, Dr. Unger suggested a study based on intermittent use, as this would mimic actual use in the marketed setting, using some type of quality of life metric. The sponsor replied this would be difficult because of lower power and difficulties with dropouts and recall difficulties.

The sponsor asked if the Division was open to accepting other controlled studies conducted outside of ones Chelsea sponsored that revealed improvement in symptom and blood pressure in the short-term. Dr. Stockbridge noted acceptance would be dependent on the possibility of generating a list of all studies, published or not, positive or not, and also the quality and symptomatic endpoints. For approval, this would require symptomatic benefit, to include how the study(ies) were conducted and the clinical endpoints selected.

**Action Items:**

Both parties agreed that the site 507 data warrant further inquiry to determine their veracity. Chelsea agreed to consider FDA’s comments on study 306B, and provide additional explanation, as requested.

**ATTACHMENTS AND HANDOUTS**

Slide presentation enclosed below.

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/s/  
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ANNA J PARK  
05/15/2012

ELLIS F UNGER  
05/16/2012



NDA 203202

**MEETING PRELIMINARY COMMENTS**

Chelsea Therapeutics, Inc.  
Attention: Rex Horton  
Director of Regulatory Affairs  
3530 Toringdon Way, Suite 200  
Charlotte, NC 28277

Dear Mr. Horton:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for NORTHERA (droxidopa) 100 mg, 200 mg and 300 mg Capsules.

We also refer to your April 4, 2012 correspondence requesting a meeting to discuss the necessary steps before the application can be approved.

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for **May 2, 2012 from 3:00 PM – 4:30 PM, EST in Bldg 22 Room 1311** between **Chelsea Therapeutics, Inc.** and the **Division of Cardiovascular and Renal Products**. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting

**1. Background**

On September 23, 2011, Chelsea Therapeutics, Inc. submitted their New Drug Application for Droxidopa, a new molecular entity, 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). Droxidopa is currently approved in Japan for the treatment of neurogenic orthostatic hypotension.

**Summary of Key Regulatory Milestones:**

January 2007	Orphan drug designation granted for the NOH indication
February 2008	Agreement on a Special Protocol Assessment for study 301
August 2008	Fast Track designation granted
November 2009	Type C Meeting – discussion of sponsor’s planned modifications of study 301. The Division noted that study 302 could not be used as one of two studies to support efficacy because it failed on its primary endpoint
January 2010	Correspondence to sponsor – FDA agreed upon a change in the primary endpoint of study 301 from the Orthostatic Hypotension Symptoms Assessment (OHSA) Item 1 to the Orthostatic Hypotension Questionnaire (OHQ)
December 2010	Pre-NDA meeting – FDA reminded Chelsea that one trial is not usually sufficient for approval. FDA requested validation data for the PRO instruments used in the studies, as well as support for the view that the observed effect size in study 301 is clinically meaningful
September 2011	NDA submitted
February 2012	NDA presented at the Cardiovascular and Renal Drugs Advisory Committee Meeting
March 28, 2012	Complete Response Letter issued

**2.1. Accelerated Approval**

**Question 1a:** Does the Agency agree that submission of results from Study 306B followed by an adequate and well-designed post-approval study to confirm durability of effect (as proposed above) will provide sufficient data for accelerated approval for droxidopa for the proposed indication?

**Question 1b:** Does the Agency agree that Study 306B would no longer be considered an exploratory study and would be considered supportive of efficacy and included in labeling under accelerated approval?

**FDA Response:** In our correspondence of 4/11/2011 we explained to you that “Study NOH306B will not be useful as an efficacy trial regardless of the results.” Our position on this issue has not changed.

In your submission, dated April 23, 2012, you proposed the endpoint for Study 306B be changed to OHSA Item 1. You also proposed that study 306B be considered as one of two efficacy trials for an accelerated approval. However, because study 306B has included an unblinded interim analysis and subsequent changes to both the primary efficacy endpoint and sample size, it is not possible to consider this trial as a pivotal efficacy trial. Therefore, you will need to conduct an additional adequate and well-controlled trial in order to have droxidopa considered for approval.

2.2. *Clinical and Statistical*

**Question 2:** Does the Agency agree with the proposal that, *in lieu* of a Black Box Warning, specific language may be added to the product labeling (b) (4)

**FDA Response:** A Box Warning will likely be used to convey the importance of the 30-degree elevation.

2.3. *Clinical Pharmacology/Bioequivalence*

**Question 3:** Can the Agency clarify the issue and confirm that the responses to the 483 observations were adequate?

**FDA Response:** The records at (b) (4) lacked complete data for the preparation of the droxidopa solutions, and we have therefore concluded that the bioanalytical data in the bioequivalence part of Study 101 are not reliable. This study will need to be re-done.

2.4. *Chemistry, Manufacturing and Controls/ Product Quality*

**Question 4:** Does the Agency agree that the stability data proposed (including the proposed stability matrix for additional batches) is sufficient for approval of the (b) (4) commercial batch size?

**FDA Response:** The proposed stability plan for all three dosage strengths of drug product is acceptable with respect to the selection of the batch size and number of batches. However, for stability studies for additional batches of all three strengths, we recommend that you apply the same stability protocol as used for previous primary stability batches. This way, we will be able to compare directly the new stability data with the previous data. In addition, since you are proposing to place the additional batches of commercial scale on stability, you will be able to use the

**data from these commercial batches as a part of post-approval stability commitment.**

**Question 5:** Does the Agency agree that 6 months data from additional stability batches proposed at the time of resubmission is sufficient?

**FDA Response:** You may be able to submit less data at the time of resubmission; however, the long-term data for additional stability batches should cover a minimum 12-month testing period by the mid-point of the resubmission review cycle. You may be able to submit these additional data prior to the mid-cycle of the review cycle.

2.5. *Additional Regulatory Considerations*

**Question 6:** Does the Agency Agree with the proposal for expedited review of the resubmission?

**FDA Response:** If you plan is to submit new efficacy studies (not including Study 306) for the NOH indication, it is likely that the NDA review would be considered to be a class 2 resubmission with a 6-month goal date. If the indication substantially changes, the new submission would be considered to be a new NDA (with a 6- or 10-month goal date depending on the indication).

**Question 7:** Can the Agency confirm that there are no additional items other than the issues and deficiencies outlined in the Complete Response letter that are required for approval?

**FDA Response:** No additional issues have been identified to date. **If additional issues arise, they will be reported promptly to you.**

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, please call Anna Park, Regulatory Project Manager, at (301) 796-1129.

Sincerely,

*{See appended electronic signature page}*

Ellis F. Unger, M.D.  
Acting Director  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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ELLIS F UNGER  
04/27/2012



NDA 203202

**MEETING REQUEST GRANTED**

Chelsea Therapeutics, Inc.  
Attention: Rex Horton  
Director of Regulatory Affairs  
3530 Toringdon Way, Suite 200  
Charlotte, NC 28277

Dear Mr. Horton:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NORTHERA (droxidopa) 100 mg, 200 mg and 300 mg Capsules.

We also refer to your April 4, 2012 correspondence requesting an End of Conference to discuss the necessary steps before the application may be approved. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting.

The meeting is scheduled as follows:

**Date:** May 2, 2012  
**Time:** 3:00 PM – 4:30 PM, EST  
**Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1311  
Silver Spring, Maryland 20903

**CDER participants:**

Ellis Unger, M.D. Acting Director, Office of Drug Evaluation I

Division of Cardiovascular and Renal Products

Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardiovascular and Renal Products
Stephen Grant, M.D.	Deputy Director, DCaRP
Shari Targum, M.D.	Medical Team Leader
Melanie Blank, M.D.	Medical Officer
Thomas Papoian, Ph.D.	Pharmacology Team Leader
Donald Jensen, DVM., M.S.	Pharmacology Reviewer
Edward Fromm, R.Ph., RAC	Chief, Project Management Staff
Anna Park, R.Ph.	Regulatory Project Manager

Office of Clinical Pharmacology

Rajnikanth Madabushi, Ph.D.                      Clinical Pharmacology and Biopharmaceutics Team  
Leader  
Sabarinath Sreedharan, Ph.D.                      Clinical Pharmacology Reviewer

Office of Biostatistics

James Hung, Ph.D.                                      Director, Division of Biometrics I, Office of  
Biostatistics (OB)  
Jialu Zhang, Ph.D.                                      Statistician

Office of New Drug Assessment and Quality Assurance

Kasturi Srinivasachar, Ph.D.                      Pharmaceutical Assessment Lead, Division of  
Premarketing Assessment I  
Lyudmila Soldatova, Ph.D.                      Product Quality Reviewer

Study Endpoints and Labeling Development (SEALD)

Elektra Papadopoulos, M.D., MPH              Medical Officer

Please e-mail me any updates to your attendees at [anna.park@fda.hhs.gov](mailto:anna.park@fda.hhs.gov), at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is defined as any non-U.S. citizen or dual citizen who does not have a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Anna Park at (301)796-1129.

Submit background information for the meeting (three paper copies or one electronic copy to the application and 20 desk copies to me) at least two weeks prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by April 18, 2012, we may cancel or reschedule the meeting.

Submit the 20 desk copies to the following address:

Anna Park  
Food and Drug Administration  
Center for Drug Evaluation and Research  
White Oak Building 22, Room: 4167  
10903 New Hampshire Avenue  
Silver Spring, Maryland  
*Use zip code **20903** if shipping via United States Postal Service (USPS).*  
*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

If you have any questions, please call Anna Park, Regulatory Project Manager at (301) 796-1129.

Sincerely,

*{See appended electronic signature page}*

LCDR Anna Park, R.Ph.  
Senior Regulatory Project Management Officer  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

ENCLOSURE: Foreign Visitor Data Request Form

## FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	May 2, 2012 3:00 PM, EST
MEETING ENDING DATE AND TIME	May 2, 2012 4:30 PM, EST
PURPOSE OF MEETING	Guidance
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	Bldg 22 Room 1311
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	no
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	LCDR Anna Park Senior Regulatory Management Officer Bldg 22 Room 4167 301-796-1129
ESCORT INFORMATION (If different from Hosting Official)	

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/s/  
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ANNA J PARK  
04/11/2012



NDA 203202

**MEETING DENIED**

Chelsea Therapeutics, Inc.  
Attention: Rex Horton  
Director of Regulatory Affairs  
3530 Toringdon Way, Suite 200  
Charlotte, NC 28277

Dear Mr. Horton:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Northera (droxidopa) Capsules.

We also refer to your March 6, 2012 correspondence requesting a meeting to discuss consideration for approval under Subpart-H provision, or discuss other options (including ideal post-approval study designs), that would allow the product to meet the significant medical need that currently exists.

After consulting with Dr. Unger, Acting Director, Office of Drug Evaluation I, the Division has decided not to grant your meeting request. Because of the time constraints of a Priority Review with an Advisory Committee Meeting, we are still finalizing our reviews of your application for droxidopa. A decision on the regulatory action to be taken will not be determined before all reviews are complete.

If you have any questions, please call Anna Park, Regulatory Project Manager at (301) 796-1129.

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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NORMAN L STOCKBRIDGE  
03/08/2012



NDA 203202

**INFORMATION REQUEST**

Chelsea Therapeutics, Inc.  
Attention: Rex Horton, Director, Regulatory Affairs  
3530 Toringdon Way, Suite 200  
Charlotte, NC 28277

Dear Mr. Horton:

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

We reviewed your response to January 13, 2012 Information Request Letter provided in the Amendment dated January 31, 2012, and have the following comments and information requests. We request a prompt written response by March 8, 2012 in order to continue our evaluation of your NDA.

1. The Amendment for DMF (b) (4) dated January 6, 2012 has been reviewed, and part of the responses for Deficiency Letter dated December 16, 2011 was found unsatisfactory. As a result, DMF (b) (4) that you are referencing for droxidopa synthesis remains deficient. In order to have an approval of the submitted NDA, DMF (b) (4) should receive an adequate status.
2. Inclusion of a limit for the control of impurities is a standard quality attribute. Moreover, a change in the source of (b) (4) and (b) (4) might result in the different level of the individual impurities in these starting materials. Therefore, you should include a limit of NMT (b) (4) for "Any Individual Impurity" in the specification of (b) (4) and (b) (4)
3. The (b) (4) droxidopa synthesis intermediates should be controlled by assay limits as well as by purity to control the quality of each intermediate. The purity determination can not be used in place of assay. Therefore, we strongly recommend that you include assay limits in the specifications for all intermediates of the droxidopa synthesis.
4. Regarding the (b) (4) provide the data, assumptions and calculations that were used to derive the estimates of exposure to this metabolite during the rat carcinogenicity study and in patients treated with droxidopa. Provide copies of any publications or study reports that were used to support these estimates.
5. In your January 31, 2012 response, you propose a limit of (b) (4) for (b) (4). We agree that the combined repeat-dose and reproductive toxicity study in rats (performed by (b) (4)) that you have selected for your calculation provides the most appropriate data. However, in the equation for Permissible Daily Exposure (PDE) from the ICH Q3C guidance, the NOEL should be specified as (b) (4)

(b) (4) (the repeat-dose NOEL observed during this study) rather than (b) (4) (the reproductive toxicity NOEL) and F3 should be (b) (4) because length of exposure was 35 days in males and approximately 40 days in females. With these changes, the PDE in patients is (b) (4). For a maximum recommended daily dose of 1800 mg/day, this requires a limit of NMT (b) (4). Reduce the limit for (b) (4) in the drug substance specification accordingly.

6. Propose a limit lower than (b) (4) for undesired (b) (4) in the (b) (4) drug substance specification, and justify the proposed limit. A limit that is lower than or equal to the actual impurity levels in the drug substance batches used for preclinical studies and for clinical studies would be most consistent with the recommendations provided in, "FDA's Policy Statement for the Development of New Stereoisomeric Drugs", (5/1/92, Revised 1/3/97).

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

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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RAMESH K SOOD  
03/02/2012



NDA 203202

**MEETING MINUTES**

Chelsea Therapeutics, Inc.  
Attention: Rex Horton  
Director of Regulatory Affairs  
3530 Toringdon Way, Suite 200  
Charlotte, NC 28277

Dear Mr. Horton:

Please refer to your New Drug Application (NDA) dated September 23, 2011, received September 28, 2011 under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for Northera (Droxidopa) 100 mg, 200 mg, and 300 mg oral capsules.

We also refer to the telecon between representatives of your firm and the FDA on February 1, 2012. The purpose of the meeting was to discuss any issues pertaining to the upcoming Advisory Committee Meeting.

A copy of the official minutes of the telecon is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Anna Park, Regulatory Project Manager at (301) 796-1129.

Sincerely,

*{See appended electronic signature page}*

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

ENCLOSURE:  
Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF TELCONFERENCE MINUTES**

**Meeting Date and Time:** February 1, 2012 3:00 PM – 4:00 PM, EST

**Application Number:** NDA 203202

**Product Name:** Droxidopa

**Indication:** 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 (D $\beta$ H) Deficiency and Non-Diabetic Autonomic Neuropathy (NDAN)

**Sponsor/Applicant Name:** Chelsea Therapeutics, Inc.

**Meeting Chair:** Norman Stockbridge, M.D., Ph.D.

**Meeting Recorder:** Anna Park, R.Ph.

**FDA ATTENDEES**

Ellis Unger, M.D.	Director (acting), Office of Drug Evaluation I
Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardiovascular and Renal Products
Shari Targum, M.D.	Medical Team Leader
Melanie Blank, M.D.	Medical Officer
Thomas Papoian, Ph.D.	Pharmacology Team Leader
Sreedharan Sabarinath, Ph.D.	Clinical Pharmacology Reviewer
Elektra Papadopoulos, M.D., MPH	SEALD Endpoints Reviewer
Mary Ross Southworth, Pharm.D.	Deputy Director of Safety
Jovita Randall-Thompson, Ph.D.	Control Substance Staff Reviewer
Megan Moncur, M.S.	Social Science Reviewer
Edward Fromm, R.Ph., RAC	Chief, Project Management Staff
Lori Wachter, RN., BSN	Regulatory Project Manager for Safety
Anna Park, R.Ph.	Regulatory Project Manager

**SPONSOR ATTENDEES**

Simon Pedder, Ph.D.	President and CEO
Bill Schwieterman, M.D.	Chief Medical Officer
Art Hewitt, Ph.D.	Chief Scientific Officer
Gerry Rowse, Ph.D.	Sr. Director, Pharmaceutical Science and Pre-clinical Programs

## **BACKGROUND**

Chelsea Therapeutics, Inc. submitted a 505(b)(1) NDA for Droxidopa, an orally administered, synthetic catecholamine acid pro-drug that is converted to norepinephrine (NE). The proposed indication for Droxidopa is 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 (D $\beta$ H) Deficiency and Non-Diabetic Autonomic Neuropathy (NDAN).

Droxidopa was granted Orphan Designation on January 17, 2007 and Fast-Track Designation on August 7, 2008 for the treatment of symptomatic NOH.

The sponsor's clinical development program included 3 studies, Study 301, 302 and 303, to assess the efficacy of Droxidopa. Study 301 is the pivotal efficacy trial in the Droxidopa development program, and the efficacy results from this study are the predominant focus of this NDA.

On November 3, 2011, the sponsor was notified of the Agency's decision to take Droxidopa to the Cardiovascular and Renal Drugs Advisory Committee (CRDAC) on February 23, 2012. A request was made on January 24, 2012 for a teleconference with Chelsea Therapeutics, Inc. to allow for an open dialogue to discuss any pending issues prior to the CRDAC meeting. The Agency received Chelsea's Advisory Committee Briefing Package on January 24, 2012 and the Division provided their "Topics for Discussion" to the sponsor on February 1, 2012. Additional feedback was received by the Division prior to the teleconference to the Agency's proposed questions. Please see the attached documents.

