

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**201656Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 201656	NDA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: NOCTIVA Established/Proper Name: desmopressin Dosage Form: nasal spray		Applicant: Serenity Pharmaceuticals Agent for Applicant (if applicable): N/A
RPM: Nenita Crisostomo		Division: Division of Bone, Reproductive and Urologic Products
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)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b> <ul style="list-style-type: none"> <li><b>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</b></li> <li><b>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</b> <ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> No changes</li> <li><input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i></li> </ul> </li> </ul> Date of check:
<b>❖ Actions</b>		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>March 3, 2017, after a 3-month review extension</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
<b>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?</b> 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 <b>This is not an accelerated approval.</b>		<input type="checkbox"/> Received <b>This is not an accelerated approval.</b>
<b>❖ Application Characteristics<sup>3</sup></b>		

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, 505(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).

<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.

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only): Type 5  
*(confirm chemical classification at time of approval)*

- |   |   |
|---|---|
| <input type="checkbox"/> Fast Track                       | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input type="checkbox"/> Rolling Review                   | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation |   |

**(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))**

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)  
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR  
 Submitted in response to a PMC  
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS:  MedGuide  
 Communication Plan  
 ETASU  
 MedGuide w/o REMS  
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<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 (approvals only)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Approval : <b>March 3, 2017</b>
Labeling	
❖ 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 <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input checked="" 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 <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ 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>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ 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> </ul>	5/27/16 5/26/16
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: 3/1/17  DMEPA: 11/16/16, 11/23/16, 2/2/17, 2/14/17, 2/28/17  DMPP/OPDP: 11/22/16  DRISK: <input checked="" type="checkbox"/> None  OPDP: 11/10/16  SEALD: <input checked="" type="checkbox"/> None  CSS: <input checked="" type="checkbox"/> None  Product Quality: 2/24/17, addendum of IQA  Other: <input type="checkbox"/> None
Administrative / Regulatory Documents	

❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting ( <i>indicate date of each review</i> )	3/1/17
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	10/26/16
❖ NDAs/NDA supplements only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input checked="" type="checkbox"/> Completed ( <b>Do not include</b> )
❖ 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>	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
○ If yes, Center Director's Exception for Review memo ( <i>indicate date</i> )	
○ If yes, OC clearance for approval ( <i>indicate date of clearance communication</i> )	<input type="checkbox"/> Not an AP action
❖ Pediatrics ( <i>approvals only</i> )	
• Date reviewed by PeRC <u>9/28/16</u> If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	<input checked="" type="checkbox"/> N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) ( <i>include only the completed template(s) and not the meeting minutes</i> )	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) ( <i>include only the completed template(s) and not the meeting minutes</i> )  ( <i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the <a href="#">MPC SharePoint Site</a></i> )	

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

<p>❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) <i>(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)</i></p>	<p>2/16/16 3/16/16 – 2 3/19/16 3/30/16 4/12/16 4/15/16 4/25/16 4/27/16 5/3/16 5/5/16 5/27/16 6/20/16 6/22/16 6/24/16 6/28/16 7/11/16 7/22/16 – 2 7/25/16 8/5/16 8/11/16 8/12/16 8/21/16 8/23/16 9/6/16 9/9/16 9/12/16 9/13/16 – 2 9/22/16 10/3/16 10/21/16 10/28/16 - 2 11/2/16 - 2 11/4/16 11/16/16 – 2 11/18/16 11/23/16 – 2 12/5/16 12/7/16 12/8/16 1/9/17 1/26/17 1/27/17 2/2/17 2/13/17 2/17/17 2/24/17 3/1/17- 2</p>
<p>❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)</p>	
<p>❖ Minutes of Meetings</p>	
<p>• If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i></p>	<p><input checked="" type="checkbox"/> N/A or no mtg</p>
<p>• Pre-NDA meeting <i>(indicate date of mtg)</i></p>	<p>7/28/10</p>
<p>• EOP2 meeting <i>(indicate date of mtg)</i></p>	<p>2/19/09</p>
<p>• Mid-cycle Communication <i>(indicate date of mtg)</i></p>	<p><input checked="" type="checkbox"/> N/A</p>
<p>• Late-cycle Meeting <i>(indicate date of mtg)</i></p>	<p><input checked="" type="checkbox"/> N/A</p>

<ul style="list-style-type: none"> <li>Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) <i>(indicate dates of mtgs)</i></li> </ul>	8/18/15, Guidance
❖ Advisory Committee Meeting(s)	
<ul style="list-style-type: none"> <li>Date of Meeting</li> </ul>	10/19/16
<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>	3/3/17
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	2/28/17
PMR/PMC Development Templates <i>(indicate total number)</i>	1
<b>Clinical</b>	
❖ Clinical Reviews	
<ul style="list-style-type: none"> <li>Clinical Team Leader Review(s) <i>(indicate date for each review)</i></li> </ul>	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> <li>Clinical review: Efficacy <i>(indicate date for each review)</i></li> </ul>	3/2/17: Final review 3/31/16: Filing
<ul style="list-style-type: none"> <li>Clinical Review: Safety <i>(indicate date for each review)</i></li> </ul>	3/2/17: Final review 2/17/17: Filing
<ul style="list-style-type: none"> <li>Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i></li> </ul>	<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>	See Clinical Review dated 3/2/17, Section 13.3, Appendix III
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i> <sup>5</sup> <ul style="list-style-type: none"> <li>Clinical Outcomes Assessment</li> </ul>	11/4/17
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and REMS Supporting Document <i>(indicate date(s) of submission(s))</i></li> <li>REMS Memo(s) and letter(s) <i>(indicate date(s))</i></li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) <i>(indicate date of each review and indicate location/date if incorporated into another review)</i></li> </ul>	2/4/16 None 2/23/17
❖ OSI Clinical Inspection Review Summary(ies) <i>(include copies of OSI letters to investigators)</i>	Summary: 11/2/16 Letter-Dr. Edelman: 10/25/16 Letter-Dr. Mills: 9/29/16

<sup>5</sup> For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).

<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	See Product Quality Review, 2/15/17
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) <i>(indicate date for each review)</i>	Filing: 3/25/16 Final: 1/11/17
<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"/> No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	Filing: 3/25/16 Final: 1/18/17
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input type="checkbox"/> None requested
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	9/16/16
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	Filing: 3/28/16 Final: 8/31/16 Final, revised: 10/7/16
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	Referenced review dated 10/17/06, under IND (b) (4), by Herman Rhee
❖ 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 11/2/15 request under IND 76667 for Carcinogenicity waiver granted, included in P/T review, page31
❖ 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 <sup>6</sup>	
• Tertiary review <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <i>(indicate date for each review)</i>	Filing: 9/12/16 IQA: 2/15/17 IQA, addendum: 2/24/17
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team <i>(indicate date of each review)</i>	See IQA dated 2/15/17 Drug Substance: 9/7/16

<sup>6</sup> Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	1/11/17, Drug Product Review, pg. 63
<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"/> Facilities inspections ( <i>indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter</i> ) ( <i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i> )	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>	<input checked="" type="checkbox"/> No changes <input checked="" type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
<ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>	<input checked="" type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> <li>• Notify the CDER BT Program Manager</li> </ul>	<input checked="" type="checkbox"/> N/A ( <i>Send email to CDER OND IO</i> )
❖ For products that need to be added to the flush list (generally opioids): <a href="#">Flush List</a> <ul style="list-style-type: none"> <li>• Notify the Division of Online Communications, Office of Communications</li> </ul>	<input checked="" type="checkbox"/> N/A
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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/s/  
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NENITA I CRISOSTOMO  
03/03/2017

MEMORANDUM

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

**DATE:** March 1, 2017

**TO:** Memo to File

**THROUGH:**

**FROM:** Nenita Crisostomo – Regulatory Health Project Manager

**SUBJECT:** Clinical Information Request – Glucocorticoids

**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo is to document the Information Request sent to Serenity Pharmaceuticals, LL via email on March 1, 2017.

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**From:** Crisostomo, Nenita

**Sent:** Wednesday, March 01, 2017 4:01 PM

**To:** Linda Cheng (lcheng@serenitypharma.com)

**Subject:** NDA201656 desmopressin: Clinical Information Request: Glucocorticoids

Hi Linda,

Below are questions from the review team. Please email to me your response as soon as possible today.

- Why did you exclude patients on oral or inhaled glucocorticoids from your trials?
- What is the scientific basis for increased risk of hyponatremia when glucocorticoids are used with desmopressin products?

Thank you,  
Nita

*Nenita Crisostomo, R.N.  
Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
Center for Drug Evaluation and Research  
Ph: 301-796-0875*

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/s/  
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NENITA I CRISOSTOMO  
03/01/2017

MEMORANDUM

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

**DATE:** March 1, 2017  
**TO:** Memo to File  
**FROM:** Nenita Crisostomo – Regulatory Health Project Manager  
**SUBJECT:** Clinical Information Request – Information for Use

**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo is to document the Information Request sent to Serenity Pharmaceuticals, LL via email on March 1, 2017.

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**From:** Crisostomo, Nenita  
**Sent:** Wednesday, March 01, 2017 3:17 PM  
**To:** Linda Cheng (lcheng@serenitypharma.com)  
**Subject:** NDA201656 desmopressin: FDA edits on IFU

Hi Linda,

Attached is the Information for Use labeling that contains our additional edits. For our immediate review, please email to me your response as soon as possible today, while enroute for official submission. In the cover letter of your official submission, please note that the version that you are submitting remains unchanged from the emailed version. This will allow us to officially review your emailed version.

The Medication Guide and the Package Insert will soon follow.

If you have any questions, please feel free to contact me.

Thank you,  
Nita

*Nenita Crisostomo, R.N.  
Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
Center for Drug Evaluation and Research  
Ph: 301-796-0875*

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/s/  
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NENITA I CRISOSTOMO  
03/01/2017

MEMORANDUM

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

**DATE:** February 24, 2017  
**TO:** Memo to File  
**FROM:** Nenita Crisostomo – Regulatory Health Project Manager  
**SUBJECT:** Information Request, Package Insert – FDA Edits #3

**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo is to document the Information Request sent to Serenity Pharmaceuticals, LLC via email on February 24, 2017.

**From:** Crisostomo, Nenita  
**Sent:** Friday, February 24, 2017 12:08 PM  
**To:** Linda Cheng (lcheng@serenitypharma.com)  
**Subject:** NDA 201656 desmopressin: Package Insert - FDA Edits

Hi Linda,

Attached is the Package Insert containing our recommendations. While enroute for official submission, please email to me your revised version of the labeling as soon as possible, or by close of business on Monday, February 27, 2017. Please indicate on the cover letter of your submission that what is being submitted is the exact version as what is being sent via email. This will allow us to officially review your emailed document.

If you have any questions, please feel free to contact me.

Best Regards,  
nita

*Nenita Crisostomo, R.N.  
Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
Center for Drug Evaluation and Research  
Ph: 301-796-0875*

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

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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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NENITA I CRISOSTOMO  
02/24/2017

MEMORANDUM

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

**DATE:** February 17, 2017  
**TO:** Memo to File  
**FROM:** Nenita Crisostomo – Regulatory Health Project Manager  
**SUBJECT:** Information Request – DMEPA: Human Factors, IFU, Carton labeling  
**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo is to document the Information Request sent to Serenity Pharmaceuticals, LL via email on February 17, 2017, as follows:

**From:** Crisostomo, Nenita  
**Sent:** Friday, February 17, 2017 1:09 PM  
**To:** 'Linda Cheng'  
**Subject:** RE: NDA 201656 NOCTIVA (desmopressin): DMEPA Information Request - Human Factors, IFU, Carton labeling

Hi Linda,

Just to clarify, the second request refers to a change on the top flap, i.e., consider revising the statement “IMPORTANT: Read Enclosed Instructions for Use Before Using” to read “IMPORTANT: Read enclosed instructions”.

Thank you,  
nita

**From:** Crisostomo, Nenita  
**Sent:** Friday, February 17, 2017 1:03 PM  
**To:** 'Linda Cheng'  
**Subject:** RE: NDA 201656 NOCTIVA (desmopressin): DMEPA Information Request - Human Factors, IFU, Carton labeling

Hi Linda,

The previous request below pertains to the side panel to be revised to the clearer language: “IMPORTANT: Read enclosed instructions for dosing, priming, and re-priming information” or “IMPORTANT: Before using read enclosed instructions for dosing, priming, and re-priming information”.

In addition, consider revising the statement “IMPORTANT: Read Enclosed Instructions for Use Before Using” to read “IMPORTANT: Read enclosed instructions”.

Thank you so much,  
Nita

*Nenita Crisostomo, R.N.  
Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
Center for Drug Evaluation and Research  
Ph: 301-796-0875*

**From:** Linda Cheng [<mailto:lcheng@serenitypharma.com>]  
**Sent:** Friday, February 17, 2017 12:43 PM  
**To:** Crisostomo, Nenita  
**Subject:** RE: NDA 201656 NOCTIVA (desmopressin): DMEPA Information Request - Human Factors, IFU, Carton labeling  
**Importance:** High

Dear Nita:

This is to capture our discussion this morning to seek clarification on the top flap of the carton label. Based on the request below concerning the “IMPORTANT” message on the top flap of the carton label, it is our understanding that DMEPA accepts the language as stated in the attached document. If on the other hand, DMEPA wants the language on the top flap to be the same as suggested for the side panel, we want to indicate that there is no enough room to put all the verbiage on the top flap without shrinking the font size on the message.

For clarity, Serenity accepts DMEPA’s request concerning the suggested language on the side panel. We will update the language as proposed accordingly.

Regards,

Linda

Linda Cheng  
V-P, Project Management  
Serenity Pharmaceuticals, LLC  
120 North Main Street  
Suite 400  
New City, New York 10956

Phone: 845-639-6760, Ext. 11

Fax: 845-639-1703

[lcheng@serenitypharma.com](mailto:lcheng@serenitypharma.com)

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**From:** Crisostomo, Nenita [<mailto:Nenita.Crisostomo@fda.hhs.gov>]

**Sent:** Friday, February 17, 2017 11:07 AM

**To:** Linda Cheng <[lcheng@serenitypharma.com](mailto:lcheng@serenitypharma.com)>

**Subject:** NDA 201656 NOCTIVA (desmopressin): DMEPA Information Request - Human Factors, IFU, Carton labeling

Hi Linda,

We refer to your January 13, 2017, submission containing the Human Factors study data. We have completed our review and we recommend implementation of the changes below prior to approval of this supplement. These modifications will not require additional human factors testing:

A. Instructions for Use (IFU)

1. You propose that the IFU be limited to one page to minimize the risk that users may overlook or do not read important steps to use your product safely and effectively. We agree with your proposal. Alternatively, if it is necessary to use more than one page, we agree to your inclusion of a 'cue' to the reader to indicate that there is additional information on subsequent pages.
2. We recognize that the information about priming and re-priming is critical, and three of the study participants in the HF validation study 2 did not notice these instructions. We notice that, as currently presented, the font weight and size of the statements for priming and re-priming are identical to that for non-critical information. We recommend you improve the prominence of these statements further by bolding them or by other means.
3. Please address the following beginning with the box titled "Before your first use":
  - a. As proposed, the headings used do not accurately reflect the contents of the sections. In particular, the heading "Before your first use" does not sufficiently convey that this section of the IFU also includes instructions for preparing the device for priming as well as for the priming step. Your study results indicated that three study participants in the HF validation study 2 did not notice the priming instructions and two study participants in the HF

validation study 2 did not perform the priming steps correctly. We suggest you consider revising the headings to better reflect the section contents. For example, revise the heading (which appears in the box with Figure B) “Before your First Use” to read “Before your first use, follow these instructions to prime the product”.

- b. In addition, we ask that you modify this section to include a step number prior to each statement. For example, the statement “Pull the cap off and set aside” should be preceded by the statement ‘Step 1’.
4. The specific statement on how to prime the nasal spray prior to use is unclear. The inability to properly prime the device may lead to the risk of under-dosing. We recommend you consider revising the language in the IFU from “Pump the nasal applicator 5 times by squeezing your fingers and thumb together (see Figure E)” to read “Completely press the nasal applicator 5 times by squeezing your . . .”
  5. Please address the following regarding the instructions contained in the re-priming section of the IFU:
    - a. Based on the study results, we find that these instructions are not clear and may lead to wrong technique errors resulting in under dosing and reduced efficacy. We recommend that you consider changing the language from “(b) (4)” to read “Completely pump the nasal applicator 2 times” to minimize the risk of under-dosing when re-priming.
    - b. The re-priming section lacks instructions to inform the user of actions to take in the event of a missed dose. One participant in the HF validation study 2 administered two doses in one day to make up for a missed dose. Given the criteria for re-priming (non-use for over 3 days), we are concerned that users may decide to give multiple doses. To mitigate such errors, we recommend the inclusion of a statement in the re-priming section of the IFU which instructs the user on what actions to take if a dose is missed. Consider adding the following statement or something similar: “If a dose is missed, you should not double the dose at the next use”. This statement should follow the statement: “If you do not use Noctiva for more than 3 days, you will need to re-prime . . .”

## B. Carton labeling

1. Based on participant feedback, the instructions on the carton labeling are not clear and may be misinterpreted. We agree with your proposed language for inclusion on the carton labeling and on the top flap to instruct the user to access the IFU. For more clarity, consider revising the statement “IMPORTANT: Read enclosed instructions (b) (4) for dosing, priming, and re-priming information” to read

“IMPORTANT: Read enclosed instructions for dosing, priming, and re-priming information” or “IMPORTANT: Before using read enclosed instructions for dosing, priming, and re-priming information”.

Please submit your response on or before 12Noon on Tuesday, February 21, 2017. If you have any questions, please feel free to contact me.

Thank you,  
nita

*Nenita Crisostomo, R.N.  
Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
Center for Drug Evaluation and Research  
Ph: 301-796-0875*

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NENITA I CRISOSTOMO  
02/17/2017

MEMORANDUM

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

**DATE:** February 13, 2017

**TO:** Memo to File

**FROM:** Nenita Crisostomo, Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products

**SUBJECT:** Clinical Pharmacology Information Request: Postmarketing Requirement

**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin acetate) Nasal Spray

This Memorandum documents to Information Request sent to Serenity Pharmaceuticals via email on January 9, 2017, as follows:

**From:** Crisostomo, Nenita  
**Sent:** Monday, January 09, 2017 2:48 PM  
**To:** Linda Cheng (lcheng@serenitypharma.com)  
**Subject:** RE: NDA 201656 desmopressin: PMR

Dear Linda,

Please propose a synopsis of your study plan for the PMR below. Please include milestone dates (month/year) as follows:

- Final Protocol Submission:
- Study Completion:
- Final Report Submission:

If you have any questions, please feel free to contact me.

Best Regards,  
Nita

*Nenita Crisostomo, R.N.  
Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
Center for Drug Evaluation and Research  
Ph: 301-796-0875*

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NENITA I CRISOSTOMO  
02/13/2017

MEMORANDUM

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

**DATE:** February 13, 2017

**TO:** Memo to File

**FROM:** Nenita Crisostomo, Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products

**SUBJECT:** Product Quality Information Request: Carton/Container Labeling

**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin acetate) Nasal Spray

This Memorandum documents to Information Request sent to Serenity Pharmaceuticals via email on February 13, 2017, as follows:

**From:** Crisostomo, Nenita  
**Sent:** Monday, February 13, 2017 11:07 AM  
**To:** Linda Cheng (lcheng@serenitypharma.com)  
**Subject:** NDA 201656 NOCTIVA (desmopressin): Product Quality Information Request - Carton/Container labeling

Hi Linda,

We refer to your February 9, 2017, submission of the carton/container labeling in response to our February 2, 2017 recommendations. Below is a request from our Product Quality Team for further revision of the labeling:

*Revise the established name presentation from [REDACTED] (b) (4) to “(desmopressin acetate) Nasal Spray” in the carton labels. Make sure the established name presentations are consistent in both container and carton labels.*

Please submit your response as soon as possible, at the latest, by close of business on February 14, 2017.

Thank you,  
Nita  
*Nenita Crisostomo, R.N.  
Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
Center for Drug Evaluation and Research  
Ph: 301-796-0875*

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NENITA I CRISOSTOMO  
02/13/2017

MEMORANDUM

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

**DATE:** 2/2/2017

**TO:** Linda Cheng

**THROUGH:** Sarah Harris, Safety RPM, DMEPA; Denise Baugh, DMEPA

**FROM:** Jennifer Dao

**SUBJECT:** NDA 201656 Noctiva (desmopressin) Carton and Container Label Information Request

**APPLICATION/DRUG:** (desmopressin)

This email was sent to the sponsor to through DMEPA to send comments regarding the Carton and Container Label submitted on 12/1/16.

**From:** [Dao, Jennifer](#)  
**To:** "[Linda Cheng](#)"  
**Cc:** [Mercier, Jennifer L](#); [Crisostomo, Nenita](#); [Roule, Jeannie](#)  
**Subject:** RE: NDA 201656 Noctiva (desmopressin) Carton and Container label Information Request  
**Date:** Friday, February 03, 2017 10:21:46 AM

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Yes, the IR is based on the attached carton and container labels.

Thanks,  
Jennifer

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**From:** Linda Cheng [mailto:[lcheng@serenitypharma.com](mailto:lcheng@serenitypharma.com)]  
**Sent:** Thursday, February 02, 2017 5:32 PM  
**To:** Dao, Jennifer  
**Cc:** Mercier, Jennifer L; Crisostomo, Nenita  
**Subject:** RE: NDA 201656 Noctiva (desmopressin) Carton and Container label Information Request

Dear Jennifer:

We are in receipt of the IR. Just want to confirm that the below IR was generated based on the review of the attached carton and vial labels submitted under Serial 0048 on 12-1-16.

Regards,

Linda

Linda Cheng  
V-P, Project Management  
Serenity Pharmaceuticals, LLC  
120 North Main Street  
Suite 400  
New City, New York 10956

Phone: 845-639-6760, Ext. 11  
Fax: 845-639-1703

[lcheng@serenitypharma.com](mailto:lcheng@serenitypharma.com)

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**From:** Dao, Jennifer [mailto:[Jennifer.Dao@fda.hhs.gov](mailto:Jennifer.Dao@fda.hhs.gov)]  
**Sent:** Thursday, February 02, 2017 4:35 PM  
**To:** Linda Cheng <[lcheng@serenitypharma.com](mailto:lcheng@serenitypharma.com)>  
**Cc:** Mercier, Jennifer L <[Jennifer.Mercier@fda.hhs.gov](mailto:Jennifer.Mercier@fda.hhs.gov)>; Crisostomo, Nenita <[Nenita.Crisostomo@fda.hhs.gov](mailto:Nenita.Crisostomo@fda.hhs.gov)>

**Subject:** NDA 201656 Noctiva (desmopressin) Carton and Container label Information Request

Hello Ms. Cheng,

We have the following information requests for the NDA mentioned above regarding the Carton and Container labeling:

1. There is a lack of differentiation between the two strengths on the container label and carton labeling. The strength statements for both strengths have (b) (4) presentations (b) (4) (b) (4) which may result in wrong strength errors. Revise the (b) (4) so that the strength appears (b) (4) does not overlap with (b) (4) the trade dress. Alternatively, you may consider (b) (4) other means to better differentiate between the strengths. We recommend this revision to improve upon the strength differentiation and to increase the prominence of the strength statement.
2. The established name (desmopressin acetate) lacks prominence commensurate with the proprietary name (Noctiva). Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2). We recommend you revise the established name to be at least half the size of the proprietary name in accordance with 21 CFR 201.10(g)(2).

Please submit your response to the NDA by February 9<sup>th</sup>. Please confirm the receipt.

Thank you,  
Jennifer

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/s/  
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JENNIFER M DAO  
02/03/2017

MEMORANDUM

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

DATE: 1/27/2017

**TO:** Linda Cheng, Serenity Pharma

**THROUGH:** Suresh Kaul, M.D., Martin Kauffman, M.D., Denise Baugh

**FROM:** Jennifer Dao

**SUBJECT:** NDA 201656 Clinical Information Request

**APPLICATION/DRUG:** NDA 201656 Noctiva (desmopressin) nasal spray

This was a clinical information request sent by the clinical review team and DMEPA.

**From:** Dao, Jennifer

**To:** lcheng@serenitypharma.com

**Cc:** Crisostomo, Nenita

**Subject:** NDA 201656 Noctiva (desmopressin) Information Request

**Date:** Friday, January 27, 2017 8:22:36 AM

Hello Ms. Cheng,

Please refer to your New Drug Application submitted for Noctiva (desmopressin) nasal spray. Listed below are Information Request from our Clinical Team:

- In DB3 and DB4 subjects had baseline serum sodium assessments during Screening and at the Day 1 visit. Provide an analysis of the number of subjects who were screen failures based on baseline sodium concentrations (e.g., how many patients had 1 normal sodium and 1 low sodium, etc).
- Provide a subgroup analyses of the primary endpoints for the 0.75 mcg dose in subjects 65 years of age or older with nocturnal polyuria for DB3 and for DB4.

We also refer to your Human Factors re-validation study report for NDA 201656 Noctiva (desmopressin acetate) nasal spray submitted January 13, 2017. Your submission includes several versions of your Instructions for Use (IFU) presented in two different formats. For example, the submission includes a single page IFU on page 126, a multiple page prior IFU on page 183, a revised IFU on page 186, and a multiple page recommended changes IFU on page 192. We are unclear regarding the version of IFU used during your validation study and what you intend to market with your combination product. We ask that you clarify the following for

your Noctiva nasal spray product:

- State which version of the IFU was used in your validation study.
- State which version of the IFU you intend to market.
- To better inform our review of your human factors validation study results, inform us on what specific page of your submission we may locate these IFU's .
- 

We ask for a reply no later than COB January 30, 2017. Please confirm the receipt.

Thank you,  
Jennifer Dao

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JENNIFER M DAO  
01/27/2017

MEMORANDUM

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

DATE: 1/26/2017

**TO:** Linda Cheng, Serenity Pharma

**THROUGH:** Christine Nguyen

**FROM:** Jennifer Dao

**SUBJECT:** NDA 201656 PMR Information Request

**APPLICATION/DRUG:** NDA 201656 Noctiva (desmopressin) nasal spray

This information request was sent regarding the milestones for their PK PMR.

**From:** Dao, Jennifer

**Sent:** Thursday, January 26, 2017 2:09 PM

**To:** 'lcheng@serenitypharma.com'

**Cc:** Crisostomo, Nenita

**Subject:** NDA 201656 Noctiva (desmopressin) PMR Information Request

Hello Ms. Cheng,

I will be covering for Nita while she is on leave. We refer you to the amendment dated January 17, 2017, submitted to NDA 210656. This amendment contained your proposed study synopsis and milestone dates for a postmarket required pharmacokinetic study of SER120 to compare systemic exposures of two sprays of 0.83 mcg and one spray of 1.66 mcg in healthy subjects. The protocol is under review; however, we noted that the study milestone dates should be revised to the following schedule:

Final Protocol: September 2017

Study Completion: March 2018

Final Study Report: September 2018

Please submit an amendment to NDA 210656, indicating your agreement with these three key milestone dates.

Please confirm the receipt. We will also be sending a clinical information request to you shortly.

Thank you,

**Jennifer Dao**

Regulatory Health Project Manager  
Division of Bone, Reproductive, and Urologic Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
**Email:** Jennifer.dao@fda.hhs.gov  
**Phone:** 301-796-8189

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JENNIFER M DAO  
01/26/2017

MEMORANDUM

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

**DATE:** December 8, 2016  
**TO:** Memo To File  
**FROM:** Nenita Crisostomo, Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
**SUBJECT:** DMPP Information Request: MedGuide, IFU

**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo documents the DMPP Information Request sent to Serenity Pharmaceuticals on December 8, 2016, via email, as follows:

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**From:** Crisostomo, Nenita  
**Sent:** Thursday, December 08, 2016 5:26 PM  
**To:** Linda Cheng (lcheng@serenitypharma.com)  
**Subject:** NDA 201656 desmopressin: Additional edits to the IFU and MG, HF protocol

Hi Linda,

As we discussed over the phone a few minutes ago, here are additional revisions to the labeling:

Information for Use:

- On Page 5, Storage section, 3<sup>rd</sup> bullet, the last sentence should read as follows: Write the date the bottle (b) (4) is opened on the bottle label.

Medication Guide:

- On Page 2, **How should I store NOCTIVA?** section, the last sentence should read: Write the date the bottle is opened on the bottle label.

Also, I have been informed by DMEPA that there are no further comments on the Human Factors protocol.

