

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125511Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION<sup>1</sup>

BLA # 125511		
Proprietary Name: Natpara Established/Proper Name: parathyroid hormone Dosage Form: injection		Applicant: NPS Pharmaceuticals
RPM: Elizabeth Chen/Meghna Jairath		Division: Division of Metabolism and Endocrinology Products
BLA Application Type: <input checked="" type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><b>For ALL 505(b)(2) applications, two months prior to EVERY action:</b></p> <ul style="list-style-type: none"> <li>• Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul> <p style="margin-left: 20px;"> <input type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity (notify CDER OND IO)          Date of check:       </p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
<b>Actions</b>		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>January 24, 2015</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 (specify type and date for each action taken)</li> </ul>		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<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).

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

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only):  
*(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 checked="" type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation   |   |

NDAs: Subpart H  
 Accelerated approval (21 CFR 314.510)  
 Restricted distribution (21 CFR 314.520)

BLAs: Subpart E  
 Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)

Subpart I  
 Approval based on animal studies

Subpart H  
 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

- 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 <i>(approvals only)</i>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
❖ Public communications <i>(approvals only)</i>	
• 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) N/A	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input 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 <i>(approvals only)</i>	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

<b>Action Letters</b>	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action and date: Approval (January 23, 2015)
<b>Labeling</b>	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> <li>• Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input checked="" type="checkbox"/> Included See approval letter dated <b>January 23, 2015 for final labeling</b>
<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 checked="" 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 See approval letter dated <b>January 23, 2015 for final labeling</b>
<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 See approval letter dated <b>January 23, 2015 for final labeling</b>
❖ 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>	Letter: 1/19/2014 Review: 1/10/2014
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: 01/07/2014 DMEPA: 10/03/2014, 04/21/2014 DMPP/PLT (DRISK): 01/02/2015 OPDP: 01/15/2015, 01/09/2015 SEALD: <input type="checkbox"/> None CSS: <input type="checkbox"/> None Other: <input type="checkbox"/> None
<b>Administrative / Regulatory Documents</b>	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting <i>(indicate date of each review)</i>	01/08/2014 <b>NOT AN NDA</b>
❖ <del>All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee</del>	<input type="checkbox"/> Not a (b)(2)
❖ <del>NDA's only: Exclusivity Summary <i>(signed by Division Director)</i></del>	<input type="checkbox"/> Included <b>NOT AN NDA</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>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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

<ul style="list-style-type: none"> <li>• This application is on the AIP             <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)             <ul style="list-style-type: none"> <li>• Date reviewed by PeRC _____</li> <li>If PeRC review not necessary, explain: <u>Orphan-designated product</u></li> </ul> </li> </ul>	
<ul style="list-style-type: none"> <li>❖ 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, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)</li> </ul>	<ul style="list-style-type: none"> <li>❖ 12/04/2013 - Acknowledgement</li> <li>❖ 01/06/2014 - Filing - Issues Identified</li> <li>❖ 01/17/2014</li> <li>❖ 01/28/2014 - Labeling Formatting Issues</li> <li>❖ 02/03/2014 (2)</li> <li>❖ 02/11/2014 (2)</li> <li>❖ 02/28/2014 (2)</li> <li>❖ 03/16/2014</li> <li>❖ 03/18/2014 (3)</li> <li>❖ 03/21/2014</li> <li>❖ 04/01/2014 (2)</li> <li>❖ 04/16/2014</li> <li>❖ 04/28/2014 - IR</li> <li>❖ 05/07/2014 (3)</li> <li>❖ 05/19/2014 (2)</li> <li>❖ 05/22/2014</li> <li>❖ 05/27/2014 - Exclusion of Columbia Data</li> <li>❖ 05/29/2014 (3)</li> <li>❖ 06/03/2014</li> <li>❖ 10/22/2014 - Major Amendment/PDUFA Clock Extension</li> <li>❖ 11/18/2014 - PMR-PMC forms</li> <li>❖ 12/15/2014 - REMS Communication</li> <li>❖ 12/22/2014 - PMR-PMC forms</li> <li>❖ 12/24/2014 - PMR-PMC forms</li> <li>❖ 12/29/2014 - REMS Communication</li> <li>❖ 01/05/2014 - REMS Communication</li> <li>❖</li> </ul>
<ul style="list-style-type: none"> <li>❖ 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)</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Minutes of Meetings</li> </ul>	
<ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg    March 15, 2012

• EOP2 meeting ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> No mtg
• Mid-cycle Communication ( <i>indicate date of mtg</i> )	April 2, 2014
• Late-cycle Meeting ( <i>indicate date of mtg</i> )	July 31, 2014
• Other milestone meetings (e.g., EOP2a, CMC pilots) ( <i>indicate dates of mtgs</i> )	None
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	September 12, 2014
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 01/23/2015
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 01/23/2015
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 1/6/2015
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input type="checkbox"/> None 01/23/2015
<b>Clinical</b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Clinical review(s) ( <i>indicate date for each review</i> )	Primary: 7/13/2014
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	Addressed in Clinical Review (07/13/2014, Page 19)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	09/12/2014 (Immunogenicity) 09/09/2014 (CDRH human factors) 06/09/2014 (QT-IRT review) 06/03/2014 (SEALD endpoints)
❖ 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>	REMS Document: Attached to approval letter REMS Supporting Document: Submitted 01/23/2015 (by e-mail) REMS Memo: 01/23/2015 Risk Management Memos: 1/23/2015 (3), 1/16, 2015, 12/28/2014, 06/19/2014
❖ OSI Clinical Inspection Review Summaries ( <i>include copies of OSI letters to investigators</i> )	Inspections Summary 08/24/2014 Inspection Waiver Recommendation (2) 06/11/2014 VAI Letters (2) 10/03/2014 VAI Letter 10/14/2014 NAI Letter 11/19/2014 NIDPOE/Consent agreement

	1/12/2015
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (indicate date for each review)	06/26/2014, 01/08/2014
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (indicate date for each review)	09/09/2014, 5/20/2014
❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None requested
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	10/10/2014
• Supervisory Review(s) (indicate date for each review)	07/31/2014
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	07/31/2014, 12/23/2013
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	09/29/2014, 06/27/2014, 11/20/2013
❖ Microbiology Reviews	
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)	
<input checked="" type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (indicate date of each review)	Filing: 12/23/2013 Primary: 07/25/2014, 08/22/2014
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input type="checkbox"/> None CDRH: 09/08/2014(2)

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> )	See page 208 of product quality review dated 06/27/2014
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within <b>30 days</b> of action date) ( <i>original and supplemental BLAs</i> )	Date completed: 09/26/2014 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation Included: Panorama Inspection Management Recommendation, accessed 01/08/2015

<b>Day of Approval Activities</b>	
<ul style="list-style-type: none"> <li>❖ For all 505(b)(2) applications: N/A               <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul> </li> </ul>	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
<ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment N/A</li> </ul>	<input type="checkbox"/> Done
❖ 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 N/A	<input type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

**From:** Chen, Elizabeth  
**To:** ["Jehan D. Rowlands"](mailto:JRowlands@npsp.com)  
**Subject:** RE: Final NATPARA Proposed - NPS (Clean and Changes Tracked) Versions - Dated 21 JAN 2015  
**Date:** Friday, January 23, 2015 3:55:00 PM

---

Dear Jehan,

We accept your revisions to the labeling dated January 21, 2015.

Regards,  
Elizabeth

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**From:** Jehan D. Rowlands [mailto:JRowlands@npsp.com]  
**Sent:** Wednesday, January 21, 2015 4:45 PM  
**To:** Chen, Elizabeth  
**Subject:** Final NATPARA Proposed - NPS (Clean and Changes Tracked) Versions - Dated 21 JAN 2015

Dear Elizabeth,

As discussed, attached is the NATPARA proposed label. We consider this to be final. We have accepted all of the FDA changes. We have just corrected typos, formatting, and for accuracy. All of our changes can be seen in the "changes tracked" version (attached). I have also attached a "clean" version.

As a reminder, we await to receive the U.S. License Number from the FDA, as it goes in the label and the carton/container labeling.

Please let me know if you have any questions.

