

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203389Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 203389

SUPPL #

HFD # 180

Trade Name Procysbi

Generic Name cysteamine bitartrate

Applicant Name Raptor Therapeutics

Approval Date, If Known 4/30/2013

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES  NO

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

505(b)(2)

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

YES  NO

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

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?

3 years

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# 20392

Cystagon

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:

Investigation #1: RP103-01  
Investigation #2: RP103-02  
Investigation #3: RP103-03  
Investigation #4: RP103-04  
Investigation #5: RP103-05  
Investigation #6: RP103-06

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 <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #3	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #4	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #5	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #6	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

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 <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #3	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #4	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #5	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #6	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

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

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

All investigations listed in #2(c) were necessary for approval

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

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

Investigations #1 thru #6

IND # 103694      YES       NO   
 Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

(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:

=====

Name of person completing form: Jessica Benjamin  
Title: Senior Regulatory Project Manager  
Date:

Name of Office/Division Director signing form:  
Andrew E. Mulberg, MD  
Title: Deputy Director, DGIEP

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/  
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JESSICA M BENJAMIN  
04/25/2013

ANDREW E MULBERG  
04/25/2013

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 203389 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: PROCYSBI Established/Proper Name: cysteamine bitartrate Dosage Form: capsules		Applicant: Raptor Therapeutics Agent for Applicant (if applicable):
RPM: Jessica M. Benjamin		Division: DGIEP
<p><b><u>NDA and NDA Efficacy Supplements:</u></b></p> <p>NDA Application Type:    <input type="checkbox"/> 505(b)(1)    <input checked="" type="checkbox"/> 505(b)(2)                      Efficacy Supplement:    <input type="checkbox"/> 505(b)(1)    <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>	<p><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>NDA 20392 Cystagon</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>Delayed release formulation – more favorable dosing regimen</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>	
<b>❖ Actions</b>		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>April 30, 2013</u></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 checked="" type="checkbox"/> None	

<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>	<p><input type="checkbox"/> Received</p>
<p>❖ Application Characteristics <sup>3</sup></p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority                  Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input checked="" type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDA: Subpart H <span style="margin-left: 200px;">BLAs: Subpart E</span>  <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <span style="margin-left: 100px;"><input type="checkbox"/> Accelerated approval (21 CFR 601.41)</span>  <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <span style="margin-left: 100px;"><input type="checkbox"/> Restricted distribution (21 CFR 601.42)</span></p> <p>Subpart I <span style="margin-left: 200px;">Subpart H</span>  <input type="checkbox"/> Approval based on animal studies <span style="margin-left: 100px;"><input type="checkbox"/> Approval based on animal studies</span></p> <p><input type="checkbox"/> Submitted in response to a PMR <span style="margin-left: 200px;">REMS: <input type="checkbox"/> MedGuide</span>  <input type="checkbox"/> Submitted in response to a PMC <span style="margin-left: 100px;"><input type="checkbox"/> Communication Plan</span>  <input type="checkbox"/> Submitted in response to a Pediatric Written Request <span style="margin-left: 100px;"><input type="checkbox"/> ETASU</span>  <span style="margin-left: 400px;"><input type="checkbox"/> MedGuide w/o REMS</span>  <span style="margin-left: 400px;"><input checked="" type="checkbox"/> REMS not required</span></p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<p><input type="checkbox"/> Yes, dates</p>
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> <li>• Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> <li>• Press Office notified of action (by OEP)</li> </ul>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> <li>• Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<p><input type="checkbox"/> None  <input checked="" type="checkbox"/> HHS Press Release  <input type="checkbox"/> FDA Talk Paper  <input type="checkbox"/> CDER Q&amp;As  <input type="checkbox"/> Other</p>

<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 checked="" 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 checked="" 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 checked="" 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 checked="" type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input checked="" 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 checked="" 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 checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

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

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

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

Yes  No

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

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

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

Yes  No

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

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

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

Yes  No

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

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

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

Yes  No

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

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

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
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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) Approval 4/30/13
<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>		4/29/13
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>		3/30/12
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>		Cystagon 6/6/07

<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 type="checkbox"/> Medication Guide <input checked="" 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>	4/29/13
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	n/a
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	Cystagon 6/6/07 – included in package insert section
<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>	4/24/13
<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>	6/28/12 3/12/13; 6/28/12
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input checked="" type="checkbox"/> RPM 12/3/12 <input checked="" type="checkbox"/> DMEPA 10/22/12 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 4/26/13 <input checked="" type="checkbox"/> ODPD (DDMAC) 4/26/13 <input checked="" type="checkbox"/> SEALD 4/29/13 <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>	2/21/13
<ul style="list-style-type: none"> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> </ul>	<input type="checkbox"/> Not a (b)(2) 4/8/13
<ul style="list-style-type: none"> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	<input type="checkbox"/> Not a (b)(2) 4/26/13
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<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: <u>orphan designation</u></li> <li>• Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ 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>)</li> </ul>	<input checked="" type="checkbox"/> Verified, statement is acceptable

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

❖ Outgoing communications ( <i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i> )	4/3/13; 4/1/13; 3/13/13; 2/13/13; 12/19/12; 11/9/12; 9/7/12; 9/5/12; 8/17/12; 6/12/12; 5/18/12; 4/10/12
❖ 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 checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg 10/25/11
• EOP2 meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg 1/28/10
• Other milestone meetings (e.g., EOP2a, CMC pilots) ( <i>indicate dates of mtgs</i> )	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available ( <i>do not include transcript</i> )	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4/30/13
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4/29/13
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input type="checkbox"/> None 1 PMC
<b>Clinical Information<sup>6</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	
• Clinical review(s) ( <i>indicate date for each review</i> )	4/26/13; 6/1/12
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	Pg 19 of clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input type="checkbox"/> None PMHS 4/16/13
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement ( <i>indicate date(s) of submission(s)</i> )	
• REMS Memo(s) and letter(s) ( <i>indicate date(s)</i> )	
• Risk management review(s) and recommendations (including those by OSE and CSS) ( <i>indicate date of each review and indicate location/date if incorporated into another review</i> )	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	<input type="checkbox"/> None requested 2/26/13; 12/7/12

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

<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Statistical Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 4/26/13; 6/5/12
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 4/4/13
❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input type="checkbox"/> None 4/9/13
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 4/22/13; 3/8/13; 5/9/12
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 4/24/13; 3/5/13; 5/24/12
❖ Microbiology Reviews	<input checked="" type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input type="checkbox"/> None Biopharmaceutics: 2/14/13; 5/10/12

❖ 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> )	CMC review dated 3/5/13, pg 160
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) ( <i>date completed must be within 2 years of action date</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: 9/24/12 – pgs 166-167 of CMC review dated 3/5/13 <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 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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JESSICA M BENJAMIN  
05/03/2013



NDA 203389

**LABELING PMR/PMC DISCUSSION COMMENTS**

Raptor Therapeutics, Inc.  
9 Commercial Boulevard, Suite 200  
Novato, CA 94949

Dear Ms. Kim:

Please refer to your March 30, 2012, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Procysbi (cysteamine bitartrate) Delayed-Release Capsules.

We also refer to our December 19, 2012, letter in which we notified you of our target date of April 2, 2013 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012."

On November 30, 2012, we received your November 30, 2012 proposed labeling submission to this application, and have proposed revisions that are included as an enclosure.

If you have any questions, call me at (301) 796-3924.

Sincerely,

*{See appended electronic signature page}*

Jessica M. Benjamin, MPH  
Senior Regulatory Project Manager  
Division of Gastroenterology and Inborn  
Errors Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

ENCLOSURE: Content of Labeling

18 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS)  
immediately following this page

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/s/  
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JESSICA M BENJAMIN  
04/03/2013

**From:** Benjamin, Jessica  
**To:** Yvonne Kim  
**Cc:** Benjamin, Jessica  
**Subject:** NDA 203389 - Carton/Container Information Request  
**Date:** Monday, April 01, 2013 2:26:49 PM

---

Hi Yvonne,

Please refer to NDA 203389 and your recent submission dated March 29, 2013, containing updated carton and container labels. Please address the following comments:

- 1. Decrease the prominence of the strength. As currently presented, the strength competes for prominence with the proprietary name and established name.**
- 2. The established name does not have a prominence commensurate to that of the proprietary name. Revise the established name per 21 CFR 201.10(g)(2) which states: The established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.**
- 3. Relocate the quantity statement to the bottom of the principal display panel and away from the strength. As currently presented at the top of the panel it may cause confusion with the strength.**
- 4. The 'Delayed-Release' statement does not appear bolded. Ensure that the statement is bolded to highlight the difference between Procysbi (Cysteamine Bitartrate) Delayed-release Capsules and Cystagon (Cysteamine Bitartrate).**
- 5. Remove the (b) (4)**
- 6. Remove the (b) (4) around the statement 'Capsules should be swallowed whole...' to decrease clutter.**
- 7. Relocate the statement 'Rx Only' to the bottom of the principle display panel**
- 8. Although the agency agreed to keep the capsule colors as a light blue body and a very dark blue cap (75 mg) and a light blue body and a light blue cap (25 mg) as you proposed, we recommend that you revise the container labels to increase the visual differentiation between the strengths by using a unique color scheme for each strength to prevent selection errors.**
- 9. Relocate the statement 'Dispense only in the original packaging' to the bottom of the principal display panel to decrease clutter.**

We appreciate a prompt response to this request.

Let me know if you have any questions.

Regards,  
Jessica

Jessica M. Benjamin, MPH  
Senior Regulatory Project Manager  
Division of Gastroenterology and Inborn Errors Products

Office of New Drugs III  
Center for Drug Evaluation and Research  
301-796-3924 *office*  
301-796-9904 *fax*

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-3924. Thank you.

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/s/  
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JESSICA M BENJAMIN

04/01/2013



NDA 203389

**INFORMATION REQUEST**

Raptor Therapeutics, Inc.  
9 Commercial Boulevard, Suite 200  
Novato, CA 94949

Dear Ms. Kim:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Procysbi (cysteamine bitartrate) delayed-release capsules.

We also refer to your NDA dated March 30, 2012.