Thank you and have a great evening,  
nita

*Nenita Crisostomo, R.N.*  
*Regulatory Health Project Manager*  
*Division of Bone, Reproductive and Urologic Products*  
*Center for Drug Evaluation and Research*  
*Ph: 301-796-0875*

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NENITA I CRISOSTOMO  
12/09/2016

MEMORANDUM

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

**DATE:** December 7, 2016  
**TO:** Memo to File  
**FROM:** Nenita Crisostomo – Regulatory Health Project Manager  
**SUBJECT:** Information Request – Package Insert: FDA edits #1

**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo is to document the first set of recommendations to revise the Package Insert sent to Serenity Pharmaceuticals, LLC via email on November 2, 2016.

**From:** Crisostomo, Nenita  
**Sent:** Wednesday, November 02, 2016 11:46 PM  
**To:** Linda Cheng (lcheng@serenitypharma.com)  
**Subject:** NDA 201656desmopressin: Labeling - FDA edits#1

Dear Linda,

Attached is the DRAFT labeling containing our first set of comments and recommendations. Please note that reviews are ongoing and further labeling edits will be forthcoming in subsequent labeling rounds.

Please accept all of our changes to the labeling, show your new edits and provide rationale/comments for your changes using the Track Changes command, and email to me your edited version on or before 12Noon on November 9, 2016.

If you have any questions, please feel free to contact me.

Best Regards,  
nita

*Nenita Crisostomo  
Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
Center for Drug Evaluation and Research  
Ph: 301-796-0875*

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

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NENITA I CRISOSTOMO  
12/07/2016

MEMORANDUM

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

**DATE:** December 7, 2016  
**TO:** Memo To File  
**FROM:** Nenita Crisostomo, Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
**SUBJECT:** CMC Information Request: Re-Priming

**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo documents the CMC Information Request sent to Serenity Pharmaceuticals on November 18, 2016, via email, as follows:

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**From:** Crisostomo, Nenita  
**Sent:** Friday, November 18, 2016 4:09 PM  
**To:** Linda Cheng (lcheng@serenitypharma.com)  
**Subject:** NDA201656 desmopressin: Response to 11/17/16 submission re: Re-priming

Hi Linda,

We have reviewed your November 17, 2016, submission in response to our November 16, 2016, Information Request regarding strength statements and re-priming and we have the following comments and recommendations:

- The data submitted in report TTP-SFU-M0043, Product Characterization: Effect of Priming and Re-priming Study for Desmopressin Acetate Nasal Spray (SER-120) dated February 25, 2015, suggest that re-priming is not necessary for product stored, unused at (b) (4) days. Nevertheless, there is a clear trend that shot weight decreases when unused for (b) (4) days.

The data, albeit limited, from the in-use stability study, however, consistently showed a larger decrease in shot weight when stored unused at room temperature for (b) (4) days. No explanation for this observation was provided. It is unknown if shot weight continues to decrease when product is stored unused at room temperature for longer than (b) (4) days.

In the absence of evidence that re-priming of product stored unused at room temperature for more than (b) (4) days is not necessary, labeling should include directions for re-priming.

Subsequent to approval, you may submit a supplemental NDA, with supporting data, to remove the language about re-priming.

Please submit your response to the NDA by Monday, before 12 Noon.

Thank you so much and have a great weekend!

--nita

*Nenita Crisostomo, R.N.  
Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
Center for Drug Evaluation and Research  
Ph: 301-796-0875*

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NENITA I CRISOSTOMO  
12/07/2016

MEMORANDUM

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

**DATE:** December 7, 2016  
**TO:** Memo to File  
**FROM:** Nenita Crisostomo – Regulatory Health Project Manager  
**SUBJECT:** CMC/DMEPA Information Request – Carton and Container Labeling & Information for Use

**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo is to document the recommendations to revise the carton and container labeling, and the Information for Use sent to Serenity Pharmaceuticals, LLC via email on December 7, 2016.

**From:** Crisostomo, Nenita  
**Sent:** Wednesday, December 07, 2016 12:46 PM  
**To:** Linda Cheng (lcheng@serenitypharma.com)  
**Subject:** NDA 201656 desmopressin: IFU and carton/container label

Hi Linda,

We refer to your submission dated December 2, 2017, containing your response to our November 23, 2016, communications to you containing our recommendations to revise the Human Factors protocol, Medication Guide, Information for Use, and carton/container labeling. We also refer to our email communication with you on December 5, 2017, containing our comments and recommendations for the revision of the Medication Guide.

Contained in this email are our comments for the Information for Use, as attached, and for the container and carton labeling as follows:

Container and Carton Labels:

1. Revise the equivalency statement for both strengths. Below is the presentation by using 1.66mcg/0.1 mL strength as an example:

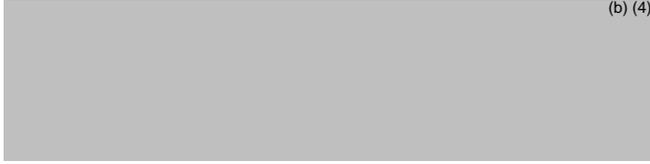
Revise from

(b) (4)

to

“Each 0.1 mL contains: desmopressin acetate 1.66 mcg (equivalent to 1.5 mcg desmopressin)”.

2. Revise the Storage condition statement on the immediate container labels from



to

“Storage: Store at 20°C to 25°C (68°F to 77°F) after opening.

Discard the unused portion after 60 days from opening.

Date of First Opening \_\_/\_\_/\_\_.”

Please submit your response to the Electronic Document Room as soon as possible. Please be reminded that the final agreed-upon labeling must be received by the Division before you start the Human Factors Study. We will update you regarding the Human Factors protocol if further comments will be forthcoming to you.

Please feel free to contact me if you have any questions.

Thank you,  
Nita

*Nenita Crisostomo, R.N.  
Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
Center for Drug Evaluation and Research  
Ph: 301-796-0875*

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NENITA I CRISOSTOMO  
12/07/2016

MEMORANDUM

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

**DATE:** December 7, 2016  
**TO:** Memo to File  
**FROM:** Nenita Crisostomo – Regulatory Health Project Manager  
**SUBJECT:** Information Request – Medication Guide: FDA Edits #2

**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo is to document the recommendations to revise the Medication Guide sent to Serenity Pharmaceuticals, LLC via email on December 5, 2016.

**From:** Crisostomo, Nenita  
**Sent:** Monday, December 05, 2016 2:05 PM  
**To:** 'Linda Cheng'  
**Subject:** NDA 201656 desmopressin: MedGuide - FDA Edits #2

Hello Linda,

We refer to your submission dated December 2, 2016, containing your responses to our November 23, 2016, Advice letters containing our recommendations to the Human Factors protocol, Information for Use, container/carton labeling and Medication Guide.

Attached is the Medication Guide containing our additional recommendations in response to your December 2, 2016, comments (also emailed on November 28, 2016). If you have additional revisions to this version, please accept all of our revisions and mark your additional edits and comments on the document using Track Changes command (not strikethroughs and underlines) and submit both CLEAN and MARKED copies, both in WORD and PDF versions. Likewise, if you agree with our recommendations, please accept all of our edits and submit clean copy, both in WORD and PDF versions, to EDR.

As stated in the document, please note that there may be further edits to the Medication Guide as the review of the Package Insert progresses.

The other documents are currently under review and we will let you know of any further comments. If you have any questions, please feel free to contact me.

Thank you,  
Nita

*Nenita Crisostomo, R.N.*  
*Regulatory Health Project Manager*  
*Division of Bone, Reproductive and Urologic Products*  
*Center for Drug Evaluation and Research*  
*Ph: 301-796-0875*

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NENITA I CRISOSTOMO  
12/07/2016

MEMORANDUM

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

**DATE:** November 29, 2016  
**TO:** Memo to File  
**FROM:** Nenita Crisostomo – Regulatory Health Project Manager  
**SUBJECT:** Information Request – DMEPA  
Repeat Human Factors study data for validation of revised IFU

**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo is to document the Information Request sent to Serenity Pharmaceuticals, LL via email on October 28, 2016, as follows:

**From:** Crisostomo, Nenita  
**Sent:** Friday, October 28, 2016 3:21 PM  
**To:** Linda Cheng (lcheng@serenitypharma.com)  
**Subject:** NDA 201656 NOCTIVA (desmopressin) - DMEPA Information Requests: Human Factors Study Results

Hi Linda,

We refer to your submission dated and received September 26, 2016, containing your Human Factors summative validation study. After review of your submission, the Division of Medication Error Prevention and Analysis have the following information requests:

- Your human factors (HF) validation study results showed multiple risk-related use errors: failure to properly prime the product (for first use only), failure to read and understand the Instructions for Use, and failure to hold the bottle upright (or at slight tilt from vertical) during administration. Based on these results, you determined to modify the Instructions for Use (IFU) to address the use errors seen in the study. However, you have not submitted additional validation data to demonstrate that the changes to the IFU effectively address the use errors and do not introduce new risks. We ask that you perform an additional simulated-use HF validation study with at least 15 representative users per distinct user group performing tasks necessary to deliver the product. Given our timeline, we ask that you submit the additional simulated-use HF validation study data no later than Monday, November 28, 2016.

If you have any questions, please feel free to contact me.

Have a great weekend!

--nita

*Nenita Crisostomo, R.N.  
Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
Center for Drug Evaluation and Research  
Ph: 301-796-0875*

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NENITA I CRISOSTOMO  
11/29/2016

MEMORANDUM

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

**DATE:** November 29, 2016  
**TO:** Memo to File  
**FROM:** Nenita Crisostomo – Regulatory Health Project Manager  
**SUBJECT:** Information Request – DMEPA  
Human Factors and IFU

**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo is to document an email sent to Serenity Pharmaceuticals, LL on November 4, 2016, regarding human factors protocol and Information for Patient.

**From:** Crisostomo, Nenita  
**Sent:** Friday, November 04, 2016 11:26 AM  
**To:** 'Linda Cheng'  
**Subject:** NDA 201656 desmopressin: Human Factors Study - Protocol and IFU

Hi Linda,

Please provide an update as to when you will be submitting the protocol for your new Human Factors validation study. Please note that your revised Instructions for Use (IFU) that you plan to test in the Human Factors study should be included with the protocol.

Please submit these documents officially to the Electronic Document Room.

If you have any questions, please feel free to contact me.

Thank you,  
Nita

*Nenita Crisostomo, R.N.  
Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
Center for Drug Evaluation and Research  
Ph: 301-796-0875*

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NENITA I CRISOSTOMO  
11/29/2016

MEMORANDUM

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

**DATE:** November 23, 2016  
**TO:** Memo to File  
**FROM:** Nenita Crisostomo – Regulatory Health Project Manager  
**SUBJECT:** Information Request, Biostatistics – Bar Plots: Mean Reduction on Nocturic Voids and INTU Overall Impact Scores Bar Graphs

**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo is to document the Information Request sent to Serenity Pharmaceuticals, LLC via email on October 3, 2016, regarding the bar plots of the mean reduction on nocturic voids and INTU overall impact scores.

---

**From:** Crisostomo, Nenita  
**Sent:** Monday, October 03, 2016 2:46 PM  
**To:** Linda Cheng (lcheng@serenitypharma.com)  
**Subject:** RE: NDA 201656 desmopressin: Biostatistics Information Requests - Bar plots

Hi Linda,

As we discussed over the phone, here is the clarification:

Below is the SAS code that defines the categories for Mean Reduction in Nocturic Episodes.

```
if chg>=0 then reduction_c='No Reduction';  
else if 0>chg>-1 then reduction_c='0< to <1';  
else if -2<chg<=-1 then chg_c='1<= to <2';  
else if -3<chg<=-2 then chg_c='2<= to <3';  
else if -4<chg<=-3 then chg_c='3<= to <4';  
else if -5<chg<=-4 then chg_c='4<= to <5';  
else if .<chg<=-5 then chg_c='>=5';
```

The reduction in INTU overall impact score categories are defined in a similar way with respect to “<=” and “<”.

This request for verification is only for the 1.5 mcg group; not needed for the .75 mcg group.

If you need further clarification, please do not hesitate to call.

Thank you,  
Nita

*Nenita Crisostomo, R.N.  
Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
Center for Drug Evaluation and Research  
Ph: 301-796-0875*

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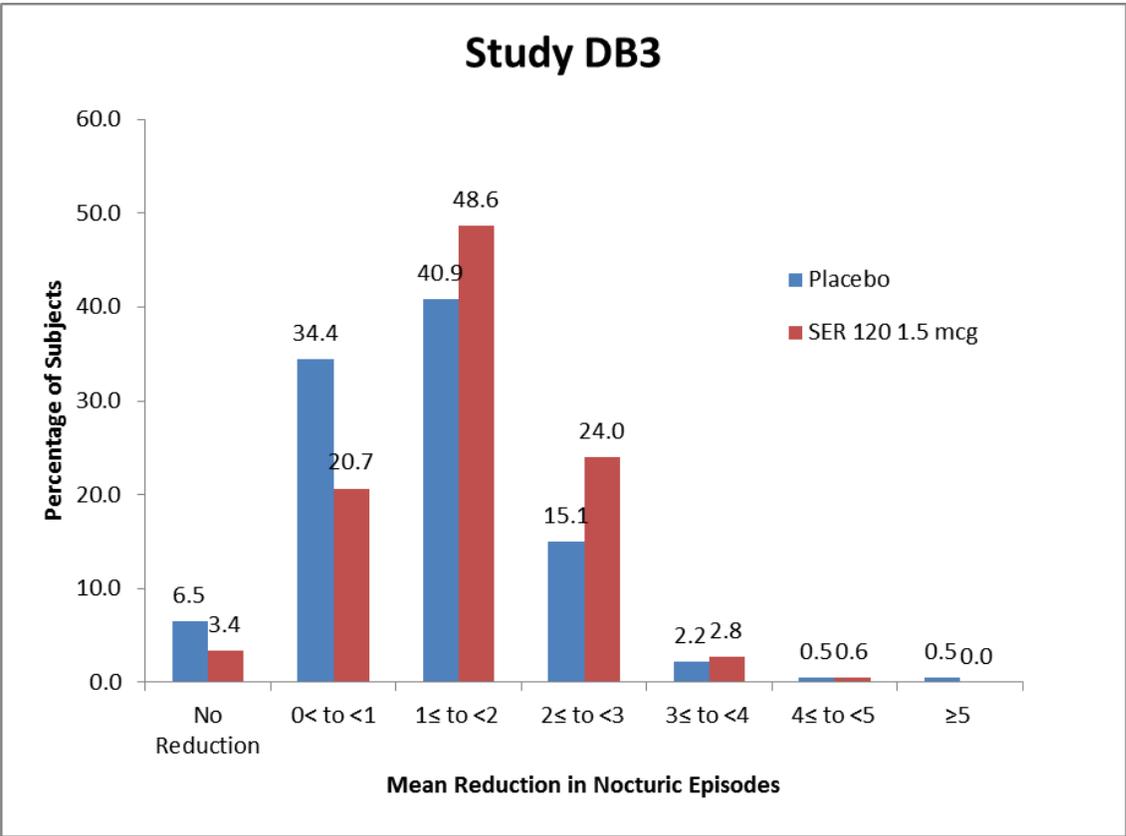
**From:** Crisostomo, Nenita  
**Sent:** Monday, October 03, 2016 9:16 AM  
**To:** Linda Cheng ([lcheng@serenitypharma.com](mailto:lcheng@serenitypharma.com))  
**Subject:** NDA 201656 desmopressin: Biostatistics Information Requests - Bar plots

Hi Linda,

Below is an Information Request from our Biostatistics Team. Please provide your response by or before close of business on October 4, 2016.

- Please verify the numbers on the three bar plots, as attached.

The Y-axis is for the percentage of subjects in each defined category on X-axis by treatment group (ITT population). The X-axis is the categories defined based on the reduction on the nocturic episodes from baseline and reduction (for Study DB3 and DB4) on INTU overall impact score from baseline (Study DB4 only), respectively.



Please feel free to contact me for any questions.

Thank you,  
Nita

*Nenita Crisostomo, R.N.*  
*Regulatory Health Project Manager*  
*Division of Bone, Reproductive and Urologic Products*  
*Center for Drug Evaluation and Research*  
*Ph: 301-796-0875*

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/s/  
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NENITA I CRISOSTOMO  
11/23/2016

MEMORANDUM

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

**DATE:** November 22, 2016  
**TO:** Memo To File  
**FROM:** Nenita Crisostomo, Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
**SUBJECT:** Clinical Information Request: Analysis of Co-primary & Secondary Endpoints for Patients with Nocturnal Polyuria

**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo documents the Clinical Information Request sent to Serenity Pharmaceuticals on October 21, 2016, via email, as follows:

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**From:** Crisostomo, Nenita  
**Sent:** Friday, October 21, 2016 11:51 AM  
**To:** Linda Cheng (lcheng@serenitypharma.com)  
**Subject:** NDA 201656 desmopressin: Clinical Information Request - Analysis of Co-Primary and secondary endpoints

Hi Linda,

Hope all is well with you. It was great meeting you briefly at the recent Advisory Committee Meeting.

Below is a request from the Clinical Team. Please submit your response on/before close of business on Tuesday, October 25, 2016.

- Please provide an analysis of the co-primary and secondary efficacy endpoints for patients who had nocturnal polyuria as defined by the 24-hour urine volume criterion at screening (i.e.>33% of urine produced at night). Use the ITT population.

If you have any questions, please feel free to contact me.

Thank you,  
Nita  
*Nenita Crisostomo, R.N.*  
*Regulatory Health Project Manager*  
*Division of Bone, Reproductive and Urologic Products*  
*Center for Drug Evaluation and Research*  
*Ph: 301-796-0875*

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/s/

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NENITA I CRISOSTOMO  
11/23/2016

MEMORANDUM

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

**DATE:** November 23, 2016  
**TO:** Memo to File  
**FROM:** Nenita Crisostomo – Regulatory Health Project Manager  
**SUBJECT:** Information Request, Biostatistics – CDF Plot of Nocturic Episodes  
**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo is to document the Information Request sent to Serenity Pharmaceuticals, LLC via email on November 2, 2016.

**From:** Crisostomo, Nenita  
**Sent:** Wednesday, November 02, 2016 1:18 PM  
**To:** Linda Cheng (lcheng@serenitypharma.com)  
**Subject:** RE: NDA201656 desmopressin: Biostatistics Information Request - CDF plot of nocturic episodes

Hello Linda,

Thank you so much for your call earlier, inquiring the clarification of the request below.

Yes, it is similar to Figure 2 and 3 in the 8/16 submission. However, the resolution of the graphs in that submission is too low. This needs to be fixed in the current request. Please be reminded that the study population should be restricted to ITT nocturnal polyuria patients.

If you have any further questions, please feel free to contact me.

Best Regards,  
Nita

*Nenita Crisostomo, R.N.  
Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
Center for Drug Evaluation and Research  
Ph: 301-796-0875*

**From:** Crisostomo, Nenita

**Sent:** Wednesday, November 02, 2016 12:40 PM

**To:** Linda Cheng ([licheng@serenitypharma.com](mailto:licheng@serenitypharma.com))

**Subject:** NDA201656 desmopressin: Biostatistics Information Request - CDF plot of nocturic episodes

Hi Linda,

Below is an Information Request from the biostatistics Team:

- Please create a CDF plot for mean change of nocturic episodes per night by treatment groups (placebo, 0.75 mcg and 1.5 mcg) for each study (DB3, DB4). For each study, the CDF plot should have three CDF curves corresponding to three treatment groups.

Please submit your response on or before 12Noon on November 4, 2016.

Thank you so much,

Nita

*Nenita Crisostomo, R.N.*

*Regulatory Health Project Manager*

*Division of Bone, Reproductive and Urologic Products*

*Center for Drug Evaluation and Research*

*Ph: 301-796-0875*

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NENITA I CRISOSTOMO  
11/23/2016



NDA 201656

**GENERAL ADVICE**

Serenity Pharmaceuticals, LLC  
Attention: Seymour Fein, M.D.  
Chief Medical Officer  
120 N. Main Street, Suite 400  
New City, NY 10956

Dear Dr. Fein:

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

We also refer to your September 8, 2016, submission, containing your response to our September 6, 2016, request to provide for higher resolution of the carton and container labels.

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

A. Carton Labeling and Container Label

1. Refer to FDA comments dated November 16, 2016, for the correct presentation of the drug product established name and the strengths. Revise the presentation of the drug product name and its strengths to the following:

Noctiva (desmopressin acetate) Nasal Spray, 0.83 mcg/0.1mL\*

(b) (4)

\*each spray contains 0.1 mL

*and*

Noctiva (desmopressin acetate) Nasal Spray, 1.66 mcg/0.1mL\*

(equivalent to 1.5 mcg/0.1 mL of desmopressin)

\*each spray contains 0.1 mL

2. The drug-identifying information for your product (established name, dosage form, and strength) is difficult to read. This important drug-identifying information is presented on one line, in thin font and closely spaced. We recommend that you re-locate the statement of strength to the next line and increase the spacing between the letters of the established name and dosage form to improve readability.
3. There is a lack of differentiation between the two strengths on the container label and carton labeling. The statements for both strengths have (b) (4) presentations (b) (4) which may result in wrong strength

errors. Revise the (b) (4) so that each strength appears (b) (4) does not overlap with (b) (4) the trade dress. We recommend this revision to improve upon the strength differentiation and to increase prominence of the strength statement.

4. As proposed, the net quantity does not appear on the principal display panel. We recommend you add the net quantity to the principal display panel in accordance with 21 CFR 201.51 and our guidance for industry “Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors”  
<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf>
5. Net content should be stated as “Net content: 3.8g or 30 doses.”
6. As currently proposed, there is a placeholder (“XXXX-XXXX-XX”) where the NDC number should be. NDC numbers are often used as an additional verification prior to drug dispensing in the pharmacy and it is an important safety feature that should be prominently displayed on the labeling. Revise the container label and carton labeling to reflect the actual NDC number to be used for each of the strengths in accordance with 21 CFR 207.35(b)(3)(i).
7. Storage conditions should be revised to reflect the updated Package Insert (see below). The storage conditions can be abbreviated in the immediate container label, if space is limited.

Storage Conditions:

- Before opening, store upright in a refrigerator, 2°C to 8°C (36°F to 46°F); excursion permitted between 0°C and 15°C (32°F and 59°F) [See USP Controlled Cold Temperature].
  - After opening, store upright at room temperature 20°C to 25°C (68°F to 77°F).
  - Discard NOCTIVA 60 days after opening. (See comment 8 below)
8. We note the statement (b) (4) on the container and carton lacks clarity, thus there is a risk that the user will use your product beyond 60 days. Consider revising the statement to read: “Date of first opening \_/ \_/. Discard unused portion 60 days after first opening”. To allow space for this information, consider revising the ‘Usual dosage’ statement on the container and the carton to read “See Package Insert”.

B. Carton Labeling

1. The statement (b) (4) may lead to confusion when preparing to administer the product. Revise the statement to better convey when priming should occur with this product and to minimize user confusion.

2. “(b) (4)” should be revised to “citric acid, anhydrous” and “sodium citrate dihydrate”, respectively.

Please submit the revised container label and carton labeling for our review and comment by November 30, 2016.

If you have any questions, call Nenita Crisostomo, Regulatory Health Project Manager, at (301) 796-0875.

Sincerely,

*{See appended electronic signature page}*

Hylton V. Joffe, M.D., M.M.Sc  
Director  
Division of Bone, Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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HYLTON V JOFFE  
11/23/2016



Serenity Pharmaceuticals, LLC  
Attention: Seymour Fein, M.D.  
Chief Medical Officer  
120 N. Main Street, Suite 400  
New City, NY 10956

Dear Dr. Fein:

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

We also refer to your February 4, 2016, submission containing your proposed Medication Guide. We further refer to your November 7, 2016, submission, containing the proposed protocol for the Human Factors study and the Instructions for Use.

We have completed our review of the above submissions and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA. Please submit the revised Human Factors protocol, Medication Guide and Instructions For Use (IFU) on or before November 30, 2016.

#### Human Factors Study

Address the following prior to conducting your Human Factors validation study.

##### 1. User Groups

- a. Your protocol identifies one user group, which is further divided into age categories, but the use tasks are identical. Your rationale is unclear for specifying the different categories and whether the categorization is representative of the user population. In addition, your protocol does not clearly identify if any naïve users (users that do not have any experience in using nasal sprays) are included in your user group. Given the proposed indications and the associated intended users, we expect that there should be two distinct user groups enrolled in your study. Modify your protocol to include 15 naïve user and 15 experienced users.

##### 2. Training

- a. Your facilitator script includes language which is 'leading' and does not reflect real world scenarios that simulate what happens when a patient picks up a prescription. Specifically, on page 25 ("Introduction") of the facilitator script, the facilitator tells the participant that "the product you will be using is packaged with a label, and includes a

product insert with Instructions for Use. You may refer to the Instructions as often as you wish when using the product”. We expect that participants should be given the product without any advance discussion of the package contents to realistically represent receipt of the product from the pharmacy. Modify your facilitator script to remove leading language and to allow the study participants to interact with the product naturally.

- b. In addition, in your facilitator script (page 25, “Usability Trials”), you refer to individual ‘task sheets,’ which are given to the user during the Human Factors study (see “Appendix C: Test Session Facilitator Script” in the Human Factors protocol submission). We expect that the user would only be given the ‘to-be-marketed’ product (device and its associated labeling including the IFU) in a real world scenario. Therefore, ‘task sheets’ should not be used in the study since they are not part of ‘to be marketed’ labeling for your product.

### 3. Data Collection

- a. Note that results focusing on ‘ease of use’ do not constitute as necessary human factors validation data that the Agency will take into consideration when assessing the effective and safe use of your product. A product that is viewed as ‘easy to use’ does not necessarily convey that it has been used safely or effectively and thus, medical care may be compromised despite the ‘ease of use’ of the product. Therefore, any assessments of ease of use, for example, Sections 9.2 (System Usability Scale) and 9.3 (Ease of Use) are not included in our analysis. Similarly, as defined in Section 10 (Data Analysis), ‘mean SUS scores’ and ‘structured interview’ will not be included in our analysis.
- b. As currently proposed, the tasks listed in Table 3 (page 10, titled “Primary Operating Functions as per IFU”) do not state what specific user actions would constitute success, failure, close call or use difficulty. These details are needed to determine task success, failures, and whether the participants experience any close call and use difficulties while using this product. Ensure that your final protocol includes the definition of task success and failure at the task level.
- c. In addition, task completion accuracy is stated to be “accurate or inaccurate completion of the task with or without assistance” (Section 9.1 Task Completion Accuracy). These definitions do not clearly define the term ‘accurate’ and providing assistance to participants during the trial may compromise the goal of the study which is to see if users can use your product safely and effectively using only the ‘to be marketed’ labeling. We recommend you revise the categories for task completion accuracy (Section 9.1) to read “success”, “failure”, “close call” and “use difficulties”. This information is needed as the basis for data collection so that the study observer correctly categorizes use task performance.
- d. As proposed in Appendix F (page 29, ‘Structured Cognitive Interview’, the questions are broadly stated (“What was difficult about using the . . . product”?) and not focused on specific task performance. While it may be appropriate to collect data on the general use experience from study participants, we ask that you revise your questions to focus on

obtaining the subjective feedback from study participants on any use errors, close calls, or use difficulties that may be observed during the study.

- e. Your protocol does not assess the re-priming of your product. Re-priming is a critical task for the use of your product and is required if the product is not used in three days. We expect the final Human Factors protocol to include the assessment of the performance and knowledge on the steps of re-priming of the nasal spray at the appropriate interval of time.

#### 4. Carton Labeling

We remind you that we provided carton labeling and container label recommendations under a separate letter, however, in addition, we have the following recommendation.

- a. We find the abbreviated IFU on the side panel of the carton labeling as presented to be misleading and may lead to improper dosing. Generally, the FDA does not support affixing instructions from the IFU onto carton labeling if the instructions must be abbreviated as a result of the limited space. Abbreviated instructions may result in ineffective or unsafe use of the product because the user is unlikely to refer to the more detailed and complete instructions packaged with the product. As such, they pose a risk of wrong technique errors. We recommend the abbreviated instructions be removed to decrease risk of medication error.

#### Medication Guide and Instructions for Use

Please see attached labeling marked with our recommendations.

We request that you resubmit labeling (in editable Microsoft Word format) that addresses these issues on or before November 30, 2016.

If you have any questions, please contact Nenita Crisostomo, Regulatory Health Project Manager, at (301) 796-0875.