Kind regards,

Jehan

**Jehan Rowlands, PharmD** | Director, Regulatory Affairs | NPS Pharma | Phone: 908.450.5537 | [jrowlands@npsp.com](mailto:jrowlands@npsp.com)



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/s/  
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ELIZABETH R CHEN  
01/23/2015

**From:** Chen, Elizabeth  
**To:** ["Jehan D. Rowlands"](mailto:Jehan.D.Rowlands)  
**Subject:** RE: BLA 125511 - Natpara REMS documents (NPS-proposed changes)  
**Date:** Monday, January 05, 2015 3:29:00 PM  
**Attachments:** [2014 23 12 Appendix 1 NATPARA REMS Document FDARevised NPS changes tracked.docx](#)

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Dear Jehan,

I am attaching a document containing additional comments regarding the REMS. Please let me know if you have any questions.

Regards,  
Elizabeth

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**From:** Jehan D. Rowlands [mailto:JRowlands@npsp.com]  
**Sent:** Wednesday, December 31, 2014 1:52 PM  
**To:** Chen, Elizabeth  
**Subject:** RE: BLA 125511 - Natpara REMS documents (NPS-proposed changes)

Dear Elizabeth,

Thank you for providing the FDA comments on the REMS documents.

For the most part, NPS has accepted all of the FDA proposed changes. We have proposed some changes to the attached "Patient-Prescriber Acknowledgement Form" and the "Appendix 1 NATPARA REMS Document" to reflect mainly updates to current process or to simplify from a logistical standpoint. These proposed changes are tracked in the attached documents as well as described in the table below.

Please let me know if these changes are acceptable to the FDA. Since we are planning to update and submit the remaining REMS documents to FDA by the middle of next week, we would appreciate confirmation on the NPS-proposed changes before then.

<b>Natpara REMS: Summary of Changes</b>	
<b>NPS revisions/comments</b>	
<b>12/31/2014</b>	
Global/General comments	
<i>Comment 1</i>	For the most part, NPS has accepted all of the FDA-proposed changes; the below NPS-proposed changes mainly reflect updates to current process/logistics
Appendix 1 NATPARA REMS Document	
<i>Comment 2</i>	Proposed update to process for pharmacy to verify that the prescriber is certified in the NATPARA REMS program:

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Thank you.

Kind regards,

Jehan

**Jehan Rowlands, PharmD** | Director, Regulatory Affairs | NPS Pharma | Phone: 908.450.5537 | [jrowlands@npsp.com](mailto:jrowlands@npsp.com)



**From:** Chen, Elizabeth [<mailto:Elizabeth.Chen@fda.hhs.gov>]  
**Sent:** Monday, December 29, 2014 12:43 PM  
**To:** Jehan D. Rowlands  
**Subject:** BLA 125511 - Natpara REMS documents

Dear Jehan,

I am attaching further comments and documents for the Natpara REMS:

The first document (filename: *BLA 125511 – REMS Comments 2.doc*) contains specific comments for the REMS. References in this document to Appendices are referring to the other attachments in the e-mail.

The other documents (the Appendices mentioned above) included in this e-mail are listed below.

- **REMS Document:** filename '*2014 23 12 Appendix 1 Natpara REMS Document FDARevised.docx*'
- **Acknowledgement Form:** filename '*2014 23 12 Appendix 2 Patient Prescriber Acknowledgement Form FDARevised.docx*'
- **Sample REMS Assessment Plan:** filename '*2014 23 12 Appendix 3 Draft REMS Assessment Plan for Natpara FDA.docx*'

Please let me know if any clarification is needed.

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

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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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ELIZABETH R CHEN  
01/05/2015

**From:** Chen, Elizabeth  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Subject:** BLA 125511 - Natpara REMS documents  
**Date:** Monday, December 29, 2014 12:42:00 PM  
**Attachments:** [BLA 125511 - REMS Comments 2.doc](#)  
[2014 23 12 Appendix 1 NATPARA REMS Document FDARevised.docx](#)  
[2014 23 12 Appendix 2 Natpara REMS Patient Prescriber Acknowledgement Form FDARevised.docx](#)  
[2014 23 12 Appendix 3 Draft REMS Assessment Plan for Natpara FDA.docx](#)

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Dear Jehan,

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- **REMS Document:** filename '*2014 23 12 Appendix 1 Natpara REMS Document FDARevised.docx*'
- **Acknowledgement Form:** filename '*2014 23 12 Appendix 2 Patient Prescriber Acknowledgement Form FDARevised.docx*'
- **Sample REMS Assessment Plan:** filename '*2014 23 12 Appendix 3 Draft REMS Assessment Plan for Natpara FDA.docx*'

Please let me know if any clarification is needed.

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

**BLA 125511 – Natpara REMS Comments  
December 29, 2014**

**COMMENTS FOR THE APPLICANT**

1. FDA acknowledges receiving on November 6, 2014 your proposal for Natpara REMS and a proposal for the Natpara REMS Patient-Prescriber Acknowledgement Form received via email on December 22, 2014.
2. The Natpara REMS proposal submitted by NPS on November 6, 2014 requires numerous revisions. To facilitate the review process, FDA is providing a clean copy of the draft REMS for Natpara which includes all FDA-proposed revisions to the REMS document submitted by NPS on November 6. See appendix 1. For subsequent submissions, FDA requests that, in addition to providing a tracked changes version of the REMS document included in appendix 1, NPS summarizes in table format all changes the company proposes and the rationale for these (see below).
3. A revised version of the Natpara REMS Patient-Prescriber Acknowledgement Form is included in Appendix 2.
4. A draft REMS Assessment Plan for Natpara is included in appendix 3.
5. Additional comments
  - a. Education or communication provided as part of a REMS should emphasize the safety messages important for the safe use of the product.
  - b. Product marketing materials generally are not appropriate to educate about product risks.
  - c. When addressing comments from FDA reviewers, in addition to tracking changes in the REMS documents, please provide a summary table in MS Word listing all revisions proposed by NPS to REMS documents and rationale for the change. (See example provided below).

<b>Natpara REMS: Summary of Changes</b>	
<b>NPS revisions/comments mm/dd/yyyy</b>	<b>FDA revisions/comments mm/dd/yyyy</b>
Global/General comments	
<i>Comment</i>	
<i>Comment</i>	
REMS Document	
<i>Comment</i>	
<i>Comment</i>	
REMS Letter for Prescribers	
<i>Comment</i>	
<i>Comment</i>	
REMS Letter for Pharmacies	
<i>Comment</i>	
<i>Comment</i>	
REMS Letter for Professional Societies	
<i>Comment</i>	
<i>Comment</i>	
Training Module for Prescribers	

**BLA 125511 – Natpara REMS Comments**  
**December 29, 2014**

<i>Comment</i>	
<i>Comment</i>	
Training Module for Pharmacy Representatives	
<i>Comment</i>	
<i>Comment</i>	
Prescriber Enrollment Form	
<i>Comment</i>	
<i>Comment</i>	
Pharmacy Enrollment Form	
<i>Comment</i>	
<i>Comment</i>	
Patient Brochure	
<i>Comment</i>	
<i>Comment</i>	
Patient-Prescriber Acknowledgement Form	
<i>Comment</i>	
<i>Comment</i>	
REMS Website (landing page)	
<i>Comment</i>	
<i>Comment</i>	

Appended Materials

Appendix 1 – Natpara REMS Document

Appendix 2 – Natpara REMS Patient-Prescriber Acknowledgement Form

Appendix 3 – Draft REMS Assessment Plan

**BLA 125511 – Natpara REMS Comments  
December 29, 2014**

Appendix 1 – Natpara REMS Document

**BLA 125511 – Natpara REMS Comments**  
**December 29, 2014**

Appendix 2 – Natpara REMS Patient-Prescriber Acknowledgement Form

**BLA 125511 – Natpara REMS Comments  
December 29, 2014**

Appendix 3 – Draft Natpara REMS Assessment Plan

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/s/  
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ELIZABETH R CHEN  
12/29/2014

**From:** Chen, Elizabeth  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Subject:** BLA 125511 - General Updates  
**Date:** Wednesday, December 24, 2014 4:36:00 PM  
**Attachments:** [Natpara PMRs.doc](#)

---

Dear Jehan,

I am attaching a copy PMR form you submitted; we have accepted your minor revision. We now consider this final. Please submit this officially to the application.

I also have an update regarding the established name for Natpara. We consider the final established name for the product to be "NATPARA® (parathyroid hormone) for injection". [rDNA] should not be part of the established name.

Please let me know if you have any additional questions. I will be working December 29-31, 2014.