## **DISCUSSION**

After brief introductions, Dr. Stockbridge reiterated the goal of the teleconference was to allow for an open and useful exchange of ideas to facilitate discussions to assist Dr. Unger with his regulatory decision. The decision was made to share the Agency's draft questions and no changes were anticipated as most of primary reviews were complete. Furthermore, questions identified major areas where the committee input was deemed necessary.

The sponsor expressed some concern with the Agency decision to include Study 303 with Studies 301 and 302, as it was a small study not powered to demonstrate efficacy. Dr. Stockbridge felt Study 303 was useful as it revealed how big the effect size was after three months of therapy relative to placebo even though it failed to meet its primary endpoint.

The sponsor requested further clarification to the following question proposed by the Agency as the sponsor believed it was addressed by their long-term data.

***“How important is it that a symptomatic treatment for a chronic condition be shown effective for more than two weeks?”***

Dr. Stockbridge felt the sponsor had insufficient long-term data to address the question of durability of effect

(b) (4)

(b) (4) When asked if the sponsor had additional long-term data to correlate blood pressure effects with long-term effectiveness or any evidence that benefit tracks with changes in blood pressure, (b) (4)

Although there was no comparator arm, the sponsor felt that Study 303 was useful to assess long-term benefit, and that the pharmacodynamic measure supported the overall efficacy of Droxidopa. When further asked what the pharmacodynamic measurement represented, the sponsor stated it represented the change in systolic blood pressure from baseline in Study 303. The sponsor acknowledged that the placebo arm also showed a change in systolic blood pressure from baseline in Study 303 and that the systolic BP in the droxidopa arm in Study 303 decreased 8 mmHg after randomization while the systolic BP in the placebo arm remained unchanged. If long-term effectiveness cannot be shown for chronic conditions, Dr. Stockbridge proposed that the sponsor make a case for approval based on short-term efficacy and safety, (b) (4)

Dr. Unger further recommended looking at examples of drugs intended for the treatment of chronic conditions, where approval was based upon short-term efficacy assessments.

For the CRDAC, the sponsor's primary focus will be on the randomized data, clinical data, risk and benefit of therapy, and the unmet medical need. When asked about the extent of the Agency's safety concerns, Dr. Stockbridge stated the sponsor would need to address the limitations of what the safety database was capable of detecting, and the overall experience with their foreign post-marketing studies, particularly mortality and neuroleptic malignant syndrome (NMS) in Japan. Dr. Blank recommended obtaining as much information on the Japanese cases of NMS, especially the non-Parkinson's disease cases.

The sponsor is proposing a registry for their Phase 4 Study, but requested further guidance on how best to optimize their study. Dr. Stockbridge recommended getting further guidance from the CRDAC, and using results from their studies and the Japanese post-marketing experience to inform the design of their study and the information they will capture.

The sponsor was informed that a neurologist will be participating on the Advisory Committee.

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/s/  
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ANNA J PARK  
02/06/2012

NORMAN L STOCKBRIDGE  
02/07/2012



NDA 203202

**METHODS VALIDATION  
MATERIALS RECEIVED**

Chelsea Therapeutics  
Attention: Rex Horton  
Director, Regulatory Affairs  
3530 Toringdon Way  
Suite 200  
Charlotte, NC 28277

Dear Rex Horton:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for northera (droxidopa) Capsules, 100 mg, 200 mg and 300 mg and to our 12/02/2011, letter requesting sample materials for methods validation testing.

We acknowledge receipt on 1/25/2012, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

James F. Allgire  
Team Leader  
Division of Pharmaceutical Analysis, HFD-920  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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/s/  
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JAMES F ALLGIRE  
01/26/2012



NDA 203202

**GENERAL ADVICE**

Chelsea Therapeutics, Inc.  
Attention: Rex Horton  
Director of Regulatory Affairs  
3530 Toringdon Way, Suite 200  
Charlotte, NC 28277

Dear Mr. Horton:

Please refer to your New Drug Application (NDA) dated September 23, 2011, received September 28, 2011 under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for Northera (Droxidopa) 100 mg, 200 mg, and 300 mg oral capsules.

We also refer to your December 8, 2011 and January 5, 2012 submissions containing draft labeling.

Using Failure Mode and Effects Analysis<sup>1</sup>, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Professional Sample Container Label submitted December 8, 2011
- Trade Container Labels submitted December 8, 2011 and January 5, 2012
- Insert Labeling submitted December 8, 2011

DMEPA has completed their review and have the following comments/recommendations:

The proposed label and labeling introduce vulnerability that can lead to medication errors. We found the container and carton labeling had an inadequate prominence of the established name, strength, and medication guide statement. In addition, use of error-prone abbreviations, symbols, acronyms are used throughout the labeling. We advise that the following recommendations be implemented prior to approval:

**A. Professional Sample Container Label (100 mg, 200mg, 300 mg - 9 count and 21 count)**

1. The graphic design in front of the proprietary name is too prominent and distracting. The graphic can be misread as an upper case 'I' or bold font lower case 'i' before the proprietary name Northera. Remove this graphic from the label or relocate and minimize this graphic so that it does not appear with the proprietary name.
2. Revise the presentation of the proprietary name so that it is presented in a single color. Select a color for the proprietary name that is unique and not previously used in the strength differentiation.

3. We note that the established name is ½ the size of the proprietary name however, lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors including typography, layout, contrast and other printing factors in accordance with 21 CFR 201.10 (g)(2).
4. The established name includes the active ingredient but lacks the finished dosage form. We request that you add the dosage form “Capsules” to appear after “Droxidopa” on the primary display panel.
5. The primary display panel does not have a Medication Guide statement to ensure that a medication guide is dispensed to every patient by every dispenser of Northera. Revise to include medication guide statement on the primary display panel in a prominent and conspicuous manner in accordance with 21 CFR 208.24 (d).
6. The strength statement is not prominently displayed on the primary display panel. Relocate the strength statement directly below the proprietary name and established name.
7. Revise the strength statement to read 100 mg per capsule, 200 mg per capsule, or 300 mg per capsule.
8. Decrease the prominence of the “Rx Only” statement on the primary display panel.
9. Revise Usual dosage statement from (b) (4) to read “See Prescribing Information” to decrease clutter on the side display panel.
10. Remove (b) (4) statement to decrease clutter on the left display panel.
11. Revise (b) (4) to read “Store at 25 °C (77 °F): excursions permitted from 15 °C to 30 °C (59 °F to 86 °F); Dispense in a tight, light-resistant container.” Use the same prominence of the Usual Dosage statement on the side display panel to increase readability.
12. Relocate the “Patient Samples-Not for Sale” to the area under the “Rx Only” statement at the lowest portion of the label.

**B. Trade Container Labels (100 mg , 200 mg, and 300 mg 90 capsules count)**

1. See comment in A 1 through A 7 and A8 through A 11 above.
2. Move the medication guide statement to the primary display panel per above in accordance with 21 CFR 208.24 (d).

3. Remove [REDACTED] (b) (4) statement from the side display panel to decrease clutter and increase readability.

**C. Blister Pack Outer Carton, Blister Pack Front and Back Label (100 mg, 200 mg, and [REDACTED] (b) (4) Unit of Use-9 Capsules each containing Ten Blister Packs)**

1. See comment in A 1 through A 9 above.
2. Remove the “[REDACTED] (b) (4)” and “[REDACTED] (b) (4)” from the Outer Carton and the Blister Pack Front.
3. Increase the font size or use color for the strength statement on the Blister Pack Back foils to differentiate the 100 mg, 200 mg, [REDACTED] (b) (4) capsule.

**D. Insert Labeling**

1. General Comments:  
The applicant has used throughout the **HIGHLIGHTS OF PRESCRIBING INFORMATION**, and **FULL PRESCRIBING INFORMATION** error-prone abbreviations. The symbols  $<$ ,  $\leq$ ,  $>$ ,  $\geq$  were utilized in the insert labeling to represent “less than,” “less than or equal to,” “greater than,” or “greater than or equal to,” respectively. These symbols can be misinterpreted as the opposite of the intended symbol or mistakenly used as the incorrect symbol. As part of a national campaign to decrease the use of dangerous symbols<sup>2</sup>, the FDA agreed not to use such error-prone symbols in the approved labeling of products because these abbreviations can be carried over to prescribing. Therefore, DMEPA recommends that  $<$  be replaced with “less than,”  $\leq$  be replaced with “less than or equal to,”  $>$  be replaced with “greater than,” and  $\geq$  be replaced with “greater than or equal to.”
2. Define all abbreviations and acronyms for clarity. For example in table 1 reads “...Adverse Events...” and in table 2 “...AEs...” Revise table 1 to “...Adverse Events (AE)...” for consistency throughout the insert labeling.
3. When writing numbers with symbols or units, insert a space between the number, symbol, or unit for better readability. For example in section 5.1 Supine Hypertension revise “2.5%” to read “2.5 %.”
4. Provide each unit of measure with each number. In section 8.1 **Pregnancy**, please revise “60, 200, and 600 mg/kg/day” to read “60 mg/kg/day, 200 mg/kg/day, and 600 mg/kg/day.”
5. Consider stating numbers greater or equal to 1,000 with a comma to prevent the reader from misinterpreting thousands “1000” as hundreds “100.” In section 10.1 Symptoms revise “...7700 mg...” to read “...7,700 mg...”
6. In the **DOSAGE AND ADMINISTRATION** section 2 does not state that Northera (droxidopa) can be opened and sprinkled on food or that it should be taken whole. Revise to include information on whether the capsules should be taken whole or other directions consistent with the intended use of Northera (droxidopa).

7. In the ***DOSAGE FORMS AND STRENGTHS*** section 3, the capsules are imprinted with (b) (4). The imprint (b) (4) on the capsule body implies the name of the drug is (b) (4) and is misleading. Remove (b) (4) from the capsule body

If you have any questions, please call Anna Park, Regulatory Project Manager, at (301) 796-1129.

Sincerely,

*{See appended electronic signature page}*

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

<sup>1</sup>Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

<sup>2</sup>Institute for Safe Medication Practices (ISMP). ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations. ISMP: 2010

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/s/  
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NORMAN L STOCKBRIDGE  
01/26/2012



NDA 203202

**INFORMATION REQUEST**

Chelsea Therapeutics, Inc.  
Attention: Rex Horton  
Director of Regulatory Affairs  
3530 Toringdon Way, Suite 200  
Charlotte, NC 28277

Dear Mr. Horton:

Please refer to your New Drug Application (NDA) dated September 23, 2011, received September 28, 2011 under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for Northera (Droxidopa) 100 mg, 200 mg, and 300 mg oral capsules.

We are reviewing your application and have the following comment and information request. We request a prompt written response in order to continue our evaluation of your NDA.

As you may be aware, DOPAL (3,4-dihydroxyphenylacetaldehyde) has been reported to possess neurotoxic effects both in vitro and in vivo. Also, it has been shown to be detected in human plasma after oral administration of droxidopa, and is markedly elevated in Parkinson's Disease patients treated with droxidopa (see references below). Given that droxidopa crosses the blood-brain-barrier and is likely to be converted into DOPAL in the CNS, we would like you to address this safety concern. Please include the following in your response: (1) the adequacy of the existing clinical and nonclinical evidence demonstrating lack of neurotoxic effects after droxidopa administration, (2) levels, if known, of DOPAL produced in animals and/or humans after administration of droxidopa, particularly in those with Parkinson's Disease, and (3) what additional clinical and nonclinical studies may be conducted, if needed, to address this issue.

References:

Burke WJ et al.; 3,4-dihydroxyphenylacetaldehyde is the toxic dopamine metabolite in vivo: implications for Parkinson's disease pathogenesis; Brain Res. 2003; 989:205-213.

Goldstein DS; L-dihydrophenylserine (L-DOPS): a norepinephrine prodrug; Cardiovasc. Drug Rev. 2006; 24:189-203.

Goldstein DS, et al.; Catechols in post-mortem brain of patients with Parkinson disease; Eur J Neurol. 2011;18:703-10.

Holmes C et al.; Contamination of the norepinehprine prodrug droxidopa by dihydroxyphenylacetaldehyde; Clin. Chem. 2010; 56:832-838.

Kristal BS et al.; Selective dopaminergic vulnerability: 3,4-dihydroxyphenylacetaldehyde targets mitochondria; Free Radical Biol. Med. 2001; 30:924-931.

Li SW et al.; 3,4-dihydroxyphenylacetaldehyde and hydrogen peroxide generate a hydroxyl radical: possible role in Parkinson's disease pathogenesis; Mol. Brain res. 2001; 93:1-7.

Panneton WM et al.; The neurotoxicity of DOPAL: behavioral and stereological evidence for its role in Parkinson disease pathogenesis; Plos One 2010; 5(12):e15251.

If you have any questions, please call Anna Park, Regulatory Project Manager, at (301) 796-1129.

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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NORMAN L STOCKBRIDGE  
01/17/2012



NDA 203202

**INFORMATION REQUEST**

Chelsea Therapeutics, Inc.  
Attention: Rex Horton  
Director of Regulatory Affairs  
3530 Toringdon Way, Suite 200  
Charlotte, NC 28277

Dear Mr. Horton:

Please refer to your New Drug Application (NDA) dated September 23, 2011, received September 28, 2011 under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for Northera (Droxidopa) 100 mg, 200 mg, and 300 mg oral capsules.

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

**DRUG SUBSTANCE**

(b) (4) Manufacturing Process of Droxidopa

1. The (b) (4) DMF (b) (4) that you are referencing for droxidopa synthesis is currently deficient. A Deficiency Letter dated December 16, 2011 was sent to the DMF holder. In order to have an approval of the submitted NDA, DMF (b) (4) should receive an adequate status.
2. Include a chiral identity test for droxidopa in the drug substance specifications for droxidopa.
3. Since there are no specified impurities in the drug substance specification for droxidopa produced by (b) (4) process, change the name for (b) (4) to "Any individual impurity".

(b) (4) Manufacturing Process of Droxidopa

4. Include Identification test in the specification of the starting material (b) (4) for (b) (4) manufacturing process.
5. Include limits for individual and total impurities in the specifications of the starting materials (b) (4) and (b) (4)
6. Provide representative Certificates of Analysis for starting materials (b) (4) and (b) (4)

7. Include a test and acceptance limit for Assay and Optical Purity in the (b) (4) specification.
8. Include assay limits in the specifications for all intermediates of the droxidopa synthesis.
9. Provide the overlaid XRPD spectra of droxidopa samples crystallized from different solvents.
10. Several potentially genotoxic droxidopa impurities have been identified by structural alerts and computational toxicology assessment. They are: (b) (4)  
(b) (4) Each of these impurities would need to be either controlled in the drug substance at a level that allows a maximum daily intake of (b) (4) or determined to be negative by a structural activity relationship (SAR) assessment. Such a determination may include a review of the available literature, a similar computational toxicology assessment, or an in vitro mutation assay (i.e., bacterial reverse mutation assay) (see Guidance for Industry: Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches; Dec. 2008; <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079235.pdf>). In case you choose to control the levels of these impurities in the drug substance specification, you should provide appropriate validation data to demonstrate that the analytical procedure is capable of quantifying these impurities at the respective level.
11. Set the limits for (b) (4) and (b) (4) in the drug substance specification based on the safety consideration, and provide the appropriate justification.
12. Consolidate the droxidopa specifications from two manufacturing processes, (b) (4) methods, into one set of regulatory specifications. Suitable notations can be used to denote tests (e.g. tests for specific residual solvents, impurities, etc.) that are applicable to an individual source of the drug substance.
13. Include a value of the system suitability criteria for tailing factor for (b) (4) analytical methods “Assay by HPLC” and “Related Substances by HPLC”.
14. Provide evidence that (b) (4) analytical method “Related Substances by HPLC” is capable of resolving all potential process and degradation impurities listed in the Section S.3.2 of the NDA submission, including potentially genotoxic impurities (b) (4)  
(b) (4) Provide the HPLC chromatogram demonstrating acceptable resolution of all potential impurities.
15. Provide the LOQ for related substances expressed as percentage, in the Analytical Method for Determination of Related Substances.
16. Provide the LOD and LOQ for Analytical Method for Optical Purity by HPLC.
17. Provide a comparison of the physico-chemical characteristics (i.e., solubility, melting point, optical rotation, XRPD spectrum, DSC spectrum, etc.) for batches manufactured using the (b) (4) routes of synthesis.

## DRUG PRODUCT

1. Confirm that the drug product as a whole (i.e. including the excipients) conforms to levels of the residual solvents recommended by ICH guidance Q3C.
2. Provide information on the drug product batch (i.e., batch number, production scale, and synthetic process of the drug substance used to manufacture this batch) that was used in the bioequivalence (BE) study No. 101.
3. Provide the particle size distribution ( $D_{10}$ ,  $D_{50}$  and  $D_{90}$ ) after (b) (4) for drug substance batches from (b) (4) process) and from (b) (4) process, and respective dissolution data for drug product batches.
4. Demonstrate that (b) (4)
5. Provide the in-process control for (b) (4) operation of droxidopa, i.e. control of the particle size distribution ( $D_{10}$ ,  $D_{50}$  and  $D_{90}$ ) after (b) (4)
6. Include the accelerated testing at 40°C/75% RH for 6 months, and the 9-month time point for long term condition in the stability protocol for first three commercial scale batches.
7. Provide representative packaging batch records for the three strengths of droxidopa capsules.
8. As per ICH Q1A(R2), the selection of batches for primary stability studies should include at least two pilot scale batches and the third one can be a smaller batch. The pilot scale batches are defined as one-tenth that of a full production scale or 100,000 capsules, whichever is larger. You have provided stability data for only one primary stability batch each of pilot scale for 100 mg and 200 mg droxidopa capsules, and no pilot scale batches for 300 mg. The stability data are not sufficient for granting the expiration period for drug product of 100, 200, and 300 mg. Provide stability data for one additional primary stability batch of pilot scale for each 100 mg and 200 mg capsules in all packaging configurations, and for two primary stability batches of pilot scale for 300 mg in all packaging configurations, so that we can determine the expiration period as per ICH Q1A(R2) guidance. In addition, provide the values of Water Vapor Transmission Rate (WVTR) for each bottle/fill configuration to justify the bracketing design of the stability studies as per Advice Letter dated May 30, 2008.