Sincerely,

*{See appended electronic signature page}*

Hylton V. Joffe, M.D., M.M.Sc.  
Director  
Division of Bone, Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Attachments: Medication Guide  
Instructions for Use

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/s/  
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HYLTON V JOFFE  
11/23/2016

MEMORANDUM

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

**DATE:** November 23, 2016

**TO:** Memo To File

**FROM:** Nenita Crisostomo, Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products

**SUBJECT:** Biostatistical and Clinical Outcomes Assessments Information Request:  
Results of INTU Impact Scores, Coprimary Endpoint Analysis &  
Snapshots

**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo documents the Biostatistical Information and Clinical Outcomes Assessments Information Requests sent to Serenity Pharmaceuticals on October 28, 2016, via email, as follows:

---

**From:** Crisostomo, Nenita

**Sent:** Friday, October 28, 2016 3:07 PM

**To:** Linda Cheng (lcheng@serenitypharma.com)

**Subject:** RE: NDA201656 desmopressin: Biostatistics Information Request: coprimary endpoint analysis & snapshots - nocturnal polyuria

Hello again Linda,

It was our pleasure to have spoken with your Team via teleconference to clarify the requests sent to you earlier today. As we indicated, a third request is forthcoming and is outlined below:

- Provide results for the INTU Overall Impact score, Nighttime Impact domain score, and Daytime Impact domain score for the 0.75mcg, 1.5mcg, and placebo arms for the following two subgroup patient populations:
  - a. Nocturnal Polyuria only (DB4, ITT)
  - b. No Nocturnal Polyuria only (DB4, ITT)

As discussed, for our immediate review, please email to me your responses regarding the INTU and the subgroup analysis, at the latest, by close of business on Tuesday, November 1, 2016, and the snapshots on or before November 4, 2016. These documents may then be submitted officially to the Electronic Document Room.

In your submission, please indicate in the cover letter that the documents being submitted officially remain unchanged from the documents sent via email on November 1 and November 4,

2016. This will allow us to officially review the emailed documents.

Thank you so much,  
Nita

*Nenita Crisostomo, R.N.*  
*Regulatory Health Project Manager*  
*Division of Bone, Reproductive and Urologic Products*  
*Center for Drug Evaluation and Research*  
*Ph: 301-796-0875*

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**From:** Crisostomo, Nenita  
**Sent:** Friday, October 28, 2016 11:35 AM  
**To:** Linda Cheng ([lcheng@serenitypharma.com](mailto:lcheng@serenitypharma.com))  
**Subject:** NDA201656 desmopressin: Biostatistics Information Request: coprimary endpoint analysis & snapshots - nocturnal polyuria

Hello Linda,

Listed below are requests from our Biostatistics review team. Please submit your response on or before close of business on November 1, 2016.

1. Please conduct subgroup analysis for the co-primary efficacy endpoints by age groups, gender and race groups as predefined in the SAP for the nocturnal polyuria ITT population in each study (DB3, DB4).
2. Produce the snapshots for nocturnal polyuria ITT population. Please refer to the 74-day letter request for formatting. The snapshots should be done for each individual study (DB3, DB4) and pooled studies (DB3 and DB4) respectively.

Please contact me if you have any questions.

Have a great weekend!  
--nita

*Nenita Crisostomo, R.N.*  
*Regulatory Health Project Manager*  
*Division of Bone, Reproductive and Urologic Products*  
*Center for Drug Evaluation and Research*  
*Ph: 301-796-0875*

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/s/  
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NENITA I CRISOSTOMO  
11/23/2016

MEMORANDUM

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

**DATE:** November 22, 2016

**TO:** Memo To File

**FROM:** Nenita Crisostomo, Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products

**SUBJECT:** Clinical Information Request: Nocturic Episodes and Etiology

**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo documents the Clinical Information Request sent to Serenity Pharmaceuticals on September 9, 2016, via email, as follows:

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**From:** Crisostomo, Nenita  
**Sent:** Friday, September 09, 2016 10:41 AM  
**To:** Linda Cheng (lcheng@serenitypharma.com)  
**Subject:** NDA 201656 desmopressin: Clinical Information Request - nocturic episodes and etiology

Hi Linda

Listed below are Information Requests from the Clinical Team. Please submit your responses on or before September 13, 2016.

- 1) Can you explain the rationale for requiring a mean of at least 2.16 nocturic episodes per night documented in the 3-day voiding diary each week during screening for study eligibility?
- 2) Can you clarify how investigators determined "probable etiology of nocturia"? Was this based on review of medical records? Or were other assessments used?

If you have any questions, please feel free to contact me.

Thank you so much,  
Nita

*Nenita Crisostomo, R.N.  
Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
Center for Drug Evaluation and Research  
Ph: 301-796-0875*

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NENITA I CRISOSTOMO  
11/22/2016

MEMORANDUM

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

**DATE:** November 22, 2016

**TO:** Memo To File

**FROM:** Nenita Crisostomo, Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products

**SUBJECT:** Clinical Information Request: Time of Sleep

**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo documents the Clinical Information Request sent to Serenity Pharmaceuticals on September 12, 2016, via email, as follows:

---

**From:** Crisostomo, Nenita  
**Sent:** Monday, September 12, 2016 2:26 PM  
**To:** Linda Cheng (lcheng@serenitypharma.com)  
**Subject:** NDA 201656 desmopressin: Clinical Information Request - tinme of sleep

Hi Linda,

Below is a request from the Clinical Team. Please submit your response to the NDA on or before close of business tomorrow, September 13, 2016.

- The voiding diary captures the “time patient went to sleep.” Please confirm that this phrase refers to the time patients went to bed with the intention of falling asleep.

If you have any questions, please feel free to contact me.

Thank you so much,  
Nita

*Nenita Crisostomo, R.N.  
Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
Center for Drug Evaluation and Research  
Ph: 301-796-0875*

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NENITA I CRISOSTOMO  
11/22/2016

MEMORANDUM

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

**DATE:** November 22, 2016

**TO:** Memo To File

**FROM:** Nenita Crisostomo, Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products

**SUBJECT:** Clinical Information Request: Per Patient Basis with Secondary Endpoints

**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo documents the Clinical Information Request sent to Serenity Pharmaceuticals on September 13, 2016, via email, as follows:

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**From:** Crisostomo, Nenita  
**Sent:** Tuesday, September 13, 2016 12:49 AM  
**To:** Linda Cheng (lcheng@serenitypharma.com)  
**Subject:** NDA 201656 desmopressin: Clinical Information Request - "per patient basis" re secondary efficacy endpoints

Hi Linda,

The Clinical Team has the following request. Please submit your response, along with our most recent request (as attached), on or before close of business today, Tuesday, September 13, 2016.

- **Please clarify what is meant by "on a per patient basis" when referring to the secondary efficacy endpoints of percentage of nights with 0 or <1 nocturia episodes.**

Thank you so much for all your help. Have a great night!

Regards,  
Nita

*Nenita Crisostomo, R.N.  
Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
Center for Drug Evaluation and Research  
Ph: 301-796-0875*

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NENITA I CRISOSTOMO  
11/22/2016

MEMORANDUM

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

**DATE:** November 22, 2016

**TO:** Memo To File

**FROM:** Nenita Crisostomo, Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products

**SUBJECT:** Biostatistics Information Request: Missing Data Handling in DB4

**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo documents the Biostatistics Information Request sent to Serenity Pharmaceuticals on September 13, 2016, via email, as follows:

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**From:** Crisostomo, Nenita  
**Sent:** Tuesday, September 13, 2016 10:41 AM  
**To:** Linda Cheng (lcheng@serenitypharma.com)  
**Subject:** NDA201656 desmopressin: Biostatistics Information Request - missing data handling in DB4

Hi Linda,

Below is an Information Request from the Biostatistician. Please email your response to me, while enroute for official submission, by close of business today, Tuesday, September 13, 2016.

In study DB4 SAP, section 7.7 stated "If a subject has at least three post-baseline assessments for at least one time point but is missing sufficient diary data for one or more post-baseline time points the "missing data" will be imputed using the multiple imputation method." Please clarify what "sufficient" exactly means. For one time point, if a subject only had 1 or 2 completed diaries, would that be considered as missing for that time point?

If you have any questions, please feel free to contact me.

Have a great day,  
Nita

*Nenita Crisostomo, R.N.  
Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
Center for Drug Evaluation and Research  
Ph: 301-796-0875*

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NENITA I CRISOSTOMO  
11/22/2016

MEMORANDUM

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

**DATE:** September 12, 2016

**TO:** Memo To File

**FROM:** Nenita Crisostomo, Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products

**SUBJECT:** DMEPA Information Request: Human Factors Risk Analysis

**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo documents the DMEPA Information Request sent to Serenity Pharmaceuticals on September 22, 2016, via email, as follows:

---

**From:** Crisostomo, Nenita  
**Sent:** Thursday, September 22, 2016 5:58 PM  
**To:** Linda Cheng (lcheng@serenitypharma.com)  
**Subject:** NDA 201656 desmopressin - DMEPA Information Request: Human Factors Risk Analysis

Hi Linda,

We refer to your NDA 201656 for Noctiva (desmopressin) nasal spray and also to the teleconference held on April 5, 2016 and your Human Factors Risk Analysis submitted April 29, 2016.

1. Your submission of use-related risk analysis does not provide sufficient data to support your conclusion that no human factors validation study is needed. To proceed with our review, please provide your risk analysis in a tabular format and for each column, please provide the following:
  - a. The use steps that are involved in using your product (based on the task analysis)
  - b. The use errors and task failures that may occur
  - c. The potential negative clinical consequences of use errors and task failures
  - d. The risk mitigation strategies that you employed to reduce the risks you have identified
2. You indicate that your proposed nasal spray shares the same device platform as several other currently approved nasal sprays. However, your April 29, 2016 submission lists only products that are marketed outside of the U.S. Please update the list to include the products that are approved in the U.S.
3. In addition, your submission did not provide adequate justification for why a human factors validation study is not needed beyond your intent to reference the clinical data,

which we had communicated that will not be sufficient during our meeting with you on April 5, 2016. As part of your justification, you may consider describing the similarities/differences of your product user interface, user tasks, use-related risks, and other aspects of the product use as compared to other approved US products (as requested per question 2).

Please provide your response no later than close of business on September 26, 2016.

If you have any questions, please feel free to contact me.

Regards,

Nita

*Nenita Crisostomo, R.N.  
Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
Center for Drug Evaluation and Research  
Ph: 301-796-0875*

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NENITA I CRISOSTOMO  
11/22/2016



NDA 201656

**REVIEW EXTENSION –  
MAJOR AMENDMENT**

Serenity Pharmaceuticals, LLC  
Attention: Seymour Fein, M.D.  
Chief Medical Officer  
120 North Main Street, Suite 400  
New City, NY 10956

Dear Dr. Fein:

Please refer to your New Drug Application (NDA) dated and received February 4, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for desmopressin.

We also refer to your submission dated November 4, 2016, that responds to our October 28, 2016, information request.

Your November 4, 2016, submission provided extensive data focusing on the subgroup of patients in your clinical trials who had nocturnal polyuria at baseline. These are important data for FDA to review because the advisory committee convened on October 19, 2016, recommended limiting the indication for your product to those with nocturnal polyuria. We have determined that this submission is a major amendment to your application. 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 March 4, 2017.

In addition, we acknowledge your submission dated November 7, 2016, for a proposed Human Factor study protocol and revised Instructions for Use. We strongly recommend that you await our comments before implementing the study. Please note that you will need to submit the completed Human Factor study prior to February 1, 2017, in order to allow sufficient time for FDA to consider the findings from the study during this review cycle.

If you have any questions, please call Nenita Crisostomo, Regulatory Health Project Manager, at (301) 796-0875.

Sincerely,

*{See appended electronic signature page}*

Jennifer Mercier  
Chief, Project Management Staff  
Division of Bone, Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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JENNIFER L MERCIER  
11/16/2016

MEMORANDUM

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

**DATE:** September 12, 2016

**TO:** Memo To File

**THROUGH:**

**FROM:** Nenita Crisostomo, Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products

**SUBJECT:** Clinical Information Request: Pooled Etiology (ITT Population)

**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo documents the Clinical Information Request sent to Serenity Pharmaceuticals on August 23, 2016, via email, as follows:

---

**From:** Crisostomo, Nenita  
**Sent:** Tuesday, August 23, 2016 2:37 AM  
**To:** Linda Cheng (lcheng@serenitypharma.com)  
**Cc:** Williamson, Charlene  
**Subject:** NDA 201656 desmopressin: Please complete the Table

Hi Linda,

Please complete the Table below and submit on or before close of business on Thursday, August 25, 2016. Please email Charlene Williamson who is CC'd here and is kindly covering for me while I am on leave until August 26, 2016, so that she can make sure to forward your response to the Clinical Team as soon as possible.

Etiology of Nocturia (studies DB3 and DB4), ITT population

	SER120 1.5 mcg	SER120 0.75 mcg	Placebo
N (%)	439 (100)	448 (100)	446 (100)
Nocturia etiology (investigator assigned)			
>1 etiology			
Nocturnal polyuria only			
OAB only			
BPH only			
Polyuria only			
Nocturnal polyuria (based on 24-hour urine collection during screening)			
Present			
Absent			

Charlene may also be contacted at 301-796-1025.

Thank you so much,  
Nita

*Nenita Crisostomo, R.N.  
Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
Center for Drug Evaluation and Research  
Ph: 301-796-0875*

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NENITA I CRISOSTOMO  
09/12/2016

MEMORANDUM

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

**DATE:** September 12, 2016

**TO:** Memo To File

**FROM:** Nenita Crisostomo, Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products

**SUBJECT:** DMEPA Information Request: Container Labels

**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo documents the Clinical Information Request sent to Serenity Pharmaceuticals on September 6, 2016, via email, as follows:

---

**From:** Crisostomo, Nenita

**Sent:** Tuesday, September 06, 2016 5:56 PM

**To:** Linda Cheng (lcheng@serenitypharma.com)

**Subject:** NDA 201656 Noctiva Container Label and Carton Labeling - DMEPA Information Request

Dear Linda,

The Division of Medication Error Prevention and Analysis (DMEPA) of the Office of Surveillance and Epidemiology have the following comments and request

- **The container label and carton labeling submitted February 4, 2016 for NDA 201656 do not have sufficient resolution for our review. Re-submit the container label and carton labeling such that all of the statements on the principal display panel, side panels, and back panel is clear and reviewable.**
- **Please re-submit the container label and carton labeling on or before 12Noon on September 9, 2016.**

If you have any questions, please feel free to contact me.

Regards,

Nita

*Nenita Crisostomo, R.N.*

*Regulatory Health Project Manager*

*Division of Bone, Reproductive and Urologic Products*

*Center for Drug Evaluation and Research*

*Ph: 301-796-0875*

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NENITA I CRISOSTOMO  
09/12/2016

MEMORANDUM

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

**DATE:** September 1, 2016  
**TO:** Memo to File  
**FROM:** Nenita Crisostomo – Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
**SUBJECT:** Dosing for patients on co-medication of any drug via nasal route

**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo is to document the Information Request sent to Serenity Pharmaceuticals, LLC via email on August 21, 2016, as follows:

**From:** Crisostomo, Nenita  
**Sent:** Sunday, August 21, 2016 12:02 AM  
**To:** Linda Cheng (lcheng@serenitypharma.com)  
**Subject:** NDA 201656 Noctiva (desmopressin): ClinPharm Information Request - Dosing for concomitant use

Hello Linda,

Below are comments and Information Requests from the Clinical Pharmacology Team. Please submit your response on or before close of business on Wednesday, August 24, 2016.

**Concomitant use of other drugs via the nasal route such as nasal decongestants may affect the absorption profile of desmopressin after administration of desmopressin nasal spray. However, you did not propose any precaution or dosing guidance regarding concomitant medication through the nasal cavity.**

**In addition, there is no pharmacokinetic information of desmopressin nasal spray in patients with rhinitis and in a situation when used concomitantly with a drug via the nasal route.**

- **Provide dosing guidance for desmopressin nasal spray in patients who are on co-medication of any drug via nasal route.**
- **Provide data and rationale to support your proposal.**

This information will be helpful for our review to move forward. Please feel free to contact me if you

have any questions.

Thank you very much,  
nita

*Nenita Crisostomo*  
*Regulatory Health Project Manager*  
*Division of Bone, Reproductive and Urologic Products*  
*Center for Drug Evaluation and Research*  
*Ph: 301-796-0875*

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NENITA I CRISOSTOMO  
09/01/2016

MEMORANDUM

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

**DATE:** August 12, 2016  
**TO:** Memo to File  
**FROM:** Nenita Crisostomo – Regulatory Health Project Manager  
**SUBJECT:** Clinical Information Request – ITT versus mITT

**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo is to document the email communications between Serenity Pharmaceuticals, LLC and the Division of Bone, and Reproductive and Urologic Products on August 12, 2016, regarding the focus of ITT versus mITT.

**From:** Linda Cheng [mailto:lcheng@serenitypharma.com]  
**Sent:** Friday, August 12, 2016 12:00 PM  
**To:** Crisostomo, Nenita  
**Subject:** RE: NDA 201656 NOCTIVA (desmopressin) nasal spray: Information Request - ITT

Dear Nita:

Thanks for sending the email concerning focusing on the ITT population. Serenity understands the FDA's interest and reasoning in this matter and agrees to your proposal.

Regards,

Linda

Linda Cheng  
V-P, Project Management  
Serenity Pharmaceuticals, LLC  
120 North Main Street  
Suite 400  
New City, New York 10956

Phone: 845-639-6760, Ext. 11  
Fax: 845-639-1703

[lcheng@serenitypharma.com](mailto:lcheng@serenitypharma.com)

**From:** Crisostomo, Nenita

**Sent:** Friday, August 12, 2016 11:36 AM

**To:** Linda Cheng (lcheng@serenitypharma.com)

**Subject:** NDA 201656 NOCTIVA (desmopressin) nasal spray: Information Request - ITT

Hi Linda,

Below is a request from the Review Team. Please provide your thoughts on the following by the close of business on Tuesday, August 16, 2016.

We are preparing our briefing document and slides for the upcoming advisory committee meeting and would like to propose that both the FDA and sponsor focus only the ITT data for the efficacy endpoints in these materials. We propose that both the FDA and sponsor have the mITT data only in backup slides. We acknowledge that you were previously advised to use the mITT population as the primary statistical population for your key efficacy endpoints but propose focusing only on the ITT analyses for the following reasons:

1. In your phase 3 trials, you randomized all patients to drug vs. placebo, including patients who turned out to be placebo responders. Randomization did not take into account the placebo-responder status. Therefore, we view the ITT as scientifically more valid because the ITT accounts for all patients who were randomized, whereas the mITT is essentially a subgroup analysis of randomized patients.
2. The mITT and ITT results are similar. However, a focus on the mITT analyses (i.e., placebo non-responders) will require discussions about whether and how to identify such patients in clinical practice.
3. We note that your proposed label focuses on the more scientifically valid ITT population.
4. For the reasons noted above, we do not believe there is added value in complicating the briefing document and slide presentation with extensive results from both populations.

Are you agreeable to showing only the ITT data in the advisory committee materials (briefing document and slides) and keeping the mITT data in backup slides? With this approach, we would envision mentioning that the mITT was prespecified as the primary statistical population based upon prior advice of the FDA but that we view the ITT population as more scientifically valid because it uses data from all randomized patients, and therefore will be focusing on the ITT results.

If you have any questions, please feel free to contact me.

Best Regards,  
Nita

*Nenita Crisostomo, R.N.*  
*Regulatory Health Project Manager*

*Division of Bone, Reproductive and Urologic Products  
Center for Drug Evaluation and Research  
Ph: 301-796-0875*

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NENITA I CRISOSTOMO  
08/12/2016

MEMORANDUM

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

**DATE:** August 11, 2016

**TO:** Memo To File

**THROUGH:**

**FROM:** Nenita Crisostomo, Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products

**SUBJECT:** Clinical Information Request: BP, hyponatremia, approvals

**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo documents the Clinical Information Request sent to Serenity Pharmaceuticals on August 11, 2016, via email, as follows:

---

**From:** Crisostomo, Nenita  
**Sent:** Thursday, August 11, 2016 1:40 PM  
**To:** Linda Cheng (lcheng@serenitypharma.com)  
**Subject:** NDA 201656 NOCTIVA (desmopressin) nasal spray: Clinical Information Request

Hi Linda,

Listed below are Information Requests from the Clinical Team. Please submit your response on or before August 17, 2016.

1. Provide a table (similar to Table 28.1 on pages 661-665 of CSR DB4) showing mean blood pressure at baseline and each visit, and change from baseline at each visit for the pooled data from DB3 and DB4 (placebo, 0.75 µg, and 1.5 µg dose). Provide a separate table for systolic blood pressure and diastolic blood pressure.
2. Confirm that no subjects, other than subjects 11S014/DB4 and 42S033/DB4, received treatment for hyponatremia (other than discontinuation of the study drug).
3. Provide a list of the countries outside the US where desmopressin has been approved for nocturia. Include the dosage, route of administration, and patient population (e.g., any restrictions) specified in the approvals. Also include a copy of the prescribing information.

If you have any questions, please feel free to contact me.

Regards,  
Nita

*Nenita Crisostomo, R.N.  
Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
Center for Drug Evaluation and Research  
Ph: 301-796-0875*

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NENITA I CRISOSTOMO  
08/11/2016

MEMORANDUM

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

**DATE:** August 5, 2016  
**TO:** Memo to File  
**FROM:** Nenita Crisostomo – Regulatory Health Project Manager  
**SUBJECT:** Clinical Information Request – INTU

**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo is to document the Clinical Information Request sent to Serenity Pharmaceuticals, LLC via email on August 5, 2016, regarding the INTU PRO.

**From:** Crisostomo, Nenita  
**Sent:** Friday, August 05, 2016 12:48 PM  
**To:** Linda Cheng (lcheng@serenitypharma.com)  
**Subject:** NDA 201656 Noctiva (desmopressin): COA Information Request - INTU

Hi Linda,

We have the following Information Requests from the Clinical Outcomes Assessment Team. Please submit your response by close of business on Thursday, August 11, 2016.

1. For comparison with the pre-specified INTU efficacy results, as a sensitivity analysis, rerun the INTU efficacy analysis in both the mITT and ITT populations separately by recalculating the INTU overall impact score in a different way. First, calculate the mean of all ten transformed INTU items (onto the 0-100 scale) and then use that new INTU overall impact score (i.e., 10-item mean) in the efficacy analysis.
2. Provide the transformed score for each INTU item and provide the SAS program that generates the INTU analysis data set (submitted on 07/05).
3. For INTU items, please provide any missing data patterns for each individual item (e.g., one item is consistently skipped by patients).
4. Provide CDF plots for the three separate INTU scores (overall impact, nighttime impact, and daytime impact) for the 3-day average scores for week 14. There should be three CDF plots with three curves in each plot – each curve corresponding to the 1.5mcg, 0.75mcg, and placebo groups separately).

5. Specify how the mean INTU Overall Impact Score was calculated for the first row of Table 26 (from your INTU evidence dossier dated December 2015) and the CDF plot (from your INTU CDF memo dated October 6, 2015), both shown below. Confirm whether it was or was not calculated in the same way as the INTU Overall Impact Score endpoint in the DB4 trial (i.e., first averaging the nighttime and daytime impact items separately and then taking the overall average of those two average scores).

**Table 26. Interpretation of scores (additional analysis): Change in INTU scores between week 1 and week 2 by response groups**

INTU Score <sup>[1]</sup>	Improved [2,3,4]							
	1-Grade Change in PGI-C (N=193)		2-Grade Change in PGI-C (N=193)		50% Reduction in Nocturic Events		Mean Decrease of One Nocturic Event (N=193)	
	n	Mean Change Score (SD)	n	Mean Change Score (SD)	n	Mean Change Score (SD)	n	Mean Change Score (SD)
INTU Overall Impact Score #1 (average)	63	-3.20 (10.99)	17	-8.58 (12.90)	14	-9.87 (14.00)	38	-5.83 (11.91)
INTU Overall Impact Score #1 (worst)		-3.00 (12.58)		-9.15 (12.50)		-8.98 (14.16)		-6.32 (12.38)
INTU Overall Impact Score #2 (average)		-2.77 (10.15)		-7.99 (12.50)		-8.95 (12.40)		-5.39 (11.48)
INTU Overall Impact Score #2 (worst)		-2.78 (12.00)		-8.60 (12.78)		-7.91 (13.98)		-5.41 (13.08)
INTU Nighttime Score (average)		-4.48 (13.41)		-10.68 (15.26)		-12.57 (17.95)		-7.80 (14.15)
INTU Nighttime Score (Worst)		-4.66 (15.34)		-11.18 (14.99)		-12.78 (18.55)		-9.04 (15.15)

[1] INTU scores are calculated as the average/worst score over week 1 (days 4–8) and week 2 (days 11–13). INTU scores range from 0 to 100, with higher scores associated with greater negative impact of nighttime urination on HRQoL. Overall Impact Score #1: Average of Daytime (items 1–4, 6, 10) and Nighttime Scores (items 5, 7–9), Overall Impact Score #2: Average of Daytime (items 1–4) and Nighttime Scores (items 5–10), INTU Nighttime Score: items 5–10.

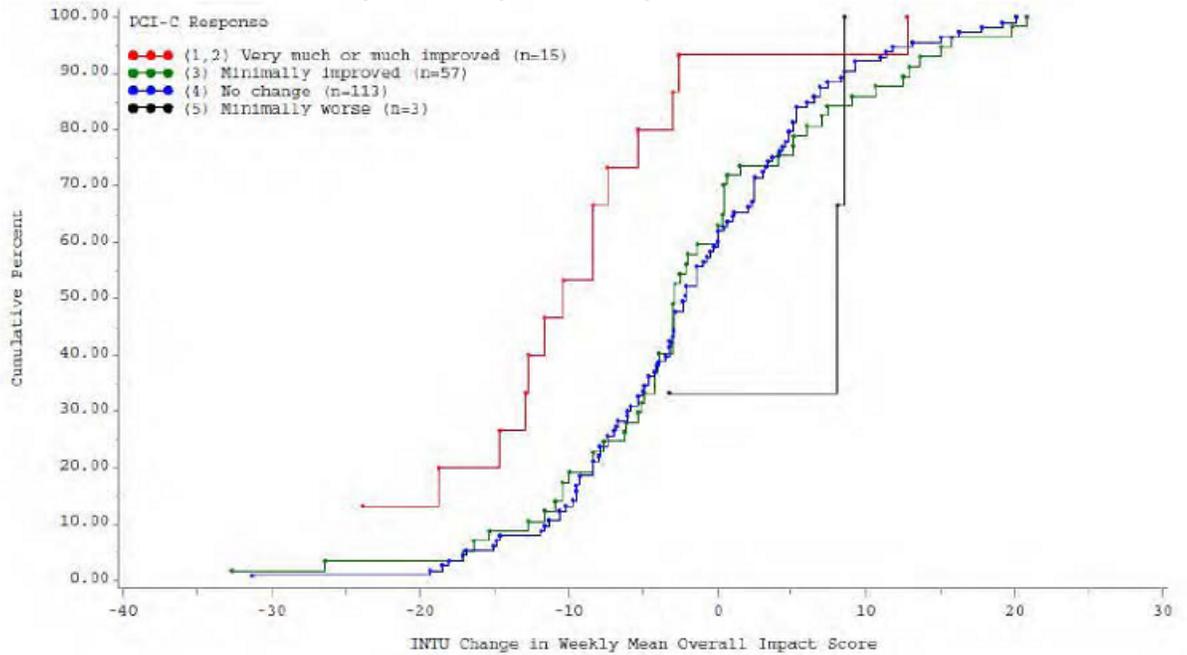
[2] Response “Improvement” defined as a one-grade improvement in PGI-C response from day 8 to day 13.

[3] Response “Improvement” defined as a two-grade improvement in PGI-C response from day 8 to day 13.

[4] Response “Improvement” defined as a 50% reduction in nocturic events between week 1 and week 2 based on the nightly urinary voiding diary.

Source table: Appendix J, Table 4.2.1, 4.2.2, 4.2.3, 4.2.4 (Additional Analysis)

Figure 3. Cumulative Distribution Function for INTU Change in Weekly Mean Overall Impact Score between Week 1 and Week 2 by PGI-C Response at Day 15



Note: INTU scores range from 0-100 with higher scores associated with greater impact of nighttime urination. Negative change scores indicate improvement from week 1.  
 Note: The PGI-C asks patients to rate how their nocturia symptoms have changed over the past 7 days on a Likert-type scale from 1 (Very much improved) to 7 (Very much worse). No patients in the study responded to the 6 (Much worse) or 7 (Very much worse) categories.

Please contact me if you have any questions. Have a great weekend!

Best Regards,  
 Nita

*Nenita Crisostomo, R.N.*  
*Regulatory Health Project Manager*  
*Division of Bone, Reproductive and Urologic Products*  
*Center for Drug Evaluation and Research*  
*Ph: 301-796-0875*

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/s/  
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NENITA I CRISOSTOMO  
08/05/2016

MEMORANDUM

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

**DATE:** July 25, 2016  
**TO:** Memo to File  
**FROM:** Nenita Crisostomo – Regulatory Health Project Manager  
**SUBJECT:** Clinical Information Request – Analysis of Co-Primary Endpoints for ITT  
**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo is to document the Clinical Information Request sent to Serenity Pharmaceuticals, LLC via email on July 25, 2016, regarding co-primary efficacy endpoints for ITT.