Happy holidays,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

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/s/  
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ELIZABETH R CHEN  
12/24/2014

**From:** Chen, Elizabeth  
**To:** ["Jehan D. Rowlands"](mailto:Jehan.D.Rowlands)  
**Subject:** RE: BLA 125511 - PMR list  
**Date:** Monday, December 22, 2014 7:55:00 AM  
**Attachments:** [Natpara PMRs.doc](#)

---

Dear Jehan,

I am attaching a new PMR/PMC form with changes made by FDA. I know this is a rush, but please provide responses by December 30, 2014.

Regards,  
Elizabeth

---

**From:** Jehan D. Rowlands [mailto:[JRowlands@npsp.com](mailto:JRowlands@npsp.com)]  
**Sent:** Tuesday, November 25, 2014 11:55 AM  
**To:** Chen, Elizabeth  
**Subject:** RE: BLA 125511 - PMR list

Dear Elizabeth,

As discussed, attached is the PMR/PMC form with the requested information added in by NPS. All additions/changes are provided with "tracking" for ease of FDA review.

Please let me know if you have any questions.

Thank you.

Kind regards,

Jehan

**Jehan Rowlands, PharmD** | Director, Regulatory Affairs | NPS Pharma | Phone: 908.450.5537 | [jrowlands@npsp.com](mailto:jrowlands@npsp.com)



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**From:** Chen, Elizabeth [mailto:[Elizabeth.Chen@fda.hhs.gov](mailto:Elizabeth.Chen@fda.hhs.gov)]  
**Sent:** Tuesday, November 18, 2014 3:57 PM  
**To:** Jehan D. Rowlands  
**Subject:** BLA 125511 - PMR list

Dear Jehan,

Please see the attached form related to PMRs and PMCs associated with the Natpara (parathyroid Hormone (1-84) Human Recombinant injection) product. We would appreciate a response by COB on Monday, December 1, 2014.

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

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

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This message may contain confidential information. It is intended only for the use of the addressee(s) named above and may contain information that is legally privileged. If you are not the addressee, you are hereby notified that reading, disseminating, distributing or copying this message is strictly prohibited. If you have received this message by mistake, please notify us by replying to the message and delete the original message immediately thereafter.

**PMR/PMC list for BLA 125511**  
**NATPARA (parathyroid Hormone (1-84) Human Recombinant injection)**

While review of your application continues, we are sending you a draft list of PMRs/PMCs based on the data and internal analyses available to date. These brief study/trial summaries are intended to describe the main objective and study/trial characteristics of interest.

Please submit by email a copy of the PMR and PMC studies/trials to us with milestone dates, which include **Final Protocol Submission**, **Study Completion** and **Final Report Submission**.

- Note that milestone dates only need month and year
- For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.
- Note that the "Final Protocol Submission" date is the date by which you have submitted a complete protocol that has already received full concurrence by FDA.
- For PMCs, include a statement that you agree to conduct these studies/trials.

**Postmarketing Requirements**

- 1) A clinical pharmacology study to assess the effect of Natpara dose and dosing regimen on the control of serum calcium and normalization of calcium excretion in urine. Modeling and simulation using mechanistic model-based assessment of prior PK/PD data should be used to design this study.

Final Protocol Submission: 11/2015  
Study Completion: 9/2016  
Final Report Submission: 3/2017

- 2) A study in Fischer 344 rats to ascertain the effect of different Natpara dosing regimens on osteoblast proliferation, as an indicator of relative osteosarcoma risk. (b) (4)

Final Protocol Submission: 11/2015<sup>(b) (4)</sup>  
Study Completion: 8/2016<sup>(b) (4)</sup>  
Final Report Submission: 11/2016<sup>(b) (4)</sup>

- 3) A 26-week randomized, controlled clinical trial to evaluate the (b) (4) -safety and effect of an alternative dose(s) and/or dosing regimen(s) of Natpara. This trial should not be initiated until the results from the clinical pharmacology study and the nonclinical study have been submitted to and reviewed by the Agency.

Final Protocol Submission (b) (4) 11/2017<sup>(b) (4)</sup>  
Trial Completion: (b) (4) 11/2021<sup>(b) (4)</sup>  
Final Report Submission (b) (4) 5/2021<sup>(b) (4)</sup>

- 4) An enhanced pharmacovigilance program for reports of osteosarcoma in patients with hypoparathyroidism treated with Natpara for a period of 15 years from the date of approval. The program will include assessment and analysis of spontaneous reports of osteosarcoma in patients treated with Natpara, with specialized follow-up to collect additional information on these cases.

Final Protocol Submission (b) (4) 7/2015

Trial Completion: 3/2030

Final Report Submission: 9/2030

#### **Postmarketing Commitments:**

- 5) Provide bioburden method qualification data from two additional lots of the (b) (4) and the drug substance. In addition, provide method qualification data from three lots of the (b) (4)

Study Completion: 11/2015

Final Report Submission: 12/2015

- 6) Establish a bioburden limit for the (b) (4) after the bioburden monitoring results for 10 more batches are available.

Study Completion: 1/2020

Final Report Submission: 2/2020

- 7) Provide LAL kinetic chromogenic method qualification data from two additional lots of drug substance. Provide LAL gel clot method qualification data from two additional lots of the (b) (4)

Study Completion: 11/2015

Final Report Submission: 12/2015

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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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ELIZABETH R CHEN  
12/22/2014

**From:** Chen, Elizabeth  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Subject:** BLA 125511 - Natpara REMS  
**Date:** Friday, December 12, 2014 2:21:00 PM  
**Attachments:** [BLA 125511 - REMS Comments.doc](#)  
[2014 12 12 Appendix 1 REMS Message Mps FDA templates.doc](#)  
[2014 12 12 Appendix 2\\_1 Natpara REMS Letter Prescriber email FDA templat....docx](#)  
[2014 12 12 Appendix 2\\_2 Natpara REMS Letter Prescribers print FDA templa....docx](#)  
[2014 12 12 Appendix 3 Natpara Training Module Prescriber FDA template.ppt](#)  
[2014 12 12 Appendix 4 Natpara Prescriber Enrollment Form FDA template.doc](#)  
[2014 12 12 Appendix 5 Natpara REMS Program An Introduction FDA template.doc](#)  
[2014 12 12 Appendix 6 Natpara Pharmacy Reps Training Module FDA template.ppt](#)  
[2014 12 12 Appendix 7 Natpara Pharmacy Enrollment Form FDA template.doc](#)  
[2014 12 12 Appendix 8 Natpara Patient Brochure FDA template.pub](#)  
[2014 12 12 Appendix 9 Natpara Patient Prescriber Acknowledgement Form FDA template.doc](#)  
[2014 12 12 Appendix 10 Natpara REMS Webpage FDA template.docm](#)

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Dear Jehan,

I am attaching our comments and template documents for the Natpara REMS.

The first document (filename: *BLA 125511 – REMS Comments*) contains the specific comments for the REMS. Any references in this document to Appendices are referring to the other attachments in the e-mail.

The other documents (the Appendices mentioned above) included in this e-mail are listed below.

- **REMS Message Maps:** filename '*2014 12 12 Appendix 1 REMS Message Maps FDA templates.docx*'
- **REMS Letter** (email version): filename '*2014 12 12 Appendix 2\_1 Natpara REMS Letter Prescriber email FDA template.docx*'
- **REMS Letter** (print version): filename '*2014 12 12 Appendix 2\_2 Natpara REMS Letter Prescriber print FDA template.docx*'
- **Prescriber Training Module:** filename '*2014 12 12 Appendix 3 Natpara Training Module Prescriber FDA template.ppt*'
- **Prescriber Enrollment Form:** filename '*2014 12 12 Appendix 4 Natpara Prescriber Enrollment Form FDA template.doc*'
- **REMS Introduction sheet** (like a factsheet): filename '*2014 12 12 Appendix 5 Natpara REMS Program\_An Introduction FDA template.doc*'
- **Pharmacy Rep Training Module:** filename '*2014 12 12 Appendix 6 Natpara Pharmacy Reps Training Module FDA template.ppt*'
- **Pharmacy Enrollment Form:** filename '*2014 12 12 Appendix 7 Natpara Pharmacy Enrollment Form FDA template.doc*'
- **Patient Brochure:** filename '*2014 12 12 Appendix 8 Natpara Patient Brochure FDA template.pub*'
- **Acknowledgement Form:** filename '*2014 12 12 Appendix 9 Patient Prescriber Acknowledgement Form FDA template.doc*'
- **REMS Webpage:** filename '*2014 12 12 Appendix 10 REMS Webpage FDA template.docm*'

As always, please feel free to call for whatever clarification is needed.