We are reviewing the carton and container labels of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Product Design

a) Per the "How Supplied" Section of the insert, the 25 mg and 75 mg strengths are

[Redacted text block containing (b) (4) information]

2. Container Label

- a) [Redacted text block containing (b) (4) information] To prevent selection errors, increase the visual differentiation of the proposed strengths using a unique color scheme for each strength. The colors chosen can also be reflected in the capsule color to ensure improved strength identification.
- b) Relocate the strength so that it appears beneath the established name.
- c) Relocate the quantity statement so that it appears toward the bottom of the principal display panel and away from the product strength.
- d) Remove the [Redacted text block containing (b) (4) information] of the capsule on the principal display panel that appears beneath the strength, [Redacted text block containing (b) (4) information]

(b) (4)

- e) Relocate the “Dispense only in original packaging” statement so that it appears on the principal display panel and highlight the information by color blocking it.
- f) Decrease the prominence of the “Raptor” logo and the address by decreasing the size of the letters and removing the (b) (4).  
Additionally, relocate this information to the back panel so that important safety information is conveyed on the principal display panel
- g) Bold the “Delayed-release” statement to ensure that this difference between Procysbi (Cysteamine Bitartrate) Delayed Release Capsules and Cystagon (Cysteamine Bitartrate) is highlighted.
- h) Add the statement, “Capsules should be swallowed whole. Do not crush or chew” and locate it below the dosage form on the principal display panel.
- i) Consider including that Procysbi is taken twice daily in the usual dose statement if space permits, because this is a delayed release formulation of a currently marketed product that is taken four times daily.
- j) If additional space is needed on the side panel, consider revising the statement that reads, “KEEP THIS AND ALL....” from all caps to title case.

If you have any questions, call Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,

*{See appended electronic signature page}*

R. Wesley Ishihara  
Chief, Project Management Staff  
Division of Gastroenterology and Inborn  
Errors Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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RICHARD W ISHIHARA  
03/13/2013

**Tran-Zwanetz, Catherine**

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**From:** Yvonne Kim [ykim@raptorpharma.com]  
**Sent:** Tuesday, February 12, 2013 11:25 PM  
**To:** Tran-Zwanetz, Catherine  
**Cc:** Benjamin, Jessica  
**Subject:** RE: NDA 203389 CMC Information Request  
**Attachments:** SN0027 Response to Information Request - CMC.pdf; emfalert.txt

Dear Cathy,

I have attached a PDF of Raptor's response to your request for CMC information for your preliminary review. It is in queue with our publishers for an electronic submission on Feb 13, 2013. Please let me know if you have any further questions.

Thanks,  
Yvonne

Yvonne Kim  
Director, Regulatory Affairs  
Raptor Pharmaceuticals  
510-304-8770 (mobile)  
415-382-8002 (fax)  
[www.raptorpharma.com](http://www.raptorpharma.com)



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**From:** Tran-Zwanetz, Catherine [mailto:Catherine.TranZwanetz@fda.hhs.gov]  
**Sent:** Tuesday, February 12, 2013 11:26 AM  
**To:** Yvonne Kim  
**Cc:** Benjamin, Jessica  
**Subject:** NDA 203389 CMC Information Request

Hi Ms. Kim,

We are reviewing the Chemistry, Manufacturing and Controls section of your NDA application submitted March 30, 2012. We have the following information request:

**Based on the mean in-vitro dissolution profiles for all strengths from clinical batches at release and under long term (18 months) stability, the following dissolution acceptance criterion for the buffer stage is recommended: Q = (b) (4) at 20 minutes. We recommend you to revise the dissolution acceptance criterion accordingly and submit an updated sheet of specifications for the drug product by February 13, 2013.**

Please let me know if you have any questions or comments.

Thanks,  
Cathy Tran-Zwanetz  
Regulatory Project Manager  
(301) 796-3877

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/s/  
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CATHERINE A TRAN-ZWANETZ  
02/13/2013



NDA 203389

**REVIEW EXTENSION –  
MAJOR AMENDMENT**

Raptor Therapeutics, Inc.  
9 Commercial Boulevard, Suite 200  
Novato, CA 94949

Dear Ms. Kim:

Please refer to your March 30, 2012, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Procysbi (cysteamine bitartrate delayed-release capsules).

On December 14, 2012, we received your December 14, 2012, solicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is April 30, 2013.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by April 2, 2012.

If you have any questions, call Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,

*{See appended electronic signature page}*

R. Wesley Ishihara  
Chief, Project Management Staff  
Division of Gastroenterology and Inborn  
Errors Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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RICHARD W ISHIHARA  
12/19/2012



NDA 203389

**INFORMATION REQUEST**

Raptor Therapeutics Inc.  
Attention: Yvonne Kim  
Director, Regulatory Affairs  
9 Commercial Blvd. Ste 200  
Novato, CA 94949

Dear Ms. Kim:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Procysbi (cysteamine bitartrate) Delayed-Release Capsules.

We also refer to your March 30, 2012, April 30, 2012, May 29, 2012, June 26, 2012, September 5, 2012, September 7, 2012, October 5, 2012, October 9, 2012, October 16, 2012 and November 1, 2012 NDA submissions.

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

1. Please commit to perform testing of the drug substance by (b) (4) for cysteamine free base, cystamine, (b) (4) and (b) (4) for every lot of the drug substance to be used for manufacture of the drug product. This is because a significant discrepancy in assay values of cysteamine free base on anhydrous and salt-free basis was observed between your data and the data provided in DMF (b) (4)

Revise the drug substance specification as following:

- a. Delete the (b) (4) from the cysteamine bitartrate regulatory specification. The analytical procedures by (b) (4) for these tests are to be used for the regulatory specification.
- b. Include an upper limit of (b) (4) for cysteamine free base on anhydrous and salt-free basis.
2. Regarding drug substance analytical procedures:
  - a. Regarding TM.1741, please provide method specificity data to show that cystamine does not interfere with the determination of (b) (4)
  - b. Regarding 20.0801, revise the system suitability acceptance criterion from NMT (b) (4) to NMT (b) (4) for (b) (4) injections and all injections of standard solution.
3. Regarding drug product analytical procedure 883011:

- a. Please clarify the concentration of [REDACTED] (b) (4) The concentration as described in the procedure, [REDACTED] (b) (4) [REDACTED] (b) (4)
  - b. Clarify whether procedure 883011 also replaces procedure 919210 for assay of bead samples (in-process controls). If so, please include preparation of bead samples in procedure 883011.
  - c. Please clarify how the relative response factor (RRF) for cystamine, which is listed as [REDACTED] (b) (4) in Attachment 3.2.P.5.3-12 and Attachment 3.2.P.5.2-8 (page 7), respectively, is calculated. The values are inconsistent with the ratio [REDACTED] (b) (4) of the slope of cystamine [REDACTED] (b) (4) to the slope of cysteamine [REDACTED] (b) (4) from linear regression analyses.
  - d. Revise Procedure 5.1.8 to include [REDACTED] (b) (4) [REDACTED]
4. Please provide a statement to certify that [REDACTED] (b) (4) (the component used in 400 cc HDPE bottle) and [REDACTED] (b) (4) (the component used in 400 cc and 50 cc HDPE bottles), comply with the current federal regulations for contact with food products. A reference to specific sections of the federal regulations should be provided.
  5. Please provide recalculated assay stability data for Lots 3085959, 3088699, 3085998, 3085999, 3088702, and 3088703 for the time points analyzed after November 2011. The assay data should be recalculated based on the newly adopted (since November 2011) reference standard certification. The information is to confirm that the strengths of the capsules remain acceptable.
  6. Please either provide a master batch record for commercial product or confirm that the manufacturing equipment as provided in the executed batch records in Section 3.2.R, such as [REDACTED] (b) (4) is intended to be used for the manufacture of the commercial product.

If you have any questions, call Cathy Tran-Zwanetz, Regulatory Project Manager, at (301) 796-3877.

Sincerely,

*{See appended electronic signature page}*

Moo-Jhong Rhee, Ph.D.  
Branch Chief, Branch IV  
Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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MOO JHONG RHEE  
11/09/2012  
Chief, Branch IV



NDA 203389

**INFORMATION REQUEST**

Raptor Therapeutics Inc.  
Attention: Yvonne Kim  
Director, Regulatory Affairs  
9 Commercial Blvd. Ste 200  
Novato, CA 94949

Dear Ms. Kim:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Procysbi (cysteamine bitartrate) Delayed-Release Capsules.

We also refer to your March 30, 2012, April 30, 2012, May 29, 2012, and September 5, 2012 NDA submissions.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response by October 8, 2012 in order to continue our evaluation of your NDA.

1. Please revise the drug substance specification as following:
  - a. Revise the acceptance criterion of Impurity (b) (4) to NMT (b) (4) unless data (e.g. nonclinical data) are provided to justify the proposed limit of NMT (b) (4). This is to minimize exposure of the impurity because of the chronic use for the drug at the proposed maximum daily dose of (b) (4).
  - b. Revise the acceptance criterion for heavy metals to NMT (b) (4) based on permitted daily exposure (PDE) of 10 µg, per USP Draft Chapter <232> Metals and Limits published in Pharmacopeial Forum 36 (1).
2. Please revise the acceptance criterion for each unspecified impurity from (b) (4) in the drug product specification per ICH Q3B.
3. Please revise your practice for recertification of cysteamine bitartrate reference standard. All tests listed on the certificate of analysis, including appearance, identification, (b) (4), residual solvents, residue on ignition, (b) (4), HPLC purity, and (b) (4) should be performed for recertification.
4. Please provide mock-up container and carton labels bearing the proprietary name Procysbi for both strengths of the drug product. The carton labels have not been provided.

If you have any questions, call Cathy Tran-Zwanetz, Regulatory Project Manager, at (301) 796-3877.

Sincerely,

*{See appended electronic signature page}*

Moo-Jhong Rhee, Ph.D.  
Branch Chief, Branch IV  
Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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MOO JHONG RHEE  
09/07/2012  
Chief, Branch IV



NDA 203389

## INFORMATION REQUEST

Raptor Therapeutics, Inc.  
9 Commercial Boulevard, Suite 200  
Novato, CA 94949

Dear Ms. Kim:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Procybsi (cysteamine bitartrate delayed-release capsules).