**From:** Crisostomo, Nenita  
**Sent:** Monday, July 25, 2016 2:10 PM  
**To:** Linda Cheng (lcheng@serenitypharma.com)  
**Subject:** NDA 201656 NOCTIVA (desmopressin): Clinical Information Request: Analysis of Co-Primary Endpoints for ITT

Hi Linda,

Below is an Information Request from the Clinical Team. Please submit your response on or before the close of business on Monday, August 1, 2016:

- Analyze the co-primary efficacy endpoints according to baseline nocturia severity (using categories of  $\leq 3$  voids per night and  $> 3$  voids per night) for the ITT population (pooled from DB3 and DB4).

If you have any questions, please feel free to contact me.

Best Regards,  
Nita

*Nenita Crisostomo, R.N.  
Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
Center for Drug Evaluation and Research  
Ph: 301-796-0875*

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NENITA I CRISOSTOMO  
08/05/2016

MEMORANDUM

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

**DATE:** July 22, 2016  
**TO:** Memo to File  
**FROM:** Nenita Crisostomo – Regulatory Health Project Manager  
**SUBJECT:** Clinical Information Request – LUTS

**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo is to document the Clinical Information Request sent to Serenity Pharmaceuticals, LLC via email on July 22, 2016, regarding objective criteria for LUTS.

**From:** Crisostomo, Nenita  
**Sent:** Friday, July 22, 2016 12:13 PM  
**To:** Linda Cheng (lcheng@serenitypharma.com)  
**Subject:** NDA 201656 NOCTIVA (desmopressin): Clinical Information Request - LUTS criteria

Hi Linda,

The Clinical Team has the following Information Request. Please provide your response *on or before* close of business on Monday, July 25, 2016. For our immediate review, please email it to me as soon as possible, while enroute for official submission.

- Please clarify whether investigators used objective criteria to qualify a subject as having “severe” LUTS during screening.

Please feel free to contact me if you have any questions.

Best Regards,  
Nita

*Nenita Crisostomo, R.N.  
Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
Center for Drug Evaluation and Research  
Ph: 301-796-0875*

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/s/  
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NENITA I CRISOSTOMO  
08/05/2016

MEMORANDUM

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

DATE: July 11, 2016

TO: Memo To File

THROUGH:

FROM: Nenita Crisostomo, Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products

SUBJECT: Clinical Information Request: Safety - Deaths

APPLICATION/DRUG: NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo documents the Clinical Information Request sent to Serenity Pharmaceuticals on July 11, 2016, via email, as follows:

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**From:** Crisostomo, Nenita  
**Sent:** Monday, July 11, 2016 2:56 PM  
**To:** Linda Cheng (lcheng@serenitypharma.com)  
**Subject:** NDA 201656 Desmopressin Nasal Spray: Clinical Information Request - Deaths

Hi Linda,

The information below is from our Clinical Team. Please submit your response on or before July 18, 2016.

- Provide all available information (e.g., coroner and/or autopsy reports, death certificates, medical records) for the deaths that occurred during the clinical studies of SER120.

If you have any questions, please feel free to contact me.

Regards,  
Nita  
*Nenita Crisostomo, R.N.*  
*Regulatory Health Project Manager*  
*Division of Bone, Reproductive and Urologic Products*  
*Center for Drug Evaluation and Research*  
*Ph: 301-796-0875*

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NENITA I CRISOSTOMO  
07/11/2016

MEMORANDUM

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

**DATE:** July1, 2016  
**TO:** Memo to File  
**FROM:** Nenita Crisostomo – Regulatory Health Project Manager  
**SUBJECT:** Clinical Information Request – Primary Efficacy Variables for ITT from DB3 & DB4

**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo is to document the Information Request sent to Serenity Pharmaceuticals, LLC via email on June 22, 2016, as follows:

**From:** Crisostomo, Nenita  
**Sent:** Wednesday, June 22, 2016 7:59 AM  
**To:** Linda Cheng (lcheng@serenitypharma.com)  
**Subject:** NDA 201656 NOCTIVA (desmopressin): Information Request - Clinical

Hi Linda,

Below is a request from the Clinical Team. Please submit your response on or before close of business on June 30, 2016:

- Provide results of primary efficacy variables for ITT population from studies DB3 and DB4 (pooled) at treatment days 15, 29, 43, 57, 71, and 85.

If you have any questions, please feel free to contact me. Have a great day!

Regards,  
Nita

*Nenita Crisostomo, R.N.  
Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
Center for Drug Evaluation and Research  
Ph: 301-796-0875*

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NENITA I CRISOSTOMO  
07/01/2016

MEMORANDUM

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

**DATE:** July1, 2016  
**TO:** Memo to File  
**FROM:** Nenita Crisostomo – Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
**SUBJECT:** Clinical Outcomes Analysis Request – INTU

**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo is to document the Information Request sent to Serenity Pharmaceuticals, LLC via email on June 24, 2016, as follows:

**From:** Crisostomo, Nenita  
**Sent:** Friday, June 24, 2016 2:45 PM  
**To:** 'Linda Cheng'  
**Subject:** RE: NDA 201656 NOCTIVA desmopressin: Information Request - COA

Hi Linda,

These Information Requests serve as clarification to our original requests sent to you on June 20, 2016, and should replace our original requests.

Please submit your response on or before 12 Noon on July 1, 2016.

1. For Study DB4, in addition to the submitted INTU analysis data, provide an updated analysis dataset ADINTU.xpt which should include the following:
  - Daily INTU total score, nighttime domain score, and daytime domain score for each of three days by Week, i.e. for Week 8 and Week 14 respectively.
  - Average INTU total score, nighttime domain score, and daytime domain score over the three days by Week, i.e. for Week 8 and Week 14 respectively.
2. Provide INTU psychometric evaluation analyses (i.e., reliability, validity, ability to detect change) using DB4 phase 3 trial data in order to allow comparison with the INTU measurement properties you obtained in your 2-week observational study (that you have already submitted as part of your INTU PRO evidence dossier).

3. Provide CDF plots using the TBS anchor scale for the three separate INTU scores (total, nighttime, and daytime) for the 3-day average scores for week 14. There should be three CDF plots for each total and domain scores.

Thank you,  
Nita

*Nenita Crisostomo, R.N.  
Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
Center for Drug Evaluation and Research  
Ph: 301-796-0875*

**From:** Linda Cheng [<mailto:lcheng@serenitypharma.com>]  
**Sent:** Monday, June 20, 2016 12:05 PM  
**To:** Crisostomo, Nenita  
**Subject:** RE: NDA 201656 NOCTIVA desmopressin: Information Request - COA

Dear Nita:

Per our discussion this morning, attached is a copy of the comparative document which should capture the request from Questions # 1 and 2. These data were submitted in NDA 201656 under Section 1.11.3. Please confirm that these are the data that the reviewer is requesting and if not, kindly clarify the request and we will do the analysis per request. As discussed, we should be able to submit the new analysis by June 28, 2016.

Also attached in this email is a copy of the training material to the study sites for diary and INTU collection as well as an exact copy of the INTU provided to patients.

Please let us know if the Division would like us to submit documents from Questions # 3 and 4 as an amendment to the NDA.

Regards,

Linda

Linda Cheng  
V-P, Project Management  
Serenity Pharmaceuticals, LLC  
120 North Main Street  
Suite 400  
New City, New York 10956

Phone: 845-639-6760, Ext. 11  
Fax: 845-639-1703

[lcheng@serenitypharma.com](mailto:lcheng@serenitypharma.com)

**From:** Crisostomo, Nenita [<mailto:Nenita.Crisostomo@fda.hhs.gov>]  
**Sent:** Monday, June 20, 2016 10:12 AM  
**To:** Linda Cheng  
**Subject:** NDA 201656 NOCTIVA desmopressin: Information Request - COA

Hi Linda,

As soon as possible, or at the latest, by close of business on June 23, 2016, please submit the following:

Submit the following information from the DB4 phase 3 trial:

1. Psychometric analysis report including measurement properties of the INTU (reliability, validity, ability to detect change, etc.) based on the longitudinal DB4 data. The psychometric analysis report included in the Evidence Dossier is a cross-sectional analysis of psychometric properties specific to the 2-week observational, non-interventional study. We consider these findings to be preliminary psychometric data and would like you to confirm the cross-sectional analyses with longitudinal analyses.
2. Anchor-based analyses conducted with DB4 data to confirm responder definitions (clinically meaningful change from baseline) found in the observational study for the INTU total score, nighttime score, and daytime score. Submit data using the TBS as the anchor scale, and submit only relevant cumulative distribution function (CDF) plots that provide support for the responder definitions you are proposing
3. Any INTU training materials used in the phase 3 trial for the site, investigator, and patient
4. Exact copies of the INTU questionnaire as was administered to patients in the DB4 trial (e.g., paper version, electronic screen shots, etc.)

If you have any questions, please feel free to contact me.

Regards,  
Nita

*Nenita Crisostomo, R.N.  
Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
Center for Drug Evaluation and Research  
Ph: 301-796-0875*

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/s/  
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NENITA I CRISOSTOMO  
07/01/2016

MEMORANDUM

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

**DATE:** July 1, 2016

**TO:** Memo to File

**FROM:** Nenita Crisostomo – Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products

**SUBJECT:** Clinical Information Request – Treatment duration, patient disposition and dose escalation

**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo is to document the Information Request sent to Serenity Pharmaceuticals, LLC via email on June 28, 2016.

**From:** Crisostomo, Nenita [<mailto:Nenita.Crisostomo@fda.hhs.gov>]  
**Sent:** Tuesday, June 28, 2016 10:02 AM  
**To:** Linda Cheng  
**Subject:** NDA 201656 NOCTIVA: Information Request - Clinical

Hi Linda,

Below are requests from the Clinical Team. Please submit your response as soon as possible, or by close of business on July 6, 2016.

- 1) For study DB3-201101-A2, did any patients complete and exit the trial prior to initiation of Amendment #2.1 or Amendment #2.2? i.e., their discontinuation was not premature, but was consistent with protocol duration at that time.**

2) Please provide a table of patient disposition according to Group in study 201101a2:

	Group 1	Group 2	Group 3
<b>N completing 122 week maintenance phase</b>			
<b>Primary reason for early discontinuation (before 122 weeks):</b>			
<b>Completed 30 weeks and exited study per protocol, prior to amendment 2.1</b>			
<b>Completed 78 weeks and exited study per protocol, prior to amendment 2.2</b>			
<b>Lack of efficacy</b>			
<b>Adverse event</b>			
<b>Withdrawal of consent</b>			
<b>Lost to follow-up</b>			

3) Please explain Table 3 (Summary of Patient Disposition) in the 201101a2 study report found on page 63 of the study. The difference between “1.5 mcg dose and...” and “1.0/1.5 mcg dose and...” is unclear. It is the reviewer’s understanding that all subjects except one initiated treatment with 1.0 mcg SER120 with dose titration to 1.5 mcg possible at Day 15 of follow-up.

4) Also, please clarify how the decision to dose escalate to 1.5 mcg was reached – was the decision based on objective data? for example, lack of response according to diary data?

Thank you,  
Nita

*Nenita Crisostomo, R.N.*  
*Regulatory Health Project Manager*  
*Division of Bone, Reproductive and Urologic Products*  
*Center for Drug Evaluation and Research*  
*Ph: 301-796-0875*

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NENITA I CRISOSTOMO  
07/01/2016

MEMORANDUM

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

**DATE:** June 25, 2016  
**TO:** Memo to File  
**FROM:** Nenita Crisostomo – Regulatory Health Project Manager  
**SUBJECT:** Clinical Information Request – Analysis of Primary and Secondary Endpoints  
**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo is to document the Information Request sent to Serenity Pharmaceuticals, LLC via email on June 20, 2016, as follows:

**From:** Crisostomo, Nenita  
**Sent:** Monday, June 20, 2016 5:23 PM  
**To:** Linda Cheng (lcheng@serenitypharma.com)  
**Subject:** NDA 201656 NOCTIVA: Information Request - Clinical

Hi Linda,

By or before close of business on June 28, 2016, please send an analysis of primary and secondary efficacy endpoints from data pooled from the two phase 3 trials DB3 and DB4 according to the presence or absence of nocturnal polyuria at baseline (nocturnal polyuria as diagnosed by 24-hour urine collection at baseline) (see Table below).

	SER120 15 mcg/mL	SER120 7.5 mcg/mL	placebo
--	------------------	-------------------	---------

<b>Nocturnal polyuria present based on 24-hour urine collection at screening</b>			
Primary efficacy endpoint #1			
Primary efficacy endpoint #2			
Secondary efficacy endpoints...			
<b>Nocturnal polyuria absent based on 24-hour urine collection at screening</b>			
Primary efficacy endpoint #1			
Primary efficacy endpoint #2			
Secondary efficacy endpoints...			

Best Regards,  
Nita

*Nenita Crisostomo, R.N.*  
*Regulatory Health Project Manager*  
*Division of Bone, Reproductive and Urologic Products*  
*Center for Drug Evaluation and Research*  
*Ph: 301-796-0875*

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/s/  
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NENITA I CRISOSTOMO  
06/25/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

NDA 201656

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Serenity Pharmaceuticals, LLC  
120 North Main Street  
Suite 400  
New City, New York 10956

ATTENTION: Seymour Fein, M.D.  
Chief Medical Officer

Dear Dr. Fein:

Please refer to your New Drug Application (NDA) dated and received February 4, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Desmopressin, Nasal Spray, 7.5 mcg/mL and 15 mcg/mL.

We also refer to your correspondence, dated and received March 14, 2016, requesting review of your proposed proprietary name, Noctiva.

We have completed our review of the proposed proprietary name, Noctiva and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your March 14, 2016, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names  
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,  
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Shawnetta Jackson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4952. For any other information regarding this application, contact Nenita Crisostomo, Regulatory Project Manager in the Office of New Drugs, at (301) 796-0875.

Sincerely,

*{See appended electronic signature page}*

Todd Bridges, 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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TODD D BRIDGES  
05/27/2016

MEMORANDUM

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

**DATE:** May 5, 2016  
**TO:** Memo to File  
**FROM:** Nenita Crisostomo – Regulatory Health Project Manager  
**SUBJECT:** Information Request, Biostatistics – Placebo Lead-In Period  
**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo is to document the Information Request sent to Serenity Pharmaceuticals, LLC via email on April 27, 2016, regarding dataset of the mean nocturic episodes in the placebo lead-in period.

---

**From:** Crisostomo, Nenita  
**Sent:** Wednesday, April 27, 2016 12:03 PM  
**To:** Linda Cheng (lcheng@serenitypharma.com)  
**Cc:** Maria Cheng (mcheng@serenitypharma.com); Seymour Fein (sfein@serenitypharma.com)  
**Subject:** NDA201656 NOCTIVA (desmopressin): Statistical Information Request

Hello Linda,

Below is another Information Request from our Biostatistics Team. Please submit the information on or before May 2, 2016.

- ***Please provide a dataset of the mean nocturic episodes in the placebo lead-in period by subject for ITT population. This applies to both studies DB3 and DB4.***

Thank you,

Nita

*Nenita Crisostomo, R.N.  
Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
Center for Drug Evaluation and Research  
Ph: 301-796-0875*

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NENITA I CRISOSTOMO  
05/05/2016

MEMORANDUM

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

**DATE:** May 5, 2016  
**TO:** Memo to File  
**FROM:** Nenita Crisostomo – Regulatory Health Project Manager  
**SUBJECT:** Information Request, Biostatistics – Placebo Lead-In Period  
**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo is to document the Information Request sent to Serenity Pharmaceuticals, LLC via email on April 27, 2016, regarding dataset of the mean nocturic episodes in the placebo lead-in period.

---

**From:** Crisostomo, Nenita  
**Sent:** Wednesday, April 27, 2016 12:03 PM  
**To:** Linda Cheng (lcheng@serenitypharma.com)  
**Cc:** Maria Cheng (mcheng@serenitypharma.com); Seymour Fein (sfein@serenitypharma.com)  
**Subject:** NDA201656 NOCTIVA (desmopressin): Statistical Information Request

Hello Linda,

Below is another Information Request from our Biostatistics Team. Please submit the information on or before May 2, 2016.

- ***Please provide a dataset of the mean nocturic episodes in the placebo lead-in period by subject for ITT population. This applies to both studies DB3 and DB4.***

Thank you,

Nita

*Nenita Crisostomo, R.N.  
Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
Center for Drug Evaluation and Research  
Ph: 301-796-0875*

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NENITA I CRISOSTOMO  
05/05/2016

MEMORANDUM

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

**DATE:** May 5, 2016  
**TO:** Memo to File  
**FROM:** Nenita Crisostomo – Regulatory Health Project Manager  
**SUBJECT:** Clinical Information Request – Diagnosis of nocturnal polyuria  
**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo is to document the Information Request sent to Serenity Pharmaceuticals, LLC via email on May 3, 2016, regarding the diagnosis of nocturnal polyuria.

**From:** Crisostomo, Nenita  
**Sent:** Tuesday, May 03, 2016 4:27 PM  
**To:** Linda Cheng (lcheng@serenitypharma.com)  
**Cc:** Maria Cheng (mcheng@serenitypharma.com); Seymour Fein (sfein@serenitypharma.com)  
**Subject:** NDA 201656 desmopressin: Clinical Information Request - Diagnosis

Hi Linda,

The request below is from the Clinical Team:

- Clarify how you made the diagnosis of nocturnal polyuria.
- Specifically, did you calculate volume of urine excreted at night from the 24-hour fractionated urine collected during screening to make the determination that etiology of nocturia was nocturnal polyuria?

Please submit your response to the NDA on or before close of business of May 5, 2016. If you have any questions, please feel free to contact me.

Best Regards,  
--nita

*Nenita Crisostomo, R.N.  
Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
Center for Drug Evaluation and Research  
Ph: 301-796-0875*

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NENITA I CRISOSTOMO  
05/06/2016

MEMORANDUM

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

**DATE:** April 25, 2016  
**TO:** Memo to File  
**FROM:** Nenita Crisostomo – Regulatory Health Project Manager  
**SUBJECT:** Information Request, Biostatistics – Type I Error Control

**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo is to document the Information Request sent to Serenity Pharmaceuticals, LLC via email on April 25, 2016, regarding the Type I error control.

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**From:** Crisostomo, Nenita  
**Sent:** Monday, April 25, 2016 3:24 PM  
**To:** Linda Cheng (lcheng@serenitypharma.com)  
**Cc:** Seymour Fein (sfein@serenitypharma.com); Maria Cheng (mcheng@serenitypharma.com)  
**Subject:** NDA201656 NOCTIVA (desmopressin): Statistical Information Request

Hi Linda,

Below is an Information Request from the Biostatistics Team. Please submit your response on or before close of business on April 28, 2016.

Your overall type I error control is not clear to the reviewer. For example, if the highest dose showed statistical significance on the first primary endpoint using mITT population, was your next test conducted on the next highest dose on the same endpoint using mITT population OR on the highest dose using ITT population? Please clarify the exact order of the testing with respect to the three doses and two analysis populations (mITT and ITT).

If you have any questions, please feel free to contact me.

Best Regards,  
Nita

*Nenita Crisostomo, R.N.  
Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
Center for Drug Evaluation and Research  
Ph: 301-796-0875*

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/s/  
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NENITA I CRISOSTOMO  
04/25/2016



NDA 201656

**FILING COMMUNICATION -  
FILING REVIEW ISSUES IDENTIFIED**

Serenity Pharmaceuticals, LLC  
Attention: Seymour Fein, M.D.  
Chief Medical Officer  
120 N. Main Street, Suite 400  
New City, NY 10956

Dear Dr. Fein:

Please refer to your New Drug Application (NDA) dated and received February 4, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for NOCTIVA™ (desmopressin) nasal spray, 7.5 mcg/mL and 15 mcg/mL.

We also refer to your amendments dated February 19, March 14 and 21, and April 12, 2016.

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 December 4, 2016.

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, mid-cycle, 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 November 2, 2016. This date conforms to the 21<sup>st</sup> Century Review timeline for your application.

We acknowledge receipt of your October 7, 2015, submission to your corresponding IND (076667). The objective of that submission was to address concerns raised by FDA at the August 18, 2015, Type C Guidance meeting regarding the apparent benefit/risk profile of your product. Specifically, the FDA noted that preliminary review of the data in the briefing package for your August 18, 2015, meeting suggested a similar benefit/risk profile to that of Nocdurna,

which an advisory committee recently found to be unfavorable. You did not await our response to your October 7, 2015, submission before submitting your NDA. We also note that you did not have a Pre-NDA meeting prior to NDA submission.

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

### Clinical

- 1) Whether you have provided adequate evidence of clinical benefit with your product is an important review issue. The absolute reduction in nocturia frequency with your drug compared to placebo appears small. In addition, with respect to the responder co-primary efficacy endpoint, the 7.5 mcg dose was statistically significant only in the modified intent-to-treat (mITT) population of study DB4.

Whether the INTU instrument provides adequate support that the treatment effects are clinically meaningful will be an important review issue. We note that you failed to show a statistically significant difference in the INTU total score in the mITT population (for the 1.5 mcg dose) and in either the mITT or intent-to-treat (ITT) population (for the 0.75 mcg dose). The clinical meaningfulness of the magnitude of the difference between treatment and placebo groups in the INTU total score and nighttime and daytime domain scores will also be a review issue.

- 2) The mITT population was the primary efficacy analysis population for both trials. The discrepant efficacy results for the mITT and ITT populations will be a review issue.
- 3) Nocturia is a symptom of many diverse conditions. We have concerns with your proposed indication of treatment of nocturia, which is broad and does not take into consideration the underlying cause of the nocturia.
- 4) The effect of gender and underlying etiology of nocturia on product efficacy will be review issues.
- 5) You propose a target patient population of adults (b) (4). However, your pivotal trials only enrolled patients 50 years of age or older. These trials do not appear to support use of your product in adults under 50 years of age.
- 6) Hyponatremia appears to be an important risk with your product. The incidence and severity of hyponatremia will be a review issue.

### Clinical Pharmacology

- 1) The appropriateness of your proposed dosing regimen for the elderly population will be a review issue.
- 2) The proposed regimen for patients with renal impairment including the contraindication for patients with a calculated glomerular filtration rate (GFR) below 50 mL/min/1.73 m<sup>2</sup> will be a review issue.
- 3) You propose that the initial dose of 0.75 mcg can be titrated to 1.5 mcg based on individual patient efficacy and tolerability. However, there is no specific guidance on when dose escalation is warranted. In addition, the pivotal phase 3 studies (Study DB3 and DB4) used

fixed doses of study medication and did not use a titration scheme. This will be a review issue.

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

We also have the following requests for information.

#### Biostatistics

- 1) In the study protocol and statistical analysis plan for DB3, you pre-specified that the “missing data will be imputed as being equal to the data that are available”. Clarify what this means.
- 2) Submit the statistical programs for conducting the efficacy analyses.
- 3) Provide analysis results for efficacy endpoints by race for DB3 and DB4.

#### Environmental Assessment:

You submitted a claim of categorical exclusion from an environmental assessment, but did not provide an explicit statement that, to your knowledge, no extraordinary circumstances exist, as required by 21 CFR 25.15 and described in 21 CFR 25.21. This statement is required if an exclusion will continue to be claimed.

#### Engineering:

- 1) Within the NDA, we are unable to locate the biocompatibility test reports and results on the final finished mechanical multi-dose nasal pump spray. Submit this information promptly if it is not already included in the NDA. If this information is included in the NDA, identify its location. If you are relying on data in a master file, identify the master file number and location of the data.
- 2) Clarify if the (b) (4) mechanical multi-dose nasal pump spray has been used in other combination product applications. If so, identify the names of the marketed products.

#### Manufacturing Process – Combination Product:

Combination products are subject to 21 CFR Part 4 *Current Good Manufacturing Practice Requirements for Combination Products* accessible at <https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products>

- 1) Provide a detailed summary of your company’s management structure with executive responsibility for staff who manage, perform, and assess work affecting quality of the product and related controls to ensure that the firm’s quality policies are appropriately implemented and followed and the product is appropriately designed and manufactured in

conformance with Current Good Manufacturing Practice (CGMP) requirements, including quality system requirements as per 21 CFR 820.20.

- 2) Provide a detailed summary of your company's design control system as per 21 CFR 820.30 for the device constituent part and combination product. Although you provided some design information, it does not appear that all the items associated with design controls were addressed. The design control information should include initial design, planning and development, design input, design output, design review, design transfer, design verification, design validation that meets the proposed intended use of the final combination product, design changes, and design history file. For changes made to the device constituent part of the combination product, the impact of the design changes on the overall combination product performance should be considered and documented. All the design control activities must be documented in the Design History File (DHF) and subjected for design reviews. In addition, provide the location of the DHF for the facility inspection determination.
- 3) Provide a detailed summary of information pertaining to the Purchasing Control as per 21 CFR 820.50 to demonstrate controls and documentation for components, products, or services (example sterilization) received at the sponsor's facility for use in the manufacture of the combination product. The summary should include the applicant's evaluation process of their suppliers that meet the manufacturing acceptance criteria of the combination product specifications. Notification of changes by the suppliers should be considered in your Purchasing/Supplier agreement as changes to incoming specification can impact the safety and effectiveness of the final combination product. If you have considered supplier evaluation as per 21 CFR 211.84 Testing and approval or rejection of components, drug product containers, and closures, this information may be leveraged to augment the requirements for 21 CFR 820.50 and 21 CFR Part 4.
- 4) Provide a detailed summary of information related to Corrective and Preventive Actions (CAPA) as per the requirement of 21 CFR 820.100. CAPA procedures are used to determine the cause of problems and non-conformances, and the appropriate measures used to correct and prevent such problems and non-conformances from recurring. The CAPA system must account for investigations into failures in the device constituent. CAPA activities for the analysis of sources of quality data to identify existing and potential cause of nonconformances, related investigations, and actions considered to correct and prevent recurrences of problems and non-conformances, including the verification or validation of the actions should be documented under the firm's CAPA System as described in 21 CFR 820.100.

Microbiology:

- 1) On page 11 of the proposed labeling, the following storage instructions (PATIENT) are provided: (b) (4) ". We note that the drug product formulation does not contain an antimicrobial preservative and that the drug product is intended to deliver multiple doses over a (b) (4) month period. Provide data demonstrating that the drug product meets USP<51> acceptance criteria for a category 2 product over the duration of the in-use period.
- 2) Non-sterile aqueous drug products may potentially be contaminated with organisms in the Burkholderia cepacia complex (BCC). BCC strains have a well-documented ability to

ferment a wide variety of substrates and are known to proliferate in the presence of many traditional preservative systems. Thus, despite the presence of otherwise adequate preservative systems, BCC strains can survive and even proliferate in product during storage. For a recent review of FDA's perspective on BCC please see PDA J Pharm Sci Tech 2011; 65(5): 535-43.

In order to control for the presence of BCC in your product you should consider the following:

- a. Identify potential sources for introduction of BCC during the manufacturing process and describe the steps to minimize the risk of BCC organisms in the final drug product. We recommend that potential sources are examined and sampled as process controls. These may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria.
- b. Provide test methods and acceptance criteria to demonstrate the drug product is free of BCC. Your test method should be validated and a discussion of those methods should be provided. Test method validation should address multiple strains of the species and cells should be acclimated to the conditions in the manufacturing environment (e.g., temperature) before testing.

As there are currently no compendial methods for detection of BCC, we have provided suggestions for a potential validation approach and some points to consider when designing your validation studies. However, any validated method capable of detecting BCC organisms would be adequate. It is currently sufficient to precondition representative strain(s) of BCC in water and/or your drug product without preservatives to demonstrate that your proposed method is capable of detecting small numbers of BCC. Your submission should describe the preconditioning step (time, temperature, and solution(s) used), the total number of inoculated organisms, and the detailed test method to include growth medium and incubation conditions. It is essential that sufficient preconditioning of the organisms occurs during these method validation studies to insure that the proposed recovery methods are adequate to recover organisms potentially present in the environment.

For more information, we refer you to *Envir Microbiol* 2011; 13(1):1-12 and *J. Appl Microbiol* 1997; 83(3):322-6.

- 3) Reference is made to the FDA Response to Question 7 for the March 10, 2014, Meeting Minutes for the associated IND 076667, where it was stated that the microbial enumeration test would be acceptable for the drug product at release and shelf-life "in the event you choose not to assess microbiological quality using the USP<71>sterility test". Furthermore, the specification provided in Section P.5.1 of your NDA indicates that the sterility test will be performed for release and stability; however, the stability data provided in Section P.8.3, includes microbial enumeration testing performed as per USP<61> and <62>. Thus, confirm that, as stated in Section P.5.1, the sterility test is the method that will be used to test the microbial quality of the drug product during its shelf-life. Alternatively, provide a revised stability protocol indicating the preferred method to assess the microbiological attributes of the drug product at shelf-life.