Regards,

## Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

**BLA 125511 – Natpara REMS Comments**  
**December 12, 2014**

1. FDA acknowledges receiving (via email) on November 6, 2014 your draft proposal for Natpara REMS. The REMS proposed by NPS includes the key elements FDA considers necessary for the Natpara REMS (i.e., prescriber certification, pharmacy certification, and documentation of safe use condition); however, the proposed REMS requires additional modifications. The REMS document is undergoing internal FDA evaluation. Once the review process is completed, FDA will send NPS the revised version. The Natpara REMS Program must include prescriber certification, pharmacy certification and documentation of safe use condition. The following comments will assist you in the development of a REMS for Natpara.
2. REMS message maps for prescribers, pharmacy representatives, and patients – The REMS message maps contain the key risk messages to be addressed by the Natpara REMS. The messages included in these maps must be consistent with the product label (not necessarily verbatim) and will be used to guide the development of all REMS-related documents, including REMS assessment survey questions. A copy of the REMS message maps should be included in the Natpara REMS Supporting Document. See appendix 1 for examples of REMS message maps.
3. *Natpara REMS Letter for Prescribers* – A REMS Letter for Prescribers is a shorter, REMS message-focused communication (b) (4) See appendix 2 which includes two examples of the *Natpara REMS Letter for Prescribers*; one is intended for email use and the other version is intended for printing, depending on NPS' decision to use email or regular mail (print format) to distribute REMS Letters along with other REMS materials among prescribers who attempt to prescribe Natpara and are not yet certified, or inquire about how to become certified.
4. Prescriber certification – Prescriber certification consists of training and enrollment. To become certified in the Natpara REMS Program, prescribers must:
  - review the Prescribing Information for Natpara, and *Natpara REMS Program: An Introduction* sheet mentioned above.
  - complete the *Natpara REMS Training Module for Prescribers*, and
  - complete and sign the *Natpara REMS Prescriber Enrollment Form* and submit it to the Natpara REMS Program Coordinating Center.NPS will establish the Natpara REMS Program Coordinating Center and will send prescribers confirmation of certification.
  - a. *Natpara REMS Training Module for Prescribers* – An example of the training module part of the prescriber certification process is included in appendix 3.
  - b. *Natpara REMS Prescriber Enrollment Form* – An example of the Prescriber Enrollment Form part of the prescriber certification process is included in appendix 4.
  - c. *Natpara REMS Program: An Introduction* – This is a REMS Program introduction sheet which summarizes all the key components of the Natpara REMS Program. See appendix 5.

## **BLA 125511 – Natpara REMS Comments**

### **December 12, 2014**

5. Pharmacy certification – Pharmacy certification entails the selection of a Pharmacy Representative who will receive training and enroll the pharmacy in the Natpara REMS Program. The Pharmacy Representative must:
  - review the Prescribing Information for Natpara, and *Natpara REMS Program: An Introduction* sheet
  - complete the *Natpara REMS Training Module for Pharmacy Representatives*, and
  - complete and sign the *Natpara REMS Pharmacy Enrollment Form* and submit it to the Natpara REMS Program Coordinating Center.

NPS will send confirmation of pharmacy certification to the Pharmacy Representative. Prior to dispensing Natpara, the pharmacy will: (1) verify the prescriber is certified in the Natpara REMS Program by contacting the Natpara REMS Program Coordinating Center prior to dispensing Natpara and (2) verify that a *Natpara REMS Patient-Prescriber Acknowledgement Form* is on record for the corresponding patient and prescriber by contacting the Natpara REMS Program Coordinating Center.

- a. *Natpara REMS Training Module for Pharmacy Representatives* – An example of the training module part of the pharmacy certification process is included in appendix 6.
  - b. *Natpara REMS Pharmacy Enrollment Form* – An example of the Natpara Pharmacy Enrollment Form part of the prescriber certification process is included in appendix 7.
  - c. *Natpara REMS Program: An Introduction* – see comment above.
6. *Natpara Patient Brochure* – Prescribers will use the *Natpara Patient Brochure* as a counseling tool to assist in the benefit:risk discussion that must take place prior to initiation of treatment with Natpara. See an example of the patient brochure in appendix 8.
  7. *Natpara REMS Prescriber-Patient Acknowledgement Form* – Prescriber and pharmacy certification alone does not guarantee that each patient will be informed about the benefits and potential risk for osteosarcoma associated to Natpara. The patients and prescriber will complete and sign a *Natpara REMS Patient-Prescriber Acknowledgement Form* documenting the discussion of the benefits and risks associated to Natpara occurred prior to the initiation of therapy. Once completed, the *Natpara REMS Patient-Prescriber Acknowledgement Form* is faxed or sent electronically via email to the Natpara REMS Program Coordinating Center. See appendix 9.

The *Natpara REMS Prescriber-Patient Acknowledgement Form* and the *Natpara Patient Brochure* should be included in as one.PDF file. The intent is that the prescriber can print both documents at the same time and provide the patient with the Patient Brochure when the patient signs the Patient-Prescriber Acknowledgement Form.

8. *Natpara REMS Website* – The REMS website should be available via a prominent, REMS-specific link in the Natpara commercial website for the duration of the REMS.

**BLA 125511 – Natpara REMS Comments  
December 12, 2014**

This link should direct users to a separate webpage that describes the REMS program and lists only approved REMS materials. The separate REMS website should contain background information on the REMS along with the REMS appended materials. The Natpara REMS website will include the option to print versions of the Natpara REMS materials. The content of the website should be easily viewed in a handheld device. Ensure the REMS website (www.NATPARAREMS.com) is independent of links to the promotional and/or commercial website and non-REMS materials about the product. Do not include a link from the REMS website back to the commercial website (www.NATPARA.com). The REMS website should also be accessible directly through a search engine. See appendix 10 for an example of a REMS landing page.

9. General comments

- a. Education or communication provided as part of a REMS should emphasize the safety messages important for the safe use of the product.
- b. Product marketing materials generally are not appropriate to educate about product risks.
- c. Please submit all planned materials (e.g., proposed communications, education materials, and REMS website) identified within the plan that will be necessary to implement your proposal.
- d. When feasible, we recommend pre-testing all REMS materials.
- e. Submit all revisions to the REMS documents in track changes and clean MS Word versions.

When addressing comments from FDA reviewers, in addition to tracking changes in the REMS documents, please provide a summary table in MS Word listing all revisions proposed by NPS to REMS documents and rationale for the change. (See example provided below).

<b>Natpara REMS: Summary of Changes</b>	
<b>NPS revisions/comments</b> mm/dd/yyyy	<b>FDA revisions/comments</b> mm/dd/yyyy
<b>Global/General comments</b>	
<i>Comment</i>	
<i>Comment</i>	
<b>REMS Document</b>	
<i>Line #X-Y: Comment</i>	
<i>Line #X-Y: Comment</i>	
<b>Natpara REMS Letter for Prescribers</b>	
<i>Line #X-Y: Comment</i>	
<i>Line #X-Y: Comment</i>	
<b>Natpara REMS Program: An Introduction</b>	
<i>Line #X-Y: Comment</i>	
<i>Line #X-Y: Comment</i>	
<b>Natpara REMS Training Module for Prescribers</b>	
<i>Line #X-Y: Comment</i>	
<i>Line #X-Y: Comment</i>	

**BLA 125511 – Natpara REMS Comments**  
**December 12, 2014**

<b>Natpara REMS Training Module for Pharmacy Representatives</b>	
<i>Line #X-Y: Comment</i>	
<i>Line #X-Y: Comment</i>	
<b>Natpara REMS Prescriber Enrollment Form</b>	
<i>Line #X-Y: Comment</i>	
<i>Line #X-Y: Comment</i>	
<b>Natpara REMS Pharmacy Enrollment Form</b>	
<i>Line #X-Y: Comment</i>	
<i>Line #X-Y: Comment</i>	
<b>Natpara Patient Brochure</b>	
<i>Line #X-Y: Comment</i>	
<i>Line #X-Y: Comment</i>	
<b>Natpara REMS Patient-Prescriber Acknowledgement Form</b>	
<i>Line #X-Y: Comment</i>	
<i>Line #X-Y: Comment</i>	
<b>Natpara REMS Website (landing page)</b>	
<i>Line #X-Y: Comment</i>	
<i>Line #X-Y: Comment</i>	