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

1. Submit analysis datasets with all available exact dose amounts, body surface area assessments, and white blood cell (WBC) measurements and the corresponding dates for each individual in Study RP103-04.
2. Submit the Phoenix Software (Pharsight, Inc) project files (including datasets) used for the final population pharmacokinetic (PK) and PK/pharmacodynamic (PD) analyses.
3. The use of [REDACTED] <sup>(b) (4)</sup> to evaluate the acid resistance and dissolution of your product is not acceptable. Conduct the acid resistance and dissolution testing [REDACTED] <sup>(b) (4)</sup> as described in the USP<711>, Delayed-Release Dosage Forms.
4. Revise the dissolution test for your delayed release product as per USP<711> and provide the complete dissolution profile data for the acid and buffer stages for the clinical batches of your proposed product (*raw data and mean values*). For the stability registration batches (*remaining stability time points*), conduct the dissolution profile testing and provide the data using both the proposed and the USP methods.
5. Based on the data using the same set of capsules as per USP<711>, provide a proposal for the dissolution acceptance criteria (*acidic and buffer stages*) for your product.
6. Clarify when you plan to submit 12 month safety data for patients enrolled in Study RP103-04 and specify what datasets will be included in your submission.

If you have any questions, call Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,

*{See appended electronic signature page}*

R. Wesley Ishihara  
Chief, Project Management Staff  
Division of Gastroenterology and Inborn  
Errors Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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RICHARD W ISHIHARA  
09/05/2012



NDA 203389

**INFORMATION REQUEST**

Raptor Therapeutics Inc.  
Attention: Yvonne Kim  
Director, Regulatory Affairs  
9 Commercial Blvd. Ste 200  
Novato, CA 94949

Dear Ms. Kim:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for cysteamine bitartrate delayed-release capsules.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. In order to continue our evaluation of your NDA, please provide a written response for Item 1 by September 5, 2012. For all other items, please provide your written response by October 8, 2012.

1. Regarding cysteamine bitartrate reference standard:
  - a. Revise the definition for the term (b) (4) as described in page 3 of Section 3.2.S.5 and Attachment 3.2.P.5.4-21 to exclude (b) (4)
  - b. Please provide data to support the practice of annual recertification of cysteamine bitartrate reference standard. The equation presented in the aforementioned sections for determination of cysteamine free base content (wt%) at time of use is valid only if total related substances, including (b) (4), remained unchanged. Data for recertification of Lot CBT0611-04, which is due for recertification in August 2012, may be used to support the practice.
  - c. Clarify the tests to which the values of (b) (4) and (b) (4) for calculation of cysteamine free base content in the reference standard, Lot CBT0611-04, correspond. The value of (b) (4) is included in the equation in Table 6 (Step 1) of Section 3.2.P.5.4. The value of (b) (4) is included in the equation for calculation of Weight % (free base) in the certificate of analysis. The tests to which these values correspond should be included in the certificate of analysis.
2. Please provide a table for the drug substance regulatory specification, which should include all tests provided in Tables 1 and 2 of Section 3.2.S.4.1. The specification should include analytical procedures by (b) (4) for appearance, identification by IR, (b) (4), cysteamine free base, (b) (4) free base, and related substances, by (b) (4) for (b) (4), by USP <231> for heavy metals, as well as by (b) (4) for all other tests.

Furthermore, revise the specification as following:

(b) (4)

- b. Revise the acceptance criterion of cysteamine free base (w/w%) on “as-is” basis (i.e. relative to cysteamine bitartrate) from (b) (4) to “report value”.
- c. Revise the acceptance criterion for cysteamine free base as relative to cysteamine free base with a limit of NMT (b) (4). The degradant is calculated by the following equation:

(b) (4)

3. Regarding the analytical procedures for the drug substance:
- For (b) (4) TM.41 for identification test by IR, clarify how the sample is prepared, (b) (4)
  - For (b) (4) 17.0801, revise the definition of the term (b) (4) for calculation of (b) (4) content as “weight of sample in mg” instead of (b) (4). Furthermore, add the definition for the term (b) (4) as (b) (4) content in the reference standard”.
4. Provide the source and lot number of cysteamine dihydrochloride reference standard.
5. Regarding the manufacture of the drug product:
- Please provide information on the design and operating principles of (b) (4). In Section 3.2.P.3.3, it is stated that an (b) (4) may be identified for the (b) (4).
  - Please clarify whether a (b) (4) using (b) (4) for cysteamine bitartrate, hypromellose (b) (4) sodium lauryl sulfate, and microcrystalline cellulose is included in (b) (4). If the (b) (4) is included, please include the information in Section 3.2.P.3.3 and provide the (b) (4) for (b) (4).
  - Please establish an upper limit for (b) (4).
6. Typically, validation protocols are not submitted within the application since the application is not the appropriate location for such protocols. The actual protocols, acceptance criteria, and study outcomes would be evaluated during an inspection. It is the company’s responsibility to conduct all studies necessary to assure the commercial manufacturing process is capable of consistently delivering high quality product. Therefore, during the course of the NDA review we cannot assess the process validation protocols provided in Section 3.2.P.3.5 of your NDA.
7. Please address the following issues regarding the drug product analytical procedures:

- a. For procedure 870210, please clarify whether the absorption band at [REDACTED] (b) (4) is required for identification of the drug product. This band is included in the acceptance criteria in Section 3.2.P.5.2, but not in Section 3.2.P.5.3.
  - b. For Procedure 868422, please provide additional data to demonstrate linearity at concentrations below the proposed limit of [REDACTED] (b) (4). The linearity range of [REDACTED] (b) (4) corresponds to [REDACTED] (b) (4) of the maximum concentration for 25-mg capsule.
  - c. For Procedure 868321:
    - i. Provide method specificity data to demonstrate that capsule shell does not interfere with the dissolution assay.
    - ii. Provide method precision data (repeatability and intermediate precision) for 25-mg capsules.
8. Please provide a statement to certify that each component [REDACTED] (b) (4) of the drug product container closure system that is in contact with the drug product complies with the current federal regulations for contact with food products. A reference to specific sections of the federal regulations for each component should be provided.
9. Please provide the long-term stability data, including the recalculated assay data, for the 12-month time point for drug product Lots 3086999, 3088702, and 3088703. Recalculated assay data should be calculated based on the newly adopted (since November 2011) reference standard certification. The long-term stability data provided to date, which include 18 months for two batches and 6 month for one batch for each strength and packaging configuration, are not sufficient to support the proposed 18 months expiration dating period.
10. The expiration dating period of the drug product should be calculated from no later than the [REDACTED] (b) (4) unless stability data are provided for three lots of each strength packaged in the commercial configuration after the [REDACTED] (b) (4) hold time.

If you have any questions, call Cathy Tran-Zwanetz, Regulatory Project Manager, at (301) 796-3877.

Sincerely,

*{See appended electronic signature page}*

Moo-Jhong Rhee, Ph.D.  
Branch Chief, Branch IV  
Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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MOO JHONG RHEE  
08/17/2012  
Chief, Branch IV



NDA 203389

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Raptor Therapeutics, Inc.  
9 Commercial Boulevard  
Suite 200  
Novato, CA 94949

ATTENTION: Yvonne Kim  
Director, Regulatory Affairs

Dear Ms. Kim:

Please refer to your New Drug Application (NDA) dated and received March 30, 2012, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Cysteamine Bitartrate Delayed-release Capsules, 25 mg and 75 mg.

We also refer to your April 9, 2012, correspondence, received April 9, 2012, requesting review of your proposed proprietary name, Procysbi. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, Procysbi 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 April 9, 2012 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 Nitin Patel, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5412. For any other information regarding this application, contact Jessica Benjamin, Office of New Drugs Regulatory Project Manager, at (301) 796-3924.

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  
06/28/2012



NDA 203389

**FILING COMMUNICATION**

Raptor Therapeutics, Inc.  
9 Commercial Boulevard, Suite 200  
Novato, CA 94949

Dear Ms. Kim:

Please refer to your New Drug Application (NDA) dated March 30, 2012, received March 30, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for cysteamine bitartrate delayed-release capsules.

We also refer to your amendment dated April 30, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is January 30, 2013.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by January 2, 2013.

We request that you submit the following information:

1. For the RP103-03 study, re-conduct the primary analysis by further adjusting the analysis by the two-level stratification variable used in the randomization (WBC cystine level Group L /WBC cystine level Group H). This re-analysis should be administered separately for the Efficacy Analysis Set and the Per Protocol Analysis Set. In addition, for further sensitivity analysis purposes, this re-analysis should also be administered on an All-Randomized (n=43) Analysis Set of patients.

2. For the RP103-03 study, present the primary analysis results by gender. This analysis should be adjusted by the two-level stratification variable used in the randomization (WBC cystine level Group L / WBC cystine level Group H) and should be administered on an All-Randomized (n=43) Analysis Set of patients.
3. For the RP103-03 study, submit the SAS programs used to generate the analysis datasets and all efficacy tables found within the finalized RP103-03 Clinical Study Report. These SAS programs should be submitted in their original \*.sas format.
4. For the forty RP103-03 patients who enrolled in the RP103-04 study, provide a figure which plots the mean ( $\pm$  standard deviation) concentration of WBC Cystine over time while these patients are being administered RP103 (Cystagon WBC Cystine levels are not necessary for this figure). Time should range from the beginning of the RP103-03 study (i.e. Randomization) through the point of last data cutoff in the RP103-04 study.

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

1. The following verbatim statement or appropriate modification should precede the presentation of adverse reactions from clinical trials:

*“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.”*

2. The following verbatim statement or appropriate modification should precede the presentation of adverse reactions from postmarketing experience:

*“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”*

3. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must be referenced in Section 17 (Patient Counseling Information). Additionally, the patient labeling should not be included as a subsection under Section 17, and instead must be printed immediately following Section 17 of the package insert. Include the following statement within Section 17.

*“See FDA-approved patient labeling (Patient Information)”*

We request that you resubmit labeling that addresses these issues by June 29, 2012. The resubmitted labeling will be used for further labeling discussions.