Drug Product:

- 1) Provide a table for all drug product batches used for the clinical studies with their corresponding sources of the drug substance and product (lots and batches), manufacture scales, container closure systems including the mechanical multi-dose nasal spray devices. In addition, specify the drug product formulations and strengths. Particularly, specify if there is a difference in those properties from the proposed to-be-marketed products.
- 2) Provide a tabular summary with the list of time points and tests conducted for the drug product batches under the storage condition of both proposed long term and “Arm Switching Stability”.
- 3) You indicated that the proposed to-be-marketed drug product formulation is an oil-in-water emulsion. Clarify whether there is a phase separation of the final formulation at drug release and by the proposed end of shelf life under the long term proposed refrigerated storage condition.
- 4) You propose for the patient to store the drug product at room temperature 20°C to 25°C (68°F to 77°F) and discard 60 days after opening. Provide in-use stability data according to Instructions for Use (IFU) to ensure the drug product strength, purity and quality. This applies to both drug product formulation and pump performance.
- 5) Provide drug product samples (eight sets for each strength) for review.

Non-Clinical Pharmacology/Toxicology:

- 1) Clarify if you intend to rely on any published literature to satisfy nonclinical requirements. If you do, provide a list tabulating the published literature with the corresponding specific nonclinical requirement.
- 2) Two toxicology studies with CPD are included in Module 4.2.3.7.7. (the 6 month rat study conducted by (b) (4), and the 28 day rat nasal study conducted by (b) (4) for which a letter of authorization appears not to be available. Clarify the right of reference for these studies and submit a letter of authorization.

Clinical Pharmacology:

- 1) Provide the dose-response relationship analysis for efficacy and safety supporting your proposed regimen. Include the dataset(s) and analysis scripts used for the dose-response analyses.
- 2) Also include hyponatremia safety analyses based on other age cut-off points such as 75 years or older.
- 3) Provide supporting information for safe use of your product in patients with rhinitis.
- 4) You submitted the Canadian product monographs for desmopressin products and one published article on *in vitro* metabolism of vasopressin to support that your product does not have any effect on nine cytochrome P450 enzymes. However, the submitted information does not contain any direct evidence to support the lack of interaction potential. Submit the relevant information.

Division of Medication Error and Prevention Analysis:

- 1) Submit a comprehensive use-related risk analysis and justification for not conducting a human factors validation study.

Clinical:

- 1) Your product is intended to increase water resorption from the kidney at night. It is unclear whether this will in turn lead to an increase in water delivery to the bladder the next morning after the effects of your medication wane. If this were to occur, the increase in water delivery could potentially exacerbate symptoms of the underlying condition, such as incontinence, urgency, or frequency in patients with overactive bladder, and urinary retention in patients with benign prostatic hyperplasia. Are there any data that address this concern?

Other:

- 1) As part of the FDA Safety and Innovation Act (FDASIA) of 2012, information on demographic subgroups in clinical trials for newly-approved drugs and biologics will be made publicly available on [www.fda.gov/drugtrialssnapshot](http://www.fda.gov/drugtrialssnapshot).

The website will include information on study design, results of efficacy and safety studies, and whether there were any differences in efficacy and side effects within sex, race, and age subgroups. The website is not intended to replace or replicate the package insert, and will contain the following:

- Information written in consumer-friendly language
- “MORE INFORMATION” sections that provide more technical, data-heavy information
- Information that focuses on subgroup data and analyses
- Links to the package insert for the product and to the FDA reviews at [Drugs@FDA](mailto:Drugs@FDA)

To ensure we have the needed information in a readily accessible format in the event that your drug is approved, we request that you populate the following tables.

**Table 1. Baseline Demographics, Pooled DB3 and BD4**

Demographic Parameters	Treatment Group(s)				Total (N=XX) n (%)
	7.5 µg/mL (N=XX) n (%)*	10 µg/mL (N=XX) n (%)*	15 µg/mL (N=XX) n (%)*	Placebo (N=XX) n (%)*	
<b>Sex</b>					
Male					
Female					
<b>Age</b>					
Mean years (SD)					
Median (years)					
Min, Max (years)					
<b>Age Group</b>					
<65 years					
≥65 years					
<b>Race</b>					
White					
Black or African American					
Asian					
Hispanic					
Other					

Source:

\*Percentages are calculated based on the total number of subjects in the respective arm.

**Table 2 Subgroup Analysis of Each Co-primary Endpoint, Pooled DB3 and BD4**

Subgroup	7.5 µg/mL	10 µg/mL	15 µg/mL
	(N=xx)	(N=xx)	(N=xx)
<b>Endpoint</b>			
<b>Sex</b>			
Male	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Female	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
<b>Age Group</b>			
<65 years	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
≥65 years	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
<b>Race</b>			
White	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Black or African American	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Asian	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Hispanic	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Other	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)

Source:

xx (xx, xx) is the treatment effect vs. placebo and the 95% CI.

**Table 3 Subgroup Analysis of Adverse Events, Pooled DB3 and BD4**

Subgroup	7.5 µg/mL (N=xxx)		10 µg/mL (N=xxx)		15 µg/mL (N=xxx)		placebo (N=xxx)	
	x (%)**	Total, n	x (%)**	Total, n	x (%)**	Total, n	x (%)**	Total, n
<b>Any TEAEs</b>								
<b>Sex</b>								
Male								
Female								
<b>Age Group</b>								
<65 years								
≥65 years								
<b>Race</b>								
White								
Black or African American								
Asian								
Hispanic								
Other								

Source:

\*\* Percentages are calculated based on the number of subjects in the subgroup per arm.

Provide a separate table in the same format as Table 3 for hyponatremia.

**PRESCRIBING INFORMATION** Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances, and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

- 1) The nonclinical pharmacology/toxicology sections of the label should include human dose multiples that are based on nasal cavity surface area.
- 2) The Highlights section is about one inch longer than ½ a page. The length of Highlights must be one-half page or less unless a waiver has been granted.

- 3) The section and subsection headings in the Table of Contents (TOC) must match the section and subsection headings in the full PI.
- Section 5.5 should be: Concomitant Use of Systemic or Inhaled Pulmonary Corticosteroids May Increase the Risk of Hyponatremia
  - Section 8.2 Lactation is not listed in the TOC.
  - Section 8.3 Nursing Mothers in the TOC does not appear in the Full PI.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by May 9, 2016. The resubmitted labeling will be used for further labeling discussions if deficiencies do not preclude approval. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

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), Medication Guide, and Instructions for Use. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the PI, Medication Guide, and Instructions for Use, and you believe the labeling is close to the final version.

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

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. We reference the waiver granted on August 10, 2015, for the pediatric study requirement for this application.

If you have any questions, please call Nenita Crisostomo, Regulatory Health Project Manager, at (301) 796-0875.

Sincerely,

*{See appended electronic signature page}*

Hylton V. Joffe, M.D., M.M.Sc.  
Director  
Division of Bone, Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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HYLTON V JOFFE  
04/18/2016

MEMORANDUM

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

**DATE:** April 12, 2016  
**TO:** Memo to File  
**FROM:** Nenita Crisostomo – Regulatory Health Project Manager  
**SUBJECT:** Information Request – Narratives of Adverse Event dropouts

**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo is to document the Information Request sent to Serenity Pharmaceuticals, LLC via email on March 30, 2016, regarding the narratives of the AE dropouts from all of their supporting studies.

**From:** Crisostomo, Nenita  
**Sent:** Wednesday, March 30, 2016 2:15 PM  
**To:** 'Linda Cheng'  
**Cc:** Maria Cheng; Seymour Fein  
**Subject:** RE: NDA 201656 Desmopressin: Clinical Information Request

Hello Linda,

Please submit the data in the narrative format for all the studies. The narratives should be appended to the study reports and include Studies OL1, ELD, DB1, DB2, DB3, DB3 A2, and DB4.

Thank you,  
Nita

*Nenita Crisostomo, R.N.  
Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
Center for Drug Evaluation and Research  
Ph: 301-796-0875*

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/s/  
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NENITA I CRISOSTOMO  
04/12/2016

MEMORANDUM

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

**DATE:** April 12, 2016

**TO:** Memo to File

**FROM:** Nenita Crisostomo – Regulatory Health Project Manager

**SUBJECT:** Clinical Information Request – Protocol Deviations

**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo is to document the Information Request sent to Serenity Pharmaceuticals, LLC via email on April 12, 2016, regarding protocol deviations.

**From:** Crisostomo, Nenita  
**Sent:** Tuesday, April 12, 2016 5:15 PM  
**To:** Linda Cheng (lcheng@serenitypharma.com)  
**Cc:** Seymour Fein (sfein@serenitypharma.com)  
**Subject:** FW: NDA 201656 NOCTIVA (desmopressin): Clinical Information Request

Hi Linda,

To clarify the request, we are seeking for number of patients for each category. Please see the revised table immediately below:

**N(%) Protocol Deviations**

	SER120 1.5 ug	SER120 1.0 ug	SER120 0.75 ug	Placebo
<b>Study DB3</b>				
Total N				
Non-compliance				
Entry criteria				
Prohibited medications				
Visit outside visit window				
Missing visit				
Missing visit procedures				
<b>Study DB4</b>				
Total N				
Non-compliance				
Entry criteria				
Prohibited medications				
Visit outside visit window				
Missing visit				
Missing visit procedures				

Thank you so much,  
Nita

*Nenita Crisostomo, R.N.*  
*Regulatory Health Project Manager*  
*Division of Bone, Reproductive and Urologic Products*  
*Center for Drug Evaluation and Research*

**From:** Crisostomo, Nenita  
**Sent:** Tuesday, April 12, 2016 4:52 PM  
**To:** Linda Cheng ([lcheng@serenitypharma.com](mailto:lcheng@serenitypharma.com))  
**Cc:** Seymour Fein ([sfein@serenitypharma.com](mailto:sfein@serenitypharma.com))  
**Subject:** NDA 201656 NOCTIVA (desmopressin): Clinical Information Request

Hello Linda,

Please submit a table with **all** the protocol deviations, not just the major deviations, for both Studies DB3 and DB4. An example of this request is shown below:

	SER120 1.5 ug	SER120 1.0 ug	SER120 0.75 ug	Placebo
DB3				
Non-compliance				
Entry criteria				
Prohibited medications				
Visit outside visit window				
Missing visit				
Missing visit procedures				
DB4				
Non-compliance				
Entry criteria				
Prohibited medications				
Visit outside visit window				
Missing visit				
Missing visit procedures				

For our immediate review, please email to me your response on or before the close of business on April 20, 2016.

If you have any questions, please feel free to contact me.

Best regards,  
Nita

*Nenita Crisostomo, R.N.*

*Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
Center for Drug Evaluation and Research  
Ph: 301-796-0875*

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/s/  
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NENITA I CRISOSTOMO  
04/12/2016

MEMORANDUM

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

**DATE:** March 16, 2016  
**TO:** Memo to File  
**FROM:** Nenita Crisostomo – Regulatory Health Project Manager  
**SUBJECT:** Information Request – DMEPA  
Regarding Human Factors

**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo is to document the Information Request sent to Serenity Pharmaceuticals, LL via email on March 16, 2016, regarding human factors.

**From:** Crisostomo, Nenita [<mailto:Nenita.Crisostomo@fda.hhs.gov>]  
**Sent:** Monday, March 21, 2016 2:29 PM  
**To:** Linda Cheng  
**Cc:** Maria Cheng; Seymour Fein; Ron Nardi; Samuel Herschkowitz ([docsam122@gmail.com](mailto:docsam122@gmail.com))  
([docsam122@gmail.com](mailto:docsam122@gmail.com))  
**Subject:** RE: TC with FDA on Human Factor Risk Management

Hi Linda,

I just confirmed with the reviewer that this is not a Filing issue. We'll wait until we hear from DMEPA and let you know further. Thank you so much, Linda for the follow-up.

Regards,  
nita

**From:** Linda Cheng [<mailto:lcheng@serenitypharma.com>]  
**Sent:** Monday, March 21, 2016 1:52 PM  
**To:** Crisostomo, Nenita  
**Cc:** Maria Cheng; Seymour Fein; Ron Nardi; Samuel Herschkowitz ([docsam122@gmail.com](mailto:docsam122@gmail.com))  
([docsam122@gmail.com](mailto:docsam122@gmail.com))  
**Subject:** RE: TC with FDA on Human Factor Risk Management

Dear Nita:

Thanks for getting back to me. We are preparing additional materials based on our extensive clinical in-use program which we think will be fully responsive to the request from DMEPA. However, we are unclear as to whether this issue is a NDA filing matter or a review matter. The original NDA submitted

on February 4, 2016 contains human factor information under Section 3.2.P.2.4.4. If needed for filing, we are happy to submit the supplemental information/material as an NDA amendment whenever it is needed for that purpose. If, however, this is a NDA review issue and you would prefer that we have a discussion with DMEPA first, please let us know.

To date, we have over 2,000 patients with human factor experience using the (b) (4) pump in the SER120 clinical program with no issue on compliance and risk of misuse. In addition, the (b) (4) pump which is manufactured by (b) (4) the leading maker of nasal spray pumps, has been on the market for 10 years and used for a variety of products worldwide.

Regards,

Linda

Linda Cheng  
V-P, Project Management  
Serenity Pharmaceuticals, LLC  
120 North Main Street  
Suite 400  
New City, New York 10956

Phone: 845-639-6760, Ext. 11  
Fax: 845-639-1703

[licheng@serenitypharma.com](mailto:licheng@serenitypharma.com)

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-----Original Appointment-----

**From:** Crisostomo, Nenita [<mailto:Nenita.Crisostomo@fda.hhs.gov>]

**Sent:** Monday, March 21, 2016 1:04 PM

**To:** Linda Cheng

**Subject:** Declined: TC with FDA on Human Factor Risk Management

**When:** Monday, March 21, 2016 2:30 PM-3:30 PM (UTC-05:00) Eastern Time (US & Canada).

**Where:** (b) (4)

Hi Linda,

As per previous email, I will get back with you on the new date/time of the call. One of the key DMEPA Team members will not be available this week. The March 24 due date will be re-assessed.

Thanks,

Nita

*Nenita Crisostomo, R.N.  
Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
Center for Drug Evaluation and Research  
Ph: 301-796-0875*

**From:** Linda Cheng [mailto:lcheng@serenitypharma.com]  
**Sent:** Saturday, March 19, 2016 6:35 PM  
**To:** Crisostomo, Nenita  
**Cc:** Maria Cheng  
**Subject:** Re: NDA 201656 desmopressin Nasal Spray: DMEPA Information Request - use-related risk analysis

Dear Nita:

I would like to give you a call on Monday to discuss. Will you be at 11 am?

Linda

---

**From:** Crisostomo, Nenita  
**Sent:** Saturday, March 19, 2016 9:55 AM  
**To:** Linda Cheng (lcheng@serenitypharma.com)  
**Cc:** Maria Cheng (mcheng@serenitypharma.com)  
**Subject:** NDA 201656 desmopressin Nasal Spray: DMEPA Information Request - use-related risk analysis

Hi Linda,

Please refer to your NDA 201656 submitted under section 505(b) on February 4, 2016 for desmopressin nasal spray. Please also refer to the meeting held with representatives of your firm and the FDA on August 18, 2015. We understand that you are planning to use desmopressin nasal spray to treat nocturia in adults who wake up 2 or more times per night to void. However, we note that you have not submitted a comprehensive use-related risk analysis or your plans for a Human Factors (HF) validation study per Agency request at the August 18, 2015 meeting. If you have determined that an HF validation study is not needed for your product, submit your use-related risk analysis and justification for not conducting the HF validation study to the Agency for review under the NDA.

We request a response no later than 12Noon, Thursday, March 24, 2016. For our immediate review, please email to me your response while enroute for official submission.

If you have any questions, please contact me.

Thank you,  
Nita

*Nenita Crisostomo, R.N.*  
*Regulatory Health Project Manager*  
*Division of Bone, Reproductive and Urologic Products*  
*Center for Drug Evaluation and Research*  
*Ph: 301-796-0875*

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/s/  
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NENITA I CRISOSTOMO  
03/21/2016

MEMORANDUM

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

**DATE:** March 16, 2016  
**TO:** Memo to File  
**THROUGH:**  
**FROM:** Nenita Crisostomo – Regulatory Health Project Manager  
**SUBJECT:** Information Request – Clinical Pharmacology  
**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo is to document the Information Request sent to Serenity Pharmaceuticals, LL via email on March 16, 2016.

**From:** Crisostomo, Nenita  
**Sent:** Wednesday, March 16, 2016 1:08 PM  
**To:** Linda Cheng (lcheng@serenitypharma.com)  
**Subject:** NDA 201656 NOCTIVA (desmopressin): Clinical Pharmacology Information Request

Hi Linda,

We are currently reviewing your NDA. Listed below are requests from our Clinical Pharmacology Team. Please submit your response, as soon as possible, or on/before close of business on March 21, 2016. For our immediate review, please email your response to me while enroute for submission.

- 1) We request that you submit the following information
  - The data file in the xpt format of the serum concentrations and PK parameters of desmopressin in the PK studies (at least, dataset for the study DB3 and the pooled PK analysis)
  - If the Sponsor already submitted them, indicate the location of those files in the NDA package.
  
- 2) The proposed label in 12.3 Pharmacokinetics describes that desmopressin did not show any effect on any of the 9 CYP 450 subtypes.

Indicate the location of the supporting study report in the NDA package.

If you have any questions, please feel free to contact me.

Thank you,  
Nita

*Nenita Crisostomo, R.N.  
Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
Center for Drug Evaluation and Research  
Ph: 301-796-0875*

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/s/  
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NENITA I CRISOSTOMO  
03/21/2016

MEMORANDUM

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

**DATE:** March 16, 2016  
**TO:** Memo to File  
**FROM:** Nenita Crisostomo – Regulatory Health Project Manager  
**SUBJECT:** Information Request – Debarment Statement

**APPLICATION/DRUG:** NDA 201656 NOCTIVA (desmopressin) nasal spray

This Memo is to document the Information Request sent to Serenity Pharmaceuticals, LL via email on March 16, 2016, regarding the debarment statement.

**From:** Crisostomo, Nenita  
**Sent:** Wednesday, March 16, 2016 4:54 PM  
**To:** Linda Cheng (lcheng@serenitypharma.com)  
**Subject:** NDA 201656 desmopressin: Debarment Certification

Hello Linda,

The Debarment Certification is incorrectly worded.

Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”

Please re-submit the certification with the correct wording.

Thanks,  
nita

*Nenita Crisostomo, R.N.  
Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
Center for Drug Evaluation and Research  
Ph: 301-796-0875*

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/s/  
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NENITA I CRISOSTOMO  
03/21/2016



NDA 201656

**NDA ACKNOWLEDGMENT**

Serenity Pharmaceuticals, LLC  
Attention: Seymour Fein, M.D.  
Chief Medical Officer  
120 N. Main Street, Suite 400  
New City, NY 10956

Dear Dr. Fein:

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

Name of Drug Product: NOCTIVA (desmopressin) nasal spray

Date of Application: February 4, 2016

Date of Receipt: February 4, 2016

Our Reference Number: NDA 201656

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 April 4, 2016, 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 Bone, Reproductive and Urologic Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

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, please call me at (301) 796-0875.

Sincerely,

*{See appended electronic signature page}*

Nenita Crisostomo, R.N.  
Regulatory Health Project Manager  
Division of Bone, Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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NENITA I CRISOSTOMO  
02/16/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 076667

MEETING MINUTES

Serenity Pharmaceuticals, LLC  
Attention: Seymour Fein, M.D.  
Chief Medical Officer  
120 N. Main Street, Suite 400  
New City, NY 10956

Dear Dr. Fein:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SER120 (desmopressin acetate nasal spray), 7.5 µg/mL and 15 µg/mL.

We also refer to the meeting between representatives of your firm and the FDA on August 18, 2015. The purpose of the meeting was to discuss your plans to file a 505(b)(2) marketing application for desmopressin nasal spray.

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

If you have any questions, please call Nenita Crisostomo, Senior Regulatory Health Project Manager at (301) 796-796-0875.

Sincerely,

*{See appended electronic signature page}*

Suresh Kaul, M.D., M.P.H.  
Medical Team Leader  
Division of Bone, Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes

**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** C  
**Meeting Category:** Guidance Meeting

**Meeting Date and Time:** August 18, 2015 @ 2:00 PM  
**Meeting Location:** CDER, White Oak Campus, Building 22, Room 1421

**Application Number:** IND 076667  
**Product Name:** SER120 (desmopressin acetate nasal spray), 7.5 µg/mL and 15 µg/mL.  
**Indication:** Treatment of adult nocturia  
**Sponsor/Applicant Name:** Serenity Pharmaceuticals, LLC

**Meeting Chair:** Suresh Kaul, M.D., M.P.H.  
**Meeting Recorder:** Eufrecina DeGuia

**FDA ATTENDEES**

Hylton V. Joffe, M.D., M.M.Sc. – Director, Division of Bone, Reproductive and Urologic Products (DBRUP)  
Suresh Kaul, M.D., MPH – Medical Team Leader, Urology, DBRUP  
Martin Kaufman, DPM, MBA – Clinical Analyst, DBRUP  
Eufrecina DeGuia – Senior Regulatory Health Project Manager, DBRUP  
Mahboob Sobhan, Ph.D. – Statistical Team Leader, Division of Biometrics III (DBIII)  
Kate Dwyer, Ph.D. – Statistical Reviewer, DBIII  
Elektra Papadopoulos, M.D., M.P.H. – Acting Associate Director, Clinical Outcome Assessments (COA) Staff, OND  
Sarrit Kovacs, Ph.D. – Reviewer, COA Staff, OND  
Jihong Shon, Ph.D. – Clinical Pharmacology Reviewer, Division of Clinical Pharmacology (DCP) III  
Gemma Kuijpers, Ph.D. – Pharmacology and Toxicology Reviewer, DBRUP  
Deepa Rao, D.V.M., Ph.D. - Pharmacology and Toxicology Reviewer, DBRUP  
Maria Walsh, R.N. – Associate Director for Regulatory Affairs, Office of Drug Evaluation III  
Peyton Myers, Ph.D. – Acting Team Leader, DBRUP  
Mark Seggel, Ph.D. – CMC Lead, Office of New Drug Products (ONDP), Office of Product Quality (OPQ)  
Yaodong Huang, Ph.D. – Chemical Engineer, Office of Process and Facilities (OPF), OPQ  
Derek Smith, Ph.D. - OPF, OPQ  
Kendra Worthy, Pharm.D. – Team Leader, Division of Medication Error and Prevention Analysis (DMEPA), Office of Surveillance and Epidemiology (OSE)  
Nandini Bhattacharya, Ph.D. – Microbiology Reviewer, OPQ  
Shawnetta Jackson – Project Manager, OSE

**SERENITY PHARMACEUTICALS, INC. ATTENDEES**

Sam Hershkowitz, M.D. – Chief Executive Officer  
Seymour Fein, M.D. – Chief Medical Officer  
Linda Cheng, M.S. – V.P. of Project Management

## 1.0 BACKGROUND

Serenity Pharmaceuticals, LLC submitted IND 076667 to the Division of Reproductive and Urologic Products (now the Division of Bone, Reproductive and Urologic Products or DBRUP) on May 30, 2008. The IND was transferred to the Division of Metabolism and Endocrinology Products (DMEP) on February 25, 2009, and was transferred back to DBRUP on April 21, 2014.

Desmopressin is a synthetic analog of the human pituitary hormone, vasopressin. Desmopressin has been in medical use for several decades as replacement therapy for patients with central diabetes insipidus and to treat bedwetting in children. Desmopressin is marketed worldwide in several dosage forms, including a nasal spray, oral tablet of multiple strengths, and injection solution.

SER120 (desmopressin acetate nasal spray) is intended to be administered at bedtime and is proposed for the treatment of adult nocturia. The product is a new emulsion formulation containing the excipient cyclopentadecanolide (CPD) [REDACTED] (b) (4) [REDACTED]. This is the first product where CPD is included in a nasal spray formulation.

An End-of-Phase 2 meeting was held with the Division of Reproductive and Urologic Products on February 19, 2009.

On July 28, 2010, DMEP provided the Sponsor with Preliminary Comments for the Pre-NDA meeting, scheduled on July 30, 2010. The comments included recommendations regarding the submission requirements for an NDA application, including those for a 505(b)(2) application.

Since then, Studies DB3, DB4 and Extension Study A.2, conducted with higher doses of desmopressin, have been completed and are summarized in the current meeting information package.

Serenity requested this meeting to discuss the clinical, non-clinical, and Chemistry/Manufacturing/Controls sections of the planned NDA application.

Preliminary comments were provided to the Sponsor on August 17, 2015, in response to questions posed in the July 15, 2015, Meeting Package. The Sponsor's questions from the meeting package are presented below in *italicized* font, followed by the Division's responses in regular font. Additional discussion and comments made at the meeting are in **bolded font**. Post-Meeting comments are in ***bolded and italicized*** font.

## 2.0 DISCUSSION

### **Introductory Comments:**

Based on the information provided in your meeting package, the clinical benefit of treating nocturia with SER120 continues to be unclear. For the co-primary efficacy endpoints, the placebo subtracted treatment effect seen in Study SPC-SER120-DB4-201301 (DB4) is small and similar to what was seen in Study SPC-SER120-DB3-201101 (DB3). Although DB4 included the Impact of Night Time Urination (INTU) Questionnaire, the brief overview of results provided in your meeting package indicate that the change in the INTU overall impact score compared to placebo was not statistically significant for either dose in the Modified-Intent-To-Treat (mITT) population.

As you are aware, FDA convened an advisory committee meeting in January 2015 to discuss Nocdurna, a desmopressin drug product, proposed for the treatment of nocturia due to nocturnal polyuria. The committee members expressed concerns with the small treatment effects of unclear clinical significance and the serious risk of hyponatremia, and voted against approval. Based on our preliminary review of the data in your meeting package, it appears that the safety and efficacy of SER120 demonstrated in DB3 and DB4 are similar to the results seen with Nocdurna that were presented to the advisory committee. Therefore, it appears that your product has a similar benefit/risk profile to that of Nocdurna, which the advisory committee concluded was unfavorable.

Before we can agree that you are ready for NDA submission, we request that you submit written materials that provide more details on your safety and efficacy data for SER 120 with an emphasis on how the safety and efficacy of your product differs from the Nocdurna product that was presented at the recent advisory committee meeting. Therefore, we believe that a Pre-NDA meeting at this time is premature and have designated your requested meeting as a guidance meeting, rather than a Pre-NDA meeting. In addition, we have

concerns with your proposed indication that will need to be resolved (see our response to Question 7).

Although, it is premature for you to submit an NDA at this time, we have provided general responses to your specific questions below. We defer more detailed responses until we determine that a Pre-NDA meeting is appropriate.

**Discussion at the meeting:** The meeting commenced with Serenity providing an overview of the SER120 clinical program; how it started in DRUP, then moved to DMEP, then transferred back to DBRUP. The Sponsor stated that they complied with all of FDA's recommendations when designing the pivotal efficacy and safety trials. The Sponsor stated that they conducted confirmatory trials, DB3 and DB4, and worked with the Clinical Outcome Assessments (COA) staff to develop a validated instrument, the Impact of Night Time Urination (INTU) questionnaire, which was incorporated in the DB4 trial.

The Division stated that based on the information provided in the meeting package, it appears that SER 120 has a similar benefit/risk profile to that of Nocdurna, which was presented at a recent advisory committee meeting and received an unfavorable vote. The Sponsor stated that, in their view, there are important differences between the Nocdurna program and the Serenity program that should be considered, (b) (4)

The Division requested that the Sponsor submit written materials providing a more detailed comparison to the efficacy and safety of Nocdurna with an emphasis on why the Sponsor believes their Serenity product has a more favorable benefit/risk profile. The Division recommended that the Sponsor focus on the Nocdurna materials presented/provided to the Nocdurna advisory committee panel, because those data were the basis of the unfavorable Nocdurna vote. In addition, the Division requested that the written materials include a discussion of the plans for monitoring for hyponatremia, and clarification on the Modified-Intent-To-Treat (mITT) and ITT populations, including which population was pre-specified for the various key efficacy endpoints. The information provided in the Briefing Package indicated that the change in the INTU overall impact score compared to placebo was not statistically significant for either dose in the mITT population. In the written materials, Serenity should also clarify why they believe the INTU questionnaire has demonstrated a statistically and clinically significant impact on the nighttime voiding assessment.