**BLA 125511 – Natpara REMS Comments  
December 12, 2014**

Appended Materials

Appendix 1 – Natpara REMS Message Maps

Appendix 2 – Natpara REMS Letter for Prescribers

Appendix 3 – Natpara REMS Training Module for Prescribers

Appendix 4 – Natpara REMS Prescriber Enrollment Form

Appendix 5 – Natpara REMS Program: An Introduction

Appendix 6 – Natpara REMS Training Module for Pharmacy Representatives

Appendix 7 – Natpara REMS Pharmacy Enrollment Form

Appendix 8 – Natpara Patient Brochure

Appendix 9 – Natpara REMS Patient-Prescriber Acknowledgement Form

Appendix 10 – Natpara REMS Website

**BLA 125511 – Natpara REMS Comments  
December 12, 2014**

Appendix 1 – Natpara REMS Message Maps

**BLA 125511 – Natpara REMS Comments  
December 12, 2014**

Appendix 2 – Natpara REMS Letter for Prescribers

Email Format

**BLA 125511 – Natpara REMS Comments  
December 12, 2014**

Print Format

**BLA 125511 – Natpara REMS Comments**  
**December 12, 2014**

Appendix 3 – Natpara REMS Training Module for Prescribers

**BLA 125511 – Natpara REMS Comments  
December 12, 2014**

Appendix 4 – Natpara REMS Prescriber Enrollment Form

**BLA 125511 – Natpara REMS Comments  
December 12, 2014**

Appendix 5 – Natpara REMS Program: An Introduction

**BLA 125511 – Natpara REMS Comments  
December 12, 2014**

Appendix 6 – Natpara REMS Training Module for Pharmacy Representatives

**BLA 125511 – Natpara REMS Comments**  
**December 12, 2014**

Appendix 7 – Natpara REMS Pharmacy Enrollment Form

**BLA 125511 – Natpara REMS Comments  
December 12, 2014**

Appendix 8 – Natpara Patient Brochure

**BLA 125511 – Natpara REMS Comments**  
**December 12, 2014**

Appendix 9 – Natpara REMS Patient-Prescriber Acknowledgement Form

**BLA 125511 – Natpara REMS Comments  
December 12, 2014**

Appendix 10 – Natpara REMS Website – landing 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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ELIZABETH R CHEN  
12/15/2014

**From:** Chen, Elizabeth  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Subject:** BLA 125511 - PMR list  
**Date:** Tuesday, November 18, 2014 3:57:00 PM  
**Attachments:** [Natpara - PMRs and PMCs.doc](#)

---

Dear Jehan,

Please see the attached form related to PMRs and PMCs associated with the Natpara (parathyroid Hormone (1-84) Human Recombinant injection) product. We would appreciate a response by COB on Monday, December 1, 2014.

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

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

**PMR/PMC list for BLA 125511**  
**NATPARA (parathyroid Hormone (1-84) Human Recombinant injection)**

While review of your application continues, we are sending you a draft list of PMRs/PMCs based on the data and internal analyses available to date. These brief study/trial summaries are intended to describe the main objective and study/trial characteristics of interest.

Please submit by email a copy of the PMR and PMC studies/trials to us with milestone dates, which include **Final Protocol Submission, Study Completion** and **Final Report Submission**.

- Note that milestone dates only need month and year
- For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.
- Note that the "Final Protocol Submission" date is the date by which you have submitted a complete protocol that has already received full concurrence by FDA.
- For PMCs, include a statement that you agree to conduct these studies/trials.

**Postmarketing Requirements**

- 1) A clinical pharmacology study to assess the effect of Natpara dose and dosing regimen on the control of serum calcium and normalization of calcium excretion in urine. Modeling and simulation using mechanistic model-based assessment of prior PK/PD data should be used to design this study.

Final Protocol Submission:

Study Completion:

Final Report Submission:

- 2) A study in Fischer 344 rats to ascertain the effect of different Natpara dosing regimens on osteoblast proliferation, as an indicator of relative osteosarcoma risk. This study should not be initiated until the results from the clinical pharmacology study have been submitted to and reviewed by the Agency.

Final Protocol Submission:

Study Completion:

Final Report Submission:

- 3) A 26-week randomized, controlled clinical trial to evaluate the efficacy and safety of an alternative dose(s) and/or dosing regimen(s) of Natpara. This trial should not be initiated until the results from the clinical pharmacology study and the nonclinical study have been submitted to and reviewed by the Agency.

Final Protocol Submission:  
Trial Completion:  
Final Report Submission:

- 4) An enhanced pharmacovigilance program for reports of osteosarcoma in patients with hypoparathyroidism treated with Natpara for a period of 15 years from the date of approval. The program will include assessment and analysis of spontaneous reports of osteosarcoma in patients treated with Natpara, with specialized follow-up to collect additional information on these cases.

Final Protocol Submission:  
Trial Completion:  
Final Report Submission:

**Postmarketing Commitments:**

- 5) Provide bioburden method qualification data from two additional lots of the (b) (4) and the drug substance. In addition, provide method qualification data from three lots of the (b) (4)

Study Completion:  
Final Report Submission:

- 6) Establish a bioburden limit for the (b) (4) after the bioburden monitoring results for 10 more batches are available.

Study Completion:  
Final Report Submission:

- 7) Provide LAL kinetic chromogenic method qualification data from two additional lots of drug substance. Provide LAL gel clot method qualification data from two additional lots of the (b) (4)

Study Completion:  
Final Report Submission:

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/s/  
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ELIZABETH R CHEN  
11/18/2014



BLA 125511

**REVIEW EXTENSION –  
MAJOR AMENDMENT**

NPS Pharmaceuticals Inc.  
Attention: Jehan Rowlands, Pharm.D.  
Director, Regulatory Affairs  
550 Hills Drive, 3rd Floor  
Bedminster, NJ 07921

Dear Dr. Rowlands:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for Natpara (parathyroid Hormone (1-84) Human Recombinant injection).

On September 19, 2014, we received your September 17, 2014, major amendment to this 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 January 24, 2015.

If you have any questions, call Elizabeth Chen, Regulatory Project Manager, at (240) 402-3729.

Sincerely,

*{See appended electronic signature page}*

Pamela Lucarelli  
Chief, Project Management Staff  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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PAMELA LUCARELLI  
10/22/2014

**From:** Chen, Elizabeth  
**To:** "[Jehan D. Rowlands](#)"  
**Subject:** RE: BLA 125511 - IR 28  
**Date:** Monday, June 02, 2014 3:03:00 PM

---

Dear Jehan,

Please submit a revised table matching the figure titled: "Summary of Adverse Events in >4% and greater in NPSP558 group compared to placebo, in decreasing order of frequency —Safety Population".

If you have any additional questions, please let me know.

Regards,  
Elizabeth

---

**From:** Jehan D. Rowlands [<mailto:JRowlands@npsp.com>]  
**Sent:** Friday, May 30, 2014 1:28 PM  
**To:** Chen, Elizabeth  
**Subject:** FW: BLA 125511 - IR 28

Dear Elizabeth,

IR 28, #7 (attached) refers to "Response to IR from February 18, 2014". We do not see any AE tables in this response. Instead, there is an AE  $\geq 2\%$  table for Q5 in IR 6. Could this be the one that the FDA is referring to? Please clarify.

Thank you,

Jehan

**Jehan Rowlands, PharmD** | Director, Regulatory Affairs | NPS Pharma | Phone: 908.450.5537 | [jrowlands@npsp.com](mailto:jrowlands@npsp.com)



---

**From:** Chen, Elizabeth [<mailto:Elizabeth.Chen@fda.hhs.gov>]  
**Sent:** Thursday, May 22, 2014 5:06 PM  
**To:** Jehan D. Rowlands  
**Subject:** BLA 125511 - IR 28

Dear Jehan,

Please see the attached information request. The Agency would also like to request an informal teleconference with NPS Pharmaceuticals *as soon as possible* (Friday, May 23 in the morning or early during the week of the 26<sup>th</sup>).

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

---

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**From:** Chen, Elizabeth  
**To:** "[Jehan D. Rowlands](#)"  
**Subject:** RE: BLA 125511 - IRs related to the revised submissions  
**Date:** Thursday, May 29, 2014 4:15:00 PM

---

Dear Jehan,

I have the following requests for information from the clinical reviewer:

- 1) Where is the revised Figure 11-11 from CSR 040?
- 2) Where is the revised Table 11-6 from CSR 040?
- 3) Where is the revised Table 12-2 from CSR 040?