### Labeling: Package Insert

1. Revise the chemical name of droxidopa to the following precise name in the Description Section: (-)-*threo*-3-(3,4-Dihydroxyphenyl)-L-serine.
2. List the components of the (b) (4) black inks as follows “The black inks contain Shellac glaze, ethanol, iron oxide black, isopropyl alcohol, *n*-butyl alcohol, propylene glycol, and ammonium hydroxide”, in the Description Section of the Package Insert and in the Medical Guide. Include also full description of the inactive ingredients of the capsule shells in the Medical Guide.
3. Change the description of the droxidopa capsules in the How supplied/ Storage and Handling section of the Package Insert to that provided in the Appearance section of the proposed drug product specification.
4. Add the NDC codes of the capsules in the How supplied/ Storage and Handling section of the Package Insert.

5. Remove the statement [REDACTED] <sup>(b) (4)</sup> in the How supplied/ Storage and Handling section of the Package Insert.

Labeling: Container Labels

1. Include the name of dosage form in all container labels as follows: Northera <sup>TM</sup> (droxidopa) Capsules.
2. Clarify why the container label is provided [REDACTED] <sup>(b) (4)</sup> in the Section P.7 Container Closure System.

We request that you provide the above information by January 31, 2012.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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RAMESH K SOOD  
01/13/2012

**Executive CAC**  
**January 9, 2012**

Committee: David Jacobson Kram, Ph.D, OND IO, Member  
Abby Jacobs, Ph.D., OND IO, Member  
Paul Brown, Ph.D., OND IO, Member  
David Joseph, Ph. D., DGIEP, Alternate Member  
Thomas Papoian, Ph.D., DCRP, Pharm Tox Supervisor  
Donald Jensen, D.V.M., DCRP, Presenting Reviewer

Author of Minutes: Donald Jensen, D.V.M.

The following information reflects a brief summary of the Committee discussion and its recommendations.

**NDA: 203,202**

**Drug Name: droxidopa**

**Sponsor: Chelsea Therapeutics, Inc.**

**Mouse Carcinogenicity Study**

An 80-week study in CD-1 mice evaluated daily doses of 30, 100, 300 and 1000 mg/kg delivered in feed. Mortality was increased at the two highest doses in both sexes. Body weight gain was modestly decreased in males at the two highest doses and food consumption was modestly decreased in the same groups between weeks 10 and 60, but not over the entire course of the study. Clinical signs were unremarkable. Mean drug intake in food closely matched desired treatment levels throughout the course of the study. Common non-neoplastic lesions included an increased incidence of amyloidosis (multiple organs) and an increased incidence of myocardial scarring, both primarily at the two highest doses. Amyloidosis was the most common cause of excess deaths at higher doses. The overall incidence of tumors was low, both in control and drug-treated groups, and likely reflected the somewhat shorter duration (i.e., 80 weeks) of the study. No drug-related increases in tumor incidence were identified.

**Rat Carcinogenicity Study**

A 104-week study in Crl:CD(SD)BR rats evaluated daily doses of 10, 30 and 100 mg/kg delivered in feed. Mortality was increased in mid- and high-dose males, but was similar among treatment groups in females. In both sexes, weight gain was similar among treatment groups. Clinical signs were unremarkable. Mean drug intake in food closely matched desired treatment levels throughout the course of the study. Mid- and high-dose males exhibited an increased incidence of renal lesions that appear to be consistent with chronic progressive nephropathy. Drug-treated males exhibited a generally dose-related increase in the incidence of myocardial inflammation and/or necrosis and an increased incidence of testicular tubular atrophy that did not appear to be dose-related. Pituitary adenomas and adenocarcinomas, which are common in most strains of rats, were the most-commonly identified cause of death in both drug-treated and control animals. No other cause of death had a high incidence. No drug-related increases in tumor incidence

were identified.

**Executive CAC Recommendations and Conclusions:**

Rat:

- The Committee concurred that the study was acceptable.
- The Committee concurred that there were no drug-related neoplasms in rats.

Mouse:

- The Committee concurred that the study was acceptable, despite the suboptimal duration.
- The Committee concurred that there were no drug-related neoplasms.

David Jacobson Kram, Ph.D.  
Chair, Executive CAC

cc:\

/Division File, DCRP  
/T. Papoian, DCRP  
/D. Jensen, DCRP  
/A. Park, DCRP  
/A. Seifried, OND IO

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/s/  
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ADELE S SEIFRIED  
01/10/2012

DAVID JACOBSON KRAM  
01/10/2012

## REQUEST FOR CONSULTATION

TO (Office/Division): QT-IRT Team

FROM (Name, Office/Division, and Phone Number of Requestor):  
Anna Park/OND1/DCRP/301796-1129

DATE  
01/10/2012

IND NO.  
077248

NDA NO.  
203202

TYPE OF DOCUMENT  
electronic

DATE OF DOCUMENT  
September 23, 2011

NAME OF DRUG  
droxidopa

PRIORITY CONSIDERATION  
P

CLASSIFICATION OF DRUG  
NME

DESIRED COMPLETION DATE  
January 31, 2012

NAME OF FIRM: Chelsea Therapeutics, Inc.

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING        |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION             |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE   |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW            |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> OTHER (SPECIFY BELOW):        |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |  |                                      |
|--|--------------------------------------|
| <input checked="" type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|--|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** The sponsor submitted a QT study protocol synopsis and statistical analysis plan in a submission dated on December 9, 2010. The QT-IRT reviewed and provided comments on January 18, 2011. An advice letter was provided to the sponsor on January 25, 2011 and on March 15, 2011, the sponsor submitted their protocol and reviewed by Drs. Balakrishnan and Zhu on April 20 and 21, 2011, respectively. On September 23, 2011, the sponsor submitted their NDA application and a Priority Review was granted. Dr. Sabarinath has requested the QT-IRT team to please review the results of the Study 102. Please click on the link below to access the NDA submission.  
NDA submission is in the EDR at: \\CDSESUB5\EVSPROD\NDA203202\203202.enx

SIGNATURE OF REQUESTOR  
Anna Park

METHOD OF DELIVERY (Check one)  
 DARRTS     EMAIL     MAIL     HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/  
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ANNA J PARK  
01/10/2012



NDA 203202

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

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

ATTENTION: Rex Horton  
Director, Regulatory Affairs

Dear Mr. Horton,

Please refer to your New Drug Application (NDA) dated September 23, 2011, received September 28, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Droxidopa Capsules, 100 mg, 200 mg, and 300 mg.

We also refer to your October 7, 2011 correspondence, received October 7, 2011, requesting review of your proposed proprietary name, Northera, and your January 2, 2012 amendment to your initial request, received January 3, 2012. We have completed our review of Northera and have concluded that it is acceptable.

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

If **any** of the proposed product characteristics as stated in your October 7, 2011 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions, contact Nina Ton, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-1648. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Anna Park at (301) 796-1129.

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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CAROL A HOLQUIST  
01/05/2012



NDA 203202

**GENERAL ADVICE**

Chelsea Therapeutics, Inc.  
Attention: Rex Horton  
Director of Regulatory Affairs  
3530 Toringdon Way, Suite 200  
Charlotte, NC 28277

Dear Mr. Horton:

Please refer to your New Drug Application (NDA) dated September 23, 2011, received September 28, 2011 under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for Northera (Droxidopa) 100 mg, 200 mg, and 300 mg oral capsules.

We have completed our computational toxicology assessment for the three major metabolites of droxidopa: 3-OM-DOPS, vanillic acid (VA), and protocatechuric acid (PA), and would like to request additional information as follows:

1. We predict fetal dysmorphogenesis with 3-OM-DOPS in the rabbit, a species in which no metabolite data are available. The absence of such data raises safety concerns regarding the adequacy of the rabbit teratology study for predicting human risk for reproductive and developmental toxicity. Please provide additional information on this issue, including an adequate metabolic profile of droxidopa for the rabbit, so that the adequacy of that study can be properly assessed.
2. In the mouse, there are serum metabolite data only for 3-OM-DOPS. Although we predict no rodent carcinogenicity in our computational toxicology assessment for 3-OM-DOPS, the other two major metabolites (VA and PA) were positive. The absence of such data raises safety concerns regarding the adequacy of the mouse carcinogenicity study for predicting human carcinogenic risk. Please provide additional information on this issue, including an adequate metabolic profile of droxidopa for the mouse, so that the adequacy of that study can be properly assessed.
3. Your examination of metabolites in human, mouse and rat serum should include an assessment of 3,4-dihydroxytoluene (HC) levels as well. This droxidopa metabolite was positive in our computational toxicology assessment for mutagenicity and carcinogenicity, and has been shown experimentally to produce tumors in rats (see Asakawa E. et al., 1994; Int. J. Cancer 56:146-152). Comparison of levels produced in humans with levels produced in mice and rats would help assess the adequacy of the rodent carcinogenicity studies for assessing risk of HC at levels produced in humans under therapeutic conditions.

If you have any questions, please call Anna Park, Regulatory Project Manager, at (301) 796-1129.

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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NORMAN L STOCKBRIDGE  
01/05/2012

**Park, Anna**

**From:** Gershon, Sharon  
**Sent:** Thursday, December 08, 2011 6:56 AM  
**To:** Park, Anna; Blank, Melanie; Targum, Shari  
**Subject:** NDA 203202 droxidopa

**Importance:** High

Hello Shari, Melanie, and Anna,

I am not sure if I'll be able to join the team meeting this morning at 11 am for NDA 203202. Therefore, I'm providing you an update with respect to OSI.

The domestic inspection assignment was issued November 30th, and the field has about 45 days to complete it. These inspections are for Sites 103 (in Scottsdale, AZ) and Site 105 (in Houston, TX).

The foreign assignment was issued November 22nd, and they have about 60 days to complete these inspections.

The inspections are for Sites 505, 507 and 513 (all in Ukraine).

We will be issuing a Sponsor inspection (Chelsea) in the next few days. The field has ~ 45 days to complete this assignment.

We'll be asking the field investigator to collect documents from EC meetings, DSMB meetings, etc. and ask or verify or confirm why the endpoint for Study 301 was changed, as well as size of enrollment for Study 301.

Let me know if you have questions. I will continue to provide you with updates as I know them.

Thanks,  
Sharon

***Sharon K. Gershon, Pharm.D.***

Captain, U.S. Public Health Service  
Good Clinical Practice Assessment Branch 2  
Office of Scientific Investigations, Bldg 51, Rm. 5360  
Office of Compliance  
CDER/FDA  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
Phone: 301-796-3404  
Fax: 301-847-8748



NDA 203202

**REQUEST FOR METHODS  
VALIDATION MATERIALS**

Chelsea Therapeutics  
Attention: Rex Horton  
Director, Regulatory Affairs  
3530 Toringdon Way  
Suite 200 Charlotte, NC 28277

Dear Mr. Rex Horton:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Northera (droxidopa) Capsules, 100mg, 200 mg and 300 mg.

We will be performing methods validation studies on Northera (droxidopa) Capsules, 100mg and 300 mg, as described in NDA 203202

In order to perform the necessary testing, we request the following sample materials and equipments:

SAMPLES AND STANDARDS

- 7.8 gram Droxidopa Drug Substance
- 25 capsules Northera 100 mg Capsules
- 35 capsules Northera 300 mg Capsules
- 50 mg (b)(4) Reference Standard
- 100 mg (b)(4) Reference Standard
- 125 mg (b)(4) Reference Standard

HPLC COLUMNS

- 1 (b)(4)
- 1 (b)(4)

Please send the MSDSs and Certificates of Analysis for the samples and standards.

Forward these materials via express or overnight mail to:

Food and Drug Administration  
Division of Pharmaceutical Analysis  
Attn: James F. Allgire  
1114 Market Street, Room 1002  
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

James F. Allgire  
Team Leader  
Division of Pharmaceutical Analysis, HFD-920  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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/s/  
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JAMES F ALLGIRE  
12/02/2011



NDA 203202

**FILING COMMUNICATION**

Chelsea Therapeutics, Inc.  
Attention: Rex Horton  
Director of Regulatory Affairs  
3530 Toringdon Way, Suite 200  
Charlotte, NC 28277

Dear Mr. Horton:

Please refer to your New Drug Application (NDA) dated September 23, 2011, received September 28, 2011 under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for Northera (Droxidopa) 100 mg, 200 mg, and 300 mg oral capsules.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is March 28, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by February 29, 2012.

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

**Clinical**

- 1. For study 301, please provide us with an analysis for the following 2 endpoints up to the last patient completed prior to the final amendment (September 28, 2009):**
  - a. OHQ**
  - b. OHSA 1**

2. **Given the results of the study 302 exploratory analysis (ANCOVA testing), why did you feel that it was necessary to resize study 301?**
3. **For study 303, please provide us with an analysis of outcomes by each question in the OHQ as you did in studies 301 and 302.**
4. **Please provide us with a “bin analysis” of results for study 301, so that we can have a better visual image of the change from baseline scores for the OHQ across the different subjects in the trial. For instance, bins should be in increments of 0.4 point changes. For, eg., : -5.4to -5.0, -4.9 to -4.5.... -0.4 to 0, 0.1 to 0.5, etc.**

### **Non-clinical**

1. **According to your submission, droxidopa increases norepinephrine levels in the brain and was judged to be positive when evaluated for potential antidepressant activity in rats, consistent with pharmacologic mechanisms of some anti-depressant drugs that inhibit the reuptake of neurotransmitters, including NE. Given these findings and potential effects, an abuse potential assessment of droxidopa should be submitted. Please consult the 2010 FDA draft guidance, “Assessment of Abuse Potential of Drugs” (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>), in order to identify the types of studies that can be performed to address this issue. Also, you indicate that the metabolic pathways for your drug consist of pathways for norepinephrine and parallel metabolic pathways for droxidopa. Please address whether any of these metabolites may bind to the various receptors identified in the abuse potential guidance that is cited here.**
2. **There is insufficient information regarding the metabolic profile of droxidopa in both animals and humans. This information is important to help address whether animals were exposed to all major metabolites formed in humans. Therefore, to address the adequacy of animal toxicity studies, please identify and quantify all major metabolites produced in toxicology study species and in man. Please specifically compare the quantitative systemic exposure to each major human metabolite (e.g., metabolites with systemic exposures  $\geq 10\%$  of parent drug exposure) in humans to the systemic exposure in each primary toxicology study species (mouse, rat, rabbit and dog). The data currently provided in your NDA is not sufficient to address this issue. Further, we note your arguments in your October 26, 2011, email response to a similar request, which indicate that you believe the metabolism of your drug is likely to be similar in animals and in man based on phylogenetically conserved metabolic pathways for catecholamines. However, droxidopa metabolites are formed that are not found with endogenous norepinephrine metabolism. Also, the limited serum metabolite data that you provide for animals and for man does not appear to be sufficient to demonstrate whether any major droxidopa-specific metabolites were identified to be present only in humans or were present at much higher levels in humans than in any of the animal species used for toxicity testing. .**

- 3. Please provide preclinical pharmacokinetic and toxicokinetic data sufficient to compare systemic drug exposures between the toxicology animal species and humans. For example, for each major toxicology study species (rat, mouse, rabbit and dog), this should include determinations of C<sub>max</sub>, T<sub>max</sub>, and AUC for multiple drug doses, plus determination of whether drug exposure increases or decreases with repeated dosing. The preclinical studies that you cite in your October 26, 2011, email response are not sufficient to address this request: The radiolabeled drug studies that you cite (D-01 and D-02) do not discriminate between parent drug and metabolites. The repeat-dose rat studies that you also cite (B-2-01 and B-3-01) sampled serum drug concentrations only at 24 hours after dosing or only at 2 and 24 hours after dosing. This infrequent sampling does not provide data sufficient to determine basic pharmacokinetic parameters so that appropriate exposure comparisons across species can be made.**
- 4. Per 21 CFR Part 58, the in-vitro mammalian cell assay for genetic toxicity that you report for your drug should either be conducted according to GLP standards, or you should provide a statement that describes in detail all deviations from Part 58 requirements.**

#### **Clinical Pharmacology**

- 1. Please provide datasets for clinical PK studies E-01 and D-08.**
- 2. Please summarize the differences between the formulations used for studies 20/1859-94 and 20/1860-94 and the final commercial formulation used in phase III trials.**
- 3. We remind you of a prior information request for datasets and scripts related to the population PK analyses.**

#### **Product Quality**

**There is a discrepancy in your application between the information on the proposed marketing packaging configuration provided in the section Container Closure System, and that in the “How Supplied” section of the draft labeling (PI). Please clarify whether the Droxidopa capsules (100 mg, 200 mg and 300 mg) will be distributed in blister packaging. Clarify which physician sample packaging configuration will be used. Clarify if only one strength (100 mg) is intended for physician's samples. Provide all appropriate container labels, if not provided.**

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

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

**1. Highlights (HL):**

- a. **Should be limited in length to one-half page. If it is longer than one-half page, a waiver must be granted or requested by the applicant in this submission.**
  - b. **Paragraphs need to be summarized and referenced to sections of FPI.**
  - c. **Use bullets throughout HL to decrease text and increase readability.**
  - d. **There is redundancy of information.**
  - e. **If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)).”**
  - f. **Bolding is reserved for section and subsection. For titles throughout the label, use italic or underline.**
  - g. **Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “side effects” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).**
  - h. **Under “Drug Interaction”, each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.**
  - i. **Under “Patient Counseling Information”, you must include the verbatim statement: “See 17 for Patient Counseling Information” or if the product has FDA-approved patient labeling: “See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”).**
  - j. **A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.**
- 2. If a section or subsection is omitted from the “Full Prescribing Information (FPI)” and “Table of Contents (TOC)”, the heading “Full Prescribing Information: Contents” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”**
- 3. When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:**
- 8.1 Pregnancy**
  - 8.3 Nursing Mothers (not 8.2)**
  - 8.4 Pediatric Use (not 8.3)**
  - 8.5 Geriatric Use (not 8.4)**
- 4. A horizontal line must separate the TOC and FPI.**
- 5. Under “Adverse Reactions”:**
- a. **The correct title is “Clinical Trials Experience”. For the “Clinical Trials Experience” subsection, the following verbatim statement should precede the presentation of adverse reactions:**
    - “Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be**

**directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”**

- b. References must be formatted appropriately per regulations.**
- 6. Please move “Effects of QTc interval” to Section 12.**
  - 7. Under “Clinical Trials”, avoid using company study titles as subsection titles. (What did study show? Why is this important?)**
  - 8. Under “Patient Counseling Information”, you must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling ...(insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example: “See FDA-approved patient labeling (Medication Guide)”**

We request that you resubmit labeling that addresses these issues by December 9, 2011. The resubmitted labeling will be used for further labeling discussions.