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

### **PROMOTIONAL MATERIAL**

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

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

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

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

### **REQUIRED PEDIATRIC ASSESSMENTS**

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

Because the drug for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,

*{See appended electronic signature page}*

Donna Griebel, M.D.  
Director  
Division of Gastroenterology and Inborn  
Errors Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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RICHARD W ISHIHARA  
06/12/2012  
Signing for Donna Griebel.



NDA 203389

**INFORMATION REQUEST**

Raptor Therapeutics, Inc.  
9 Commercial Boulevard, Suite 200  
Novato, CA 94949

Dear Ms. Kim:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for cysteamine bitartrate delayed-release capsules.

We also refer to your March 30, 2012 NDA submission.

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

1. There are insufficient data to support the adequacy of the selected dissolution method. Provide the dissolution method report supporting the selection of the proposed dissolution test. Include as part of the dissolution report the following information:
  - a. A detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters supporting the proposed dissolution method as the optimal test for your product (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.). The testing conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least 85% of drug release of the label claim or when a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable.
  - b. Data to support the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e.,  $\pm 10$ -20% change to the specification-ranges of these variables). In addition, if available, submit data showing that the selected dissolution method rejects batches that are not bioequivalent.

2. Provide complete dissolution profile data (raw data and mean values) from the pivotal clinical and primary stability batches supporting the selection of the dissolution acceptance criterion (i.e., specification-sampling time point and specification value) for the proposed product.
3. We are concerned that your delayed-release (DR) product may release its entire contents (“dose dumping”) in the stomach when co-administered with alcohol. Therefore, we recommend that you evaluate the potential for a drug-alcohol interaction with your DR product using the following *in vitro* settings:
  - Dissolution testing should be conducted using the optimal dissolution apparatus and agitation speed in 0.1 N HCl and in the proposed quality control medium. Dissolution data should be generated from 12 dosage units (n=12) at multiple time points to obtain a complete dissolution profile.
  - The following alcohol concentrations for the *in vitro* dissolution studies are recommended: 0 %, 5 %, 10 %, 20 %, and 40 %.
  - The shape of the dissolution profiles should be compared to determine if the modified release characteristics are maintained, especially in the first 2 hours.
  - The f2 values assessing the similarity (or lack thereof) between the dissolution profiles should be estimated (using 0% alcohol as the reference).
  - The report with the complete data (i.e., individual, mean, standard deviation, comparison plots, f2 values, etc.) collected during the evaluation of the *in vitro* alcohol induced dose dumping study should be provided to FDA within six weeks of the date of this letter.
4. Provide rationale for inclusion of data from non-US study sites (Sites 5, 6, 7, 8, and 9) for Studies RP103-03 and RP103-04.
5. Provide a Letter of Authorization from the DMF holder for the excipient [REDACTED] (b) (4) [REDACTED].
6. As indicated in the advice letter dated March 8, 2012, you are required to provide the detailed dose re-calculation method and results, and explain how this impacts the doses used in the clinical trials for your proposed product and the comparator product. In addition, you will also need to explain how this does or does not impact the interpretation of trial results. It is unclear whether you have submitted all the requested information. If you have done so, clarify the location in the submission. If not, submit this information as soon as possible.
7. Confirm whether the formulation of the to-be-marketed product is identical to that of the product used in the phase 3 clinical trials. If the product is different, provide a summary of the specific formulations used for each clinical trial.

If you have any questions, call Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,

*{See appended electronic signature page}*

R. Wesley Ishihara  
Chief, Project Management Staff  
Division of Gastroenterology and Inborn  
Errors Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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RICHARD W ISHIHARA  
05/18/2012



NDA 203389

**NDA ACKNOWLEDGMENT**

Raptor Therapeutics, Inc.  
9 Commercial Boulevard, Suite 200  
Novato, CA 94949

Dear Ms. Kim:

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

Name of Drug Product: cysteamine bitartrate delayed-release capsules, 25mg and 75 mg

Date of Application: March 30, 2012

Date of Receipt: March 30, 2012

Our Reference Number: NDA 203389

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 DATE 60 DAYS FROM DATE OF RECEIPT OF APPLICATION, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

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

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Gastroenterology and Inborn Errors Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

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

If you have any questions, call me at (301) 796-3924.

Sincerely,

*{See appended electronic signature page}*

Jessica M. Benjamin, MPH  
Senior Regulatory Project Manager  
Division of Gastroenterology and Inborn  
Errors Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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JESSICA M BENJAMIN  
04/10/2012



IND 103694

**MEETING MINUTES**

Raptor Therapeutics Inc.  
9 Commercial Blvd, Suite 200  
Novato, CA 94949

Attention: Yvonne Kim  
Senior Manager, Regulatory Affairs

Dear Ms. Kim:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for cysteamine bitartrate (RP103) delayed release capsules.

We also refer to the meeting between representatives of your firm and the FDA on October 25, 2011. The purpose of the meeting was to discuss specific questions relating to the Clinical and CMC sections of your planned NDA submission.

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) 796-3924.

Sincerely,

*{See appended electronic signature page}*

Jessica M. Benjamin  
Senior Regulatory Project Manager  
Division of Gastroenterology and Inborn  
Errors Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

ENCLOSURE:  
Meeting Minutes

## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** B  
**Meeting Category:** Pre-NDA meeting

**Meeting Date and Time:** October 25, 2011, 11:00 AM  
**Meeting Location:** White Oak, Building 22, Room 1309

**Application Number:** IND 103694  
**Product Name:** cysteamine bitartrate (RP103) delayed release capsules  
**Indication:** treatment of nephropathic cystinosis  
**Sponsor/Applicant Name:** Raptor Therapeutics Inc.

**Meeting Chair:** Lynne Yao, M.D.  
**Meeting Recorder:** Jessica M. Benjamin, M.P.H.

### FDA ATTENDEES

Andrew Mulberg, M.D., Deputy Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)  
Lynne Yao, M.D., Medical Team Leader, DGIEP  
Carla Epps, M.D., Medical Reviewer, DGIEP  
David Joseph, Ph.D., Pharmacology Acting Team Leader, DGIEP  
Niraj Mehta, Ph.D., Pharmacology Reviewer, DGIEP  
Insook Kim, Ph.D., Clinical Pharmacology Reviewer  
Dilara Jappar, Ph.D., Clinical Pharmacology Reviewer  
Christine Garnett, Ph.D., Office of Clinical Pharmacology  
Marie Kowblansky, Ph.D., Pharmaceutical Assessment Lead  
Khairy Malek, M.D., Office of Scientific Investigations  
Jeff Fritsch, M.D., Office of Orphan Product Development

### SPONSOR ATTENDEES

Craig Langman, M.D., RP103-03 Lead Investigator  
Chris Starr, Chief Executive Officer  
Thomas E. Daley, President  
Patrice Rioux, M.D., Chief Medical Officer  
Kathy Powell, Vice President, CMC  
Mary Jo Bagger, Director, Clinical Operations  
Erica Krainack, Director, Program Management  
Yvonne Kim, Senior Manager, Regulatory Affairs

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## 1.0 BACKGROUND

Raptor Therapeutics has requested this Pre-NDA meeting to discuss the timing, content and format of its 505(b)(2) NDA for cysteamine bitartrate delayed-release capsules (RP103), 25 mg and 75 mg, for the treatment of nephropathic cystinosis. Raptor intends to submit its application in the first quarter of 2012. The NDA will provide final reports of clinical and bioequivalence studies RP103-01, RP103-02, RP103-03 and RP103-05, an up-to-date interim report for ongoing clinical efficacy and safety study RP103-04, as well as information on the chemistry, manufacturing and controls of the final product and an integrated safety summary.

## 2. DISCUSSION

- 2.1 *Does the Agency agree that the stability program supports a bracketing packaging configuration for RP103 75 mg and 25 mg strengths [REDACTED] (b)(4) [REDACTED] and stability data is sufficient to support the filing of the application?*

**FDA Response:**

**A bracketing design for stability studies is reasonable for your product provided that significant differences in the shape and size of your container/closures are taken into consideration in the protocol design (as recommended in ICH Q1D).**

Discussion:

There was no further discussion of this point.

- 2.2 *Does the Agency agree with Raptor's approach to implementing a new APT particle size distribution method and revising the current API particle size distribution acceptance criterion?*

**FDA Response:**

**It is acceptable to revise your procedure for determining particle size distribution; however, it is critical that acceptance criteria associated with the new method be based on Phase 3 clinical trial batches.**

Discussion:

There was no further discussion of this point.

- 2.3 *Does the Agency concur that the described submissions of a dossier, based on data from the studies listed above, supports an evaluable NDA for the proposed indication?*

**FDA Response:**

**No. Based on the results you have provided in the briefing document for study RP103-02, there appears to be a clear food effect on the exposure of cysteamine. Therefore, it is not clear whether administration after a meal would provide the same exposure. We recommend that you conduct a food**

**effect study or provide specific instruction as to when the medication should be taken in relation to meal time.**

**Additionally, we recommend you to evaluate whether RP103 is substrate, inhibitor or inducer of CYP enzymes or transporter in vitro to identify potential drug-drug interaction. Based on the results of these in-vitro studies, in vivo studies may be necessary.**

Discussion:

Raptor will provide proposed labeling based on data collected in studies RP103-02, RP-103-03, RP-103-04, and RP-103-05 to support their proposed dosing recommendations. The Agency continues to express concerns regarding the ability to provide those recommendations but will review is the data that are submitted. The Agency understands that there are additional PK/PD data from study RP103-04 that will be submitted with the NDA.