Regards,  
Elizabeth

---

**From:** Chen, Elizabeth  
**Sent:** Thursday, May 29, 2014 1:24 PM  
**To:** 'Jehan D. Rowlands'  
**Subject:** RE: BLA 125511 - IRs related to the revised submissions

Dear Jehan,

Thank you for the information.

I have the following question regarding Trial 007:

How many patients were at the Columbia site? If there were none, no revised data needs to be submitted. Otherwise, please provide revised efficacy and safety data for Trial 007.

Regards,  
Elizabeth

---

**From:** Jehan D. Rowlands [<mailto:JRowlands@npsp.com>]  
**Sent:** Thursday, May 29, 2014 11:26 AM  
**To:** Chen, Elizabeth  
**Subject:** RE: BLA 125511 - IRs related to the revised submissions

Dear Elizabeth,

We are working on providing responses to the below requests as soon as possible.

For request #3 below, the revised Table 14.3.8.1 (from CSR 40) is located in the pdf file (for tables, provided on Wednesday, May 28, 2014) on pages 3119-3121 of the pdf.

Please confirm if you are able to locate this table.

Kind regards,

Jehan

---

**From:** Chen, Elizabeth [<mailto:Elizabeth.Chen@fda.hhs.gov>]  
**Sent:** Thursday, May 29, 2014 9:35 AM  
**To:** Jehan D. Rowlands  
**Subject:** BLA 125511 - IRs related to the revised submissions

Dear Jehan,

See the below questions from the clinical reviewer regarding the information that has been submitted since Tuesday. Please answer *as soon as possible*. More information requests will likely come throughout the day. It would greatly help our review if you can provide responses before the end of the day and preferably earlier than that.

- 1) Where is the revised Table 11-3 from CSR 40?
- 2) Where is the revised Table 14.4.27 from CSR 40?
- 3) Where is the revised Table 14.3.8.1 from CSR 40?
- 4) Provide a revised Figure 10-1, highlighting the differences as a result of the excluded subjects.

Regards,  
Elizabeth Chen

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
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---

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**From:** Chen, Elizabeth  
**To:** "[Jehan D. Rowlands](#)"  
**Subject:** BLA 125511 - IR 31  
**Date:** Tuesday, June 03, 2014 5:44:00 PM

---

Dear Jehan,

Thank you for this response to our device IR. I have an additional information request related to this submission:

We need real-life use data for the Haselmeier pen-injector where it had been assembled with the cartridge and stored in refrigeration when not in use. Please specify how many of your patients were using Haselmeier pen-injectors daily in your clinical trial and what were the duration of use for each patient? Were there any adverse events or medication errors attributed to device malfunctions? If yes, please provide the details surrounding the circumstances.

Please respond to this IR by **Monday, June 9** at the latest.

In addition, we have some requests related to the submitted response to IR 24. We would like to convey these requests by informal teleconference on **Thursday, June 5, 2014 (3:00 to 3:30 PM)**. Please provide a teleconference number. This teleconference is purely *device* related.

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

Regards,  
Elizabeth

---

**From:** Jehan D. Rowlands [mailto:[JRowlands@npsp.com](mailto:JRowlands@npsp.com)]  
**Sent:** Friday, May 30, 2014 11:31 PM  
**To:** Chen, Elizabeth  
**Subject:** Natpara BLA 125511: NPS Complete Response to IR 24

The following attachment has been securely sent to you.

[BLA 125511 NPS Response to IR 24 \(Sequence No. 0027\).pdf](#) (16.0 MB)

Additional download options are available at the [Pick-Up Portal](#)

The link within this message can be accessed until June 30, 2014 11:31:14 PM EDT.

Dear Elizabeth,

Please find attached NPS complete response to IR 24 (BLA Sequence No. 0027). The formal response will be submitted to the BLA via the Gateway within a few days.

Kind regards,

Jehan

**Jehan Rowlands, PharmD** | Director, Regulatory Affairs | NPS Pharma | Phone: 908.450.5537 |  
[jrowlands@npsp.com](mailto:jrowlands@npsp.com)

**From:** [Chen, Elizabeth](#)  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Subject:** BLA 125511 - Acknowledgement of receipt and additional IR (30?)  
**Date:** Monday, June 02, 2014 3:19:00 PM  
**Attachments:** [BLA 125511 IR 30.doc](#)

---

Dear Jehan,

I acknowledge receipt of revised information for IRs: 1, 2, 4, 5, 6, 8, 9, 12, 16, 18. I also acknowledge receipt of Tables, Figures, and Listings for Study 008 (RACE).

I acknowledge receipt of responses for IRs: 23, 24

Please see the attached IR with questions from clinical and immunogenicity reviewers.

We are in discussion with reviewers from CDRH regarding the response to IR 22.

If I missed a number somewhere, please let me know.

Feel free to contact me if you have additional questions.

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

**From:** Chen, Elizabeth  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Subject:** BLA 125511 - IR 36  
**Date:** Friday, July 11, 2014 1:46:00 PM

---

Dear Jehan,

I have the following question from the clinical reviewer:

Please confirm if the EU marketing authorization for Preotact was recently withdrawn. If so, explain why and whether the decision was related to any issues of safety.

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

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

**From:** Chen, Elizabeth  
**To:** "[Jehan D. Rowlands](#)"  
**Subject:** RE: BLA 125511 - IR 35  
**Date:** Tuesday, July 08, 2014 8:51:00 AM

---

Good morning Jehan,

The table is entitled: "Summary of Supplements and Selected Laboratory Assessment at Screening and Baseline—All Subjects with Both Screening and Baseline Data, Excluding Site 1002." It is from a May 28, 2014 submission, listed as Table B-14.4.5.

Please let me know if you need any additional clarification. Thank you for your responsiveness with these urgent requests.

Regards,  
Elizabeth

---

**From:** Jehan D. Rowlands [mailto:[JRowlands@npsp.com](mailto:JRowlands@npsp.com)]  
**Sent:** Monday, July 07, 2014 2:58 PM  
**To:** Chen, Elizabeth  
**Subject:** RE: BLA 125511 - IR 35

Dear Elizabeth,

For request #2 below, could you please clarify which tables the FDA reviewer is referring to?

We are working to provide the response to IR 35 by Wednesday, July 9, 2014, as requested.

Thank you.

Kind regards,

Jehan

---

**From:** Chen, Elizabeth [mailto:[Elizabeth.Chen@fda.hhs.gov](mailto:Elizabeth.Chen@fda.hhs.gov)]  
**Sent:** Monday, July 07, 2014 2:03 PM  
**To:** Jehan D. Rowlands  
**Subject:** RE: BLA 125511 - IR 35

Dear Jehan,

Please see the bolded correction to request 2 below:

2. In the revised data submitted for Trial 040, the screening and baseline data for 24-hour urine calcium is given in mmol/day **and the serum calcium is given in mmol/L**. Please resubmit with units of mg/24 hour **and mg/dL, respectively**, to be consistent with **efficacy** endpoint data.

If you have any questions, please let me know.

Regards,  
Elizabeth

---

**From:** Chen, Elizabeth  
**Sent:** Monday, July 07, 2014 12:48 PM  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Subject:** BLA 125511 - IR 35

Dear Jehan,

Please see the below questions from the reviewer. If at all possible, return your responses to these information requests by Wednesday, July 9, 2014.

1. Regarding the analysis of responder rate in Trial 008: Can you please explain the sizable difference/discrepancy between the responder rates for Week 52 and EOT? When was the EOT for most of these subjects?
2. In the revised data submitted for Trial 040, the screening and baseline data for 24-hour urine calcium is given in mmol/day. Please resubmit with units of mg/24 hour, to be consistent with exploratory endpoint data.
3. Please clarify the discrepancy between the two following tables with respect to n (%) of patients with an AE leading to discontinuation: Table B-14.1.1.5.1 from your submission dated May 27, 2014 and Table B-14.3.1.1.1 from your submission dated May 28, 2014. One lists 2 (2.4%) and the other lists 3 (3.6%).
4. Re: your submission from June 6, 2014, in which you provided subjects who required hypocalcemia-related ER visits: are all of the patients from the Natpara group?
5. The following data was extracted from the original CSR for Trial 008: Hypocalcemia was observed in 14 (26.4%) subjects (total of 23 events), hypercalcemia was observed in 6 (11.3%) subjects (total of 9 events), and hypercalciuria was observed in 4 (7.5%) subjects (total of 6 events). Please submit these statements with the revised (excluding Site 1002) data.