**Post-Meeting Comments:** *As requested by Serenity at the meeting, the following comments from COA were provided via email on August 20, 2015:*

*In the Phase 3 trial we recommend you look at the cumulative distribution function (CDF) curves, one curve for each study arm (placebo, low dose, high dose), looking at the mITT population in one graph and the ITT population in another graph. We recommend this is done for each PRO.*

*We also recommend in the Phase 3 trial that you conduct additional exploratory analyses that evaluate the Daytime Impact Score, Nighttime Impact Score, and INTU Overall Impact Score using the Treatment Benefit Scale (TBS) as an anchor. We suggest that you plot cumulative distribution function curves at different score points on the TBS. In this case, the change score of INTU domain or total score of interest would be on the x-axis and the cumulative percent of patients experiencing up to that INTU domain or total score change would be on the y-axis. For each INTU domain score or total score, there will be up to seven cumulative distribution curves (in the same figure) corresponding to the categories of TBS score. None of the anchor measures is preferable on its own, but including data from all potential anchors may provide an accumulation of evidence to help interpret a clinically meaningful change in the INTU domain and total scores. We recommend since the mITT population is the pre-specified population, this is the population that is used when plotting the cumulative distribution function curves. Curves using the ITT population may be useful as well.*

*In your two-week interventional [behavioral modification] psychometric evaluation study, we recommend that you conduct additional exploratory analyses that evaluate the Daytime Impact Score, Nighttime Impact Score, and INTU Overall Impact Score using the Patient Global Impression of Change (PGI-C) as an anchor. We suggest that you plot cumulative distribution function curves at different score points (1, 2, 3,...) on the PGI-C for day 15. Depending on the sample size you may or may not wish to also have plots that collapse some of the PGI-C score categories. In this case, the change score of INTU domain or total score of interest would be on the x-axis and the cumulative percent of patients experiencing up to that INTU domain or total score change would be on the y-axis. For each INTU domain score or total score, there will be up to seven cumulative distribution curves (in the same figure) corresponding to the categories of PGI-C score. None of the anchor measures (e.g. PGIC, change in 3-day voiding diary, N-QOL) is preferable on its own, but including data from all potential anchors may provide an accumulation of evidence to help interpret a clinically meaningful change in the INTU domain and total scores. We recommend since the mITT population is the pre-specified population, this is the population that is used when plotting the cumulative distribution function curves. Curves using the ITT population may be useful as well.*

**On September 3, 2015 Serenity emailed FDA and asked for clarification on the August 20, 2015 email.**

Follow up clarification question: “Our PRO experts are doing the analysis per request below. However we have a question with the request in the second paragraph and would like to seek clarification.

“The agency had suggested we generate cumulative distribution functions for the different score points on the TBS. In describing this figure, the request stated the change score of INTU domain or total score of interest would be on the x-axis, with the CDF on the y-axis. This would imply there would be five CDF curves corresponding to each of

the TBS scores, namely, 'much better', 'somewhat better', 'not changed', 'somewhat worse' and 'much worse'. However, in the request below [sic], it mentioned seven CDF curves rather than five, Is our understanding of what is suggested correct?"

***Post meeting follow-up email sent to the Sponsor on September 8, 2015, responding to the clarifying question:***

***Your understanding of what is suggested is correct. The number of CDF curves should match with the number of TBS response options.***

***Serenity agreed to provide all the requested information as a clinical amendment to the IND.***

***Responses to most of the clinical questions were not discussed because the focus of the meeting was on the Division's introductory comment outlined in the Preliminary Responses document provided to Serenity on August 17, 2015.***

## 2.1. CLINICAL

***Question 1:*** *On July 30, 2010, a pre-NDA meeting was held with DMEP concerning SER120 (Noctiva) for nocturia. Preliminary written responses to the questions in the briefing document were provided by the Division (FDA Preliminary Written Response to IND Amendment, Serial # 0026 Submitted on June 25, 2010) which referred to earlier clinical studies in the program performed with lower doses of SER120 (DB1, DB2, OL-1, chronic renal insufficiency and the elderly studies). Subsequently, Serenity has conducted two Phase 3 pivotal efficacy and safety trials (DB3 and DB4) (Appendix 1, Appendix 2) and a new open-label safety extension study at higher doses of SER120 (Appendix 3). These studies were much larger in size and longer in treatment duration than the earlier trials and now constitute the vast majority of the clinical database. The 2 pivotal studies contain most of the elderly patients in the program and all of these elderly patients were treated at doses of 0.75, 1.0 or 1.5 µg/day. Serenity plans to include in the integrated summary of efficacy (ISE) the pooled analysis of the 0.75 and 1.5 µg/day treatment groups from the DB3 and DB4 studies only (Appendix 4). Does FDA agree with this proposal?*

***FDA Response to Question 1:*** No. We do not agree. It is premature to comment on details of the Integrated Summary of Efficacy (ISE) but we can state at this time that it is not appropriate to "pool" efficacy data from separate phase 3 studies. The ISE should provide a separate discussion for each of the phase 3 studies and include analyses and comparisons of the study outcomes.

The ISE should also include analyses and discussion of the persistence of effect of SER120 over time.

***Discussion at the meeting:*** The Sponsor stated that they have 24 months of efficacy data and will include those data when the NDA is submitted.

*Question 2: Does FDA agree with the planned scope and presentation of safety data in the Summary of Clinical Safety and the ISS?*

FDA Response to Question 2: It is premature to comment on details of the Integrated Summary of Safety (ISS) until we have determined that NDA submission is no longer premature.

**No further discussion ensued.**

*Question 3: Serenity proposes to include the full integrated summary of safety (ISS) in Module 5, Section 5.3.5.3 and to include a further summary of safety in Module 2, Section 2.7.4. Does FDA agree with this proposal?*

FDA Response to Question 3: We defer further discussion of this Question until we have determined that NDA submission is no longer premature.

**No further discussion ensued.**

*Question 4: Does FDA agree this safety database is adequate to support NDA approval?*

FDA Response to Question 4: We are unable to answer this question at this time because of the concerns we have described in the Introductory Comments.

**No further discussion ensued.**

*Question 5: Does FDA agree to a full pediatric study waiver for SER120?*

FDA Response to Question 5: A letter was issued on August 10, 2015, agreeing with your Agreed iPSP as amended in your submission dated July 29, 2015. The Agreed iPSP must be included in the appropriate section of an NDA submission.

**No further discussion ensued.**

*Question 6: Serenity plans to include a selected literature review of published papers in which desmopressin has been used to treat patients with nocturia. We do not plan to submit a comprehensive literature review of desmopressin for other clinical indications. The preliminary responses for the July 30, 2010 meeting agreed to this proposal and requested inclusion of all available data which support clinical benefit from the reduction in nocturic episodes in adults and elderly. Does FDA remain in agreement with this plan including its earlier response?*

FDA Response to Question 6: No. We do not agree. In addition to the literature review outlined above, we also request that you include a literature review of published papers focusing on desmopressin and thrombocytopenia. This review should include all clinical

indications. We may have additional comments when we determine that NDA submission is no longer premature.

**Discussion at the meeting:** Serenity acknowledged that there was one case of thrombocytopenia in the clinical program but noted that the finding was already present prior to dosing with desmopressin. They stated that they will provide the narrative.

*Question 7. Serenity proposes to have the product label clinical indication for SER120 read as follows:* [REDACTED] (b) (4)

[REDACTED] Does FDA agree with this proposed label clinical indication?

**FDA Response to Question 7:** It is premature to agree on the specific labeling at this time. However, it is not clear how you could support use of SER120 in patients [REDACTED] (b) (4) since it appears that your phase 3 trials were conducted only in patients age 50 or older.

In addition, nocturia is a symptom of many conditions and, therefore, the proposed indication is too broad. In the written materials that you will be submitting (see Introductory Comments), clearly explain the underlying causes of nocturia in the patient population you studied in your phase 3 trials, and the causes of nocturia for which you are seeking an indication.

**Discussion at the meeting:** Serenity agreed to include the information and justification about extrapolating data from patients from 50 years and older [REDACTED] (b) (4) will be submitted. The Division indicated that this issue will need further discussion.

*Question 8: Does the agency agree with this approach for the clinical pharmacology overview section of the NDA submission?*

**FDA Response to Question 8:** As discussed previously, an NDA submission is premature. We can share the following comments at this time.

You need to clarify what the qualitative data means in your proposal. Refer to the following comments for the clinical pharmacology section of an NDA submission.

1. The pharmacokinetic (PK) profile of the to-be-marketed (TBM) formulation should be summarized from the most relevant PK studies. We note that the phase 1 and 2 studies (Studies 200801 and 200802) used a different concentration of desmopressin and different administration methods from those tested in the phase 3 studies.
2. In the NDA submission, the effect of age, gender, special populations (e.g. renal impairment), and body mass on the PK of desmopressin should be addressed based on the data from the PK studies. If you intend to rely on the published literature, the relevance of the studies and data should be scientifically justified.

3. Clarify what type of data supports the PK and pharmacodynamic information for labeling in the NDA submission. The quality of data will be a review issue.
4. The data supporting PK characteristics of the TBM product should derive from the PK studies using the validated assay method. We note that two bioanalysis methodologies were used in the PK studies. Two assay methods had different detection limits. The PK should be analyzed using the data points higher than the validated lower limit of quantitation.

**No further discussion ensued.**

#### **Additional Clinical Comments**

1. Clarify whether subjects in DB3 and DB4 were counseled or given instructions regarding night time fluid intake. The study protocols state that during the Week -2 screening visit the patient's night time fluid intake history was recorded and reviewed. How was this information used?
2. Clarify whether your review of data from DB3 and/or DB4 identified a monitoring scheme that could be used to identify patients whose serum sodium dropped to 125 mmol/L or lower.
3. Explain how dose titration was conducted during the long term open-label extension of DB3. Was lack of efficacy a criterion for up-titration from the 1.0 µg to the 1.5 µg dose?

**Discussion at the meeting: The Sponsor confirmed that night time fluid intake was not restricted in DB3 and DB4. The sponsor stated that the goal of titration in the open-label extension of DB3 was to safely escalate to the 1.5 µg dose; efficacy was not a consideration for dose escalation.**

## **2.2. DATABASE**

*Question 9: Does the Agency agree to the proposed database content and format?*

**FDA Response to Question 9:** When you are ready for NDA submission, the integrated safety ADaM datasets should also include SPC-SER120-ELD-201001 as well as any additional phase 3 studies that may be needed to conduct to support the NDA.

When you are ready for NDA submission, SAS programs related to efficacy analyses should also be included. These programs should be sufficient to duplicate your efficacy results.

**No further discussion ensued.**

*Question 10: Serenity plans to submit Case Report Forms for deaths, serious adverse events, adverse events leading to study discontinuation for any adverse event and any patient with a*

*serum sodium level  $\leq 125$  mmol/L (No symptomatic patient with sodium levels between 126 and 129 mmol/L was observed in the SER120 program) in the ISS and to include a table with CRFs grouped by those categories as per the preliminary responses for the July 30, 2010 meeting. Does FDA remain in agreement with this approach?*

**FDA Response to Question 10:** At present, we agree with your plan except that Case Report Forms (CRFs) should also be submitted for any patient with a serum sodium concentration less than 130 mmol/L. We may have additional comments when we determine that NDA submission is no longer premature.

**No further discussion ensued.**

***Question 11:** Serenity plans to include patient narratives for deaths, serious adverse events and adverse events leading to study discontinuation related to electrolyte abnormalities. Serenity also plans to prepare narratives for other significant events beyond nasal irritation and any patient with a serum sodium level  $\leq 125$  mmol/L (No symptomatic patients with sodium levels between 126 and 129 mmol/L was observed in the SER120 program) within each clinical report and in the pooled patient narratives from all Phase 3 studies in the relevant sections of the ISS as per the preliminary responses for the July 30, 2010 meeting. Does FDA remain in agreement with this proposal?*

**FDA Response to Question 11:** At present, we agree with your plan except that narratives should be prepared and submitted for any patient with a serum sodium concentration less than 130 mmol/L including patients without symptoms. Narratives should include all available serum sodium measurements, concomitant medications, and history of intercurrent illnesses. We may have additional comments when we determine that NDA submission is no longer premature.

**No further discussion ensued.**

***Question 12.** A draft high level eCTD Table of Contents for the proposed NDA is provided in this meeting information package including a risk-benefit analysis in the Clinical Overview section 2.5, a Risk Management Plan in section 1.16 and efficacy and safety analyses in section 5.3.5.3 (Appendix 7). Reports of Analyses from more than one study and a coding dictionary used for mapping investigator verbatim terms to preferred terms as a SAS transport file along with the datasets in Section 5.3.5.3. as requested in the preliminary responses for the July 30, 2010 meeting. Does FDA remain in agreement with this plan?*

**FDA Response to Question 12:** At present, we agree with your plan. We may have additional comments when we determine that NDA submission is no longer premature.

**No further discussion ensued.**

***Question 13:** Serenity plans to submit with the NDA summary level clinical site data for CDER's inspection planning as per the draft Guidance of December, 2012. These data listings will be organized by study site, study, domain and treatment group for the pivotal*

*Phase 3 studies supporting the NDA which are DB3 and DB4. Does FDA agree with this plan?*

**FDA Response to Question 13:** We are deferring a response to this question until we have determined that NDA submission is no longer premature.

**No further discussion ensued.**

### 2.3. PHARMACOLOGY / TOXICOLOGY

*Question 14: Serenity believes that the 28 day bridging toxicology study and the two chronic toxicology studies with the SER120 formulation are adequate to document the toxicity risks associated with the nasal administration of CPD in SER120. Does the FDA agree?*

**FDA Response to Question 14:** Yes. The 28-day bridging toxicology study is acceptable as a subchronic local toxicity assessment of nasal CPD administration. The 26-week rat study and 39-week dog study may be sufficient to evaluate the local tolerance to CPD.

However, the potential carcinogenicity of the excipient CPD still needs to be addressed in the NDA submission per CDER *Guidance for Industry: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*. Decisions concerning the adequacy of the sponsor's approach are made on a case-by-case basis, using a weight-of-evidence approach. A sponsor generated document providing scientific justification that carcinogenicity data are not necessary based on negative genotoxicity potential, limited systemic exposure, absence of accumulation based on nonclinical and clinical pharmacokinetic data, negative histopathology data from chronic toxicology studies (e.g. absence of preneoplastic lesions and other relevant toxicologic effects) performed at the Maximum Feasible Dose (MFD), and information on the carcinogenic potential of other excipients in the same class would be acceptable for review by the Division when you are ready for NDA submission.

Evaluation of the clinical relevance of the data from the chronic local tolerance studies should include interspecies dose comparisons based on nasal cavity surface area (cm<sup>2</sup>) rather than whole body surface area (m<sup>2</sup>). A summary table of dose comparisons between nonclinical and clinical studies should be included. Justification for dose selection and/or maximum feasible dose administration for all nonclinical studies should also be provided.

**Discussion at the meeting:** The Division reiterated that the potential carcinogenicity of the excipient CPD still needs to be addressed.

**The Sponsor stated that they plan to submit a request for a waiver for CPD carcinogenicity studies, including documentation to support the request. The Division responded that this plan is acceptable, and should include final reports of all relevant toxicology studies. The Sponsor stated that they plan to submit this information for FDA comment prior to NDA submission but may not await our comments before submitting the NDA.**

***Post meeting comment: The Division recommends that the Sponsor submit the waiver request with a cover letter clearly describing the content of the submission and a reference to this guidance meeting. The Sponsor is advised that the review of the request may include consultation with CDER's Executive Carcinogenicity Assessment Committee (ECAC).***

***Question 15:*** Serenity does not plan to include a literature review of published papers concerning desmopressin pre-clinical pharmacology, toxicology and pharmacokinetics. In the preliminary responses for the July 30, 2010 meeting, no literature review was needed for preclinical data of desmopressin. Does FDA remain in agreement with this approach?

***FDA Response to Question 15:*** In order to meet the nonclinical requirements for an NDA submitted via the 505(b)(2) regulatory pathway, you will need to rely on published literature or rely on FDA's finding of safety for a listed drug (e.g., DDAVP). You would need to establish that such reliance is appropriate by either providing a scientific justification in the case of reliance on published literature, or by establishing a bridge between your proposed drug product and the listed drug upon which you propose to rely. For additional information on submitting a 505(b)(2) NDA, see the 505(b)(2) REGULATORY PATHWAY section below.

**No additional discussion ensued.**

***Question 16:*** To facilitate the toxicology review, the study reports for CPD animal toxicology evaluations performed by other organizations will be placed in Module 4 under Other Toxicology Studies. The expert review and analysis of the two (b)(4) chronic dosing studies is also included in Module 4 under Other Toxicity Studies. Does FDA agree with this organization of the eCTD contents plan?

***FDA Response to Question 16:*** Yes. That would be acceptable when you are ready for NDA submission. Refer to this linked document for eCTD submission organization and formatting:  
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163556.pdf>

Note that bioanalytical and stability studies on CPD and CPD metabolites in rats and humans need to be included in the NDA submission. In addition, documentation on the assessment of CPD's carcinogenic potential needs to be included in the NDA (see response to Question 14).

**No additional discussion ensued.**

***Question 17:*** Serenity plans to include in Module 2 Sections 2.4 and 2.6 summary background information concerning the formulations used in the various toxicity studies included in the NDA and contextual information about the toxicity studies included under Other Toxicity Studies in Module 4. Does FDA agree with this plan?

FDA Response to Question 17: Clarification regarding ‘contextual information about the toxicity studies’ is requested.

When you are ready for NDA submission, refer to this linked document for eCTD submission organization and formatting:  
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163556.pdf>

**No additional discussion ensued.**

#### 2.4. CHEMISTRY, MANUFACTURING AND CONTROLS

*Question 18: Does FDA agree that this stability program and supporting data are sufficient for NDA submission and approval (pending data review) of a (b) (4) shelf life?*

FDA Response to Question 18: Yes. The drug product stability program appears adequate to support submission of an NDA. It is reported that the production process has “remained essentially unchanged” throughout the development program. Any differences between the clinical batch process(es) and the commercial process should be highlighted and the potential impact on product stability evaluated.

**No additional discussion ensued.**

*Question 19: Does FDA agree that the test methods and plan for setting specifications for leachables/extractables are acceptable to support the approval of the product?*

FDA Response to Question 19: Yes. The proposed plan for characterizing and setting acceptance criteria for leachables/extractables appears adequate.

An adequate toxicological risk assessment on potential leachables and extractables from the drug product formulation should be included in the NDA submission. In addition, qualification of impurities and degradants in drug substance and drug product, respectively, may be needed for the NDA. We refer to ICH Guidances for Industry Q3A and Q3B(R2) for guidance on impurity qualification.

**No additional discussion ensued.**

*Question 20: Does FDA agree that the PPQ program planned is acceptable to support the approval of this product?*

FDA Response to Question 20: FDA does not review or approve proposed matrix approaches for process performance qualification (PPQ) studies, process validation, protocols, or specific batches of different strengths used in PPQ studies, other than commercial scale process simulations for aseptically manufactured products. The actual protocols, acceptance criteria and study outcomes will be evaluated during an inspection.

Prior to marketed product distribution, it is necessary for you to justify and confirm that the proposed manufacturing process is capable of consistently delivering quality product.

**No additional discussion ensued.**

**ADDITIONAL COMMENTS:**

- **Division of Medication Error Prevention and Analysis (DMEPA)**

You should conduct a comprehensive use-related risk analysis of your proposed desmopressin nasal spray drug/device combination product. Your comprehensive risk analysis must include a comprehensive evaluation of all the steps involved in using your desmopressin nasal spray product (e.g., based on a task analysis for your device and known problems with similar marketed devices), the errors that users might commit or the tasks they might fail to perform, the potential negative clinical consequences of use errors and task failures, the risk mitigation strategies you employed to reduce any use errors or failures, and the method of validating your risk mitigation strategies. This information is needed to ensure that all potential risks involved in using your product have been considered and adequately mitigated and that all residual risks are acceptable (i.e. not easily reduced further and outweighed by the benefits of the product). Based on the comprehensive use-related risk hazard analysis, you will have a better idea of the extent to which simulated use testing is required. The risk analysis will also guide you in the design of a human factors validation protocol study for your product if it is warranted based on the risk analysis.

If a validation study is needed, to ensure your approach and methodology are acceptable, submit your use-related risk analysis and validation study protocol for review prior to study implementation for FDA review and comment. Note that we will need 90 days to review and provide comments under the IND. If you determine that no human factors validation study is required, ensure that the use risk analysis and justification for your determination is submitted to the FDA for review.

Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, available online at:

<http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm094460.htm>.

Note that we have also published three draft guidance documents that while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors and product design:

- a. *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* (Draft), available at <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM259760.pdf>

- b. *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (Draft)*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>
- c. *Safety Considerations for Product Design to Minimize Medication Errors (Draft)*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf>

**Discussion at the meeting:** Serenity stated that they have a DMF on file for the device, which is already approved, and will provide rationale for its use in their use-related risk analysis. In addition, they will also provide the instructional pamphlet.

**DMEPA stated that providing rationale in the use-related risk analysis was acceptable, and requested that the Sponsor also provide data on errors or misuse of the device. Serenity stated that as far as they know there is no evidence of misuse, but will confirm and provide the requested information.**

**Serenity also asked for clarification on the term “validation study.” DMEPA explained that simulated use and validation study are synonymous.**

### 3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance>

s/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email [pdit@fda.hhs.gov](mailto:pdit@fda.hhs.gov). For further guidance on pediatric product development, please refer to:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

#### 4.0 505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent

on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

<b>List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature</b>	
<b>Source of information (e.g., published literature, name of listed drug)</b>	<b>Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)</b>
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX "TRADENAME"</i>	<i>Previous finding of effectiveness for indication X</i>
<i>3. Example: NDA YYYYYY "TRADENAME"</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>
<i>4.</i>	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

**5.0 ISSUES REQUIRING FURTHER DISCUSSION:**

The Sponsor will submit to the IND the information requested by the Division. The Division indicated that we are amenable to holding another meeting to discuss the issues raised at this meeting after we have reviewed the IND submission.

**6.0 ACTION ITEMS**

Meeting minutes will be provided to the Sponsor within 30 days.

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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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SURESH KAUL  
09/17/2015

**Johnson, Jennifer**

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**From:** Johnson, Jennifer  
**Sent:** Wednesday, July 28, 2010 4:49 PM  
**To:** 'Linda Cheng'  
**Cc:** 'Maria Cheng'; 'Seymour Fein'  
**Subject:** IND 76667: Preliminary FDA Responses in Preparation for Pre-NDA Meeting on July 30, 2010  
**Attachments:** Pre NDA Preliminary Responses IND 76667.pdf

Dear Linda,

Please find attached our preliminary responses in preparation for this Friday's Pre-NDA meeting to discuss IND 76667, desmopressin acetate nasal spray. As indicated in the CMC section, responses from the Office of Compliance and the Center for Devices and Radiological Health (CDRH) are forthcoming.

Let me know if you have any questions or concerns. We look forward to a productive discussion on Friday.

Kind Regards,  
Jennifer

**Jennifer Johnson**  
**Regulatory Project Manager**  
**Division of Metabolism & Endocrinology Products**  
**Center for Drug Evaluation and Research**  
**Food & Drug Administration**  
**301-796-2194 phone**  
**301-796-9712 fax**  
[jennifer.johnson@fda.hhs.gov](mailto:jennifer.johnson@fda.hhs.gov)

**Application No:** IND 76667  
**Drug Name:** Desmopressin Acetate Nasal Spray  
**Sponsor:** Serenity Pharmaceuticals, LLC  
**Meeting Date:** Friday, July 30, 2010  
**Meeting Time:** 1:00 – 2:30 pm

**Preliminary Responses to Questions for Further Discussion with Sponsor**

*This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting (teleconference) scheduled for July 30, 2010, at 1:00 pm, between Serenity Pharmaceuticals, LLC and the Division of Metabolism and Endocrinology Products (DMEP). This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. **If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact Jennifer Johnson).** It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. Please note that if there are any major changes to your development plan/the purpose of the meeting/to the questions based on our responses herein, we may not be prepared to discuss or reach agreement on such changes at the meeting. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager to discuss the possibility of including these for discussion at the meeting.*

**QUESTIONS FOR THE AGENCY**

**CLINICAL QUESTIONS AND ISSUES**

1. Serenity plans to include in the integrated summary of efficacy (ISE) the two randomized, double-blind, placebo controlled studies (SPC-SER120-DB1-2009-01 and SPC-SER210-DB2-2009-02), the open-label safety extension study (SPC-SER120-OL1-2009-03), the elderly PK/PD safety study (SPC-SER120-ELD-2010-01) and the phase 2A study in nocturia patients (SPC DESMO-NS 200802). These clinical studies were not designed for pooling of efficacy data and have greater statistical value as independently analyzed databases. Therefore, we plan to present summary efficacy data from each of these studies individually and not to pool efficacy data among the studies. Serenity does not plan to prepare a statistical analysis plan for the ISE as the data are presented by individual study.

Does FDA agree with the planned scope and presentation of efficacy data in the ISE?

**FDA Preliminary Response: It is acceptable to present the individual study data separately. However, we would like to see analyses of the primary endpoint and any secondary endpoints that you consider significant using pooled data from all the Phase 3 trials (i.e., the two placebo-controlled trials, the open label extension and the elderly trial). The data should present both short-term and long-term efficacy and look at efficacy by age, gender and race sub-groups.**

2. Serenity plans to include all studies in nocturia patients in the integrated summary of safety (ISS) and to pool the summary safety data across these studies. We do not plan to integrate or present in the ISS the safety data from the first phase 1 PK/PD study in water loaded subjects, SPC DESMO-NS-200801 or the single dose phase 1 PK study in patients with moderate renal insufficiency, SPC-SER120-CRI-2010-02. The statistical analysis plan for the ISS will be submitted in August 2010.

Does FDA agree with the planned scope, presentation of safety data in the ISS and timing of the submission?

**FDA Preliminary Response: Yes, but we also request the following data in the ISS: a table listing the number and percentage of patients with serum sodium levels in the following categories < 135, 130-134, 125-129 and < 125 mmol/L, with respect to dose. Additional tables showing these data sub-grouped with respect to age (e.g., <65, ≥65, and ≥75 years), race and gender. Case narratives for all patients with serum sodium levels ≤125mmol/L, including all available sodium and serum creatinine measurements, dosing of desmopressin and concomitant medications, and history of intercurrent illnesses.**

3. Serenity proposes to put the text portion of the integrated summary of safety (ISS) in Module 2, Section 2.7.4. Only summary tables and data listings of the pooled data will be put into Module 5, Section 5.3.5.3 as per FDA guidance.

Does FDA agree with this proposal?

**FDA Preliminary Response: Yes.**

4. Serenity submitted on January 14, 2010 (IND Amendment, Serial # 0016) the statistical analysis plan (SAP) for the two pivotal phase 3 studies to FDA for review and comments. On April 12, 2010 we received an email from the Division that it had no comments on these SAPs. Based on that communication Serenity believes FDA has accepted the SAPs for these two pivotal phase 3 studies.

Does FDA confirm that it has reviewed and accepted these two SAPs?

**FDA Preliminary Response: No. We did not review the SAPs. We did review the Special Protocol for Study 200901, which we consider sufficient. We note that you modified the protocol in response to our SPA review comments, and informed us in**

**your Pre-sNDA meeting briefing document that the two pivotal Phase 3 studies have not been amended in any substantive manner since the written Special Protocol Assessment agreements were reached. The review team rarely reviews SAPs submitted after the corresponding protocol has been reviewed, particularly a Special Protocol Assessment.**

5. Serenity had submitted a statistical analysis plan on May 27, 2010 (IND Amendment, Serial # 0022) for the randomized study in elderly patients (SPC-SER120-ELD-2010-01) which assigns patients to two dose levels of active study drug. The elderly study is primarily a safety and PK trial and not powered for statistical comparison of efficacy. The analysis will consist of descriptive statistics.

Does FDA agree with this approach?

**FDA Preliminary Response: Descriptive statistics for this PK study are acceptable. However, we do request the pooled analyses, including data from the elderly patient study, as described in the response to Question 1.**

6. Serenity anticipates that at the time of initial NDA filing it will submit safety data on approximately 550 patients with exposure to the low dose desmopressin acetate nasal spray product, 450 patients with at least one month exposure, 200 patients with at least 6 months exposure and 75 patients with at least 12 months exposure. Serenity anticipates that at the time of the 120 day safety update we will submit safety data on over 250 patients with at least 6 months exposure and over 100 patients with at least 12 months exposure to the active drug product.

Does FDA agree this safety database is adequate to support NDA approval?