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

If you have any questions, please call Anna Park, Regulatory Project Manager, at (301) 796-1129.

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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NORMAN L STOCKBRIDGE  
11/16/2011

## REQUEST FOR CONSULTATION

TO (Office/Division): **Control Substance Staff**

FROM (Name, Office/Division, and Phone Number of Requestor): **Anna Park/ODE1/DCRP/301-796-1129**

DATE  
**October 28, 2011**

IND NO.

NDA NO.  
**203202**

TYPE OF DOCUMENT  
**electronic**

DATE OF DOCUMENT  
**September 28, 2011**

NAME OF DRUG  
**droxidopa**

PRIORITY CONSIDERATION  
**Priority**

CLASSIFICATION OF DRUG  
**NME**

DESIRED COMPLETION DATE  
**December 1, 2011**

NAME OF FIRM:

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** NDA 203202 is a priority review and for this reason we are asking that an evaluation of this product for abuse potential be conducted as soon as possible. Droxidopa was developed in Japan during the 1980s and has been marketed in Japan since 1989, so substantial clinical experience exists. The proposed indication for droxidopa is for chronic treatment of symptomatic neurogenic orthostatic hypotension, an orphan indication with only one approved drug (midodrine) that may soon be removed from the market. Symptomatic neurogenic orthostatic hypotension is a rare and often disabling condition that results in symptoms of dizziness, weakness, syncope and falls.

Droxidopa is an orally active synthetic amino acid norepinephrine (NE) precursor that is directly converted or metabolized to NE in a single step by DOPA-decarboxylase. The conversion of droxidopa to NE can occur peripherally and/or centrally. In addition to its function as an NE precursor, droxidopa is distributed to the brain and has been shown to promote the release of NE from the nerve endings in experiments using brain synaptosomes and slices (Nishino et al, 1987 –link to article on p. 20/61 of Clinical Overview). Further, on p. 9/33 of the Nonclinical Overview, the Sponsor states, “Central effects of droxidopa may also be relevant to its pharmacodynamic activity as droxidopa does cross the blood-brain barrier.” Potentially relevant to possible behavioral effects, it was judged to be

positive when evaluated for potential antidepressant activity in rats, consistent with the pharmacologic mechanisms of some anti-depressant drugs that inhibit the reuptake of neurotransmitters, including NE. The numbers and names of these animal studies (located in section 4.2.1.3 in module 4) are:

- 1) C-1-19: Effects on Operant Behavior, Rat/Sprague Dawley, (b) (4)
- 2) IB-1: Effects Of L-Threo-3,4-Dihydroxyphenylserine (L-Threo-Dops), An NE Precursor, On Operant Behavior In Rats, Rat/Sprague Dawley, (b) (4)
- 3) C-1-18: Involvement of Antiserotonin Action in Combination with Noradrenaline-Stimulating Action on Muricide Inhibition, Rat/Wistar; raphelesioned, (b) (4)

An abuse potential assessment was not requested in the pre-NDA phase and was not submitted with the FDA. We are currently in the process of sending a request for an abuse potential assessment from the sponsor, but anticipate that there may be no other animal studies that specifically address the potential for abuse or dependency.

Clinical study 301 is the only study in this NDA that won on its primary endpoint: the Orthostatic Hypotension Questionnaire (OHQ). The biggest difference between treatment and placebo was seen in the 2 impact assessment questions that addressed perceived ability to stand for short and long periods. Study 302 (completed before 301) was a supportive study where a post-hoc exploratory analysis of the OHQ revealed a similar win and pattern of success. (The OHQ information is located in module 5 section 5.3.5.3 in the ISE appendix 10.1). The paradoxical finding in these trials is that no difference was seen between the treatment and the placebo groups in systolic blood pressure (BP), the intended target for norepinephrine's pharmacologic activity as a vasoconstrictor. It seems unlikely that droxidopa would have a real effect on the symptoms or impact of the disease without exerting an effect on the change in systolic BP measured peripherally. However, the hemodynamic factors involved in the maintenance of cerebral blood flow are not well enough understood to rule out the potential for symptomatic benefit here due to droxidopa's CNS effects. It is also possible that droxidopa could be affecting different vascular beds that might not be measurable with an arm cuff. In clinical trial 303, a 3 1/2 month trial with a 2-week randomized withdrawal phase at the end, there was no difference between active treatment arm and the placebo arm at the end of the two week period in the OHQ scores. This result raises a concern for the development of tolerance to either the hemodynamic or symptomatic effects. The sponsor's unsupported rationale for failure in this study is that there may be a carry-over effect of Droxidopa despite its short half-life.

We would appreciate any advice you can provide to us on the potential of droxidopa for abuse or dependency, and if additional in vitro, animal and/or clinical studies should be conducted by the sponsor to help address this issue.

SIGNATURE OF REQUESTOR Anna Park	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DARRTS <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/  
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ANNA J PARK  
11/01/2011

# REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

**\*\*Please send immediately following the Filing/Planning meeting\*\***

TO: <b>CDER-DDMAC-RPM</b>	FROM: (Name/Title, Office/Division/Phone number of requestor) Anna Park/ ODE I/ DCRP/ 301-796-1129
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REQUEST DATE October 13, 2011	IND NO.	NDA/BLA NO. 203202	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
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NAME OF DRUG Droxidopa	PRIORITY CONSIDERATION Priority	CLASSIFICATION OF DRUG NME	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) February 20, 2012
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NAME OF FIRM: Chelsea Therapeutics, Inc.	PDUFA Date: March 28, 2012
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## TYPE OF LABEL TO REVIEW

<b>TYPE OF LABELING:</b> (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> CARTON/CONTAINER LABELING <input checked="" type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)	<b>TYPE OF APPLICATION/SUBMISSION</b> <input checked="" type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	<b>REASON FOR LABELING CONSULT</b> <input checked="" type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION
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**EDR link to submission:** Original NDA submission is in the EDR at: <\\CDSESUB5\EVSPROD\NDA203202\203202.enx>

**Please Note:** There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to DDMAC. Once the substantially complete labeling is received, DDMAC will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: December 20, 2011

Labeling Meetings: January 5, 30, February 13, March 5, 2012

Wrap-Up Meeting: February 27, 2012

SIGNATURE OF REQUESTER Anna Park

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) <input type="checkbox"/> eMAIL <input checked="" type="checkbox"/> DARRTS
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/s/  
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ANNA J PARK  
10/27/2011

## REQUEST FOR Patient Reported Outcomes (PRO) ENDPOINTS CONSULTATION

<b>TO: Study Endpoints and Labeling Development (SEALD)</b> <b>CDER/OND-IO White Oak Bldg 22, Mail Drop 6411</b> <a href="mailto:SEALD.ENDPOINTS@FDA.HHS.GOV">SEALD.ENDPOINTS@FDA.HHS.GOV</a>		<b>FROM: Review Division: DCRP</b> <b>Medical Reviewer: Melanie Blank, M.D.</b> <b>Project Manager: Anna Park</b>		
<b>DATE OF CONSULT REQUEST</b> October 12, 2011	<b>Application# NDA#</b> 2030202	<b>LETTER # OR SUBMISSION #</b>	<b>TYPE OF DOCUMENT</b> (Meeting; Protocol/SPA; PDUFA Product Review) PDUFA Product Review	<b>REQUESTED SEALD COMPLETION DATE*</b> December 1, 2011
<b>DRUG ESTABLISHED NAME</b> Droxidopa		<b>DRUG TRADE NAME</b> Northera	<b>NAME OF SPONSOR</b> Chelsea Therapeutics, Inc.	<b>SPONSOR SUBMIT DATE</b> September 23, 2011

**DEVELOPMENT PHASE (E.G., pre-IND/NDA/BLA; IND/BB-IND Phase 1, 2, 3; NDA/BLA):** NDA

**GOAL DATE (if NDA/BLA/SPA):** March 28, 2012

**ELECTRONIC LINK (if applicable):** This is accessible in DARRTS or at: <\\CDSESUB5\EVSPROD\NDA203202\203202.enx>

PLEASE make certain the background-briefing package is included with this consult. It should contain the following applicable information needed to start Study Endpoints Review: Protocol or Study ID; Endpoint Concept(s); Instrument(s); Indication(s); Study population(s); Prior related reviews. Division PM, please provide the following specific information on this consult form:

**Instrument(s):** 1) The Orthostatic Hypotension Questionnaire was the primary endpoint. The OHQ consists of two subcomponents, the OHSA (consists of 6 items) and the Orthostatic Hypotension Daily Activity Scale (OHDAS; consists of 4 items). The sponsor believes that this instrument meets all of the specifications for a validated PRO measure.

In order to calculate the change in OHQ score, the following procedure was done: see p. 41 of study 301 study report: The OHQ composite score, a global measure of disease activity, was calculated as the average of the OHSA composite and OHDAS composite scores. At a given time point, the OHSA composite score is the average of the symptom scores at that time for those symptoms present at Baseline (e.g., if five symptoms were marked as present at Baseline [i.e., score >0], then, the OHSA composite score is the sum of the scores of those symptoms at the specified time point divided by 5). The OHDAS composite score is the average of the activities that are scored at the same time point. Activities that were marked at Baseline as zero, or 'cannot be done for other reasons' were not included in the analysis. Where patients had a score for an OHDAS activity at Baseline (i.e., score >0), OHDAS activities marked as 'cannot be done for other reasons' or without a value at Randomization or End of Study Visits were imputed using LOCF. Each of the OHSA and OHDAS items were evaluated on a scale of 0 to 10. Thus the OHQ composite is a score that ranges from 0 to 10. A decrease in the composite score represents an improvement.

Secondary endpoints: No apparent hierarchical order: 1) OHSA, 2) OHDAS instrument, 3) Global Assessment Evaluations (CGI-S and CGI-I scales), 4) Orthostatic Standing Test (OST), 5) BP changes, 6) Subgroup analysis by underlying condition. It appears from the Clinical Overview that the BP results did not correlate with the positive OHQ results.

Droxidopa's proposed indication is for the treatment of **symptomatic neurogenic orthostatic hypotension (NOH)**.

Specific Questions/Comments for SEALD: In the Clinical Overview section the sponsor asserts that FDA agreed with using the OHQ as a primary endpoint. This is reflected in meeting minutes. Apparently, the sponsor had provided evidence demonstrating the OHQ was an appropriate and valid outcome measure of clinical benefit to substantiate efficacy claims for the treatment of symptomatic NOH. They assert that the OHQ met the requirements in the PRO measures guidance.

- 1) Is the OHQ a validated method for assessing symptoms of NOH in the patients that were enrolled in the study [Primary autonomic failure which includes Pure Autonomic Failure (same as Bradbury Eggleston), Multisystem Atrophy (same as Shy Drager), Dopamine Beta Hydroxylase deficiency, or non-diabetic symptomatic NOH-(mostly associated with Parkinson's Disease)]?

- 2) Please comment on whether the OHQ has been validated globally.
- 3) Please comment on the small effect size that was demonstrated in the context of a relatively wide SD and whether that invalidates the positive results: [Placebo OHQ score change for study 301: -0.93 (1.69) and Droxidopa OHQ score change for study 301: -1.83 (2.07). p=0.003].

Requester	
Name/Phone number/email address/office location	Anna Park, R.Ph./301-796-1129/anna.park@fda.hhs.gov/ ODE1/DCRP

Glossary: **Concept:** The specific goal of a measurement (i.e. the *thing* that is to be measured by a PRO instrument). **Instrument:** A means to capture data (e.g. questionnaire, diary) plus all the information and documentation that supports its use. Generally, that includes clearly defined methods and instructions for administration or responding, a standard format for data collection, and well-documented methods for scoring, analysis, and interpretation of results. \*For voluminous study endpoint submissions (e.g. PRO “dossier” or content validity documentation greater than 50 pages), SEALD requests 60 days after receiving the background/briefing package document to complete the review.

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/s/  
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ANNA J PARK  
10/17/2011

# REQUEST FOR CONSULTATION

TO (Office/Division): Karl Lin, Team Leader, Division of Biometrics 6 (Applications in Pharmacology/ Toxicology)

FROM (Name, Office/Division, and Phone Number of Requestor): Anna Park, ODE I/ DCRP 301-796-1129

DATE October 13, 2011	IND NO.	NDA NO. 203202	TYPE OF DOCUMENT NME	DATE OF DOCUMENT September 28, 2011
NAME OF DRUG droxidopa		PRIORITY CONSIDERATION Priority NDA	CLASSIFICATION OF DRUG NME	DESIRED COMPLETION DATE November 30, 2011

NAME OF FIRM: Chelsea Therapeutics, Inc.

## REASON FOR REQUEST

### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING        |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION             |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE   |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW            |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> OTHER (SPECIFY BELOW):        |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

### V. SCIENTIFIC INVESTIGATIONS

- |                                   |   |
|-----------------------------------|---|
| <input type="checkbox"/> CLINICAL | <input checked="" type="checkbox"/> NONCLINICAL |
|-----------------------------------|---|

**COMMENTS / SPECIAL INSTRUCTIONS:** We are requesting your assistance in the review of the carcinogenicity data for droxidopa. This datasets for this submission are located at the following links:

[\\cdsesub5\EVSPROD\NDA203202\0000\m4\datasets\ea-b-1-1\tabulations\sdtm](#) (Mouse)

[\\cdsesub5\EVSPROD\NDA203202\0000\m4\datasets\ea-b-2-1\tabulations\sdtm](#) (Rat)

The carcinogenicity data for both the mouse and rat studies arrived on September 23, 2011 in Module 4.2.3.4.1.25.1.2. The Pharmacology/ Toxicology reviewer for this IND/NDA is Donald (Nick) Jensen (301-796-1925); his supervisor is Tom Papoian. Once a statistician has been assigned, please let Nick, Tom, and me know.

This NDA will be a priority review, so this data will need to be presented to the Exec CAC during the first weeks of December, so we are hoping to have at least a draft review from your team before then. If you have any questions, please do not hesitate to contact me or Nick.