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
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**From:** Chen, Elizabeth  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Subject:** BLA 125511 - IR 32  
**Date:** Monday, June 09, 2014 4:27:00 PM

---

Dear Jehan,

See the following request/question from the clinical reviewer related to the 4-month safety update:

1. Please update exposure (Table A1-5) excluding Site 1002.
2. Are there narratives provided for the 2 additional subjects with SAEs in 008 (1010-004 and 1015-003)?

A request for clarification from the device/compliance reviewer:

Where is PD-TEM-PTH-0302 located in terms of sequence, section and date?

Please contact me with any questions. I will get back to you soon regarding the new date for the face-to-face late cycle meeting.

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

**From:** Chen, Elizabeth  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Subject:** BLA 125511 - IR 34  
**Date:** Tuesday, June 17, 2014 11:12:00 AM

---

Dear Jehan,

Please see the below request for information from CMC:

Provide an updated specification for drug substance and revise your proposed limit for

(b) (4) to NLT (b) (4).

Please respond as soon as possible.

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

**From:** Chen, Elizabeth  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Subject:** BLA 125511 - IR 35  
**Date:** Monday, July 07, 2014 12:47:00 PM

---

Dear Jehan,

Please see the below questions from the reviewer. If at all possible, return your responses to these information requests by Wednesday, July 9, 2014.

1. Regarding the analysis of responder rate in Trial 008: Can you please explain the sizable difference/discrepancy between the responder rates for Week 52 and EOT? When was the EOT for most of these subjects?
2. In the revised data submitted for Trial 040, the screening and baseline data for 24-hour urine calcium is given in mmol/day. Please resubmit with units of mg/24 hour, to be consistent with exploratory endpoint data.
3. Please clarify the discrepancy between the two following tables with respect to n (%) of patients with an AE leading to discontinuation: Table B-14.1.1.5.1 from your submission dated May 27, 2014 and Table B-14.3.1.1.1 from your submission dated May 28, 2014. One lists 2 (2.4%) and the other lists 3 (3.6%).
4. Re: your submission from June 6, 2014, in which you provided subjects who required hypocalcemia-related ER visits: are all of the patients from the Natpara group?
5. The following data was extracted from the original CSR for Trial 008: Hypocalcemia was observed in 14 (26.4%) subjects (total of 23 events), hypercalcemia was observed in 6 (11.3%) subjects (total of 9 events), and hypercalciuria was observed in 4 (7.5%) subjects (total of 6 events). Please submit these statements with the revised (excluding Site 1002) data.

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

**From:** Chen, Elizabeth  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Subject:** RE: BLA 125511 - IR 35  
**Date:** Monday, July 07, 2014 2:02:00 PM

---

Dear Jehan,

Please see the bolded correction to request 2 below:

2. In the revised data submitted for Trial 040, the screening and baseline data for 24-hour urine calcium is given in mmol/day **and the serum calcium is given in mmol/L**. Please resubmit with units of mg/24 hour **and mg/dL, respectively**, to be consistent with **efficacy** endpoint data.

If you have any questions, please let me know.

Regards,  
Elizabeth

---

**From:** Chen, Elizabeth  
**Sent:** Monday, July 07, 2014 12:48 PM  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Subject:** BLA 125511 - IR 35

Dear Jehan,

Please see the below questions from the reviewer. If at all possible, return your responses to these information requests by Wednesday, July 9, 2014.

1. Regarding the analysis of responder rate in Trial 008: Can you please explain the sizable difference/discrepancy between the responder rates for Week 52 and EOT? When was the EOT for most of these subjects?
2. In the revised data submitted for Trial 040, the screening and baseline data for 24-hour urine calcium is given in mmol/day. Please resubmit with units of mg/24 hour, to be consistent with exploratory endpoint data.
3. Please clarify the discrepancy between the two following tables with respect to n (%) of patients with an AE leading to discontinuation: Table B-14.1.1.5.1 from your submission dated May 27, 2014 and Table B-14.3.1.1.1 from your submission dated May 28, 2014. One lists 2 (2.4%) and the other lists 3 (3.6%).
4. Re: your submission from June 6, 2014, in which you provided subjects who required hypocalcemia-related ER visits: are all of the patients from the Natpara group?
5. The following data was extracted from the original CSR for Trial 008: Hypocalcemia was observed in 14 (26.4%) subjects (total of 23 events), hypercalcemia was observed in 6 (11.3%) subjects (total of 9 events), and hypercalciuria was observed in 4 (7.5%) subjects (total of 6 events). Please submit these statements with the revised (excluding Site 1002)

data.

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

**From:** Chen, Elizabeth  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Subject:** BLA 125511 - Inquiry  
**Date:** Tuesday, July 29, 2014 12:09:00 PM  
**Attachments:** [image001.png](#)

---

Dear Jehan,

I have two questions for you from the clinical reviewer. This may not require a new submission, but please return the information as soon as possible:

- 1) In Trial 040, how many subjects (per arm) were enrolled/randomized at the time of Protocol Amendment 7?
- 2) Was the graph below submitted excluding subjects from Site 1002?

**Mean Percent Change from Baseline in Active Vitamin D  
Metabolite/Analog Dose (ITT Population)**



ITT = Intent-to-Treat; n = number; SE = standard error  
Source: [Figure 14.2.3.1.1](#), [Table 14.2.2.1.3.1](#) and [Listing 16.2.6.2.1](#)

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

**From:** Chen, Elizabeth  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Subject:** BLA 125511 - more IRs  
**Date:** Thursday, July 31, 2014 10:18:00 AM

---

Dear Jehan,

Please provide the following:

- 1) For the pivotal trial: a table (or provide the location if previously sent) with the following data (excluding Site 1002): statistics for mean serum calcium for baseline through EOT, including all available intermediate timepoints. This should include actual values, not change from baseline.
- 2) For REPLACE: a graph (this was previously sent, but the link has since expired) with the scatterplot of serum phosphorus by study visit.

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

**From:** [Chen, Elizabeth](#)  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Subject:** BLA 125511 - IR 39  
**Date:** Tuesday, August 05, 2014 4:48:00 PM  
**Attachments:** [BLA 125511- IR Drug Product Microbiology.doc](#)

---

Dear Jehan,

(I hope I have the numbers correct.)

This e-mail contains two different sets of information requests. The attached file contains the IRs and possible PMRs/PMCs from the drug product microbiology reviewer mentioned during the late-cycle meeting (please respond by COB August 13).

Below are two additional IRs from the clinical reviewers:

- 1) Indicate where in your submission there is information indicating that the inclusion criterion for hypoparathyroidism was met for individual subjects.
- 2) Populate this table with data from the REPLACE trial (excluding site 1002):

**Hyperphosphatemia Incidence—ITT Population**

Serum phosphorus (mg/dl)	Titration Period Weeks 0-12		Maintenance Period Week 12-24		Trial Duration Weeks 0-24	
	Placebo N=40 n (%)	rhPTH(1-84) N=84 n (%)	Placebo N=40 n (%)	rhPTH(1-84) N=84 n (%)	Placebo N=40 n (%)	rhPTH(1-84) N=84 n (%)
>4.5 mg/dL						
>4.5 and ≤5 mg/dL						
>5 and ≤6 mg/dL						
>6 and ≤7 mg/dL						
>7 mg/dL						

**Hypophosphatemia Incidence—ITT Population**

Serum phosphorus (mg/dl)	Titration Period Weeks 0-12		Maintenance Period Week 12-24		Trial Duration Weeks 0-24	
	Placebo N=40 n (%)	rhPTH(1-84) N=84 n (%)	Placebo N=40 n (%)	rhPTH(1-84) N=84 n (%)	Placebo N=40 n (%)	rhPTH(1-84) N=84 n (%)
< 2.4 mg/dL						

The clinical information requests should be returned as soon as possible.

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

**From:** Chen, Elizabeth  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Subject:** BLA 125511 - IR ?  
**Date:** Wednesday, August 06, 2014 3:05:00 PM

---

Dear Jehan,

Please see the following IR from the clinical reviewer:

Provide summary tables of Treatment-Emergent Adverse Events Occurring in  $\geq 5\%$  in either group by Preferred Term (not by SOC) for the Safety Population, Excluding Site 1002, for the following periods (one separate table for each period) for the pivotal trial:

1. Week 0- Week 12
2. Week 12-24
3. Week 0 -24
4. Week 24 through post-treatment period

Return this IR as soon as possible.