- 2.4 *Does the Agency concur that since findings from study RP103-05 demonstrate bioequivalence of two dosing methods, i.e. intact capsule and contents mixed with applesauce, the labeling for the proposed product may contain information to permit patients who have difficulty swallowing capsules to mix the contents of the capsules with soft food (or liquid) and permit placing the mixture in a GI tube for patients for whom the dose must be administered in that manner?*

**FDA Response:**

**No. We recognize that if your product is approved it may provide a substantial improvement compared currently available treatments because of the proposed twice daily dosing schedule. However, adequate interpretability of study RP-103-05 and the ability to compare results from study RP-103-05 and the phase 3 clinical trial, RP-103-03. Furthermore, since you plan to allow mixing of the capsule contents with applesauce, (b) (4) other foods, or liquids prior to administration, you will need to specify which foods will be acceptable and establish the stability of the product in each of these vehicles. Based on the stability data, the labeling for your product will need to specify the maximum time your product may remain mixed with the applesauce (or other food vehicle) before being administered.**

**Since the product may be administered by GI-tube, you will need to include instructions for such administration in the your labeling, specifying the volume of water (or other liquid) to be used to suspend the (b) (4) and the volume to be used to rinse the container in which the suspension is prepared. You will need to submit data to demonstrate the reproducibility of the administered dose using your instructions. You should probably include a particle size limit for the enteric-coated beads (either in-process or finished product) to ensure that the particles will not clog the tube. In addition, please provide rational for using 94.12% confidence intervals instead of 90% confidence interval for BE analysis.**

Discussion:

Raptor agrees to perform a BE study in healthy volunteers to evaluate administration of an intact capsule with acidic juice compared to an open capsule with applesauce. Raptor also had concerns of the feasibility of a (b) (4). The Agency agrees that these studies may be performed as post-marketing studies; however, labeling will be restricted to only those patient populations who have been studied. Raptor has started to enroll patients less than age 6 in RP-103-04. Raptor plans to collect (b) (4) data as part of study RP103-04 on patients less than 6 years of age and will include available data as part of NDA submission.

Raptor will investigate collecting additional data in treatment naive patients post-approval.

Regarding the proposed particle size test for the enteric coated beads, Raptor will use the standard USP (b) (4) test which is acceptable to the Agency.

Raptor agrees to use 90% confidence interval in future BE studies.

- 2.5 *Does the Agency concur that the electronic data package plan described above would support, in part, a sufficient review of the planned NDA?*

**FDA Response:**

**Your proposed electronic data package plan appears to meet requirements for content areas to be included your NDA application. The final determination of the adequacy of the data to support the proposed indication will be made from our review of the data submitted in the application. Additionally, please provide the following full case report tabulation (CRT) for each adequate and well-controlled clinical study (per 21 CFR 314.126) you plan to Include in your NDA submission:**

- **All clean/locked clinical data presented in electronic datasets, submitted utilizing SAS Version 5 Transport, along with the annotated case report form (aCRF) and a thorough data definition file. We recommend that the electronic datasets, aCRF, and data definition file fully comply with the latest CDISC/SDTM, CDISC/CDASH, and CDISC/Define.XML standards respectively.**
- **All corresponding analysis data presented in electronic datasets, submitted utilizing SAS Version 5 Transport, along with a thorough data definition file. We recommend that these electronic datasets fully incorporate the modeling approaches described by both the latest CDISC/ADaM standard and the FDA Study Data Specifications document**  
**<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissions/Requirements/ElectronicSubmissions/ucm248635.htm>**. We

**recommend that the data definition file fully comply with the latest CDISC/Define.XML standard.**

- **A well commented and organized software program written for each analysis dataset and efficacy table created.**

Discussion:

There was no further discussion of this point.

- 2.6 *Does the Agency concur that safety data on approximately 38 patients with at least 6 months of safety follow-up at the time of submission of the NDA in the RP103-04 will provide sufficient information for an evaluable NDA for the proposed indication?*

**FDA Response:**

**Based on ICH-E1 guidelines, a chronically administered drug should include safety data in patients exposed to the drug for a minimum of one year. Therefore, safety data that includes only 6 months of exposure would not be acceptable. However, you state in your briefing package that you will have 12-month safety data on 32 patients that will be available at the time of the NDA submission. We strongly recommend that you submit all available safety data in patients who have been treated with RP-103 for at least one year. You should also provide the cut-off date used for safety data submitted in the NDA. We recommend that safety data to within 3 months of your submission be included in the NDA.**

Discussion:

As the PK and PD profiles for Cystagon and RP103 are comparable, Raptor intends to rely on the finding of safety for Cystagon for approval (as per FDA's Memorandum of Meeting Minutes, End-of-Phase 2, held January 28, 2010). However, Raptor will include all available safety data using a data cut-off date within 3 months of our NDA submission as requested. Raptor will continue to collect safety data on all active patients and will submit that data in annual safety updates. Raptor will submit 12 months of safety data on all patients within 3 months of the PDUFA date.

- 2.7 *Does the Agency concur with Raptor's approach regarding postapproval pharmacovigilance plans for RP103?*

**FDA Response:**

**It is premature to answer this question. Please see Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126834.pdf> for more information. We note that the guidance states that based on safety risks identified pre- or post-approval, a pharmacovigilance plan may need to include pharmacovigilance efforts "above and beyond routine postmarketing spontaneous reporting," such as the creation of a patient**

**registry, implementation of patient or health care provider surveys, or additional controlled clinical trials.**

Discussion:

There was no further discussion of this point.

- 2.8 *In this case, does the Agency consider the medication guide a part of the labeling or will the medication guide also be required as a part of the REMS program?*

**FDA Response:**

**FDA has determined that maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21 CFR 208.1.**

Discussion:

There was no further discussion of this point.

- 2.9 *Does the Agency concur that the improvement in the dosing schedule effectively addresses the issue of patient inability or unwillingness to comply with the dosing regimen of the currently available treatment, and therefore could qualify the Company's dossier for priority review?*

**FDA Response:**

**It is premature to answer this question. A determination on whether an application qualifies as a priority review is based on conditions and information available at the time the application is filed. If you are seeking a priority review based on a claim that your product will improve patient compliance compared to currently available treatments then you must provide specific clinical data demonstrating that patient compliance is improved compared to currently available treatments in your submission.**

Discussion:

As previously noted by the Agency in response to Question 2.4, Raptor agrees that RP103 may provide a substantial improvement compared to currently available treatments because of the proposed twice daily dosing schedule. Raptor believes it is not feasible to conduct a clinical study to demonstrate improved patient compliance. Thus, Raptor intends to provide unsolicited testimonials from patients, parents, clinicians, and foundations as well as literature references regarding the noncompliance with Cystagon due to the every 6 hour round-the-clock dosing schedule to support our request for priority review. The Agency agreed to review these data but reiterated that the final decision to grant priority review will be made after the application is submitted.

- 2.10 *Does the Agency concur with the described format of the application?*

**FDA Response:**

**Yes. Please see additional guidance on the format of specific sections of an NDA at**

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/NewDrugApplicationNDA/default.htm>

Discussion:

There was no further discussion of this point.

**Additional CMC Comments:**

- **Your drug substance and drug product specifications will need to include limits for all impurities whose structures have been identified and limits for unidentified and total impurities, as well. (Unidentified impurities should be identified at least by retention time.)**
- **In your April, 2010 amendment to this IND, you indicated that a number of unidentified peaks were observed in HPLC chromatograms for samples on stability testing, but you were unable to isolate or identify any of the peaks. You further state that you have determined that the unknown peaks are not product-related and consequently you would not be reporting them in future lots. You will need to explain/justify your decision. All drug-related impurities present at levels greater than the ICH reporting threshold, whether identified or not, need to be reported and there should be no other unidentified impurities in your drug product.**

Discussion:

Raptor's intent is that all unidentified impurities and known related substances will be reported and limits will be established. Peaks identified as assay artifacts will not be reported. FDA agrees with Raptor's approach.

Raptor agrees to apply to USAN for an established name. Cysteamine bitartrate is not a new molecular entity and is already approved by the FDA in Cystagon. Raptor notes that the salt, i.e., cysteamine bitartrate, is not an official USAN adopted name. However, the active moiety does have a USAN adopted name. FDA will know by the end of November whether or not Raptor will need to apply to USAN for an established name.

**Post-Meeting Clarification:**

**It is acceptable for you to use *cysteamine* as the established name for your product. It is not necessary for you to apply to USAN for an established name for *cysteamine bitartrate*.**

**3.0 PRESCRIBING INFORMATION**

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

#### 4.0 **MANUFACTURING FACILITIES**

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

## 5.0 Additional Information

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct the inspections (Item I and II).

The dataset that is requested as per Item III below, is for use in a clinical site selection model that is being piloted in CDER. 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.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 2, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

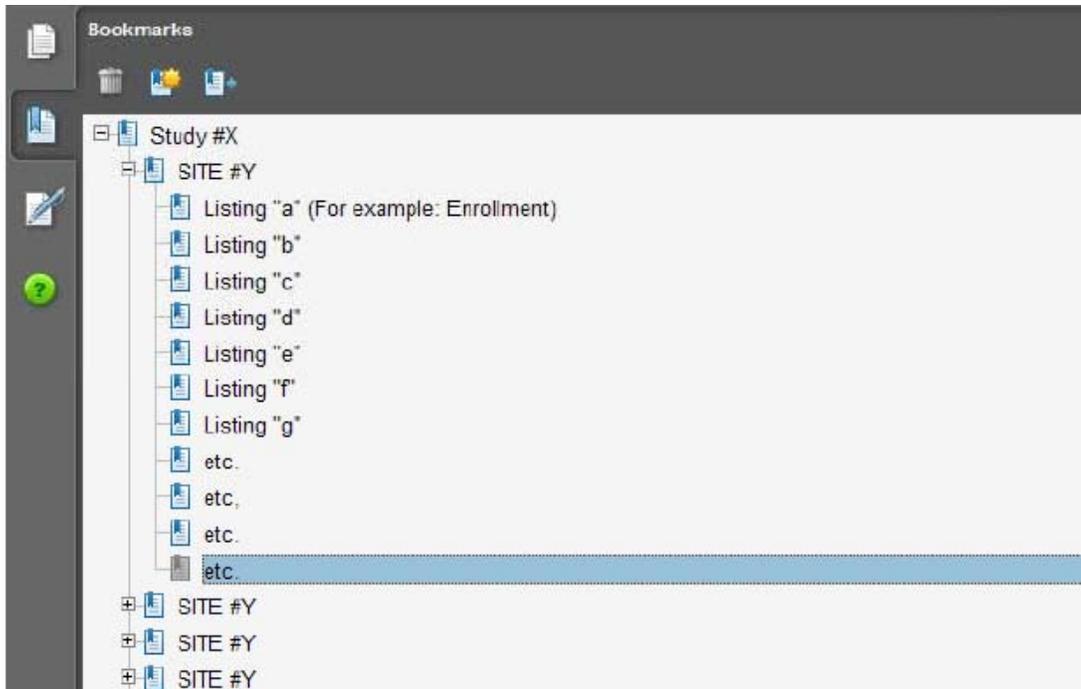
### I. Request for general study related information and specific Clinical Investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed Phase 3 clinical trials:
  - a. Site number
  - b. Principal investigator
  - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
  - d. Current Location of Principal Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
2. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 3 clinical trials:
  - a. Number of subjects screened for each site by site
  - b. Number of subjects randomized for each site by site
  - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed Phase 3 clinical trials:

- a. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
  - b. Name, address and contact information of all CROs used in the conduct of the clinical trials
  - c. 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
  - d. 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.)
4. For each pivotal trial provide a sample annotated Case Report Form (if items are provided elsewhere in submission, please describe location or provide a link to requested information).
  5. For each pivotal trial provide original protocol and all amendments (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

## **II. Request for Subject Level Data Listings by Site**

1. For each pivotal trial: Site-specific individual subject data (“line”) listings. For each site provide line listings for:
  - a. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
  - b. Subject listing for treatment assignment (randomization)
  - c. Subject listing of drop-outs and subjects that discontinued with date and reason
  - d. Evaluable subjects/ non-evaluable subjects and reason not evaluable
  - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
  - f. By subject listing, of AEs, SAEs, deaths and dates
  - g. By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
  - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
  - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
  - j. By subject listing, of laboratory tests performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



### **III. Request for Site Level Dataset:**

OSI 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 Attachment 1, “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 a dataset, as outlined, which includes requested data for each pivotal study submitted in your application.

## **Attachment 1**

### **Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions**

The purpose of this pilot for electronic submission of a single new clinical site dataset is to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process in support of the evaluation of data integrity.

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 to facilitate the evaluation of the application. 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 Standard Deviation (TRTEFFS) – the standard deviation 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 Standard Deviation (SITEEFFS) – the standard deviation 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: *Table 1 Clinical Site Data Elements Summary Listing (DE)*. 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).

Exhibit 1: Table 1 Clinical Site Data Elements Summary Listing (DE)

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter "1".	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	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
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100

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Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5
16	ENDPOINT	Endpoint	Char	String	Plain text label used to descr be the primary endpoint as described in the Define file included with each application (limit 200 characters).	Average increase in blood pressure
17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
18	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Efficacy result for each primary endpoint by treatment arm at a given site.	0, 0.25, 1, 100
19	TRTEFFS	Treatment Efficacy Result Standard Deviation	Num	Floating Point	Standard deviation of the efficacy result (TRTEFFR) for each primary endpoint by treatment arm at a given site.	0.065
20	SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	Site effect size with the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
21	SITEEFFS	Site-Specific Efficacy Effect Size Standard Deviation	Num	Floating Point	Standard deviation of the site-specific efficacy effect size (SITEEFFE).	0.065
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not applicable, enter -1.	5
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm. This value should include multiple events per subject and all event types (i.e., <u>not limited to</u> only those that are deemed related to study drug or treatment emergent events).	10
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by treatment arm. This value should include multiple events per subject.	5
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., not limited to only significant deviations).	20
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount (\$USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	20000.00
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount (\$USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parties. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	25000.00

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Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	INITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	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: Example for Clinical Site Data Elements Summary Listing (Table 1)

STUDY	STUDYTL	DOMAIN	SPONNO	SPONNAME	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	ENROLL	SCREEN	DISCONT
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	27	60	1

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FINLDISC	LASTNAME	FRSTNAME
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	45000.00	Washington	George
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45000.00	Washington	George
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	0.00	Lincoln	Abraham
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	0.00	Lincoln	Abraham

IND 103694  
Meeting Minutes

INITIAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

Attachment 2

**Technical Instructions:  
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format**

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

<b>DSI Pre-NDA Request Item<sup>1</sup></b>	<b>STF File Tag</b>	<b>Used For</b>	<b>Allowable File Formats</b>
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study  (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be

“BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: [ESUB@fda.hhs.gov](mailto:ESUB@fda.hhs.gov)

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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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JESSICA M BENJAMIN  
11/22/2011



IND 103,694

**MEETING MINUTES**

Raptor Therapeutics, Inc.  
Attention: [REDACTED] (b) (4)  
Senior Associate  
9 Commercial Blvd.  
Suite 200  
Novato, CA 94949

Dear Ms. Roberts:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Cysteamine Bitartrate Delayed-Release Capsules.

We also refer to the meeting between representatives of your firm and the FDA on January 28, 2010. The purpose of the meeting was to discuss the results of Study RP103-01.

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, call me at (301) 796-2259.

Sincerely,

*{See appended electronic signature page}*

Chantal Phillips, M.S.H.S.  
CDR, U.S. Public Health Service  
Regulatory Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** B  
**Meeting Category:** End of Phase 2

**Meeting Date and Time:** January 28, 2010 at 3:00 pm EST  
**Meeting Location:** FDA, White Oak, Bldg 22

**Application Number:** 103,694  
**Product Name:** Cysteamine Bitartrate Delayed-Release Capsules

**Indication:** Nephropathic Cystinosis  
**Sponsor/Applicant Name:** Raptor Therapeutics, Inc.

**Meeting Chair:** Dr. Lynne Yao  
**Meeting Recorder:** CDR Chantal Phillips

**FDA ATTENDEES**

Division of Gastroenterology Products

Donna Griebel, M.D., Director  
Lynne Yao, M.D., Acting Medical Team Leader  
Carla Epps, M.D., M.P.H., Medical Reviewer  
Niraj Mehta, Ph.D., Pharmacology Reviewer  
Chantal Phillips, LCDR, M.S.H.S., Regulatory Project Manager

Pre-Marketing Assessment Division II

Marie Kowblansky, Ph.D., Pharmaceutical Assessment Lead

Division of Biometrics III

Mike Welch, Ph.D, Deputy Director

Office of Orphan Products Development

Henry "Chip" Startzman, M.D., Medical Officer

Office of Clinical Pharmacology

Jane Bai, Ph.D., Reviewer

**SPONSOR ATTENDEES**

Christopher M. Starr, Ph.D., CEO, Raptor Pharmaceutical

Thomas (Ted) Daley, President, Raptor Therapeutics Inc.

Patrice P. Rioux, M.D., Ph.D., Chief Medical Officer, Raptor Therapeutics Inc.

Erica Kraynack, Ph.D., Program Management, Raptor Therapeutics Inc.

(b) (4)

\*via telephone

## 1.0 BACKGROUND

Raptor Therapeutics plans to submit a 505 (b)(2) NDA by which Cystago under NDA 20-392 will be the Referenced Listed Drug. (b)(4) submitted an End of Phase 2 meeting request on behalf of Raptor Therapeutics, Inc. on October 15, 2009. Background packages were submitted on December 22, 2009.

## 2. DISCUSSION

In response to questions in the December 22, 2009, background package, the following responses were given. The format provides the firm's questions in italics followed by FDA responses in bold lettering. Questions, responses, and additional comments are indicated with headings.

### **Chemistry, Manufacturing, and Controls Questions**

*Q1: Raptor intends to provide in the NDA at least 6 months stability data on three drug product lots in the proposed commercial container closure system stored under ICH conditions at both standard room temperature and accelerated conditions. Additional data will be provided as available during the review period. Does the Agency agree with this approach?*

#### **FDA Response:**

**It is acceptable for you to submit additional stability data while the NDA is under review, provided your data is received no later than three months prior to the PDUFA date.**

### **Bioanalytical Questions**

*Q2: Raptor will attempt to transfer the method used at UCSD to measure WBC cystine in the pilot study, to a CRO capable of performing the assays in a GLP environment. If unsuccessful, we will use the current laboratories that perform this assay.. The laboratory will evaluate the existing methodology and make any necessary modifications to develop a robust and rugged method. The results will be audited by the laboratory's Quality Assurance Unit according to all applicable GLP requirements. Samples from U.S. clinical sites would be sent to this CRO for analysis. Does the Agency agree?*

#### **FDA Response:**

**Though it is acceptable to ship your samples to a CRO for analysis, it is important the samples are packed to ensure the stability and accuracy of sample identifications.**

**Please refer to the following guidance, "Guidance for Industry Bioanalytical Method Validation (2001),"**

**<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf>**

**The analytical reports from the CRO need to address all the elements detailed in the guidance and signed by the staff involved in analytical studies including managers at the CRO.**

*Q3: Raptor intends to transfer the method developed as written to a European laboratory. Raptor will evaluate feasibility to establish a fit-for-purpose cross-validation between the laboratories. Does the Agency agree?*

**FDA Response:**

**It is acceptable that you establish cross-validation between the laboratories. Each laboratory should have its own Standard Operating Procedure (SOP) and follow the established SOP for all the analytical methods performed at each laboratory. Please refer to the guidance document cited above (see response to question 2).**

**Clinical Questions**

*Q4: Long-term data suggests that controlled trough (i.e., when cysteamine level is the lowest, just before the next dose of Cystagon<sup>®</sup> every 6 hours) WBC cystine levels correlate with better patient outcome, including reducing the rate of deterioration of renal and thyroid function. Raptor intends to support its 505(b)(2) NDA with an efficacy study (every patient being treated for at least 3 to 4 weeks of treatment with RP103), as explained in the attached protocol), based on impact on white blood cell (WBC) cystine, and an extension, safety study. Does the Agency agree?*

**FDA Response:**

**No, we do not agree. There were several limitations to your exploratory Phase 1 PK-PD study. We have identified the following limitations after reviewing the submitted information of your exploratory Phase 1 study:**

- 1. Per protocol, the patients were supposed to have a washout period of 18-24 hours prior to RP-103 administration. Patients 4 to 9 had a washout period of  $\leq$  12 hours. For example, washout period were reported as 12 hours for patient 4, 12 hours for patient 5, 6 hours for patient 6, 12 hours for patient 7, and 11.5 hours for patient 8, and 6 hours for patient 9.**