SIGNATURE OF REQUESTOR Anna Park	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DARRTS <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
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PRINTED NAME AND SIGNATURE OF RECEIVER

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/s/  
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ANNA J PARK  
10/13/2011

**REQUEST FOR CONSULTATION**

,Division/Office): <b>Mail: OSE</b>			FROM: Anna Park, ODE // DCRP/ 301-796-1129	
DATE October 13, 2011	IND NO.	NDA NO. 203202	TYPE OF DOCUMENT NDA submission	DATE OF DOCUMENT September 28, 2011
NAME OF DRUG Droxidopa		PRIORITY CONSIDERATION Priority	CLASSIFICATION OF DRUG NME	DESIRED COMPLETION DATE January 31, 2011
NAME OF FIRM:				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY				
<input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT				
<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
<b>II. BIOMETRICS</b>				
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH	
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):	
<b>III. BIOPHARMACEUTICS</b>				
DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST	
<b>IV. DRUG EXPERIENCE</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS	
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL	
COMMENTS/SPECIAL INSTRUCTIONS: Please review the carton and container label for Droxidopa.  Original NDA submission is in the EDR at: <u>\\CDSESUB5\EVSPROD\NDA203202\203202.enx</u>				
SIGNATURE OF REQUESTER Anna Park			METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> DARRTS	
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER	

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/s/  
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ANNA J PARK  
10/13/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
(Division/Office): <b>Mail: OSE and Nina Ton</b>		FROM: Anna Park, ODE II/DCRP/301-796-1129		
DATE October 13, 2011	IND NO.	NDA NO. 203202	TYPE OF DOCUMENT NDA submission	DATE OF DOCUMENT September 28, 2011
NAME OF DRUG Droxidopa	PRIORITY CONSIDERATION Priority	CLASSIFICATION OF DRUG NME	DESIRED COMPLETION DATE January 31, 2011	
NAME OF FIRM:				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY				
<input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT				
<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
<b>II. BIOMETRICS</b>				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
<b>III. BIOPHARMACEUTICS</b>				
<input checked="" type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG EXPERIENCE</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: This NDA was submitted with a REMS, to include a Medication Guide and Communication Plan. Please review the appropriate documents.  Original NDA submission is in the EDR at: <a href="#">\\CDSESUB5\EVSPROD\NDA203202\203202.enx</a>				
SIGNATURE OF REQUESTER Anna Park		METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> DARRTS		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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ANNA J PARK  
10/13/2011



NDA 203202

**NDA ACKNOWLEDGMENT**

Chelsea Therapeutics, Inc.  
Attention: Mr. J. Rex Horton  
Director, Regulatory Affairs  
3530 Toringdon Way, Suite 200  
Charlotte, NC 28277

Dear Mr. Horton:

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

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

Date of Application: September 23, 2011

Date of Receipt: September 28, 2011

Our Reference Number: NDA 203202

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 27, 2011, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

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

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

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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, please contact:

Anna Park, R.Ph.  
Regulatory Health Project Manager  
(301) 796-1129

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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EDWARD J FROMM  
10/06/2011

Form Approved: OMB No. 0910 - 0297 Expiration Date: January 31, 2013. See instructions for OMB Statement, below.					
<b>DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION</b>	<b>PRESCRIPTION DRUG USER FEE COVERSHEET</b>				
A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on FDA's website: <a href="http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm">http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm</a>					
<b>1. APPLICANT'S NAME AND ADDRESS</b>  CHELSEA THERAPEUTICS INC Rex Horton 3530 TORINGDON WAY STE 200 CHARLOTTE NC 28277 US	<b>4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER</b>  203-202				
<b>2. NAME AND TELEPHONE NUMBER OF REPRESENTATIVE</b> 704-973-4248	<b>5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?</b> <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:  <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION  <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:				
<b>3. PRODUCT NAME</b> Droxidopa	<b>6. USER FEE I.D. NUMBER</b> PD3011710				
<b>7. ARE YOU REDEEMING A PRIORITY REVIEW VOUCHER FOR THE TREATMENT OF TROPICAL DISEASES? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</b>  PRIORITY REVIEW VOUCHER NUMBER:					
<b>8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.</b> <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) <input checked="" type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY					
<b>9. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</b> If a waiver has been granted, include a copy of the official FDA notification with your submission.					
<b>OMB Statement:</b> Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:  <table style="width:100%; border: none;"> <tr> <td style="width: 33%; border: none;">                     Department of Health and Human Services                      Food and Drug Administration                      Center for Biologics Evaluation and Research                      Office of Information Management (HFA-710)                      1350 Piccard Drive, 4th Floor                      Rockville, MD 20850                 </td> <td style="width: 33%; border: none;">                     Department of Health and Human Services                      Food and Drug Administration                      Center for Drug Evaluation and Research                      Office of Information Management (HFA-710)                      1350 Piccard Drive, 4th Floor                      Rockville, MD 20850                 </td> <td style="width: 33%; border: none;">                     An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.                 </td> </tr> </table>			Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research Office of Information Management (HFA-710) 1350 Piccard Drive, 4th Floor Rockville, MD 20850	Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research Office of Information Management (HFA-710) 1350 Piccard Drive, 4th Floor Rockville, MD 20850	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research Office of Information Management (HFA-710) 1350 Piccard Drive, 4th Floor Rockville, MD 20850	Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research Office of Information Management (HFA-710) 1350 Piccard Drive, 4th Floor Rockville, MD 20850	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.			
<b>PRINTED NAME AND SIGNATURE OF AUTHORIZED REPRESENTATIVE</b> Rex Horton	<b>TITLE</b> Director, Reg. Affairs	<b>DATE</b> 9/15/2011			
<b>9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION</b> \$0.00					
Form FDA 3397 (01/10)					

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

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



**US Mail address:**

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

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**Transmitted via email to:** hewitt@chelseatherapeutics.com

**Attention:** **L. Arthur Hewitt, Ph.D.**

**Sponsor:** Chelsea Therapeutics, Inc.

**Phone:** (704) 973-4202

**Subject:** **Pre-NDA Meeting  
Minutes**

**Date:** December 17, 2010

**Pages including this sheet:** 35

**From:** **Quynh Nguyen, Pharm.D., RAC**

**Phone:** **301-796-0510**

**Fax:** **301-796-9838**

**E-mail:** **quynh.nguyen@fda.hhs.gov**

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

**Pre-NDA Meeting with Sponsor**

**Application Number:** IND 77,248  
**Sponsor:** Chelsea Therapeutics, Inc.

**Drug:** L-DOPS

**Type of Meeting:** Pre-NDA  
**Classification:** B

**Meeting Date:** December 1, 2010  
**Briefing Package Received:** November 2, 2010  
**Confirmation Date:** October 15, 2010  
**Meeting Request Received:** October 12, 2010

**Meeting Chair:** Norman Stockbridge, M.D., Ph.D.  
**Recorder:** Quynh Nguyen, Pharm.D., RAC

**List of Attendees:**

Food and Drug Administration

Ellis Unger, M.D. Deputy Director, Office of Drug Evaluation I  
Norman Stockbridge, M.D., Ph.D. Director, Division of Cardiovascular and Renal Products (DCRP)

Abraham Karkowsky, M.D., Ph.D. Clinical Team Leader, DCRP  
Shari Targum, M.D. Clinical Team Leader, DCRP  
Valeria Freidlin, Ph.D. Statistician, DBI

John Koerner, Ph.D. Pharmacology Team Leader (Acting), DCRP  
Donald Jensen, D.V.M. Pharmacologist, DCRP  
Rajnikanth Madabushi, Ph.D. Clinical Pharmacology Team Leader, Division of Clinical Pharmacology I (DCPI)  
Sreedharan Sabarinath, Ph.D. Clinical Pharmacologist, DCPI  
Edward Fromm, R.Ph., RAC Chief, Project Management Staff, DCRP  
Quynh Nguyen, Pharm.D., RAC Regulatory Health Project Manager, DCRP

Chelsea Therapeutics, Inc.

William Schwieterman, M.D. Chief Medical Officer, Chelsea  
L. Arthur Hewitt, Ph.D. Chief Scientific Officer, Chelsea  
Joseph Oliveto, M.B.A. Vice President, Operations, Chelsea  
Gerry Rowse, Ph.D. Senior Director, Preclinical Programs, Chelsea  
Cameron Szakacs, Ph.D. Senior Director, Drug Development, Chelsea  
Rita Lee, Ph.D. Regulatory Affairs Manager, Chelsea  
Loni da Silva, M.S. Regulatory Affairs Consultant to Chelsea, (b) (4)

(b) (4)

## **BACKGROUND**

L-DOPS (droxidopa) is a synthetic amino acid, which as a prodrug, is converted by dopa decarboxylase to form norepinephrine. The proposed indication is for the chronic treatment of the signs and symptoms of neurogenic orthostatic hypotension (NOH) including light-headedness, dizziness, feeling faint, fainting (syncope), blurred vision, weakness, and fatigue, and to improve patient function including activities of daily living. The droxidopa drug development program was granted Fast-Track designation on August 7, 2008. Orphan drug designation was granted on January 17, 2007. The sponsor requested this Pre-NDA meeting to discuss the adequacy and sufficiency of the nonclinical and clinical data in support of the proposed indication. The Division's Preliminary Responses were sent to the sponsor on November 23, 2010. The sponsor requested clarification of the Preliminary Responses to Questions 1, 5, 7, 8, 10, 11, and 13. The SEALD comments were also discussed as noted below.

## **DISCUSSION**

### **Clinical Questions**

1. Chelsea believes that, given the highly significant efficacy results observed in Study 301, supportive efficacy results from Study 302, and the favorable safety profile seen across the Chelsea-sponsored droxidopa development program along with clinical studies conducted by DSP and the extensive (over 20 years) clinical experience with droxidopa in Japan, the currently available efficacy and safety data adequately support the submission of an NDA for droxidopa for the chronic treatment of the signs and symptoms of NOH. Does the Division agree?

\* Data from the currently ongoing comparative efficacy trial in Parkinson's disease patients (Study 306) will not be submitted as part of the clinical portion of the NDA; however, these data will be provided to FDA as supplementary information upon the study's completion.

### **Preliminary Response**

We believe that it is reasonable to submit your currently available efficacy and safety data for our review. Please keep in mind, however, that it is not customary for the Agency to approve a new chemical entity with only one positive efficacy trial. Furthermore, because you have reported cases of angina, heart failure, and arrhythmias in your small development program, it is possible that a complete review of your safety data will suggest that the current exposure in your development program is inadequate or that the safety profile is incompatible with your established benefits.

### **Discussion during Meeting**

The sponsor acknowledged the importance of categorizing the safety profile of droxidopa and will submit the relevant cardiovascular safety data, including patient narratives, in a separate section of the NDA to address the supine hypertension and cardiovascular disease issues.

Drs. (b) (4) commented on their 30+ year experience in treating patients with autonomic dysfunction. Dr. (b) (4) noted these patients have a much higher morbidity, e.g., with falls and hip fractures. In Study 301, it was observed that patients on droxidopa had a lower incidence of falls. Dr. (b) (4) added that because of the concern with supine hypertension, the

dose is titrated based on blood pressure response. He noted however that with NOH, the blood pressure can drop dramatically when patients stand up, and therefore, the acute effects are as concerning as the hypertension. Dr. (b) (4) stated that the lack of perfusion due to hypotension represents an unmet medical need. Dr. (b) (4) added that droxidopa is unique in its selectivity in increasing standing blood pressure to a greater degree than supine.

The sponsor stated that >700 patients have been treated with at least one dose of droxidopa, almost 300 patients have been treated for longer than six months, and 165 patients have been treated for longer than one year in their clinical development program. The sponsor will submit the existing safety data from Studies 301, 302, 303, 304, and 305 as well as the safety data from Japan and Europe for the NDA.

2. Chelsea proposes the use of 3 datasets for the Integrated Summary of Safety (ISS): the Chelsea-sponsored studies; the DSP-sponsored randomized, controlled studies; and postmarketing surveillance data collected by DSP. Based on the proposed datasets and integration plans for the ISS (details below), does the Division agree that this is an acceptable approach for presenting the safety data for droxidopa?

**Preliminary Response**

Your approach to presenting the safety data seems reasonable.

3. Chelsea has reviewed the cardiovascular safety data from the droxidopa clinical development program which has demonstrated that the administration of droxidopa for the chronic treatment of the signs and symptoms of NOH generally has a safe cardiovascular profile and, specifically, is not associated with an increased risk of supine hypertension. As a result, Chelsea believes the proposed labeling language regarding the cardiovascular safety of droxidopa should include two statements (as outlined below) in the “Warnings and Precautions” section of the Prescribing Information (b) (4)  
Does the Division agree?

**Preliminary Response**

(b) (4) However, the entire NDA will need to be reviewed before this can be decided.

4. Following the approval of droxidopa for the chronic treatment of the signs and symptoms of NOH, Chelsea is prepared to implement a Risk Evaluation and Mitigation Strategy (REMS) that will consist of a Medication Guide and a Health Care Provider (HCP)-oriented Communication Plan. Does the Division agree that this initial plan is adequate in managing the potential risks of droxidopa?

**Preliminary Response**

This is a review issue; we cannot address this question without reviewing the application.

**Clinical Pharmacology and Pharmacokinetic Questions**

5. Chelsea believes that the proposed datasets and data planned for inclusion in the NDA will be sufficient to fulfill the clinical pharmacology requirements for adequate labeling information to support the proposed indication. Also, as outlined in Section 5.5, Chelsea believes the existing data support the use of droxidopa in both hepatically- and renally-impaired patients,

and has no plans for additional studies in these patient populations. Does the Division agree?

**Preliminary Response**

No, we do not agree.

Droxidopa and its metabolites are predominantly (~70%) renally cleared. Studies in rats with 1/6th of normal renal function showed 5-fold greater systemic exposure and delayed elimination than normal. With the proposed TID dosing regimen of droxidopa in humans, a significant accumulation can be expected. Therefore it is important to study the clinical pharmacology of droxidopa in renally impaired patients.

We agree that you do not need to study droxidopa in patients with hepatic impairment.

**Discussion during Meeting**

The sponsor agreed to conduct a dedicated renal study and asked if they could submit the results postmarketing. Since the drug is not given as a fixed dose, but is titrated to effect, the sponsor believes they will be able to determine the optimal dose within a reasonable period of time. The Division agreed that the sponsor could submit the study results of their renal study postmarketing. The sponsor will also provide in the NDA draft labeling to include a possible contraindication to address the safety of droxidopa in renally impaired patients until data from the dedicated study are available.

6. Chelsea has reviewed the safety and efficacy data from the droxidopa clinical development program with regard to the use of concomitant medications and will establish proposed labeling recommendations based on these results. In addition, other drug-drug interactions will either be described on a theoretical basis or taken from the approved Prescribing Information for Levophed (intravenous norepinephrine), which is indicated for blood pressure control in acute hypotensive states. Does the FDA agree with this approach for addressing drug-drug interactions in the proposed Prescribing Information for droxidopa?

**Preliminary Response**

Your approach is reasonable.

**Nonclinical Questions**

7. Chelsea believes that the DSP-sponsored carcinogenicity studies, which were conducted during the 1990s and, thus, are not reflective of all of the most current nonclinical practices, yielded results that allow for an adequate evaluation of the carcinogenicity risk relative to the proposed indication. Specifically:
  - a. Does the Agency agree that Chelsea can adequately summarize the existing data without using SAS datasets?

**Preliminary Response**

No. Submission of carcinogenicity data using the standard SAS format is required for our statistical review.

**Discussion during Meeting**

The Division agreed with the sponsor's proposal to submit only the tumorigenicity dataset in SAS format. This dataset would specifically include observed tumors, the organs the tumors are found in, the malignancy status, the cause of death, and the time of death/sacrifice.

- b. Does the Agency agree that Chelsea can adequately summarize the risk of carcinogenicity despite the absence of specific toxicokinetic data?

**Preliminary Response**

This will be a review issue. Given the lack of toxicokinetic data in both species, plus the apparent lack of any pharmacokinetic data in mice, it will be particularly important that you demonstrate that appropriate doses were selected for the carcinogenicity studies. You may wish to consult the ICH guidance, "S1C(R2) Dose Selection for Carcinogenicity Studies."

**Discussion during Meeting**

The sponsor stated that carcinogenicity studies were conducted using adequate doses and they do have pharmacokinetic data in mice. The top dose in the carcinogenicity studies was based on observed maximum tolerated dose according to the S1C(R2) ICH Guidance. The sponsor stated that 13-week dose ranging studies with drug supplied in feed were conducted to determine the appropriate doses for the carcinogenicity trial. In addition, the 18-month and 2-year carcinogenicity studies confirmed that the doses were appropriately chosen. This information will be included in the NDA.

8. Chelsea proposes that the nonclinical cardiovascular safety package outlined below is acceptable for the droxidopa NDA. Specifically, does the Agency agree that there is no need for a dedicated QTc study given existing data supporting the safety of droxidopa on cardiac conduction times?

**Preliminary Response**

The general cardiac toxicity (i.e., myocardial damage) observed during preclinical studies should be addressed by data collected during clinical trials. Clinical data should include evaluation of cardiac troponin values. No additional preclinical data are required regarding this issue.

However, we judge, based on the information you have submitted so far, that a thorough QTc study is required. If you disagree, then you will need to provide further arguments in the NDA regarding why you believe such a study is not necessary.

**Discussion during Meeting**

The sponsor asked for clarification on why a thorough QTc study was required since their data had shown an absence of any QTc effects. Dr. Stockbridge explained that the Division does not typically approve a product for chronic use without an upper bound specifiable on what the QT effect size is according to the ICH Guidance for Industry E14. The sponsor agreed to conduct a QT study and asked if they could submit the top-line study results after NDA submission at the time of the 90-day Safety Update; the Division agreed with this proposal. Additionally, the sponsor could include draft labeling crafted to address the lack of definitive data. The Division also stated that it could expedite the review of a proposed QTc study. The sponsor will include in the NDA the data from a negative hERG assay. Dr. Koerner asked about the hERG positive

control and whether it was done at the IC 50 dose. The sponsor thought so, but will follow-up on this information to the Division.

9. Chelsea proposes the following approach for characterizing renal safety. Does the Division agree?

**Preliminary Response**

The renal toxicity observed during preclinical studies should be addressed by data collected during clinical trials. No additional preclinical data is required regarding this issue.

10. Chelsea proposes that the data on metabolism in animals and humans as provided in IND Amendment SN 0026 (which will be integrated into appropriate sections of the proposed NDA submission) are sufficient to demonstrate that the exposure to metabolites is similar between animals and humans and that no further studies are required. Specifically, does the Agency agree that given existing data characterizing the metabolism of droxidopa, there is no need for a formal mass-balance study or a human metabolites in safety testing (MIST) study?

**Preliminary Response**

This will be a review issue. Please provide both complete study reports for and a thorough discussion of the studies of human and animal metabolites. The IND supplement cited above appears to provide systemic (serum) exposure data in humans only for norepinephrine plus a single metabolite (3-OM-DOPS). Can you provide data that demonstrates that human patients have no significant serum exposure to metabolites other than those present in the serum of the tox study animals? Do you have metabolite data for rabbits, a species used in reproductive toxicity studies? Do you have data for serum norepinephrine (the active drug) for species other than humans, rats and monkeys?

Neither a mass-balance study in animals nor a MIST study are required.