**FDA Preliminary Response: No, at the time of submission we require final data on at least 200 patients out to 1 year, 300-600 patients out to 6 months and 1,500 patients with total exposure.**

7. Serenity was instructed by FDA at the pre-IND meeting in December, 2007 not to conduct testing of low dose desmopressin acetate nasal spray in pediatric patient population (See Appendix 1). Serenity has observed this restriction. In addition, the adult nocturia indication for which the nasal spray product is being developed does not apply to pediatric patients. At the EOP2 meeting on February 19, 2009, FDA was considering waiving the requirements for pediatric studies (See Appendix 2). Therefore, Serenity seeks confirmation that FDA will grant a pediatric waiver for this NDA.

Does FDA plan to grant a pediatric waiver?

**FDA Preliminary Response: Your request for confirmation that FDA will grant a pediatric waiver for this NDA is premature. A waiver decision is not final until the time**

of NDA approval and requires Pediatric Review Committee (PeRC) review before an action is taken.

When you submit your NDA, a pediatric plan must be submitted which includes an outline of the studies you are planning to conduct; these must be sufficient to demonstrate dose, safety and efficacy (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy). The pediatric plan must contain a timeline for the completion of these studies, including the date the protocol will be submitted, the date studies will be completed and the date studies will be submitted.

The criteria for granting a full or partial waiver of requirements to conduct pediatric studies under the Pediatric Research Equity Act of 2007 (PREA) are limited to the following:

**(A) FULL WAIVER.**—At the request of an applicant, the Secretary shall grant a full waiver, as appropriate, of the requirement to submit assessments under this subsection if the applicant certifies and the Secretary finds that—

- i. necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed) (section 505B(a)(4)(A)(i) of the Act);
- ii. there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups (section 505B(a)(4)(A)(ii) of the Act). If a waiver is granted based upon evidence that the drug is unsafe or ineffective in pediatric populations, the applicant must include this information in the labeling for the drug or biological product (section 505B(a)(4)(D) of the Act); or
- iii. The drug or biological product-- (I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients; and (II) is not likely to be used in a substantial number of pediatric patients (section 505B(a)(4)(A)(iii) of the Act).

**(B) PARTIAL WAIVER.**—On the initiative of the Secretary or at the request of an applicant, the Secretary shall grant a partial waiver, as appropriate, of the requirement to submit assessments under this subsection with respect to a specific pediatric age group if the applicant certifies and the Secretary finds that—

- i. necessary studies are impossible or highly impracticable (because, for example, the number of patients in that age group is so small or the patients in that age group are geographically dispersed); (section 505B(a)(4)(B)(i) of the Act).
- ii. there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in that age group (section 505B(a)(4)(B)(ii) of the Act). If a waiver is granted based upon evidence that the drug is unsafe or ineffective in pediatric populations, the applicant must include this information in the labeling for the drug or biological product (section 505B(a)(4)(B)(ii) of the Act).
- iii. The drug or biological product--(I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group; and (II) is

- not likely to be used by a substantial number of pediatric patients in that age group; (section 505B(a)(4)(B)(iii) of the Act); or
- iv. The applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed (section 505B(a)(4)(B)(iv) of the Act).

**(C) PEDIATRIC FORMULATION NOT POSSIBLE—**If a waiver is granted on the ground that it is not possible to develop a pediatric formulation, the waiver shall cover only the pediatric groups requiring that formulation. An applicant seeking either a full or partial waiver shall submit to the Secretary documentation detailing why a pediatric formulation cannot be developed and, if the waiver is granted, the applicant's submission shall promptly be made available to the public in an easily accessible manner, including through posting on the Web site of the Food and Drug Administration (section 505B(a)(4)(C) of the Act).

If you are requesting a full or partial waiver, you must provide a scientific rationale supported by sufficient data to justify each applicable waiver criteria cited in your request. Such data could include, but are not limited to, epidemiological data and drug use data (for related therapies of primary nocturnal enuresis). If you are requesting a waiver based on safety concerns or lack of efficacy, you must submit proposed labeling which reflects the lack of efficacy and/or the safety concern.

8. Serenity plans to include a selected literature review of published papers in which desmopressin has been used to treat patients with nocturia. We do not plan to submit a comprehensive literature review of desmopressin for other clinical indications.

Does FDA agree with this plan?

**FDA Preliminary Response: Yes, include in the submission all available data which support clinical benefit from the reduction of nocturia in adults and the elderly.**

9. Based on the EOP2 meeting minutes, Serenity understands that product labeling will be based on the data provided in the NDA and not on data related to class labeling. Therefore, Serenity believes risk management issues can be adequately addressed through product labeling including the patient package insert.

Does FDA agree?

**FDA Preliminary Response: A complete review of the full risk management plan after the NDA is submitted will be necessary to determine whether it is acceptable, since additional information regarding risks and safe product use may emerge during the review of your NDA.**

#### DATABASE QUESTIONS AND ISSUES

10. Serenity plans to submit an application for SER120 in eCTD format in accordance with ICH eCTD specifications, version 3.2.2, dated July, 2008 using the most recent specifications as found at <http://www/fda/gov/cder/regulatory/ersr/ectd.htm> through the electronic submission gateway. Serenity is planning to submit the eCTD submission as the archival copy. All documents will be bookmarked and hyperlinked in accordance with the 1999 FDA guidance.

Does FDA agree with this approach?

**FDA Preliminary Response: Yes.**

11. Serenity plans to submit the proposed labeling text in SPL format in accordance with the current SPL schema. The proposed labeling, formatted according to 21 CFR 201.56(d) and 201.57 will also be provided in Microsoft Word. All additional labeling components will be provided as pdf files.

Does FDA agree with this approach?

**FDA Preliminary Response: Yes.**

12. Serenity plans to submit SAS raw and analysis datasets in lieu of case report tabulations, i.e. by patient data listings, for all Phase 3 clinical studies. Each dataset will be provided as a SAS transport file according to the relevant guidance. Both electronic raw and analysis datasets along with appropriate metadata and annotated CRFs will be provided. We do not plan to follow the proposed Study Data Tabulation Model Standards (CDISC- SDTM) as this is not a current requirement. The SAS datasets will be accompanied by a define.pdf file.

Does FDA agree with this approach?

**FDA Preliminary Response: The Division would appreciate if the data followed Study Data Tabulation Model Standards (CDISC-SDTM), as this would make a review of the data easier.**

13. Serenity plans to submit the draft specifications for the analysis datasets and the data listing datasets for FDA review in August/September 2010. Serenity plans to schedule a teleconference with the FDA statistician to discuss these specifications.

Does FDA agree with this approach and the timing of the planned submission of these specifications?

**FDA Preliminary Response: A teleconference is probably not necessary. Please submit to us your draft specifications for the analyses datasets and the data listing datasets for our review.**

14. Serenity plans to submit case report forms for any patient who died, had a serious adverse event or discontinued due to an adverse event to the drug product. Each case report form will be submitted as a single pdf file and will be bookmarked by visit and domain.

Does FDA agree with this approach?

**FDA Preliminary Response: Include a table with Case Report Forms (CRFs) grouped by the following categories: deaths, serious adverse events, drop-outs and any patient with a serum sodium level  $\leq 125$  mmol/L in the Integrated Summary of Safety (ISS).**

15. A draft high level eCTD Table of Contents for the proposed NDA is provided in Appendix 3. Does FDA agree with the proposed content and organization of this submission?

**FDA Preliminary Response:**

- **Include a detailed risk-benefit analysis in the Clinical Overview section 2.5.**
- **Include a Risk Management Plan in Section 1.16 if warranted.**
- **Include pooled efficacy and safety analyses requested in the responses to Questions 1 and 2 in Section 5.3.5.3 Reports of Analyses from More Than One Study.**
- **Include a coding dictionary used for mapping investigator verbatim terms to preferred terms as a SAS transport file along with the datasets in Section 5.3.5.3.25.3.**

16. Serenity plans to include patient narratives for deaths and serious adverse events within each clinical study report submitted with the NDA.

Does FDA agree with this proposal?

**FDA Preliminary Response:**

- **Include narratives for all adverse dropouts and for any patient with a serum sodium level  $\leq 125$  mmol/L (see response to Question 2) within each clinical study report.**
- **Include the pooled patient narratives from all Phase 3 studies in the relevant sections of the ISS.**

#### PHARM/TOX QUESTIONS AND ISSUES

17. FDA indicated to Serenity during the pre-IND meeting that no additional pre-clinical pharmacology or pharmacokinetic studies would be required for this program to support the NDA (See Appendix 4).

Does FDA confirm this position?

**FDA Preliminary Response: No. The mechanism of action and toxicity profile of desmopressin is well-understood. Your product uses low-dose intranasal instillation of**

desmopressin in a novel formulation with CPE-215® to increase the bioavailability of desmopressin. We acknowledge that subchronic toxicity studies with CPE-215® have been presented in IND (b) (4). However, there are no nonclinical studies conducted with your proposed intranasal product. While this information is supportive of sufficient safety to allow clinical trials under the IND it may not be sufficient to support a 505(b)(2) NDA application. See response to Question 18.

18. FDA indicated to Serenity during the pre-IND meeting that the only pre-clinical toxicology studies which were required for this program to support the NDA were the three topical nasal studies in the (b) (4) IND and to which Serenity has a right of reference through a letter of authorization sent by (b) (4) to FDA. These three studies are a 28 day rat study, a 13 week rat study and a 13 week dog study and evaluated both bland formulation containing CPE-215 and the same formulation containing (b) (4) (See Appendices 5, 6 & 7).

Does FDA confirm that this package of pre-clinical toxicology studies satisfies the requirement to support this NDA?

**FDA Preliminary Response:** No. You are proposing a 505(b)(2) nonclinical development pathway for the intranasal desmopressin spray. Although the PD/PK/Tox profiles for desmopressin are well-established in published literature, this drug product has different excipients compared to the approved desmopressin products. Even though you have referenced these excipients to IND (b) (4) (toxicity studies including one major excipient, CPE-215®), the formulations between these two IND products are also not identical. IND (b) (4) whereas IND 76667 is an intranasal desmopressin spray. There might be a difference in the impurity and degradant profiles of these two products, which may require further characterization.

Since you plan to submit a 505(b)(2) NDA application, which relies in part on FDA's finding of safety and effectiveness for an approved desmopressin product, you will be required to: (1) demonstrate sufficient similarity between your product (i.e., drug substance and drug product) and that referenced desmopressin, and (2) provide scientific justification for this reliance. Currently, there is not an established bridge between your product and the referenced product. In addition, based on potential differences in impurity/degradant profiles of your product, it is recommended that you perform a comparative, subchronic bridging toxicology study (with toxicokinetics) in a relevant species to provide this bridge and qualify any impurity/degradant differences between your product and the desmopressin product you plan to reference in your NDA application. The comparative bridging toxicology study should evaluate a standard toxicology tissue battery as well as assess local toxicity. Based on published literature indicating greater absorption of peptides to the olfactory nerve centers when administered via intranasal routes, an assessment of distribution into the brain as well as histopathology is encouraged.

19. Serenity does not plan to include a literature review of published papers concerning desmopressin pre-clinical pharmacology, toxicology and pharmacokinetics.

Does FDA agree?

**FDA Preliminary Response: Yes. Based on the clinical experience with marketed desmopressin products, no literature review is needed for preclinical data of desmopressin alone.**

#### CMC QUESTIONS AND ISSUES

20. Serenity has previously submitted drug product release test methods and specification which have been discussed with FDA. These test methods and specifications are presented in the briefing package (See Appendix 8). In addition, characterization of the drug product and formulation components using the chromatographic methods confirms that the (b) (4) peaks in the drug product are from formulation components. These validated methods and specifications have been used during development and it is our plan to use these methods and specifications for product release post approval.

Does FDA agree that these proposed release tests and specifications are acceptable for this product?

**FDA Preliminary Response: We cannot agree at this time that your proposed tests and acceptance criteria are completely adequate for your nasal spray. Upon review of your NDA we may ask you to add or modify the drug product specification as appropriate. You should consider the following advice as reflective of our current (but not final) thinking about your drug product's specification:**

- Normally, the FDA approves an assay specification of (b) (4)% of label claim or tighter. Accordingly, justify your (b) (4) acceptance criteria for the desmopressin assay.
- Your osmolality specification should also have a numerical lower limit, based on your batch data; you should explain why your nasal spray is formulated to be hypotonic.
- The CPE-215 acceptance limits should be narrowed unless you can justify your wide assay limits for this enhancer. For example, we would like to see data or other arguments that show that at the upper and lower levels of your proposed CPE-215 content there are no significant differences in the rate of absorption into the blood stream, and that your assay limits for this enhancer reasonably reflect your batch data. Additionally, have you demonstrated whether or not there is any direct-to brain-absorption of your drug; and if so is this type of absorption significantly different at the upper and lower limits of the CPE-215 enhancer?

- There are discrepancies between the drug product specification listed in your Amendment submitted on June 14, 2010 (Vol. 5, pp. 2549-2553) and the acceptance criteria provided in the meeting briefing document submitted on June 25, 2010 (Appendix 8, pp.116-117). In this connection, in addition to the % of droplets that are (b) (4)  
(b) (4)
- Your allowable limits for foreign particulate are too high and not justified by the data from the nasal sprays that you have produced. You should also explain the nature and origin of your foreign particulates.
- You do not have a specification for Individual Related Impurities and Total Related Impurities. What levels of these impurities and their total do you find in your product at release, and as a result of your long term and accelerated stability storage conditions?
- We did not see a release specification for Spray Pattern in Appendix 8 of your meeting briefing document. In accordance with our Guidance for Industry (Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products—Chemistry, Manufacturing, and Controls Documentation), a release specification should be established for the spray pattern of your drug product. In the evaluation of the spray pattern, the spray distance between the nozzle and the collection surface, number of sprays per spray pattern, position and orientation of the collection surface relative to the nozzle, and visualization procedure should be specified. The acceptance criteria for spray pattern should include the shape (e.g., ellipsoid of relative uniform density) as well as the size of the pattern (e.g., no axis is greater than x millimeters and the ratio of the longest to the shortest axes should lie in a specified range). Data should be provided to demonstrate that the collection distance selected for the spray pattern test will provide the optimal discriminatory capability.
- Microbial and endotoxin limits will be evaluated by our Microbiologist as part of the NDA Review.

**Additional preliminary product quality microbiology comments:**

IND 76,667 has not been reviewed for product quality microbiology. The CMC information provided in the meeting package was insufficient for the evaluation of product quality microbiology content. The product is a hypotonic solution with no preservative and the manufacturing process indicates that the drug product solution is (b) (4). The product description as well as the release criteria based on Microbial Limits and Bacterial Endotoxins Tests indicates that the product is not sterile. The release criteria are adequate for a non-sterile product. This meeting package did not contain container/closure information or information on how the

(b) (4) Pump operates in concert with the system. However, there was a validation report for gamma irradiation on (b) (4) Pumps. Therefore, from a microbiology product quality standpoint, the following information will be needed at the time of NDA submission:

- Include a detail description of the manufacturing process for the non-sterile product. Generally, for drug absorption through nasal passage, the drug product must have a preservative, unless the product itself has inherent antimicrobial properties. With no preservative in the product, the sponsor must provide a reasonable assurance of microbiological safety of this product over its shelf-life.
- Include a complete description of the container closure system with the operation of the (b) (4) Pump. As is the case with the (b) (4) Pump, does the sponsor intend to gamma irradiate the remaining product container closure system?
- Microbial and endotoxin testing should be carried out at release and at the end of stability time point as well as annually between these time points.
- For finished products which do not purport to be sterile, they are expected to meet the requirements of 21CFR211.113(a) Control of microbiological contamination.
- In addition, for aqueous finished products such as Desmopressin Acetate Nasal Spray that do not purport to be sterile, they should be tested for *Burkholderia cepacia* and the process controls should include tests of potential sources of this species. Provide test methods and acceptance criteria to demonstrate the product is free of the objectionable microorganism *Burkholderia cepacia*. We recommend that potential sources are examined and sampled as process controls, and these may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria. Your test method should be validated and a discussion of those methods should be provided. Test method validation should address multiple strains of the species and cells that are acclimated to the environments (e.g., warm or cold water) that may be tested. Potential sources may include raw materials and the manufacturing environment. Please see the information below on the opportunistic pathogen.

**Background Information on *Burkholderia cepacia*:**

*Burkholderia cepacia* is an opportunistic pathogen that is commonly found in water and soil. It is often present in commercial water systems as well as natural environments. It is capable of growing in distilled water. Strains of this species can grow in the presence of disinfectants and antimicrobial preservatives, and are used commercially in

**bioremediation to degrade toxic chemicals. Recent recalls due to this species in non-sterile drug and cosmetic products have been reported and it has been implicated in deaths among compromised patients. *B. cepacia* may be difficult to recover with bacteriological media when present in water that is cold (<7°C) or is very warm (>46°C).**

21. Serenity has conducted its drug product stability evaluation using protocols, testing methods and specifications previously presented to FDA. A list of the validated methods and specifications is presented in this briefing document (See Appendix 8). In addition, stability protocols that identify the array of storage conditions and sampling times evaluated were submitted to FDA in IND Amendment, Serial # 0024 on June 14, 2010.

Does FDA agree that this stability program is adequate to support the approval of this product?

**FDA Preliminary Response: Our responses to Question 20 largely apply to your proposed stability program. However, we have the following additional comments:**

- **To support your claim that the nasal spray can be stored by the patient for** (b) (4)  

- **Depending on the merits of your explanation for not having a specification for Individual Related and Total Related Impurities, you may be requested to monitor these impurities as part of your stability program.**
- **Droplet size distribution should be monitored during the** (b) (4) **stability studies.**
- **Microbial and endotoxin testing should be carried out** (b) (4), (b) (4)  

- **Leachables/extractables should be monitored** (b) (4), (b) (4)  


(b) (4)

22. The NDA will include stability data from seven batches of product used in the clinical development program and from several additional batches of product to be manufactured in 2010. Four batches contain 5 µg/mL drug concentration and three batches contain 7.5 µg/mL drug concentration. At NDA filing, storage durations will be 24 months for one batch (5 µg/mL), 18+ months for two others (one at each concentration strength), 12+months for two others (one at each concentration strength) and 9+ months for two others (one at each concentration strength). During the review period, batches will continue on stability for six of these seven lots, with five lots passing 24 months and two lots passing 18+ months on storage (See Appendix 9). All available data from these 7 batches submitted to FDA in the IND Amendment, Serial # 0024 on June 14, 2010 indicate that the product is stable for 24 months

(b) (4)

Does FDA agree that this stability program and supporting data are sufficient for NDA submission and approval (pending data review) of a 24 month shelf life

(b) (4)

?

**FDA Preliminary Response: Assuming the advice previously noted is incorporated into your stability program, as appropriate, the amount of data you plan to provide at filing appears to be adequate. If there were no differences (quantitative composition or container/closure system) between the batches in the clinical development program and the to-be-marketed products, and if at least two of these lots were pilot scale batches, they will be considered as part of the primary stability package; otherwise, data from these batches will be deemed as supporting findings. To further support your stability claim, you should also provide the results of stress testing experiments for the nasal spray.**

23. Serenity has initiated an evaluation of leachables/extractables for contact materials in the container/closure system. The extractables portion is complete and the summary data as well as the calculated total daily intake from multiple solvents tested are included in Appendices 10 and 11 of this briefing document. Also included in Appendix 12 is the summary for the targeted leachables program and the planned specifications. Samples across the stability program will be used to assess the leachables content.

Does FDA agree that the test methods and specifications for leachables/extractables are acceptable to support the approval of the product?

**FDA Preliminary Response: The leachables/extractables evaluation methods and data that you provided are adequate, except that you should justify why (b) (4) was not also employed as a solvent in your extraction procedures. The acceptance criteria for the**

**various potential leachables to be monitored on stability are review issues to be decided jointly by our CMC and Toxicology teams.**

24. Serenity has included in the briefing document product characterization protocols in Appendix 13 (please see list of test methods in Appendix 8).

Does FDA agree that the product characterization program planned is acceptable to support the approval of this product?

**FDA Preliminary Response: Your product characterization program appears to be adequate except for the proposed (b) (4) studies. In addition to the monitoring for Appearance and Droplet Size Distribution, according to our Nasal Spray Guidance, periodically throughout the (b) (4) study, and at the end of a predetermined number of cycles, the samples should be analyzed for appropriate parameters and compared with the control drug product. Test parameters (b) (4) should also include particle size distribution, microscopic evaluation, assay, Spay Content Uniformity (SCU), sterility, and functionality of pump components. A validated container closure integrity test, instead of sterility testing, can be used to assess sterility and demonstrate maintenance of the integrity of the microbial barrier provided by the container closure system. With regard to appearance of the nasal spray, you should consider, as applicable, the discoloration of the formulation, distortion of pump components, pump clogging, and adherence of the drug to the walls of the container, closure, and/or pump components.**

25. Serenity has undertaken a manufacturing process development for two dosage strengths of a low bioburden nasal spray drug product. This program included two batches made at greater than (b) (4)% commercial scale (one of each dosage strength) and four batches made at (b) (4)% of intended commercial scale (one of each dosage strength). As previously discussed with FDA, the drug products differ only by the content of the API which is present in the finished product at less than (b) (4)% of the formulation. Except for the necessary difference in the API weighing step the production processes (b) (4). Serenity has submitted a manufacturing process validation protocol in Appendix 14 of this briefing packet which includes production of four full scale batches (two of each dosage strength).

Does FDA agree that the process validation plan as described in the protocol is acceptable to support the commercial distribution of this product?

**FDA Preliminary Response: This question will be answered by the Office of Compliance.**

26. Serenity has included the validation report from (b) (4) using gamma irradiation to sterilize the (b) (4) pumps to be used in this product in Appendix 15. A right of reference to the (b) (4) DMF will be included in the NDA.

Does FDA agree that the sterility assurance level, procedures described and the use of gamma radiation meets the sterilization standard for the intended use of the (b) (4) pumps?

**FDA Preliminary Response:** This question will be answered by the staff of the Center for Devices and Radiological Health (CDRH).

27. Serenity plans to have alternative sourcing for API and CPD and proposes to utilize these alternative sources for manufacture of finished drug product based on the validated release testing of finished drug product batches containing alternate source API and CPD with certificates of analysis meeting the specifications and showing comparability among the alternative sourcing compounds (See Appendices 16 – 24).

Does FDA agree?

**FDA Preliminary Response:** We will have to see the details of your compatibility assessments between the various suppliers of desmopressin acetate and cyclopentadecanolide (CPD) before we can say that your compatibility assessments are adequate. In this regard, note the following points:

- In the NDA, provide an extensive comprehensive comparative characterization of the material from the different suppliers, including structural analysis and impurity comparison.
- The Agency will have to review all of the relevant DMF.s from the suppliers of the API and CPD after the NDA is submitted. We did not see, however, reference to a DMF for the CPD manufactured by (b) (4). If there is no DMF for this cyclopentadecanolide, your NDA should provide all of the Chemistry, Manufacturing, and Control (CMC) information for this product, in as much detail as would be required for an API.
- Since different suppliers, almost certainly, have a number of differences in their processes, different impurities may be present in the alternative APIs and CPDs. Therefore, any new impurities may necessitate additional acceptance testing and specifications; and any new impurities that have a safety concern may have to be evaluated by our toxicologists.
- You should demonstrate that your drug products meet their specifications regardless of the source of the drug substance and the enhancer by manufacturing and monitoring 4 registration batches ((b) (4) desmopressin with (b) (4) CPD, (b) (4) desmopressin with (b) (4) CPD, (b) (4) desmopressin with (b) (4) CPD, and (b) (4) desmopressin with CPD).

The use of an API from an alternate supplier, may call for additional Validation Batches, subject to a determination by the Office of Compliance.

- **If you have no significant body of data with the products from the proposed alternative suppliers, the agency would like to see data from one or two extra batches of (b) (4) desmopressin with (b) (4) CPD, (b) (4) desmopressin with (b) (4) CPD, and (b) (4) desmopressin with (b) (4) CPD from accelerated (40°C/75% RH ) stability studies.**
- **Your post-approval stability protocol should reflect drug products that you plan to market made with those combinations of desmopressin and CPD from the different suppliers.**
- **To avoid complications and possible delay in the approval of your nasal spray, you might consider qualifying the desmopressin and CPD from the alternate suppliers by means of a post-approval supplement.**

#### **Additional Clinical Pharmacology Comment**

We would like to remind you that you should adequately characterize the pharmacokinetics (PK) of desmopressin from the to-be-marketed formulation at the intended clinical doses and dosing regimen.

#### **Additional Comments Pertaining to Submission of 505(b)(2) New Drug Applications:**

- A. A 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/01p-0323-pdn0001-vol1.pdf>).**
- B. If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must**

establish that reliance on the studies described in the literature is scientifically appropriate.

- C. In your submission of a New Drug Application under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, you should clearly identify the information for the proposed drug product that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature.

In addition to identifying the source of supporting information in annotated labeling, the information may be summarized in a table such as the one below

Source of information (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
1.	
2.	
3.	
4.	

- D. Reliance on information for another product (whether a previously approved product or from published literature) must be scientifically appropriate. Describe how you bridged the proposed product to the referenced product(s); for example, BA/BE studies. Also, identify the specific (e.g., brand name) name of each listed drug named in any of the published literature on which your application relies to support approval.
- E. We remind you that your labeling must conform to the Physicians Labeling rule (PLR) format and that 505(b)(2) applications are subject to the Prescription Drug User Fee Act.
- F. Also, it will be necessary to identify the listed drug and/or literature used to support each section of your application, including the labeling. If literature is used, copies of the articles must be included and any trade/proprietary names given in those reports identified. Further, a 505(b)(2) application may not rely on any specific data for the listed drug (e.g., such as that included in a summary basis of approval). Please note that the listed drug relied upon for approval must have been approved under section 505(b) of the Federal Food, Drug, and Cosmetic Act; applications approved under section 505(j) (generics) may not be relied upon.

**Additional comments from the Office of Compliance, Division of Scientific Investigations (DSI), regarding requests for data to be submitted to the sNDA:**

**I. Request for general study related information as well as specific Clinical Investigator (CI) information to be used in site selection:**

- A. Please include the following information in a tabular format for the clinical trial:
1. Site number
  2. Primary investigator
  3. Location: City State, Country, including contact information (phone, fax, email)
- B. Please include the following information in a tabular format by site for the clinical trial:
1. Number of subjects screened at each site by site
  2. Number of subjects treated at each site by site
  3. Number of subjects treated who prematurely discontinued at each site by site
- C. Please include the following information in a tabular format for the clinical trial:
1. Name, address and contact information of all Contract Research Organizations (CROs) used in the conduct of the clinical trials
  2. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
  3. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)
- D. Sample blank case report form

**II. Request for Individual Patient Data Listings to be used for inspections:**

For the trial: Site-specific individual subject data (“line”) listings from the datasets:

1. Line listings for each site listing the subject number screened and reason for subjects who did not meet eligibility requirements
2. Line listings by site and subject, of treatment assignment and treatment administered
3. Line listings by site and subject, of drop-outs and discontinued subjects with date and reason
4. Line listings by site of evaluable subjects/ non-evaluable subjects and reason not evaluable
5. Line listings by site and subject, of AEs, SAEs, deaths and dates
6. Line listings by site and subject, of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
7. Line listings by site and subject, of the primary and secondary endpoint efficacy parameters (frequency of vaginal bleeding days, bone age advancement, growth velocity, predicted adult height, Tanner stage, uterine volume, ovarian volume, hormone levels)
8. Pharmacokinetics data
9. Line listings by site and by subject, of concomitant medications

### **III. Request for Site Level Data**

DSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to the attached document, "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" for further information. We request that you provide datasets, as outlined, for the study submitted in your application.

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

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## **I. INTRODUCTION**

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

## **II. DESCRIPTION OF THE SUMMARY LEVEL CLINICAL SITE DATASET**

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection and are not intended to support evaluation of efficacy. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

### **Site-Specific Efficacy Results**

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- Treatment Efficacy Result Variance (TRTEFFV) – the variance of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis
- Site-specific Efficacy Effect Size Variance (SITEEFFV) – the variance of the site-specific efficacy effect size (SITEEFFE)

- 
- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.
  - Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) – the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, “TRTEFFR”.

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.
- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.
- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).
- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the “endpoint” plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1.

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### **III. CREATING AND SUBMITTING THE DATA FILE (SUBMISSION TEMPLATE AND STRUCTURE)**

A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (\*.xpt). The file may be submitted electronically through the FDA Electronic Submission Gateway (ESG) referencing the active IND number or via secure CD addressed to the Division of Scientific Investigations point of contact.