**Additional Discussion for item 1:**

**The sponsor clarified that patients 4-9 did not have a washout period and that this information was submitted in a protocol amendment. The Agency reiterated that the success of your Phase 3 study will rely heavily on preliminary data (Phase 1/2 studies) that clearly establish the PK/PD relationship between your product and Cystagon.**

- 2. As a result of the limited washout period, these same patients had high pre-dose cysteamine concentrations on day 2 prior to receiving RP-103, suggesting a**

**significant carryover effect or high variability in the pharmacokinetics of RP-103. For example, patient 7 had a pre-dose concentration of 32micromol/L on day 2 prior to receiving RP-103 at a dose of 1050 mg cysteamine.**

- 3. The quality of bioanalytical method is questionable. For example, patient 7 had low cysteamine levels following administration of RP-103 despite a high RP-103 dose.**
- 4. There was inconsistent fasting or feeding conditions prior to dosing of Cystagon and RP-103 for patients 7 to 9.**

**Additional Discussion for item 4:**

**The Agency recommended that your product be taken with food to minimize gastrointestinal adverse events.**

- 5. There was inconsistent dose adjustment and lack of rationale in individual dose adjustment.**
- 6. There could be a period effect in the PK or PD data because the study was not randomized.**

**Thus, we are unable to clearly identify a dose(s) of RP-103 that could be evaluated in a Phase 3 trial. Therefore, we strongly recommend that you perform an additional Phase 2 PK-PD study prior to proceeding with your Phase 3 study. We have the following recommendations regarding this additional study:**

**We agree that WBC cystine levels are an appropriate efficacy measure. We recommend that you evaluate the PK profile of RP-103 compared with Cystagon following multiple doses and in more detail. The plasma concentration profiles of cysteamine resulting from your product should fall within the [Cmin, Cmax] bracket of Cystagon. The Cmax for RP-103 should not exceed that of Cystagon to minimize the potential for development of new safety issues based on increased exposure to cysteamine.**

**We also recommend that you evaluate the PD profile of RP-103 compared with Cystagon in more detail. According to the approved labeling for Cystagon, the WBC cystine levels approached the accepted upper bound of 1.0 nmol/half cystine/mg protein by 6 hours following Cystagon. However, the recommended dose interval of Cystagon is every six hours. From data reviewed from Study RP-103-01, your product appears to have a prolonged period (approximately 8 hours after dosing) during which cysteamine levels remained low (close to the Cmin of Cystagon). Since you did not provide a plot of both cysteamine and WBC cystine levels, it is not clear what the WBC cystine levels were between 8 and 12 hours post-dose of RP-103. Thus, we are concerned that the WBC cystine level after RP-103 administration may be higher than the desired upper bound after 8 hours following the dose. To demonstrate adequate efficacy of your extended-release product, you will need to demonstrate that WBC cystine levels are below 1.0**

**nmol/half cystine/mg protein at trough cysteamine concentrations. If necessary, you may need to redesign your extended-release formulation.**

**Additionally, we recommend that you incorporate the following procedures into the design of this study:**

- 1. The target dosing regimen of RP-103 must ensure that the plasma concentration profiles of cysteamine will fall within the cysteamine [Cmin, Cmax] bracket of Cystagon.**
- 2. There will be a 3-day run-in period with Cystagon to ensure WBC cystine levels are below 1.0 nmol/half cystine/mg protein.**
- 3. Patients should then be randomized to one of two treatment sequences:**

Sequence 1	Cystagon q6h for 3 days	RP-103 q12h for 3 days
Sequence 2	RP103 q12h for 3 days	Cystagon q6h for 3 days
- 4. Blood sampling on Day 3 of each period to quantify both cysteamine and cystine concentrations, preferably at matched time points, for PK and PD analyses.**
- 5. Adequate PK blood sampling to capture the Cmax and terminal half life of cysteamine for your product and Cystagon.**
- 6. With regard to WBC cystine sampling, you should have, at steady state, at least 5 time points for Cystagon during the 6 hour period, and at least 9 time points for your proposed product during the 12 hour period, after dosing. See our comments in question 4.**
- 7. You should evaluate the following clinical endpoints:**
  - Cmin, Cmax, and AUC of cysteamine**
  - WBC cystine level at the Cmin of cysteamine**
  - WBC cystine profiles with time points matched to those of cysteamine and determine the AUEC (area under the effect curve) of WBC cystine**
  - Average WBC at Cmin should be under 1.0 nmol/half cystine/mg protein**

**Finally, we recommend that you plot WBC cystine concentrations over the 12-hour interval for your product and Cystagon and calculate the area under the effect curve (AUEC) and determine the comparability between your product and Cystagon based on the AUEC. We recommend that you refer to the following guidance, “*Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations (March, 2003)*” for further information.**

**The adequacy of efficacy and safety data to support your application will be determined during the application review.**

**Additional Discussion:**

**No new agreements were reached between Raptor and the Agency during the meeting. The Agency recommends that a Special Protocol Assessment be submitted for review before initiating Phase 3 studies (see additional comments section below).**

*Q5: In our pilot study (RP103-01), we evaluated PK (plasma cysteamine) and PD (WBC cystine) parameters after a single dose of Cystagon<sup>®</sup> followed by a single dose of RP103. In the initial design of the protocol, patients had to follow an 18 hour washout period between these 2 single doses. We observed that for 3 patients who had to follow this washout period, the WBC cystine levels increased dramatically and very quickly during washout, as also noticed by R. Dohil in previously published studies (J Pediatr, 2006 & 2009). Since all the patients are already treated with one formulation (Cystagon<sup>®</sup>), the evaluation of a carry-over effect in a true crossover design would require a washout / re-equilibration period before administering one formulation then another washout / re-equilibration period before administering the second formulation. The minimum duration as well as the clinical impact of this washout / re-equilibration period is unknown. Thus, it is considered that the optimal design of our efficacy study is linear (i.e., a period of Cystagon<sup>®</sup> followed by a period of RP103 to demonstrate non-inferiority in WBC cystine control). This should permit greater flexibility for the optimization of dose of RP103, similar to standard clinical practice (i.e., titration of drug to effect), as described below. Does the Agency agree?*

**FDA Response:**

**It is premature to answer this question (see response to question 4). We recommend that you conduct additional Phase 2 studies that address these concerns before proceeding to a Phase 3 trial. However, we note that you have proposed an (b) (4) study design for your Phase 3 study; (b) (4)**

**As noted in the December 11, 2008 pre-IND meeting minutes, FDA stated that parallel design or a cross-over design would be acceptable for your pivotal PK study. We continue to recommend that a parallel design or cross-over design should be used for your Phase 3 trial. Additionally, we recommend that the study be designed with proper randomization and an adequate control population.**

*Q6: There are between 200 to approximately 500 patients in the U.S. and 800 patients in Europe with cystinosis. Almost all the patients without a kidney transplant are younger, school-age children. As a result of the rarity of the disease and the lack of any geographic concentration of patients, most patients have to travel considerable distances to clinical centers in order to participate in a clinical study. Additionally, because most eligible patients are children who must be accompanied by an adult or guardian, enrollment in a clinical study poses significant challenges and hardships to cystinosis patients and their family, including taking time away from work and school (Note: only 1 of 6 patients contacted was able to enroll in Raptor's RP103-01 pilot study.) Consequently, Raptor endeavors to demonstrate efficacy of the new*

*formulation with a small but sufficient sample size of patients, already under stable treatment with Cystagon<sup>®</sup>, over a short, but sufficient period of time that can assure comparable clinical efficacy.*

*The general design of this study will be as follows:*

- *Screening for eligibility.*
- *Day 1 to Day 3: Treatment Cystagon<sup>®</sup> (Q6H); Pre-dose WBC cystine measurement.*
- *Day 4 to Day 6: Treatment RP103 (Q12H); Pre-dose WBC cystine measurement.*
- *Day 7 to Day 28: Treatment RP103 (Q12H); same dose as Day 4 to Day 6 for a week and if a dose-adjustment is necessary based on WBC cystine measurements from Day 4 to 6 then, as soon as possible, RP103 (Q12H) dose will be adjusted based on cystine measurements from Day 1 to Day 6.*
- *Day 29 to Day 31: Treatment RP103 (Q12H); Pre-dose WBC cystine measurement.*

*Does the Agency agree with this design?*

#### **FDA Response:**

**It is premature to answer this question (see response to question 4). However, we have general recommendations regarding the design of future Phase 3 studies. We recommend that you measure WBC cystine levels at several timepoints. You should have, at steady state, at least 5 time points for Cystagon during the 6-hour period, and at least 9 time points for your proposed product during the 12 hour period, after dosing. Based on clinical data in patients receiving treatment for nephropathic cystinosis, WBC cystine levels should be maintained below 1.0 nmol/half cystine/mg protein. Therefore, RP-103 will also need to maintain a WBC cystine level below 1.0 nmol/half cystine/mg protein. In order to establish a comparable pharmacodynamic profile compared with Cystagon, you should evaluate the area under the curve (AUC) of the WBC cystine-time plot over a 12-hour period (AUEC). Pre-dose (trough) WBC cystine levels are not sufficient to demonstrate the comparable pharmacodynamic effect.**

**We also recommend that for future Phase 3 studies you provide a formal statistical analysis plan for review. Your protocol should include a formal statistical analysis plan that includes a clear rationale for your proposed analysis of efficacy endpoints, and plans for adaptive design strategies. We strongly recommend that you submit your final protocol, including your formal statistical analysis plan, for a special protocol assessment (SPA) before initiating your Phase 3 study.** (b) (4)

*Q7: The primary endpoint of this efficacy study will be based on the comparison of WBC cystine measurements over 3 days under steady-state, (patients on a stable dose of Cystagon<sup>®</sup> for at least 21 days) Cystagon<sup>®</sup> (Day 1 to Day 3) vs. 3 days under steady-state RP103 (Day 29 to Day 31). WBC cystine samples will always be collected just before the morning dose. If the upper bound of the 95% confidence interval for the difference in mean WBC cystine level depletion is less than 0.30, we will conclude that depletion with RP130 is comparable to Cystagon<sup>®</sup>. Does the Agency agree?*