**Discussion during Meeting**

The sponsor stated that in the human, the serum data covers droxidopa, its primary metabolite (3-OM-DOPS) and the active metabolite norepinephrine. The sponsor stated that the overall pattern of metabolites in humans based on serum data is similar to those seen in the animal species and they exist in the same relative proportions between animals and humans. The sponsor does not believe that there is a unique human metabolite, although this could not be completely ruled out. This information on the metabolites will be included in the NDA.

Regarding reproductive studies, Dr. Koerner stated that it would be helpful to have data on the pharmacokinetics of droxidopa and its metabolites in the rabbit. The sponsor stated that these data had not been collected. The sponsor does have pharmacokinetic and metabolite data in the rat, the species in which the majority of the reproductive toxicology was conducted. Dr. Koerner added that it would be helpful to assess protein binding for parent and major metabolites for which there are pharmacokinetic or toxicokinetic data.

11. Chelsea proposes that there is adequate data to demonstrate exposure of animals in the pivotal toxicology experiments and that modeling of dose exposure from previous pharmacokinetic studies is sufficient to estimate exposure. Specifically, does the Agency agree that additional toxicology studies are unnecessary given available existing data?

**Preliminary Response**

This will be a review issue. It appears that you have no toxicokinetic data from any species and that the only pharmacokinetic data you have for preclinical species is from rats. Of note, you appear to have neither toxicokinetic nor pharmacokinetic data from mice (carcinogenicity assay), from rabbits (reproductive toxicity) or from dogs (chronic, repeat-dose toxicity). Additional data would be useful.

**Discussion during Meeting**

The sponsor stated that they have some pharmacokinetic and metabolism data from all species, except the rabbit. The sponsor will include the available pharmacokinetic and pharmacodynamic data from the dog, mice, rats, and rhesus monkey species in the NDA.

**Submission Logistic Questions**

12. Chelsea proposes the following approach for NDA submission format. Does the Division agree?

**Preliminary Response**

We will accept your proposed format but note the following:

Please submit SAS data sets including the raw as well as cleaned data. For example, for adverse events we require both the original verbatim investigator-reported text as well as the final terms used for coding and reporting. Also include an analytical dataset for the efficacy endpoints and the SAS programs to reproduce the efficacy analyses. Please submit complete case report forms including SAE Medwatch or CIOMS forms, data queries, and all other clinical communications.

13. Chelsea requests a rolling NDA submission for this NDA. Does the Division agree?

**Preliminary Response**

No. We would prefer that you submit the full NDA in one complete submission. Regardless, if you have reasons for doing a rolling submission, you must submit the complete data for each discipline as one submission, e.g., all CMC data in one submission, all clinical data in one submission, etc.

**Discussion during Meeting**

The sponsor stated that they will plan to submit one complete NDA submission in the May/June 2011 instead of a rolling NDA. The 90-day Safety Update will include the QT study results.

Dr. Stockbridge noted that for Study 301, the primary endpoint was changed after 124 subjects had been enrolled and 165 subjects had been randomized. He recommended that the sponsor be as thorough as possible in providing the full documentation for the basis of that decision in their complete study report. The sponsor acknowledged this and will provide the documentation to show that they remained blinded to the study results at the time.

14. Chelsea believes that the contents described in the listing of core studies for Module 4 (Appendix 4) and Module 5 (Table 4-1), along with the rest of the information presented in the Pre-NDA Briefing Document, is acceptable to support a complete NDA and that there are no issues apparent at this time that would result in a "Refusal to File"? Does the Division

agree?

**Preliminary Response**

Please see response to question 8.

**Additional Preliminary Responses**

**Study Endpoints Team (SEALD) Comments**

The patient-reported outcome measures, the orthostatic hypotension questionnaire (OHQ) composite score and item 1 of the orthostatic hypotension symptom assessment (OHSA) were used as the primary evaluative measures to support claims of treatment benefit in your phase 3 clinical studies for L-DOPS (droxidopa).

The Agency should be provided with adequate evidence of the development and validation of each of these PRO measures according to principles set forth in the FDA's *Guidance for Industry on Patient-Reported Outcome (PRO) Measures: Use in Medical Product Development to Support Labeling Claims*. We request you to submit supportive materials for each measure as indicated in the aforementioned guidance, including:

1. A copy of the instruments as completed by the patients (including instructions to patients);
2. Investigators' and patients' study manual and/or training material and user manuals (include the scoring algorithms); and
3. Documented evidence of the measures' performance in the specific population in which it is used including but not limited to conceptual framework, content validity documentation, assessment of construct validity, reliability, and ability to detect change.

**Discussion during Meeting**

The sponsor acknowledged the need for validated PRO measures and will submit the detailed documentation for this in the NDA. The OHQ/OHSA measures were developed in 2001 prior to the FDA Guidance. Dr. (b) (4) explained that since there were no instruments to measure NOH in 2001, groups of patients, specialists physicians, biostatisticians, and others worked together to develop psychometric evaluations for the clinical trials through meetings and focus-group testing. The OHQ/OHSA measures that were developed in 2001 are close to the FDA Guidance.

Dr. Stockbridge commented that the sponsor should consider the applicability of the validation to where the study was conducted since Study 301 was conducted in North America and Europe. He also recommended that the sponsor consider the cumulative distribution score to determine which patients are high responders and they should make a case in their NDA on why their treatment effect size, i.e., 0.9, is a reasonable one. The sponsor agreed to supply all this information in their NDA.

**Division of Scientific Investigations (DSI) Comments**

Please see the attached "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" document and the DSI comments document.

**Clinical Pharmacology Comments**

Please see the attached pilot Clinical Pharmacology Summary Aid document.

**CONCLUSION**

Agreement was reached regarding the content and format of the sponsor's proposed NDA submission for droxidopa. The sponsor plans to submit a complete NDA in May/June 2011.

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

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

Rd:

N Stockbridge	12/14/10
E Fromm	12/14/10
E Unger	12/14/10
A Karkowsky	12/14/10
J Koerner	12/13/10
D Jensen	12/13/10
R Madabushi	12/13/10
S Sabarinath	12/13/10

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# Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

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## **I. INTRODUCTION**

The purpose of this electronic submission of a single new clinical site dataset is to facilitate the timely evaluation of data integrity and selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

## **II. DESCRIPTION OF THE SUMMARY LEVEL CLINICAL SITE DATASET**

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection and are not intended to support evaluation of efficacy. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

### **Site-Specific Efficacy Results**

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- Treatment Efficacy Result Variance (TRTEFFV) – the variance of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis
- Site-specific Efficacy Effect Size Variance (SITEEFFV) – the variance of the site-specific efficacy effect size (SITEEFFE)

- 
- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.
  - Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) – the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, “TRTEFFR”.

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.
- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.
- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).
- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the “endpoint” plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1.

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### **III. CREATING AND SUBMITTING THE DATA FILE (SUBMISSION TEMPLATE AND STRUCTURE)**

A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (\*.xpt). The file may be submitted electronically through the FDA Electronic Submission Gateway (ESG) referencing the active IND number or via secure CD addressed to the Division of Scientific Investigations point of contact.

**Exhibit 1: Summary Level Clinical Site Data Elements**

Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
IND	IND Number	Num/Char	6 digit identifier	FDA identification number for investigational new drug	010010
TRIAL	Trial Number	Char	String	Study or Trial identification number	ABC-123
SITEID	Site ID	Num/Char	String	Investigator site identification number	50
ARM	Treatment Arm	Num/Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters)	Active (e.g. 25mg), Comparator drug product name (e.g. Drug x), or Placebo
ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site	20
SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site	100
DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site	5
ENDPOINT	Endpoint	Char	String	Plain text label used to describe the primary endpoint as described in the Define file included with each application. (limit 200 characters)	Average increase in blood pressure
ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other)	Continuous
TRTEFFR	Treatment Efficacy Result	Num	Floating Point	The efficacy result for each primary endpoint, by treatment arm	0, 0.25, 1, 100
TRTEFFV	Treatment Efficacy Result Variance	Num	Floating Point	The variance of the efficacy result (TRTEFFR) for each primary endpoint, by treatment arm	0, 0.25, 1, 100
SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	The effect size should be the same representation as reported for the primary efficacy analysis	0, 0.25, 1, 100
SITEEFFV	Site-Specific Efficacy Effect Size Variance	Num	Floating Point	The variance of the site-specific efficacy effect size (SITEEFFE)	0.065
CENSOR	Censored Observations	Num	Integer	The number of censored observations for the given site and treatment	5
NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site. This value should include multiple events per subject.	10
SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site. This value should include multiple events per subject.	5
DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site	1

Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
PROTVIOL	Number of Protocol Violations	Num	Integer	Number of deviations from the protocol noted by the sponsor for a given site. This value should include multiple violations per subject.	20
FINLDISC	Financial Disclosure Amount	Num	Integer	Total financial disclosure amount (\$USD) by the site investigator	50000.00
LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572	Doe
FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572	John
PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator	555-555-5555, 44-555-555-5555
FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator	555-555-5555, 44-555-555-5555
EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator	john.doe@mail.com
COUNTRY	Country	Char	ISO 3166-1-alpha-2	Country in which the site is located	US
STATE	State	Char	String	Unabbreviated state or province in which the site is located	Maryland
CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located	Silver Spring
POSTAL	Postal Code	Char	String	Postal code for the site	20850
STREET	Street Address	Char	String	Street address and office number at which the site is located	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

**Exhibit 2: General Structure of Data Submission Template**

IND	TRIAL	SITEID	ARM	ENROLL	SCREEN	DISCONT	ENDPOINT	ENDTYPE	TRTEFFR
000001	Study 1	001	Active	26	61	3	Percent Responders	Binary	0.48
000001	Study 1	001	Placebo	25	61	4	Percent Responders	Binary	0.14
000001	Study 1	002	Active	23	54	2	Percent Responders	Binary	0.48
000001	Study 1	002	Placebo	25	54	4	Percent Responders	Binary	0.14
000001	Study 1	003	Active	27	62	3	Percent Responders	Binary	0.54
000001	Study 1	003	Placebo	26	62	5	Percent Responders	Binary	0.19
000001	Study 1	004	Active	26	29	2	Percent Responders	Binary	0.46
000001	Study 1	004	Placebo	27	29	1	Percent Responders	Binary	0.12

TRTEFFV	SITEEFFE	SITEEFFV	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLDISC	LASTNAME	FRSTNAME	PHONE
0.0096	0.34	0.0198	NA	0	2	0	1	0.00	Doe	John	555-123-4567
0.0049	NA	NA	NA	2	2	0	1	0.00	Doe	John	555-123-4567
0.0108	0.33	0.0204	NA	3	2	1	0	45000.00	Washington	George	020-3456-7891
0.0049	NA	NA	NA	0	2	0	3	45000.00	Washington	George	020-3456-7891
0.0092	0.35	0.0210	NA	2	2	0	1	0.00	Jefferson	Thomas	01-89-12-34-56
0.0059	NA	NA	NA	3	6	0	0	0.00	Jefferson	Thomas	01-89-12-34-56
0.0095	0.34	0.0161	NA	4	1	0	0	0.00	Lincoln	Abraham	555-987-6543
0.0038	NA	NA	NA	1	2	0	1	0.00	Lincoln	Abraham	555-987-6543

FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

DSI Comments for the preNDA meeting *IND 077248, L-DOPS, Chelsea Therapeutics, Inc., Sharon K. Gershon, Pharm.D., GCPB II/DSI/OC*

DSI has 2 types of requests for data to be submitted to the NDA; one type addresses the clinical data submitted in the NDA that will be used for the inspection as background materials (Items I and II) and the other type addresses the site selection process (Item III).

## **I. Request for general study related information and specific Clinical Investigator information**

A. Please include the following information in a tabular format in the original NDA for each of the completed Phase 3 clinical trials:

1. Site number
2. Principle investigator
3. Location: City State, Country, to include contact information (phone, fax, email)

B. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 3 clinical trials:

1. Number of subjects screened for each site by site
2. Number of subjects randomized for each site by site
3. Number of subjects treated who prematurely discontinued for each site by site

C. Please include the following information in a tabular format in the NDA for each of the completed Phase 3 clinical trials:

1. Name, address and contact information of all CROs used in the conduct of the clinical trials
2. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
3. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)

## **II. Request for Site Level Data**

1. For each site in the pivotal clinical trials: Name of primary investigator, accurate address and phone number, e-mail contact
2. For each pivotal trial: Sample blank CRF and case report data tabulations for the site with coding key
3. For each pivotal trial: Site-specific individual subject data (“line”) listings from the datasets:
  - a. Line listings for each site listing the subject/number screened and reason for subjects who did not meet eligibility requirements
  - b. Line listings by site and subject, of treatment assignment (randomization)

- c. Line listings by site and subject, of drop-outs and discontinued subjects with date and reason
- d. Line listings by site of evaluable subjects/ non-evaluable subjects and reason not evaluable
- e. Line listings by site and subject, of AEs, SAEs, deaths and dates
- f. Line listings by site and subject, of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
- g. Line listings by site and subject, of the primary and secondary endpoint efficacy parameters or events.
- h. Line listings by site and by subject, concomitant medications (as appropriate to the pivotal clinical trials)
- i. Line listings by site and by subject, of laboratory tests performed for safety monitoring

**III. Request for Individual Patient Data Listings format:**

DSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to the attached document, “Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions” for further information. We request that you provide datasets, as outlined, for each pivotal study submitted in your application.

# CLINICAL PHARMACOLOGY SUMMARY AID

## 1. Goal

In addition to summarizing the relevant findings the goal of the Clinical Pharmacology Summary is to focus sponsor and reviewer on the critical review issues of a submission. To better communicate the expectations of the Agency and to guide sponsors in creating the Clinical Pharmacology Summary in NDA and BLA submissions a Clinical Pharmacology Summary Aid was created. The document consists of a generic questionnaire and instructions clarifying what the answers to the questions should address. The questions cover the entire Clinical Pharmacology realm. The aggregate answers provided by sponsors generate the desired backbone of the Clinical Pharmacology Summary in NDA and BLA submissions. The questions and instructions included in this aid are not intended to be either inclusive of all or exclusive of any questions that specific reviews will address.

The Clinical Pharmacology Summary generated by sponsors is a **stand-alone document**, i.e. the answers to the questions including supporting evidence should be self-sufficient. Appropriate use of complementary tables and figures should be made. The sponsors' answers to the questions should be annotated with links to the detailed information in the study reports and the raw data located in SAS transport files.

## 2. Question Based Review

### 2.1 What are the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA or BLA?

All performed Clinical Pharmacology studies (*in vitro* studies with human biomaterials and *in vivo* studies) and clinical studies with PK and/or PD information along with report numbers should be tabulated. Study titles, objectives, treatments (single or multiple dose, size of the dose/interval), demographics (sex, age, race/ethnicity, body weight, creatinine clearance) and numbers of study participants should be listed. Studies whose results support the label should be marked.

### 2.2 General Attributes of the Drug

#### 2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Provide background information on the drug substance (description, chemical name, molecular formula, molecular weight, structure), physical characteristics

(Log D, solubility, pKa if applicable). Provide tabular information on the drug products, strengths, quantitative composition of ingredients and lot numbers for all formulations used in all *in vivo* studies and indicate corresponding study report numbers.

**2.2.2 What are the proposed mechanism of action and therapeutic indications?**

**2.2.3 What are the proposed dosages and routes of administration?**

**2.2.4 What drugs (substances, products) indicated for the same indication are approved in the US?**

**2.3 General Clinical Pharmacology**

**2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?**

Provide a tabular description of the designs, methodology and salient findings of the clinical pharmacology-, dose-ranging-, and pivotal studies and other clinical studies with PK and/or PD information in brief for each indication. Indicate duration of study, subjects' demographics, dose regimens, endpoints (clinical/biomarkers) and study report numbers.

**2.3.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?**

Provide a rationale for the selected clinical endpoints and biomarkers. For biomarkers indicate relationship to effectiveness and safety endpoints.

**2.3.3 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?**

Indicate circulating active moieties and their plasma and-tissue concentration range after therapeutic doses of the drug of interest. Provide evidence that sensitivity of the assay method(s) used is (are) sufficient to determine apparent terminal t1/2 and AUC.

## **2.4 Exposure-Response**

### **2.4.1 Does the exposure-response relationship support evidence of effectiveness?**

Describe briefly the method(s) used to determine the exposure-effectiveness relationship from pivotal and other appropriate trials. Provide evidence that the exposure-response analysis supports of effectiveness: e.g. a significant slope in the E-R relationship or a clear separation in effectiveness at different drug levels and placebo.

Indicate whether the selected effectiveness endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-effectiveness relationship. Indicate major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status see also 2.6/2.7) impacting the exposure-effectiveness relationship. If commonly known covariates are not identifiable, evaluate different strategies, for example therapeutic drug monitoring, to maximize effectiveness for patients with a sub-therapeutic exposure.

Provide point estimate as well as a measure of the inter-subject variability for effectiveness variables if applicable. Indicate minimum and maximum effective dose- and concentration levels (major active moieties). Provide evidence that with the proposed regimens clinically meaningful effectiveness is maintained throughout the entire dose interval or alternatively provide evidence that maintenance of effectiveness during the entire dose interval is not important. Indicate the magnitude of the effect at peak and trough concentrations with the tested dose regimens. Indicate steady-state trough and peak plasma concentrations of the major active moieties with the proposed dose regimens. Indicate whether AUC, C<sub>max</sub> or C<sub>min</sub> is more correlated with effectiveness. Show the distribution of the effect size for each dose/concentration level tested.

Justify if an analysis of the exposure-effectiveness relationship was not done.