Exhibit 1: Summary Level Clinical Site Data Elements

Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
IND	IND Number	Num/Char	6 digit identifier	FDA identification number for investigational new drug	010010
TRIAL	Trial Number	Char	String	Study or Trial identification number	ABC-123
SITEID	Site ID	Num/Char	String	Investigator site identification number	50
ARM	Treatment Arm	Num/Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters)	Active (e.g. 25mg), Comparator drug product name (e.g. Drug x), or Placebo
ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site	20
SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site	100
DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site	5
ENDPOINT	Endpoint	Char	String	Plain text label used to describe the primary endpoint as described in the Define file included with each application. (limit 200 characters)	Average increase in blood pressure
ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other)	Continuous
TRTEFFR	Treatment Efficacy Result	Num	Floating Point	The efficacy result for each primary endpoint, by treatment arm	0, 0.25, 1, 100
TRTEFFV	Treatment Efficacy Result Variance	Num	Floating Point	The variance of the efficacy result (TRTEFFR) for each primary endpoint, by treatment arm	0, 0.25, 1, 100
SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	The effect size should be the same representation as reported for the primary efficacy analysis	0, 0.25, 1, 100
SITEEFFV	Site-Specific Efficacy Effect Size Variance	Num	Floating Point	The variance of the site-specific efficacy effect size (SITEEFFE)	0.065
CENSOR	Censored Observations	Num	Integer	The number of censored observations for the given site and treatment	5
NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site. This value should include multiple events per subject.	10
SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site. This value should include multiple events per subject.	5
DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site	1

Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
PROTVIOL	Number of Protocol Violations	Num	Integer	Number of deviations from the protocol noted by the sponsor for a given site. This value should include multiple violations per subject.	20
FINLDISC	Financial Disclosure Amount	Num	Integer	Total financial disclosure amount (\$USD) by the site investigator	50000.00
LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572	Doe
FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572	John
PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator	555-555-5555, 44-555-555-5555
FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator	555-555-5555, 44-555-555-5555
EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator	john.doe@mail.com
COUNTRY	Country	Char	ISO 3166-1-alpha-2	Country in which the site is located	US
STATE	State	Char	String	Unabbreviated state or province in which the site is located	Maryland
CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located	Silver Spring
POSTAL	Postal Code	Char	String	Postal code for the site	20850
STREET	Street Address	Char	String	Street address and office number at which the site is located	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

**Exhibit 2: General Structure of Data Submission Template**

IND	TRIAL	SITEID	ARM	ENROLL	SCREEN	DISCONT	ENDPOINT	ENDTYPE	TRTEFFR
000001	Study 1	001	Active	26	61	3	Percent Responders	Binary	0.48
000001	Study 1	001	Placebo	25	61	4	Percent Responders	Binary	0.14
000001	Study 1	002	Active	23	54	2	Percent Responders	Binary	0.48
000001	Study 1	002	Placebo	25	54	4	Percent Responders	Binary	0.14
000001	Study 1	003	Active	27	62	3	Percent Responders	Binary	0.54
000001	Study 1	003	Placebo	26	62	5	Percent Responders	Binary	0.19
000001	Study 1	004	Active	26	29	2	Percent Responders	Binary	0.46
000001	Study 1	004	Placebo	27	29	1	Percent Responders	Binary	0.12

TRTEFFV	SITEEFFE	SITEEFFV	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLDISC	LASTNAME	FRSTNAME	PHONE
0.0096	0.34	0.0198	NA	0	2	0	1	0.00	Doe	John	555-123-4567
0.0049	NA	NA	NA	2	2	0	1	0.00	Doe	John	555-123-4567
0.0108	0.33	0.0204	NA	3	2	1	0	45000.00	Washington	George	020-3456-7891
0.0049	NA	NA	NA	0	2	0	3	45000.00	Washington	George	020-3456-7891
0.0092	0.35	0.0210	NA	2	2	0	1	0.00	Jefferson	Thomas	01-89-12-34-56
0.0059	NA	NA	NA	3	6	0	0	0.00	Jefferson	Thomas	01-89-12-34-56
0.0095	0.34	0.0161	NA	4	1	0	0	0.00	Lincoln	Abraham	555-987-6543
0.0038	NA	NA	NA	1	2	0	1	0.00	Lincoln	Abraham	555-987-6543

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

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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IND-76667

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GI-1

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SERENITY  
PHARMACEUTICA  
LS CORP

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DESMOPRESSIN

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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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JENNIFER L JOHNSON

07/28/2010

Preliminary comments sent to sponsor via email on July 28, 2010



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

IND 76,667

Serenity Pharmaceuticals Corporation  
Attention: Linda Cheng, M.S.  
Vice President of Project Management  
120 N. Main Street, Suite 400  
New City, NY 10956

Dear Ms. Cheng:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Desmopressin Nasal Spray.

We also refer to the meeting between representatives of your firm and the FDA on February 19, 2009. The purpose of the meeting was to discuss further clinical development of a novel formulation of low dose desmopressin nasal spray for the treatment of adult nocturia.

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 Meredith Alpert, Regulatory Project Manager at (301) 796-1218.

Sincerely,

*{See appended electronic signature page}*

Suresh Kaul, M.D.  
Acting Team Leader  
Division of Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** February 19, 2009  
**TIME:** 11 a.m.-12:30 p.m.  
**LOCATION:** White Oak Building 22, Room 1311  
**APPLICATION:** IND 76,667  
**DRUG NAME:** Desmopressin Nasal Spray  
**TYPE OF MEETING:** Type B (End of Phase II)  
**MEETING CHAIR:** Suresh Kaul, M.D.  
**MEETING RECORDER:** Meredith Alpert

### FDA ATTENDEES:

George Benson, M.D.	Deputy Director, Division of Reproductive and Urologic Products (DRUP)
Mary Parks, M.D.	Division Director, Division of Metabolism and Endocrinology Products (DMEP)
William Lubas, M.D., Ph.D.	Medical Officer, DMEP
Suresh Kaul, M.D.	Acting Medical Team Leader, DRUP
Olivia Easley, M.D.	Medical Officer, DRUP
Donna Christner, Ph.D.	Pharmaceutical Assessment Lead, Division of Pre-Marketing Assessment II (DPMA), Office of New Drug Quality Assessment (ONDQA)
Yichun Sun, Ph.D.	Chemistry Reviewer, DPMA, ONDQA
Eric Andreasen, Ph.D.	Pharmacologist, DRUP
Hae Young Ahn	Deputy Division Director, Office of Translational Sciences (OTS), Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology (DCP) III
Sandhya Apparaju, Ph.D.	Clinical Pharmacology Reviewer, OTS, OCP, DCP III
Sonia Castillo, Ph.D.	Statistical Reviewer, OTS, Office of Biostatistics (OB), Division of Biometrics III
Jennifer Mercier	Chief, Project Management Staff, DRUP
Charlene Williamson	Regulatory Health Project Manager, DRUP
Meredith Alpert, M.S.	Regulatory Health Project Manager, DRUP
Jennifer Johnson	Regulatory Health Project Manager, DMEP

### EXTERNAL CONSTITUENT ATTENDEES:

#### Serenity Pharmaceutical Corp.

Samuel Herschkowitz, M.D.	Chief Executive Officer
Seymour Fein, M.D.	Chief Medical Officer
Alain Kodsi, J.D.	V.P. of Business Development
Linda Cheng, M.S.	V.P. of Project Management

Maria Cheng, Ph.D.

V.P. of Clinical Operations

(b) (4)

**BACKGROUND:**

Serenity Pharmaceutical Corp. is developing a low-dose desmopressin nasal spray for the treatment of adult nocturia. Serenity has completed Phase I and Phase II clinical studies for the adult nocturia indication. The Phase I study in water loaded healthy volunteer subjects was completed in July, 2008, and the Phase II study in patients with nocturia was completed in November, 2008. The sponsor is planning to conduct two pivotal Phase III clinical trials during the second quarter of 2009.

On December 3, 2009, the sponsor submitted a Meeting Request to DRUP for an End of Phase II meeting to discuss the design, methodologies, and scope of the protocols for the Phase III program. DRUP emailed the Preliminary Comments to Serenity on February 17, 2009.

**MEETING OBJECTIVES:**

- To discuss the data from the Phase I and Phase II trials.
- To discuss further clinical development of a novel formulation of low dose desmopressin nasal spray for adult nocturia.
- To finalize plans for the Phase III pivotal studies between the Division and Serenity.

At the start of the meeting, DRUP informed the sponsor that IND 76,667 would be transferred to DMEP since all other existing desmopressin applications are currently held by DMEP. Any future correspondence regarding IND 76,667 should be directed to DMEP.

**General Comment:**

The Agency views the adult nocturia indication as a convenience indication and as such sponsors will be required to demonstrate efficacy with minimal safety risks. The FDA has removed the primary nocturnal enuresis indication from nasal sprays of desmopressin because of the high rate of hyponatremia associated with this method of administration. In addition, all desmopressin formulations have shown a higher rate of hyponatremia in patients over 50 years of age. Therefore, development of a nasal formulation of desmopressin for adult nocturia will need to enroll adequate numbers of elderly patients to convincingly rule out an increased risk of hyponatremia.

**Discussion:**

The sponsor acknowledged DMEP's concern regarding hyponatremia particularly in older patients. The sponsor stated that the purpose of the low dose desmopressin program was to avoid hyponatremia and clarified that the planned clinical development program would provide a database to demonstrate avoidance of this risk. The sponsor also referred to their Phase II data which demonstrated no cases of hyponatremia.

DMEP responded that in their review of U.S. post-marketing adverse event reports associated with desmopressin use, the rate of hyponatremic-seizures was higher than five-fold among users of the nasal spray than among those using oral desmopressin, and that this difference was not due to a difference in the number of prescriptions written as relatively more prescriptions were written for oral desmopressin over the time period of the review. The sponsor recognized DMEP's observations regarding hyponatremia with the nasal formulation. They stated that they were confident that their low-dose formulation would yield improved safety in terms of hyponatremia risk. They will ensure that their clinical data base contains a sufficient number of elderly subjects to ascertain the risk of hyponatremia in that population.

*Question 1. Serenity plans to conduct two pivotal phase III studies of low dose desmopressin nasal spray. Each study will enroll 300 patients and be double-blind and placebo controlled with a 3 month assessment period, followed by an open-label, 9 month safety extension study in which all patients receive desmopressin. Does FDA agree that two phase III trials of this design and sample size will be fully adequate to support NDA approval?*

**Division Response:**

The trial size will need to be recalculated using the new endpoint recommended in response to question 2.

Statistical comments regarding phase 3 protocols:

1. You define the ITT population as "all patients who receive study drug and who have some post-randomization safety data." We do not agree. The ITT population should be defined as all patients who receive any study drug. If a patient receives study drug but does not have any post-randomization data, then their baseline value should be carried forward to all time points of interest.
2. In your ANCOVA model with treatment group, study center, baseline number of nocturic episodes as covariate, and interactions between treatment group and study center and treatment group and covariate, you propose to remove any non-significant ( $p > 0.10$ ) interaction term from the final model. The final model should be pre-specified in the protocol and not derived after modeling the data. You could either keep the interaction terms in the model as is or propose that your final model is the one without interaction terms and then investigate the effect of interactions as supportive evidence.

**Discussion:**

The sponsor agreed to the statistical changes recommended by the DRUP statistical reviewer; specifically,

- Re-calculating trial size based on the two co-primary endpoints
- Defining the ITT population as all patients who receive study drug
- Using a LOCF approach to manage patients with no post-baseline data
- Pre-specifying the ANCOVA model that would be used in the Phase 3 protocol, and clarifying that the final model would be one without interaction terms and that a supportive analysis of the interaction terms would be performed.

At DMEP's request the sponsor agreed to stratify enrollment by age and gender. At the meeting DMEP had originally mentioned using 75 years for the age stratification because it was assumed that the risk of hyponatremia would be greatest in that age group. However since the sponsor expects to enroll < 10% of patients at age > 75 the Division has reevaluated and recommends that the sponsor stratify by age < 65 and ≥ 65, instead.

*Question 2. Serenity plans to designate the mean decrease in the number of nocturic episodes from a baseline lead-in period over the double-blind observation period after final dose titration as the primary efficacy endpoint for the phase III studies.*

*Does FDA agree?*

**Division Response:**

The Division recommends an endpoint which measures a clinically significant response in a substantial proportion of patients and not just a decrease in the mean number of voids per night. The efficacy of the drug should be assessed using co-primary endpoints including change from baseline to final titration visit (Day 28) in mean number of nocturnal voids, in addition to a measure of treatment success defined as greater than 33% reduction from baseline in the mean number of voids per night. Each measurement should be the average of three consecutive 24-hour periods. A statistically significant difference between groups would be required for both endpoints with each test conducted at the 5% alpha level.

**Discussion:**

The sponsor asked for clarification on DMEP's response. DMEP explained that the primary efficacy endpoints should be measured at the conclusion of the maintenance phase.

The sponsor proposed to define treatment success as % of patients with a (b) (4) % (not 33%) reduction from baseline in mean number of voids per night compared to placebo. DMEP agreed to the sponsor's proposal, but now is recommending that the sponsor consider measuring the % of patients with at least a 33% reduction from baseline compared to placebo as a secondary endpoint.

*Question 3. Serenity plans to define a nocturic episode as "A non-incontinent urinary void of any volume at night during the patient's normal hours of sleep following an initial period of sleep and, thereafter, preceded and followed by sleep or an attempt to sleep."*

*Does FDA agree?*

**Division Response:**

Yes.

**Discussion:**

**No discussion**

*Question 4. Serenity plans to designate as secondary efficacy variables the following:*

*The mean number of nocturic episodes over the double-blind observation period after final titration*

*The mean decrease in the number of nocturic episodes from baseline during the 2-week periods ending at 4, 8, and 12 weeks after final dose titration*

*Time from retiring to bed for purposes of sleep to first nocturic episode*

*Proportion of patients with a mean number of nocturic episodes of 0 to 1*

*Proportion of nights with 0 nocturic episodes*

*Proportion of nights with 1 nocturic episode*

*Proportion of nights with 0 or 1 nocturic episode*

*Quality of Life Assessment using validated instrument*

*Does FDA agree?*

**Division Response:**

The Division does not object to the evaluation of these secondary endpoints, but whether they will be included in labeling will be a review issue. In order to consider a secondary endpoint for inclusion in labeling, you will need to ensure that the study is adequately sized for the efficacy endpoint of interest and that there is control for the overall study significance level. You should propose a testing procedure to control the overall study significance level.

**Discussion:**

**The sponsor agreed that there were key secondary efficacy endpoints such as the proportion of nights with 0 nocturic episodes which would be beneficial to the patient. The sponsor proposed to select these secondary endpoints, prioritize them in order of clinical importance and then perform sequential statistical analyses allowing each succeeding endpoint to be analyzed only if the preceding one was positive. The sponsor stated that they wished to adequately size the study. DMEP agreed with the sponsor's approach** (b) (4)

*Question 5. Serenity plans to establish as an eligibility criterion for the phase III studies a minimum mean number of nocturic episodes per night of 2 during a lead-in period with diary recordings. Does FDA agree?*

**Division Response:**

Yes.

**Discussion:**

**DMEP recommended that the sponsor qualify the baseline number of nocturic voids among those patients who achieve zero nocturic episodes at study endpoint.**

*Question 6. Serenity plans to have enrollment criteria allowing patients with and being treated with drugs for overactive bladder and benign prostatic hypertrophy but still with the required nocturia symptoms to enroll in the phase III studies. In addition, Serenity plans to allow patients with modest degrees of polyuria (not caused by central diabetes insipidus, nephrogenic diabetes insipidus or severe renal impairment) on 24 hour urine collections to enroll in the phase III studies.*

*Does FDA agree?*

**Division Response:**

The Division agrees. We also recommend that you perform subgroup analyses on patients with polyuria and nocturnal polyuria (nocturnal urine volume >35%).

**Discussion:**

**The sponsor agreed with the DMEP's recommendation to perform subgroup analyses on patients with polyuria and nocturnal polyuria. The sponsor stated the recommended subgroup analyses would be for information purposes only because the number of patients with these conditions enrolled in the studies could not be anticipated beforehand. DMEP agreed.**

*Question 7. Serenity plans to provide safety data in approximately 250 patients with 12 months of drug exposure and approximately 500 patients with 6 to 9 months of drug exposure. This is based on approximately 300 patients initially randomized to receive desmopressin during the double-blind observation period and an additional group of approximately 300 patients initially randomized to placebo and then switched to desmopressin for the 9 month safety extension study. We believe this safety database which exceeds ICH safety database requirements will be fully adequate to support NDA approval.*

*Does FDA agree?*

**Division Response:**

It will depend on the age distribution of the study population. If there is an inadequate number of patients age 75 or greater, the treatment indication may be limited to those patients <75 years of age.

**Discussion:**

**The sponsor stated that the proportion of patients age 75 or greater in its Phase 2 study was 8%. They said if this proportion is maintained in the Phase 3 study, the sample size would be approximately 50 patients. DMEP responded that a sample size of 50 patients  $\geq 75$  years may be insufficient to adequately characterize the safety of low-dose desmopressin in this population. DMEP stated that they wish to confirm that the incidence**

of hyponatremia is  $\leq 3\%$ , particularly in the elderly patient population. The recommended sample size will depend on how many subjects  $\geq 75$  years are randomized to the highest dose (i.e. if  $N=50$  subjects  $\geq 75$  years on highest dose, that sample size may be sufficient). The number of patients older than 75 years exposed to each desmopressin dose will be a review issue.

DMEP recommended the minimum age for entry into the Phase 3 studies be raised to 50 years (b) (4) to ensure a larger contingent of older subjects in the clinical trials population, and the sponsor agreed to modify the lower limit of the age for study inclusion. DMEP clarified that exclusion of subjects younger than age 50 from clinical trials would not prevent the sponsor from receiving an indication for adult nocturia (i.e. the label would not limit use of desmopressin to subjects  $>50$  years, but would include subjects (b) (4) years of age).

The sponsor stated that since DMEP did not comment further on the size of the proposed Phase 3 studies, it understood this to mean that the Division agreed with the overall sample size in these trials as being an adequate safety database to support NDA registration. The Division stated that this was an accurate understanding by the sponsor.

*Question 8. In addition to the pharmacokinetic data already generated from the Phase I and Phase IIA studies, Serenity plans to obtain desmopressin plasma concentrations in the morning following bedtime doses in selected patients at various time points during one of the Phase III studies. We believe this PK database is fully adequate to support approval. Does FDA agree?*

**Division Response:**

Based on the information provided in the meeting package, it appears that the completed phase 1 and phase 2 studies have yielded some useful PK data, although not at the lower (0.5 ug) dose level due to analytical limitations. We also acknowledge your plan to conduct sparse sampling for population PK in the phase 3 clinical trial. We have the following comments:

- The phase 3 protocol synopses note that two different concentrations of the nasal spray will be used in the clinical trials to allow 4 total doses. The concentrations have not been specified. Completed clinical trials to date (including PK) have employed the 5 ug/ml formulation. We currently do not have PK data on any additional concentrations of the proposed nasal spray. We recommend that you characterize PK of any alternate strength formulation(s) prior to their use in phase 3.
- Based on the assay limitations and the short T1/2 of desmopressin, it appears that the proposed time of blood draws for population PK analyses in the phase 3 study (i.e. in the morning after bedtime doses at week 2 and week 6) may not yield detectable plasma concentrations. You should consider alternate time points to maximize analytical detection and usability of the sparse sampling to improve the current PK database.
- We encourage you to complete analysis of the blood samples obtained at the 0.5 ug dose level in the phase 1 study (protocol # SPC DESMO-NS 200801).
- You should continue your efforts to develop a more sensitive method to detect plasma desmopressin concentrations at the doses proposed for clinical use. Also clarify whether

- endogenous ADH in the non-water loaded nocturia patients of the phase 2 trial might have interfered with the RIA assay for desmopressin.
- We recommend that you ensure adequate enrollment of elderly patients in your planned phase 3 clinical trials to evaluate safety and efficacy as well as population PK of desmopressin in these patients. Since the drug is renally excreted and elderly patients have decreased renal functioning, this information will be important for labeling and appropriate dosing recommendations in specific populations.
- Prior to the phase 3 clinical trial, you should conduct a PK study in subjects with allergic rhinitis, in order to evaluate the potential influence of altered nasal mucosa on drug absorption from the nasal spray.
- The phase 3 protocols and patient instructions should clearly specify the mode of administering 2 sprays (i.e. both sprays into one nostril vs. one spray per each nostril).

**Discussion:**

The sponsor clarified that the purpose of obtaining early morning blood samples for desmopressin concentrations is to document that the level is undetectable at 12 hours post-dose, a finding that they expect would imply lowered risk for hyponatremia in adult nocturia patients. The Division indicated that this objective did not require “population PK” analyses. The sponsor agreed and indicated that this terminology would be revised. The sponsor noted that dedicated PK subset study(ies) at each dose level may be conducted at the end of the maintenance phase in the Phase 3 trials. The Division recommended that the sponsor gather PK information from elderly patients and gender subgroups during such a study. The Division requested that a formal PK evaluation be done on the higher dose concentration nasal spray used in these studies. The sponsor agreed and stated it had planned to do this.

The Division clarified that they are most interested in PK data on the following sub-populations: age, gender and renal impairment.

With regard to dosing in the presence of renal impairment, [REDACTED]

(b) (4)

[REDACTED] The Division responded that the sponsor should justify the relevance of this recommendation for their product which should achieve significantly lower systemic exposure. The Division stated that if the sponsor finds it appropriate to further investigate the safety of the new low dose nasal spray in patients with renal impairment, they might want to allow enrollment of such patients in Phase 3. The sponsor inquired whether a dedicated renal PK study in various degrees of renal impairment would be useful in providing the needed information for systemic exposure and safety in renal impairment patients. The Division stated that this would be acceptable.

The Division suggested that renal function be captured at baseline either by calculation using serum creatinine or using the 24 hour urine collections. The sponsor agreed.

The sponsor answered the Division’s question concerning the specificity of the PK assay for desmopressin and stated that the antibody used in the assay did not cross-react with vasopressin (endogenous ADH) and was specific for desmopressin. Therefore, there was no

**interference from endogenous ADH in the Phase 2 trial data.**

*Question 9. The two pivotal Phase III studies which Serenity plans to conduct are identical except for the inclusion in one of blood samples to measure desmopressin plasma concentrations in selected patients. For SPA purposes, does FDA wish to review both Phase III protocols or can the protocol with the PK assessments serve as a reference?*

**Division Response:**

The Division will review a single protocol. You should perform the PK assessments as part of the initial study, as the PK or initial efficacy subgroup analyses may lead you to consider some modifications to the second study protocol.

Additional Clinical Comments regarding Phase 3 program:

1. A sufficient number of patients at the proposed highest dose will need to be studied for 6 to 12 months to adequately assess the risk of hyponatremia at this dose.
2. Safety and efficacy analyses for the following age subgroups should be performed: <65, ≥65, and ≥75 years of age.
3. You will need to submit any Quality of Life questionnaires you propose to use prior to initiating any phase 3 studies, so that we can consult the division that deals with sleep disorders to determine the applicability and usefulness of the questionnaires in supporting a clinically relevant benefit for this treatment.
4. You should submit any data you have on the association of adult nocturia and falls leading to hip fracture, as well as any other clinically relevant data you have to justify the clinical benefit of the nocturia indication.
5. The following exclusion criteria should be added to the phase 3 protocols:
  - Urinary retention (post-void residual >150 mL)
  - Evidence of hepatic insufficiency
  - Evidence of renal insufficiency (GFR <30 mL/min)
  - Baseline hyponatremia (Na <135 mmol/L)
  - History of SIADH
  - Nephrotic syndrome
  - Evidence of significant peripheral edema on physical examination (e.g. >2+ pre-tibial edema)

**Discussion:**

**The sponsor stated that it understands and agrees with the need to evaluate safety in a sufficient number of patients at the highest dose level administered in the Phase 3 studies. The sponsor stated that it anticipates approximately 400 patients exposed to the lower dose and 200 patients treated with the higher dose in the Phase 3 studies.**

**The sponsor agreed to perform the recommended safety and efficacy analyses based on age. DMEP confirmed that the analysis of age subgroups would be considered**

informational and would not be held to rigid statistical testing procedures. DMEP also confirmed that they are most interested in an analysis of the  $\geq 75$  years subgroup.

The sponsor expressed understanding of comment #3 above regarding the quality of life questionnaires, and also that data from any Quality of Life questionnaires obtained during Phase 3 will not likely be included in labeling. DMEP added that it will be important for the sponsor to demonstrate additional clinical benefit of desmopressin beyond a reduction in nocturic voids. Demonstration of such benefit will be considered in the overall risk/benefit analysis of the drug.

The sponsor agreed to the suggested additional exclusion criteria for the Phase 3 protocols.

The sponsor also agreed to DMEP's recommendation that the Phase 3 protocols include temporary stopping criteria in the event of an acute illness (e.g. gastroenteritis) that might disrupt normal electrolyte balance.

#### CMC QUESTIONS AND ISSUES

*Question 1. Serenity plans to generate long term stability data on two concentrations of desmopressin nasal spray of approximately 5 mcg/mL and 7.5 mcg/mL. At each of these two concentrations Serenity plans to conduct stability programs on one research batch of approximately (b) (4) bottles and two conformance batches of approximately (b) (4) bottles at the same cGMP manufacturing facility which is the one planned for production of commercial batches. We believe that this stability program will be fully adequate to support NDA approval. Does FDA agree?*

**Division Response:**

As per the *Guidance for Industry: Q1A(R2) Stability Testing of New Drug Substances and Products*, (<http://www.fda.gov/cder/guidance/5635fnl.htm>), two of the three batches for each strength of the drug product used for registration stability studies should be at least pilot scale batches. If the conformance batches are at least pilot scale, this would provide adequate information to allow review of the NDA.

**Discussion:**

**There was no additional discussion.**

*Question 2. Serenity has included in this briefing packet the proposed product characterization, release and stability testing and believes this program is fully adequate to support approval. Does FDA agree?*

**Division Response:**

Although testing schedule tables were provided, the proposed product characterization, release and stability tests, and acceptance criteria of the tests for the drug product can not be found in the

briefing packet. Provide a specification table for both release and stability tests to adequately address your question. Additionally, we have the following comments:

- Based on reviewing the chromatograms provided in the amendment dated November 5, 2008, the HPLC method used for stability studies may not be adequately validated. The retention times of desmopressin in the reference standards and stability samples were very different (approximately [REDACTED] (b) (4)). Clarify this discrepancy.
- Provide results of excipient degradation studies. Additional studies may be needed to qualify the degradation products depending on the results.
- Leachable materials from the container closure system need to be evaluated using the drug product.
- Sterility of the drug product during both product shelf life and the in-use period needs to be ensured. Provide data to the NDA for evaluation by the microbiologist during the NDA review cycle.

**Discussion:**

The sponsor clarified that the reason for varying retention times in different chromatographic runs was due to the [REDACTED] (b) (4). The sponsor confirmed that the retention time of the samples for a given run is the same as the reference standards. The Division accepted this explanation.

*Question 3. Serenity plans to conduct the long term stability programs for each batch at 5, 25 and 30 degrees Celsius for this refrigerated product according to the enclosed stability program. We believe this will be fully adequate to support NDA approval. Does FDA agree?*

**Division Response:**

The proposed testing conditions (5 °C, 25°C/60% RH and 30°C/75% RH) are acceptable to allow review of the NDA. The expiration dating period will be set based on the amount and quality of the data you submit in the NDA. In addition to the stability studies needed to set an expiration dating period, photostability studies need to be performed and the results included in the NDA submission.

**Discussion:**

**No additional discussion.**

*Question 4. Serenity plans to initiate the Phase III studies with Clinical Trial Materials (CTM) from the research batches and transition to CTM from the conformance batches approximately one-third of the way through the randomized, double-blind studies. The research and conformance batches have the identical concentrations of API and the identical formulations, actuators, container-closure system, site of manufacture, release specifications and analytical methods.* [REDACTED] (b) (4)

*Does FDA agree?*

**Division Response:**

From a CMC standpoint, if the only change between batches of the CTM [REDACTED] (b) (4) and the drug products are shown to be equivalent, this would be acceptable. However, if other changes are planned, provide updated CMC information to review the option for the proposed switch.

**Discussion:**

**No additional discussion.**

**Additional meeting discussion:**

**The sponsor stated that as per the minutes of the pre-IND meeting held on December 10, 2007, and based on safety data from Phase 1 and 2 studies in adult nocturia, an initial study of the safety, and pharmacokinetics [REDACTED] (b) (4)**

[REDACTED] (b) (4)

[REDACTED] (b) (4)

**Brief summary statements were made by Drs. Lepor and Nitti regarding the importance of developing a safe and effective drug treatment for adult nocturia which they believe represents a significant public health problem.**

**ACTION ITEMS:**

- Meeting minutes due to the sponsor within 30 days of the meeting.

Linked Applications

Sponsor Name

Drug Name / Subject

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IND 76667

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SERENITY  
PHARMACEUTICALS  
CORP

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DESMOPRESSIN

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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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SURESH KAUL  
03/20/2009