**FDA Response:**

**We do have sufficient data to agree on this proposed criterion. As a general guidance, we would need WBC cystine levels prior to dosing as well as at other time points during the dosing interval. We would accept the upper bound of the 90% confidence interval of the ratio between RP-103 and Cystagon for the mean WBC cystine level set at less than 1.25. In addition, the upper bound of WBC cystine levels should be less than 1.0 nmol/half cystine/mg protein.**

**Additional discussion:**

**See additional comments section below.**

*Q8: The same criteria (i.e., if the mean WBC cystine level determined for Days 4 to 6 (RP103 PD sample days) is  $> 0.3$  nmol/half-cystine/mg protein plus the mean WBC cystine level determined for Days 1 to 3 (Cystagon<sup>®</sup> PD sample days) [i.e.,  $\Sigma$  (Days 4-6 WBC cystine)/3  $> 0.3$  +  $\Sigma$  (Days 1-3 WBC cystine)/3; units expressed as nmol/half-cystine/mg protein]) will be used to trigger potential dose-adjustment during the first week of steady state at home. If a dose increase appears necessary, the new total daily dose of RP103 will be approximately 80% of the daily dose of previous regular daily dose of Cystagon<sup>®</sup>. Does the Agency agree?*

**FDA Response:**

**Your proposed criterion to adjust the dose from 70% to 80% of the daily dose of RP-103 is acceptable as long as the WBC cystine level is maintained below 1.0 nmol/half cystine/mg protein.**

*Q9: An adaptive design will be used for the efficacy, with periodic adjustment of the sample size based on the variance of the progressive WBC cystine measurements. Although a minimum of 16 patients will be enrolled, the first 5 patients and every additional 5 patients thereafter, an estimation of the variance will be conducted. If it is found that the study will need more than 50 patients for a positive outcome, the study will be stopped and be considered as negative. Otherwise the study will be analyzed after all the patients have been treated. Does the Agency agree?*

**FDA Response:**

**From a statistical perspective, your proposed study can only be considered exploratory regarding potential efficacy conclusions. Without a proper randomization element, your trial does not meet the usual criteria for an adequate and well-controlled study and the use of statistical methods becomes problematic. Sample size adjustments based on (blinded) variance estimation may be done without alpha penalty; however without randomization, there is no clear relationship among planned effect size, sample size, power, and type I error rate.**

*Q10: The starting dose of RP103 will be based on the regression between cysteamine AUCs after Cystagon<sup>®</sup> and RP103, and as such, from Day 3 on, patients will receive a total daily dose of RP103 that is approximately 70% of their regular previous daily dose of Cystagon<sup>®</sup>. This daily dose will be divided in 2 doses, each dose taken every twelve hours. Does the Agency agree?*

**FDA Response:**

**It is premature to answer this question (see response to question 4). Your calculations were based on the results of the pilot PD study in a small number of patients (9). Therefore, we have concerns that your plan to use 70% of the Cystagon dose as the starting dose for RP-103 is not based on sufficient evidence because there are considerable variations in the PK and PD parameters reported for Cystagon. Since cysteamine has a short half life, there may be a prolonged period of time during which the plasma cysteamine level resulting from your product could be low. As a consequence, the WBC cystine level may not be maintained less than 1.0 nmol/half cystine/mg protein. From the approved labeling for Cystagon, the WBC cystine was 1.0 nmol/half cystine/mg protein) at 6 hours post dosing of Cystagon. You must demonstrate that your dosing regimen also maintains a consistently low cysteamine in the white blood cells.**

**RP-103 showed a long period of low cysteamine levels between 8 and 12 hours after dosing. You must demonstrate that RP-103 is able to maintain the WBC cystine below 1.0 nmol/half cystine/mg protein between dosing. Otherwise, you may need to redesign the formulation of RP-103.**

*Q11: Raptor intends to use 3-5 sites in the U.S. and 2-3 sites in the EU. The total number of sites is up to 6. Does the Agency have any objection to utilizing EU sites?*

**FDA Response:**

**We do not object to using EU sites as long as trials conducted at these sites meet the same regulatory requirements for trials conducted within the U.S.**

*Q12: Since an adaptive design will be used for study RP103-03, with periodic adjustment of the sample size based on the variance of the progressive WBC cystine measurements, the total number of patients in Study RP103-03 will vary between 16 and 50 patients. In order to evaluate the long-term safety profile of RP103, all patients who complete the RP103-03 efficacy study will be offered the opportunity to enroll in the extension study (RP103-04) and receive RP103 during the NDA review process, that is until Agency NDA approval or until Raptor terminates RP103 development for this indication for any reason. Does the Agency agree?*

**FDA Response:**

**Barring the identification of any new safety concerns, we encourage patients who complete RP-103-03 to enroll in an extension study.**

*Q13: The RP103-04 protocol has made provisions for enrolling additional patients who would not have participated in the previous RP103-03 study and these patients will also be followed during the NDA review process until NDA approval or until Raptor decides to terminate development of RP103. As noted above, the rarity of the disease and the lack of any geographic concentration of patients require patients to travel considerable distances to clinical centers in order to participate in a clinical study. Also, most eligible patients are likely to be children, who must be accompanied by an adult or guardian, so participation in a clinical study places significant burdens on the patient and their family including taking time away from work and school (Note: Approximately only 1 out of 6 potentially qualifying patients that were contacted was able to enroll in Raptor's RP103-01 pilot study). Due to these limitations, we do not anticipate a large number of additional patients enrolling in the study. However, the safety of cysteamine bitartrate is well known based on the currently approved Cystagon<sup>®</sup> formulation. As provided in the Integrated Safety Summary in the initial IND submission and updated with this submission (see Attachment 4), there do not seem to be significant adverse events with proper use of cysteamine bitartrate. Additionally, the pilot study showed no treatment-emergent adverse events associated with the use of RP103. Thus, we plan on submitting at least 6 months of safety data on no fewer than 16 patients (the minimum number for which efficacy could be established) and at least 3 months of safety data on all patients who completed the RP103--03 study and enrolled in the RP103-04 study, when the NDA is submitted. Safety data will continue to be collected from all enrolled patients after NDA submission and filed as an amendment at the 120 day safety update. Is this plan acceptable?*

**FDA Response:**

**It is premature to answer this question. If the PK and PD profile of RP-103 establish sufficient comparability to Cystagon (as described above), then available data for Cystagon may also be used to support the safety of RP-103. However, if there are substantive differences in the PK or PD profile of RP-103 compared with Cystagon, then additional data will be required to establish the safety profile for RP-103.**

*Q14: In this extension study, a blood sample for measuring blood cysteamine concentration and WBC cystine level will be collected every other month before the morning dose and any necessary adjustment to the dose of RP103 will be done to maintain efficacy (i.e., WBC cystine*

*level less than 1 nmol/half-cystine/mg of protein) and safety. Standard safety monitoring will be conducted in this study. Does the Agency agree?*

**FDA Response:**

**We recommend that dose adjustment should provide a comparable PD effect between your product and Cystagon; that is, maintaining WBC cystine level at less than 1.0 nmol/half cystine/mg protein (see response to question 6). Additionally, as noted in the December 11, 2008, pre-IND meeting minutes, we have concerns regarding the adequacy of safety monitoring in your clinical development program. We request that you propose specific safety monitoring based on the time course and frequency of adverse events known from experience in the clinical trials of Cystagon or those described in the literature. You have not provided justification for the proposed monitoring frequency of WBC cystine levels or other safety assessments. For example, we recommend that patients undergo monthly evaluation of WBC cystine levels and that more frequent evaluation may be required depending on the results of these values.**

**Regulatory Question**

*Q15: Since preliminary results with RP103 have shown fewer adverse events associated with RP103 than Cystagon® and RP103 will provide greater patient compliance, does the Agency believe there is a potential for a Fast Track and / or Priority Review designation? What, if any, other data would be needed to support a Fast Tack designation? Priority Review designation?*

**FDA Response:**

**Please refer to the Guidance for Industry: “Fast Track Drug Development Programs- Designation, Development, and Application Review.” You may submit a request for fast track designation at any time during the IND process or prior to NDA submission. A determination cannot be made to grant fast track designation until a request has been formally submitted and reviewed by the Agency. Also, please note that fast track designation does not guarantee a priority review for the NDA submission. A request for priority review should be made when the NDA is submitted and a decision will be made by the filing date.**

**Additional comments:**

**The Sponsor presented data at the meeting suggesting that a WBC cystine level of (b) (4) should be acceptable as the upper bound for the primary efficacy measurement. The Sponsor provided some data to suggest that clinical outcomes are not different in patients who maintain WBC cystine levels < 1.0 nmol/half cystine/mg protein compared with patients who maintain WBC cystine levels (b) (4). The Agency acknowledges that some patients may still receive benefit with a WBC cystine level of less than (b) (4). However, several publications, including one recently published study (Dohil R., Fidler M., Gangoiti JA, et**

al, *J Pediatr*, 2010) cite that the optimal WBC cystine levels in cystinosis patients receiving cysteamine is < 1.0 nmol/half cystine/mg protein. Furthermore, labeling for Cystagon states that the goal of treatment should be to maintain WBC cystine levels < 1.0 nmol/half cystine/mg protein. Therefore, we do not agree that the Sponsor's proposed WBC cystine level of [REDACTED]<sup>(b) (4)</sup> protein is appropriate as the upper bound for efficacy measurement for future studies.

### 3.0 ISSUES REQUIRING FURTHER DISCUSSION

### 4.0 ACTION ITEMS

The Agency recommends that a Special Protocol Assessment be submitted for review before initiating Phase 3 studies.

### 5.0 ATTACHMENTS AND HANDOUTS

Raptor Therapeutics provided an overview (slide presentation) of the outcome of the RP103-01 study, the unmet need in the treatment of cystinosis, the current standard of care, and general overview of FDA response and discussion points for the meeting. (Refer to the attached slide presentation).

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Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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IND-103694

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GI-1

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RAPTOR  
THERAPEUTICS  
INC

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Cysteamine Bitrartrate Delayed -  
release Capsules

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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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CHANTAL N PHILLIPS  
02/25/2010