### **2.4.2 What are the characteristics of the exposure-response relationships for safety?**

Describe briefly the method(s) used to determine the exposure-safety relationship. The analysis should focus on adverse events responsible for discontinuations and other drug related toxicities. Indicate whether the safety endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-safety relationship. Indicate the major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal

status) impacting the exposure-safety relationship. Provide point estimate as well as a measure of the inter-subject variability for relevant safety endpoints. Indicate magnitude and/or frequency of relevant adverse events at the tested dose/concentration levels. Indicate proportion of subjects with an excessive adverse response. Indicate whether AUC, C<sub>max</sub> or C<sub>min</sub> is more related to clinically relevant adverse effects. Add information on the maximum tolerated single and multiple dose regimens and the corresponding plasma levels [mean (SD) C<sub>max</sub> and AUC] of the circulating major active moieties.

Justify if an analysis of the exposure-safety relationship was not done.

### **2.4.3 Does this drug prolong QT/QTc Interval?**

Provide a brief description of the study design, regimens, population and data analysis used. Indicate whether plasma concentrations of the drug and the relevant metabolites and the positive control were measured. Give a rationale for the chosen supra-therapeutic dose regimen. Report the findings on the relationship between dose/concentration and QTc interval. Indicate point estimate and 95% confidence interval for the increase of the QTc- interval at the supra-therapeutic dose level. Discuss the relevance of the findings for safety. Provide support for the appropriateness of the selected supra-therapeutic dose, if applicable. Indicate whether the pharmacokinetics of the drug of interest at supra-therapeutic levels is different from that at therapeutic levels.

### **2.4.4 Is the dose and dosing regimen selected consistent with the known E-R relationship?**

Provide information on the criteria used to select the dose regimen (doses, dose intervals) used in the pivotal trials. Indicate the therapeutic dose and/or concentration range for the drug and provide evidence that the proposed dose regimens are optimal given the effectiveness/safety profile of the drug.

## **2.5 What are the PK characteristics of the drug?**

### **2.5.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?**

Briefly describe methods (two-stage and/or population approaches, compartment model dependent or-independent methods) in healthy subjects and in patients with the target disease used to determine the pharmacokinetic parameters of parent drug and relevant metabolites (pharmacologically active or impacting the exposure to parent drug or co-administered drugs). Provide mean, median (SD, CV%) pharmacokinetic parameters of parent drug and relevant metabolites after single doses and multiple doses at steady-state [C<sub>max</sub>, t<sub>max</sub>, AUC, C<sub>max,ss</sub>, C<sub>min,ss</sub>, C<sub>max,ss</sub>/C<sub>min,ss</sub>, t<sub>max,ss</sub>, AUC<sub>0-τ</sub>, CL/F, V/F and t<sub>1/2</sub> (half-life determining accumulation factor), accumulation factor,

fluctuation, time to steady-state]. Indicate how attainment of steady-state is determined. Provide evidence for attainment of steady-state.

**2.5.2 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?**

Compare the pharmacokinetic parameters of the drug of interest and relevant metabolites in healthy subjects and patients with the target disease. Provide a rationale for observed significant differences between healthy subjects and patients with the target disease.

**2.5.3 What is the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?**

Provide mean/median (SD, coefficient of variation, range within 5% to 95% confidence interval bracket for concentrations) about mean AUC, C<sub>max</sub>, C<sub>min</sub>, CL/F and t<sub>1/2</sub> of the parent drug and relevant metabolites after single doses and at steady-state.

**2.5.4 What are the characteristics of drug absorption?**

Indicate absolute bioavailability of drug of parent drug and relative bioavailability, lag time, t<sub>max</sub>, t<sub>max,ss</sub>, C<sub>max</sub>, C<sub>max,ss</sub> and extent of systemic absorption of parent drug and relevant metabolites in healthy subjects and patients with the target disease. Indicate mean (SD) for these parameters.

**2.5.5 What are the characteristics of drug distribution?**

Indicate mean (SD) V/F for the drug of interest in healthy subjects and patients with target disease. Provide mean (SD) blood/ plasma ratio for parent drug in healthy subjects. Briefly describe method and pH- and temperature conditions used for determining plasma protein binding for parent drug and relevant metabolites. Provide mean (SD) values of the plasma protein binding of the drug of interest and relevant metabolites measured over the therapeutic range in healthy subjects and patients with target disease and special populations.

**2.5.6 Does the mass balance study suggest renal or hepatic as the major route of elimination?**

Present total, renal and fecal recoveries as percent of the administered total radioactivity. Indicate the percentage of radioactivity excreted as unchanged parent drug in urine and feces and the percent of radioactivity excreted as metabolites in urine and feces.

**2.5.7 What is the percentage of total radioactivity in plasma identified as parent drug and metabolites?**

Provide identification for  $\geq 90\%$  of the circulating total radioactivity (AUC). If multiple small peaks are present whose individual radioactivities are too small

to be assignable to specific metabolites provide an estimate for their contribution to circulating total radioactivity.

#### **2.5.8 What are the characteristics of drug metabolism?**

Present the metabolic scheme for the drug. Provide an estimate for the contribution of metabolism to the overall elimination of the drug of interest. Indicate mean (SD) values for the non-renal clearance (mL/min) in healthy subjects and patients with the target disease. Indicate whether active metabolites constitute major circulating moieties and if so how much they contribute to effectiveness and/or whether they affect safety.

#### **2.5.9 Is there evidence for excretion of parent drug and/or metabolites into bile?**

If appropriate provide *in vitro* and/or *in vivo* evidence suggesting that parent drug and/or metabolites are excreted into bile (*in vitro*: parent drug and/or metabolites are substrates of BCRP, *in vivo*: recovery of unchanged parent drug in mass balance- and absolute bioavailability studies suggest excretion into bile)

#### **2.5.10 Is there evidence for enterohepatic recirculation for parent and/or metabolites?**

Indicate whether there are secondary peaks and humps in the plasma concentration profile correlating with food intake.

#### **2.5.11 What are the characteristics of drug excretion in urine?**

Provide an estimate of the contribution of renal excretion to the overall elimination of parent drug in healthy volunteers. Present mean values (SD) for the renal clearance (mL/min) in healthy subjects and in the target population. Using mean plasma protein binding and renal clearance values in healthy subjects estimate the respective contributions of glomerular filtration and net tubular secretion or re-absorption to renal clearance.

#### **2.5.12 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?**

Briefly describe the statistical methods used to determine the type of pharmacokinetics of the drug and its relevant metabolites (linearity, dose proportionality, non-linearity, time dependency) in healthy subjects and patients with the target disease. Identify the doses tested after single and multiple dose administrations of the drug of interest and the respective dose normalized mean (SD) C<sub>max</sub> and AUC values in healthy subjects and patients with the target

disease. Indicate whether the kinetics of the drug is linear, dose proportionate or nonlinear within the therapeutic range. In case of nonlinear or time dependent pharmacokinetics provide information on the suspected mechanisms involved.

### **2.5.13 How do the PK parameters change with time following chronic dosing?**

Indicate whether the mean ratio of AUC<sub>0-τ</sub> at steady-state to AUC after the first dose for the circulating major active moieties deviates statistically significantly from 1.0 in healthy subjects and patients with the target disease. Discuss the relevance of the findings and indicate whether an adjustment of the dose regimen is required. If the pharmacokinetics of the drug of interest changes with time provide a rationale for the underlying mechanism.

### **2.5.14 Is there evidence for a circadian rhythm of the PK?**

Indicate whether C<sub>max</sub> and C<sub>min</sub> of the parent drug after the morning and evening dose differ significantly. Discuss the relevance of the findings and whether an adjustment of the dose regimen is required for the drug of interest. Provide a rationale for the underlying mechanism for the observed circadian rhythm of the pharmacokinetics of the drug of interest. Indicate whether the dose regimens in the pivotal studies were adjusted for circadian rhythm.

## **2.6 Intrinsic Factors**

### **2.6.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, C<sub>max</sub>, C<sub>min</sub>) in patients with the target disease and how much of the variability is explained by the identified covariates?**

Provide for all studies investigating the impact of the intrinsic factors (age, sex, body weight, ethnicity/race, renal and hepatic impairment) demographics and number of study subjects, and dose regimens. Provide summaries of the results and indicate intrinsic factors that impact significantly exposure and/or efficacy and safety of the drug of interest. Provide for each major identified covariate an estimate for its contribution to the inter-subject variability and indicate how much of the inter-subject variability is explained by the identified covariates.

Provide mean (SD) parameters for AUC, C<sub>max</sub>, clearance, volume of distribution and t<sub>1/2</sub> for pairs studied: elderly vs.young, male vs.female, normal body weight vs. obese, race/ethnicity x vs. race/ethnicity y, mild vs. severe target disease

### **2.6.2 Based upon what is known about E-R relationships in the target**

## **population and their variability, what dosage regimen adjustments are recommended for each group?**

Characterize the populations (age, sex, body weight, ethnicity/race) used to determine the impact of each intrinsic factor on variability in exposure and exposure-response. Indicate for each intrinsic factor whether a dose adjustment (dose or interval) is required or not and provide a rationale for either scenario.

### **2.6.2.1 Severity of Disease State**

### **2.6.2.2 Sex**

### **2.6.2.3 Body Weight**

### **2.6.2.4 Elderly**

### **2.6.2.5 Pediatric Patients**

If available provide mean (SD, range) pharmacokinetic parameters, biomarker activity, effectiveness and safety in the pediatric sub-populations (neonates (birth-1 month), infants (1 month- 2 years), children (2-12 years) and adolescents (12- < 16 years) and define the target disease. If no information is available in the pediatric population indicate age groups to be investigated in future studies. Provide a summary stating the rationale for the studies proposed and the endpoints and age groups selected. Include a hyperlink to the development plan of the drug of interest in children.

### **2.6.2.6 Race/Ethnicity**

### **2.6.2.7 Renal Impairment**

Characterize the demographics for each subgroup (normal renal function, mild, moderate and severe renal impairment, on and off dialysis). Indicate mean (SD, range) for creatinine clearance estimated by the Cockcroft-Gaul- and MDRD equations for the stages of renal impairment investigated. Provide arithmetic mean (SD) AUC, C<sub>max</sub>, CL/F, CL<sub>r</sub>, V/F and t<sub>1/2</sub> of parent drug and relevant metabolites in the different sub-groups assessed by 2-stage or population PK approaches. Show regressions including 90% confidence intervals of AUC, C<sub>max</sub> and CL/F on CL<sub>r</sub> for parent drug and relevant metabolites. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of creatinine clearance.

Provide estimates of the contribution of glomerular filtration and net tubular secretion or re-absorption to the renal excretion of the drug of interest. Indicate whether plasma protein binding of the active moieties is significantly altered in renal impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment is required or not for each of the

sub-groups of patients with impaired renal function and provide a rationale for either scenario.

#### **2.6.2.8 Hepatic Impairment**

Characterize the demographics for each subgroup (normal hepatic function, mild, moderate and severe hepatic impairment based on Child-Pugh scores). Provide information on arithmetic mean (SD) AUC, C<sub>max</sub>, CL/F and t<sub>1/2</sub> of parent drug and relevant metabolites in the different hepatic function sub-groups assessed by two-stage or population PK approaches. Show regressions including 90% confidence intervals of C<sub>max</sub>, AUC or CL/F on the Child-Pugh score for parent drug and relevant metabolites. Indicate whether plasma protein binding of the active moieties is significantly altered in hepatic impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment is required or not for each of the subgroups of patients with impaired hepatic function and provide a rationale for either scenario. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of Child-Pugh score.

#### **2.6.2.9 What pregnancy and lactation use information is available?**

#### **2.6.3 Does genetic variation impact exposure and/or response?**

Describe the studies in which DNA samples have been collected. If no DNA samples were collected state so. Include a table with links to the studies in which DNA was analyzed and genomic/genetic information is reported. In the description of these studies include demographics, purpose of DNA analysis (effectiveness, safety, drug metabolism, rule in-out of patients, etc.), rationale for the analysis, procedures for bio-specimen sample collection and DNA isolation, genotyping methods, genotyping results in individual subjects, statistical procedures, genotype-phenotype association analysis and results, interpretation of results, conclusions. If genomic polymorphism impacts either exposure and/or response indicate the measures to be taken to safeguard efficacy and safety of the drug in subjects with varying genotypes. Indicate the contribution of genetic factors to inter-subject variability.

#### **2.6.4 Immunogenicity (NOT applicable to small molecule drugs)**

##### **2.6.4.1 What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?**

**2.6.4.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?**

**2.6.4.3 Do the anti-product antibodies have neutralizing activity?**

**2.6.4.4 What is the impact of anti-product antibodies on clinical efficacy?**

**2.6.4.5 What is the impact of anti-product antibodies on clinical safety?**

Provide information on the incidence of infusion-related reactions, hypersensitivity reactions, and cross-reactivity to endogenous counterparts.

## **2.7 Extrinsic Factors**

**2.7.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?**

Summarize the results of the *in vitro* studies performed with the drug of interest as substrate, inhibitor or inducer of relevant CYP and non-CYP enzymes and transporters. Give rationale for why based on the *in vitro* results an interaction study in humans is required or is not required

**2.7.2 Is the drug a substrate of CYP enzymes?**

Briefly describe the methods used (specific chemicals/antibodies, human recombinant CYP enzymes, human microsomes). Indicate incubate, initial rate conditions, concentration range tested relative to  $K_m$ , controls etc. Provide a summary of the results of the *in vitro* studies investigating the drug of interest as a substrate of CYP 450 and non-CYP 450 enzymes. Provide for each of the relevant enzymes a mean estimate for the % contribution to the metabolism of the drug of interest. Discuss the relevance of the *in vitro* findings for the drug of interest as a substrate for deciding which drug-drug interactions should be or need not be performed in humans. For each situation provide supporting evidence.

**2.7.3 Is the drug an inhibitor and/or an inducer of enzymes?**

Briefly describe the methods used (type and source of liver tissue, concentration range tested for the drug of interest as substrate, inhibitor and inducer, experimental conditions, pre-incubation, probe substrates, positive/negative controls. Provide summary results of the *in vitro* studies with human liver tissues for the drug of interest as a potential inhibitor or inducer of enzymes. Indicate whether the drug is a reversible inhibitor (competitive, non-competitive or un-competitive) or an irreversible inhibitor (mechanism based) and supportive evidence. Provide mean (SD) values for  $K_i$ ,  $IC_{50}$  and  $V_{max}$  for each relevant enzyme and probe substrate. Indicate the anticipated maximum total and unbound concentration of the drug of interest as inhibitor ([I]). Provide the mean (SD) % activity relative to the positive control for the drug of interest as

inducer. Discuss the relevance of the *in vitro* findings for the drug of interest as an inhibitor or inducer for deciding which drug-drug interactions should be or need not be performed *in vivo* in humans. If appropriate use the  $[I]/K_i$  ratio as a means to assess the likelihood of an *in vitro* result to be clinically relevant. For each situation provide supporting evidence.

**2.7.4 Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?**

See 2.7.2.2 and 2.7.2.3. The instructions for the interactions of the drug of interest as substrate, inhibitor or inducer of transporters are analogous to those for enzymes.

**2.7.5 Are there other metabolic/transporter pathways that may be important?**

**2.7.6 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?**

Indicate extrinsic factors that impact significantly exposure and/or effectiveness and safety of the drug. Indicate extent of increase or decrease in exposure and/or response caused by extrinsic factors. State whether an adjustment of the dose is or is not required and provide supporting evidence for either case.

**2.7.7 What are the drug-drug interactions?**

Provide a list of the drug-drug interaction studies (PK or PD based mechanism) performed and give a rationale for conducting the listed studies. Indicate the suspected mechanism responsible for the interaction. For each of the *in vivo* studies performed provide a rationale for the design selected (single or multiple dose regimens, randomized/non-randomized cross-over or parallel design for perpetrator and/or victim).

a) Drug of interest is impacted by co-administered other drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Report the 90% confidence intervals about the geometric mean ratio for AUC and C<sub>max</sub> for the drug of interest in the presence and absence of each of the co-administered drugs. Indicate whether a dose adjustment is required or not. In either case provide a rationale. Define the required adjusted dose regimens.

b) Drug of interest impacts other co-administered drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the

magnitude of the equivalence interval selected if it is greater than the default interval. Report 90% confidence intervals about the geometric mean ratio for AUC and C<sub>max</sub> of each of the co-administered drugs in the presence and absence of the drug of interest.

- 2.7.8 Does the label specify co-administration of another drug?**
- 2.7.9 What other co-medications are likely to be administered to the target population?**
- 2.7.10 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?**

## **2.8 General Biopharmaceutics**

For all *in vivo* studies performed in this section indicate study design, demographics and number of subjects enrolled, and type, composition, strength and lot number of the formulations used. Provide summary results with estimates for mean and inter-subject variability on AUC and C<sub>max</sub> after single and multiple dose administration and peak to trough fluctuation after multiple dose administration.

### **IR Product**

- 2.8.1 Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?**
- 2.8.2 How is the proposed to-be-marketed formulation linked to the clinical service formulation?**
  - 2.8.2.1 What are the safety or effectiveness issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?**
  - 2.8.2.2 If the formulation does not meet the standard criteria for bioequivalence, what clinical pharmacology and/or safety and efficacy data support the approval of the to-be-marketed product?**
- 2.8.3 What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?**

Indicate composition and calories of the food administered, and length of the

pre-dose fasting period. State whether the impact of food is on the drug substance or the inactive ingredients of the formulation. Indicate clinical relevance of findings. Indicate the temporal relationship between drug intake and food intake in the pivotal studies.

**2.8.4 Was the bioequivalence of the different strengths of the to be marketed formulation tested? If so were they bioequivalent or not?**

**2.8.5 If unapproved products or altered approved products were used as active controls, how is BE to the to be marketed product demonstrated? What is the link between the unapproved/altered and to be marketed products?**

**MR product (if an IR is already marketed)**

**2.8.6 What is the bioavailability of the MR product relative to the approved IR product? How does the plasma concentration time profile of the MR formulation compare to that of the IR formulation after single and multiple doses?**

Indicate whether or not the pharmacokinetics of the drug of interest is linear, dose proportional or nonlinear after administration of the MR formulation. Summarize data on C<sub>max</sub>, AUC and C<sub>min</sub> of the IR and MR formulations after a single dose and multiple doses at steady-state. Provide information on the fluctuation factor at steady-state.

**2.8.7 What is evidence that MR formulation *in vivo* consistently shows claimed MR characteristics?**

**2.8.8 What is evidence that MR formulation displays less variability in C<sub>max</sub>, AUC and C<sub>min</sub> than IR formulation?**

**2.8.9 Does the MR product show dose dumping *in vivo*?**

Describe design, demographics and number of subjects participating in the studies performed to determine whether dose dumping occurs with the MR formulation when given in the fed state or when given together with alcohol. Present summaries of results.

**2.8.10 Does ethanol *in vitro* have a dose-dumping effect on the MR product?**

Provide the results of the *in vitro* dissolution testing of the various strengths of the ER product in pH 1.2, 4.5 and 6.8 media containing 0, 5, 10, 20 and 40% alcohol. Discuss any dose dumping observed. If an *in vivo* study was performed report the clinical relevance of the findings.

**2.8.11 Are the MR and IR products marketed simultaneously?**

If the intention is to market both the MR and IR products, indicate how patients are converted from the IR to the MR product and vice versa.

**2.8.12 If the NDA is for an MR formulation of an approved IR product without supportive safety and effectiveness studies, what dosing regimen changes are necessary, if any, in the presence or absence of a PKPD relationship?**

**2.8.13 In the absence of effectiveness and safety data what data support the NDA for a MR formulation of an approved IR product?**

**2.9 Analytical Section**

**2.9.1 How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?**

List all assays used and briefly describe the individual methods.

**2.9.2 Which metabolites have been selected for analysis and why?**

**2.9.3 For all moieties measured, is free, bound, or total measured?**

Indicate whether free, bound or total (bound+unbound) concentrations of the drug of interest and relevant metabolites are measured and give a rationale for your selection.

**2.9.4 What bioanalytical methods are used to assess concentrations of the measured moieties?**

Identify all studies that used a particular assay method. For each assay report indicate the corresponding assay validation report.

**2.8.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?**

For each method and analyte provide concentration range of calibration curve and indicate respective concentration range for relevant moieties with therapeutic

regimens. Indicate fit type of the calibration curves.

**2.9.5.1 What are the lower and upper limits of quantitation?**

For each method and analyte indicate LLOD, LLOQ and ULOQ for undiluted and diluted samples.

**2.9.5.2 What are the accuracy, precision, and selectivity at these limits?**

For each method and analyte indicate inter-day and intra-day precision (CV%) and inter-day and intra-day accuracy (RE%).

**2.9.5.3 What is the sample stability under conditions used in the study?**

For all studies in which concentrations of the drug of interest and relevant metabolites were measured provide information on initiation date of study, date of last sample analyzed and total sample storage time. For each method and matrix provide information on the stability of the analytes, i.e. number of freeze-thaw cycles, benchtop stability at room temperature and stability during long term storage at  $\leq -20^{\circ}$  C.

**2.9.5.4 What is the plan for the QC samples and for the reanalysis of the incurred samples?**

For each study, method and analyte indicate precision (CV%) and accuracy (%RE) using the QC samples measured alongside samples with unknown concentrations. Indicate the concentrations of the QC and incurred samples used.

**Applicable to therapeutic proteins only**

**2.9.5.5 What bioanalytical methods are used to assess therapeutic protein concentrations?**

Briefly describe the methods and summarize the assay performance.

**2.9.5.6 What bioanalytical methods are used to assess the formation of the anti-product antibodies?**

Briefly describe the methods and assay performance including sensitivity, specificity, precision, cut point, interference and matrix, etc.

**2.9.5.7 What is the performance of the neutralizing assay(s)?**

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/s/  
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NORMAN L STOCKBRIDGE  
12/17/2010

**DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS  
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**Transmitted via email to:** hewitt@chelseatherapeutics.com

**Attention:** Dr. L. Arthur Hewitt

**Sponsor:** Chelsea Therapeutics

**Phone:** (704) 341-1516, ext. 102

**Subject:** **End-of-Phase 2 Meeting Minutes**

**Date:** September 20, 2007

**Pages, including this sheet:** 9

**From:** Quynh Nguyen, Pharm.D.  
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Please note that you are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

**End-of-Phase 2 Meeting with Sponsor**

**Application Number:** IND 77,248  
**Sponsor:** Chelsea Therapeutics  
**Drug:** L-DOPS (droxidopa)  
**Type of Meeting:** EOP2  
**Classification:** B  
**Meeting Date:** August 21, 2007  
**Briefing Package Received:** July 9, 2007  
**Confirmation Date:** June 4, 2007  
**Meeting Request Received:** May 21, 2007  
**Meeting Chair:** Robert Temple, M.D.  
**Recorder:** Quynh Nguyen, Pharm.D.

**List of Attendees:**

**Food and Drug Administration**

Robert Temple, M.D.	Director, Office of Drug Evaluation I
Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardiovascular and Renal Products (DCRP)
Thomas Marciniak, M.D.	Medical Team Leader, DCRP
Abraham Karkowsky, M.D., Ph.D.	Medical Team Leader, DCRP
James Hung, Ph.D., Director	Division of Biometrics I, Office of Biostatistics
Rajnikanth Madabushi, Ph.D.	Pharmacometrics Reviewer, Office of Clinical Pharmacology (OCP)
Yanning Wang, Ph.D.	Pharmacometrics Team Leader, OCP
Edward Fromm, R.Ph.	Chief, Project Management Staff, DCRP
Quynh Nguyen, Pharm.D.	Regulatory Health Project Manager, DCRP

**Chelsea Therapeutics**

L. Arthur Hewitt, Ph.D.	V.P., Drug Development
Simon Pedder, Ph.D.	CEO and President
Cameron Szakacs, Ph.D.	Director, Drug Development

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**BACKGROUND**

L-DOPS (droxidopa) is a synthetic amino acid, which as a prodrug, is converted by dopa decarboxylase to form norepinephrine. The drug is being developed for the treatment of symptomatic neurogenic orthostatic hypotension (NOH) in patients with primary autonomic failure, dopamine- $\beta$ -hydroxylase (D $\beta$ H) deficiency, or nondiabetic autonomic neuropathy. A Pre-IND meeting was held on

March 30, 2007. This End-of-Phase 2 meeting was scheduled to discuss the sponsor's proposed clinical development plan.

## **DISCUSSION**

- 1. Clinical studies designed to examine the safety and efficacy of Droxidopa have been conducted in Japan and the EU. Does the Agency agree with the sponsor that, given the availability of existing data demonstrating a meaningful clinical benefit of Droxidopa, the data generated and analyzed from the proposed Phase III studies (Protocols 301 and 302) and an open-labeled safety study (Protocol 303) may be sufficient to demonstrate the safety and efficacy of Droxidopa in support of marketing approval for this indication?**

### **Preliminary Response**

We agree.

### **Discussion during Meeting**

Dr. Stockbridge stated that two Phase 3 trials involving a clinical endpoint and some long-term data would be sufficient for approval, but further discussion was needed regarding the details of the trials (see discussion for Question 2).

- 2. Does the Agency agree with the sponsor that the Orthostatic Hypotension Symptom Assessment (OHSA) is an acceptable outcome measure for assessing symptomatic benefit in patients with neurogenic orthostatic hypotension?**

### **Preliminary Response**

We agree. However, you should also include a global assessment scale, i.e., ask patients whether they feel the same, better, or worse.

### **Discussion during Meeting**

The sponsor agreed to include a global assessment scale in their protocol.

Dr. Stockbridge stated that responder analysis was not recommended since the Division was interested in symptomatic relief rather than blood pressure (BP) effects. Therefore, BP effects should not be part of the endpoint, but the sponsor should still characterize BP effects as a function of dose and time.

There was discussion regarding the following sentence in the preamble to the OHSA scale on page 193 of the meeting package: "PLEASE RATE THE SYMPTOMS THAT ARE DUE ONLY TO YOUR LOW BLOOD PRESSURE PROBLEM." The Division was concerned with this sentence because patients should not be informed of what their blood pressure is. The sponsor explained that there will be instructions to patients to explain the kinds of symptoms that result from low BP but that patients would not be informed of their standing BP prior to being asked about their BP-related symptoms. They referred to the "Patient Instructions," which would be read aloud to patients (on page 192). The Agency agreed that if the "Patient Instructions" are read first, then the preamble to the OHSA scale would be interpretable and therefore was acceptable.

There was discussion regarding the validation procedure for the OHSA scale. The sponsor explained that there was a very good correlation between improvement in scale score and an increase in BP, and they agreed to provide this further information in the IND. Dr. Marciniak commented that a statistically significant difference would have to be observed in change in scale score between the droxidopa and placebo groups to indicate efficacy.

To characterize the effects in the population, Dr. Temple suggested that the sponsor consider looking at the distribution of effect rather than at just one number or point change in the score.

There was discussion regarding the Agency's experience with midodrine where studies failed to show a clinical benefit, even though orthostatic hypotension was decreased. The sponsor wondered whether because neurogenic orthostatic hypotension was a rare disease, perhaps some of the previous trials had included patients who should not have been entered. The Agency suggested that the study include patients who are symptomatic, potentially including patients who had participated in previous trials. In addition, it would be acceptable to enroll a smaller number of patients with severe disease.

The sponsor agreed that for Study 301, the primary endpoint would be a change of symptoms of OH. The study will compare the mean change from baseline in score on Question 1 of the OHSA in patients who received droxidopa versus patients who received placebo. The Agency agreed that Item 1 of the OHSA could be used as the primary outcome measure for the study.

- 3. Does the agency agree with the sponsor's proposal to use a co-primary endpoint that measures both symptomatic and hemodynamic (blood pressure) effects following therapy with Droxidopa?**

**Preliminary Response**

No. Only a change in symptoms of OH should be used as the primary endpoint.

**Discussion during Meeting**

See discussion under Question 2. The Division agreed that the sponsor's proposal to use both a clinical and BP endpoint was acceptable. However, a change in the BP was not needed to show effectiveness. The sponsor wished to identify patients with a change in clinical benefit and a change in BP, i.e., eliminate responders who do not have the BP effect. Dr. Temple suggested that the sponsor could perform an initial screening process to look for patients with a BP effect, i.e., an enrichment design.

- 4. Does the Agency agree with the sponsor that there is adequate justification for the sponsor's definition of response for each of the co-primary endpoints used in Protocols 301 and 302:**
- a. A change in symptoms of OH, as indicated by an improvement of 1 point on Item 1 of the OHSA , and**
  - b. Improvement in systolic blood pressure (SBP) with an increase of SBP of 10 mmHg at 3 minutes post standing?**

**Preliminary Response**

See response to Question 3.

**Discussion during Meeting**

See discussion under Questions 2 and 3.

- 5. Does the Agency agree with the sponsor that there are sufficient data to support the sponsor's choice of dose regimen, including the appropriateness of using titration to effect for the Phase III studies?**

**Preliminary Response**

We agree. Toxicity should be measured and patients should be titrated only if there is no toxicity of concern.

Blood pressure as part of the Orthostatic Standing Test should be measured sooner than 3 hours post-morning dose, i.e., at 1 hour post-dose.

**Discussion during Meeting**

The sponsor agreed that patients should be titrated only if there is no toxicity of concern and will include a statement to this effect in the protocol.

The sponsor explained that blood pressure as part of the Orthostatic Standing Test would be measured at 3 hours. As droxidopa is a prodrug, this is related to the peak concentrations of norepinephrine as determined by pharmacokinetic studies.

**6. Does the Agency agree with the sponsor that the statistical analysis plans provided in Protocols 301 and 302 are adequate to evaluate the efficacy and safety of Droxidopa?**

**Preliminary Response**

Because of the interim analysis, an alpha adjustment for the final efficacy analysis needs to be pre-specified in the protocol to ensure adequate control of type 1 error. All details of the sample size re-estimation need to be provided in the SAP and submitted considerably before initiation of the interim analysis.

There are many secondary endpoints in the protocol. If you plan to include the results of any of the secondary endpoints into labeling or promotions, a hierarchical testing procedure for the secondary endpoints may be considered to control the overall type 1 error in this case.

One primary statistical method for the primary efficacy analysis should be pre-specified in the SAP. All other methods will be supportive. You cannot have a choice of covariates for the final statistical model. All covariates in the final model need to be pre-specified.

Sites with small number of patients may be problematic in the analysis. If you intend to pool small sites for the analysis, an algorithm for pooling needs to be pre-specified.

**Discussion during Meeting**

The sponsor agreed with the above comments.

**7. Does the Agency agree with the sponsor that the proposed long-term extension for protocol 302 (Protocol 303) will provide the data necessary to demonstrate a durability of effect of Droxidopa?**

**Preliminary Response**

We agree.

**Discussion during Meeting**

See discussion under Question 8.

- 8. Chelsea's Phase III clinical program includes Protocol 301 (designed to examine the safety and efficacy of Droxidopa in 114 evaluable patients); Protocol 302 (a randomized withdrawal study in which 114 patients are equally randomized to receive Droxidopa or placebo during the withdrawal period); and Protocol 303 (an open-label long-term safety study in up to 114 patients treated for at least 3 months). Does the Agency agree with the sponsor that this clinical study program is sufficient to demonstrate safety and efficacy to support a marketing approval, given the rarity of this condition?**

**Preliminary Response**

We agree.

**Discussion during Meeting**

**Study 301**

The sponsor presented a schematic drawing of Study 301 during the meeting for the Agency's comments. Dr. Stockbridge commented that the Division would like to be able to distinguish the effects attributable to dose and time. He suggested that this could be achieved with a fixed-dose design by adding a third arm in which a group of patients would be titrated to less than 600 mg t.i.d. (perhaps 300 mg). Since the current protocol allows the dose of droxidopa to be increased until BP is 180/110 or greater, the proposed study design would allow the sponsor to determine if there is an added benefit to dosing above 300 mg t.i.d. in light of this increase in BP. The sponsor pointed out that very few patients ever receive doses between 400 and 600 mg t.i.d. Dr. Marciniak expressed concerns about the potential risk of stroke with an increased BP in this population. Drs. Marciniak suggested a crossover study design that would investigate the dose at which the maximum effect is observed. Dr. Karkowsky suggested dividing subjects to a fixed low dose group with the option of adding an additional two weeks to allow for that group to be titrated based on response. The primary metric would be the effect at the end of either two or 4 weeks.

The sponsor responded that the suggested trial design was not appropriate because patients were being titrated to a fixed dose that might not be effective. In addition, the sponsor noted that different patients have a different sensitivity to different drugs. There was also concern due to the heterogeneity of the patients, i.e., some patients have pure autonomic failure, while others have Parkinson's disease. Therefore, the sponsor stated that a fixed dose was not appropriate since each patient had to be titrated to an optimal dose. The sponsor was also concerned that the modified study design would require more patients and a longer duration, which would be burdensome.

**Study 302**

The Agency agreed that for Study 302, a duration of 7 days was acceptable to demonstrate effectiveness. However, for chronic therapy, the duration of treatment with this trial would need to be longer, or the sponsor would need to consider an open-label extension study. The sponsor stated that rather than increase the length of Study 302 (and possibly Study 301), it would add a withdrawal phase to Study 303 where patients would receive active drug for three months and then be randomized to a 2-week withdrawal period, where they would receive either placebo or continue on their dose of droxidopa. This was acceptable to the Agency.

Dr. Temple asked if there was an escape clause in Protocol 302 (and during the withdrawal stage of 303) since the study population would include patients that are very symptomatic. The sponsor agreed that this study will include an escape clause. The Agency stated that anyone who dropped out of the study during the withdrawal phase but then received rescue medication should be accounted for appropriately in the study statistical plan.

Dr. Temple asked if patients would be required to return for a clinic visit following the first week of withdrawal or would only be seen at the conclusion of the 14-day withdrawal period of Protocol 302. The sponsor noted that the protocol only had a mandatory visit at the end of the 14-day withdrawal period; however, patients could contact their study physician at any time during the withdrawal period to schedule an additional visit if they felt that their symptoms had worsened or they need to be evaluated.

**Additional Preliminary Comments**

Patients with severe OH should be recruited for the studies.

Study 302 should be longer, i.e., 6 months instead of 7 days.

Due to a potential large placebo effect, patients should not be required to score at least 4/10 on item 1 of the OSHA to enter into the study.

To avoid a regression to the mean effect, eligibility scores taken as entry criteria should not be used for the baseline.

**Discussion during Meeting**

The Agency explained that the entry score (with a tendency to be inflated to allow entry) should not be used as the baseline score, because of regression to the mean. Instead, the baseline value should be the score on day 0.

**CONCLUSION**

This End-of-Phase 2 meeting was scheduled to discuss the sponsor's proposed clinical development plan for L-DOPS. The sponsor was encouraged to submit one of the protocols for their pivotal trials as a Special Protocol Assessment (SPA). The sponsor would receive the Agency's comments on the SPA no later than 45 days from receipt. The sponsor should also include a description of the rest of their clinical development plan. The sponsor intends to file the IND with one protocol and ask for an SPA for review of their second protocol.

If you have any questions, please call:

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Sincerely,

*{See appended electronic signature page}*

Robert Temple, M.D.  
Director  
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