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

**From:** Chen, Elizabeth  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Subject:** BLA 125511 - Labeling Comments  
**Date:** Monday, August 11, 2014 1:47:00 PM

---

Dear Jehan,

Please see the following recommendations from the Division of Medication Error Prevention and Analysis (DMEPA):

A. Instructions for Use (IFU)

- a. [REDACTED] (b) (4)
- b. Delete page [REDACTED] (b) (4) in the IFU because this information is repeated in page 6 and 7.
- c. Since disposable needles, alcohol swap pad, and puncture-resistant container represents additional supplies and not part of the components for use with Natpara, add a subtitle entitled "Additional Supplies" [REDACTED] (b) (4)
- d. Increase the prominence of the statement "Do not use the medication on or after the "Discard on" date" by using a different color font or boxing the text. We recommend this based on the result of the human factors study where one participant delivered her last dose on the "discard on" date and mixed a new medication cartridge on the next day.
- e. Since two different devices (Mixing Device and Q-Cliq Pen) are used [REDACTED] (b) (4) split the section into two separate sections (e.g. A. Mixing Your Medication and B. Preparing Your Pen) to improve clarity and readability of the important instructions regarding to priming the pen.
- f. As currently presented [REDACTED] (b) (4) all human factor study participants who had difficulty with mixing the medication cartridge only read the first part of the IFU statement, which states "With the needle pointing up, turn the wheel slowly until the stoppers no longer move [REDACTED] (b) (4)". Revise this statement to "With the needle pointing up, turn the wheel slowly until the stoppers no longer move. **Make sure the wheel turns** [REDACTED] (b) (4). Bolding the statement "Make sure the wheel turns [REDACTED] (b) (4) will help mitigate errors where the participants turned the wheel until the stoppers came together but not until the wheel turned [REDACTED] (b) (4)".
- g. As currently presented on [REDACTED] (b) (4) Re-position the arrow so that it is pointed to the space between the cartridge and the pen base.
- h. Add a box statement [REDACTED] (b) (4) that states "Make sure the needle cap is pointing downward at all times during steps [REDACTED] (b) (4) since four participants in the HF study did not kept the needle cap pointing down at all times.

B. All container labels and carton labeling

- a. [REDACTED] (b) (4)
- b. Revise the presentation of the proprietary name from all upper case letters "NATPARA" to mixed

case letters “Natpara” to improve readability. Words set in upper and lower case form recognizable shapes, making them easier to read than the rectangular shape that is formed by words set in all capital letters. <sup>[1]</sup>

### C. Carton labeling

#### a. Medication cartridge, all strengths

- i. Add the following statement “Use only after training by your health care provider” to the principal display panel to ensure that patients are trained prior to first use of Natpara.
- ii. Revise the statement (b) (4) to “Must be refrigerated, store at 36°F to 46°F (2°C to 8°C)” to increase the prominence of this important information and to minimize the risk of the storage information being overlooked.
- iii. As currently presented, the net quantity statement “Contains: Two 14-dose medication cartridges of Natpara (rhPTH [1-84]) for injection” is located in the back panel. If space permits, repeat this statement on the principal display panel to increase the prominence of this net quantity statement.<sup>1</sup>  
Additionally, there is a picture of the two medication cartridges on the principal display panel with no explanation of what the picture represents. Therefore, adding the net quantity statement below this picture will help to explain what the picture represents and minimize confusion.

#### b. Q-Cliq pen

- i. See Section B.a.
- ii. Per Prescribing Information insert labeling, the Q-Cliq pen injector can be used for up to two years of daily treatment. Therefore, we recommend adding this information on the carton label for Q-Cliq pen injector.
- iii. Add the statement “Use only after training by your health care provider” because Human Factors study results demonstrate that training is essential to ensure safe use of this product and to minimize the risk of medication errors.

#### c. Mixing Device

- i. See Section B.a.
- ii. Add the statement “for use with Natpara® (rhPTH [1-84]) for Injection only” as (b) (4) was not an approved proprietary name.
- iii. Per the PI insert labeling, the Mixing Device can be used to reconstitute up to 6 Natpara medication cartridges. We recommend adding this information on the carton label for Mixing Device.
- iv. Add the statement “Use only after training by your health care provider” because Human Factors study results demonstrate that training is essential to ensure safe use of this product and to minimize the risk of medication errors.

---

[1] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

Please confirm receipt, and let me know if you have further questions or need clarification so I can speak to the reviewers from the Office of Surveillance and Epidemiology.

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

---

[\[1\]](#) Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

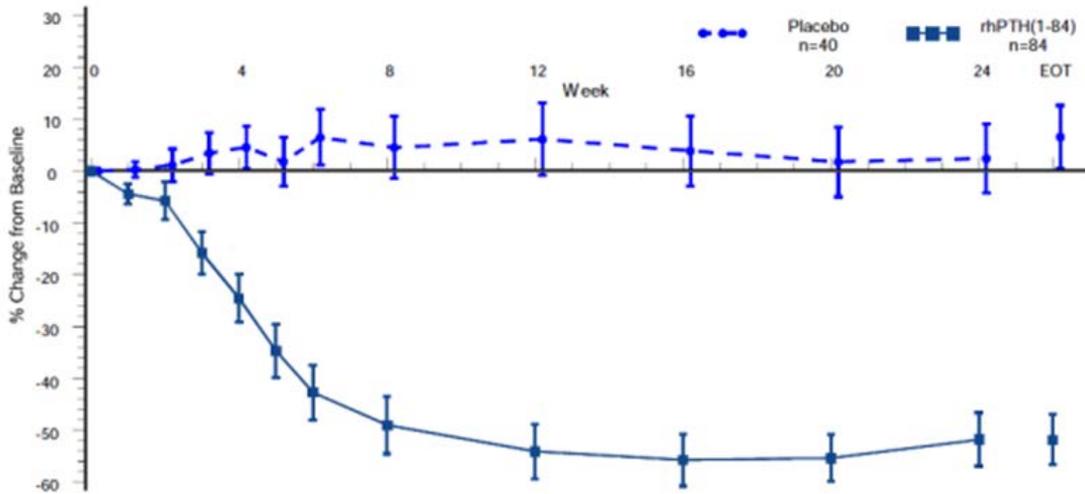
From: Chen, Elizabeth  
To: "[Jehan D. Rowlands](#)"  
Subject: RE: BLA 125511 - more IRs  
Date: Tuesday, August 12, 2014 9:18:00 AM  
Attachments: [image002.png](#)  
[image003.png](#)  
[image004.png](#)

Dear Jehan,

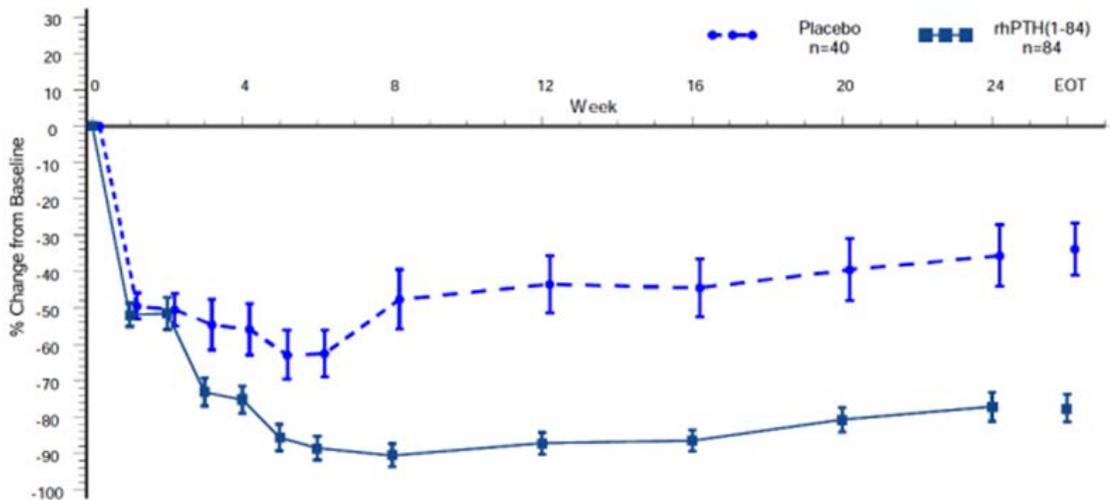
I have another request from the reviewer:

1. Can you please provide the location for the updated figure (excluding Site 1002) with the actual mean values of 24-hour urine calcium over time (not just the changes from baseline) for the pivotal trial?
2. Please confirm if the following figures are for the ITT population:

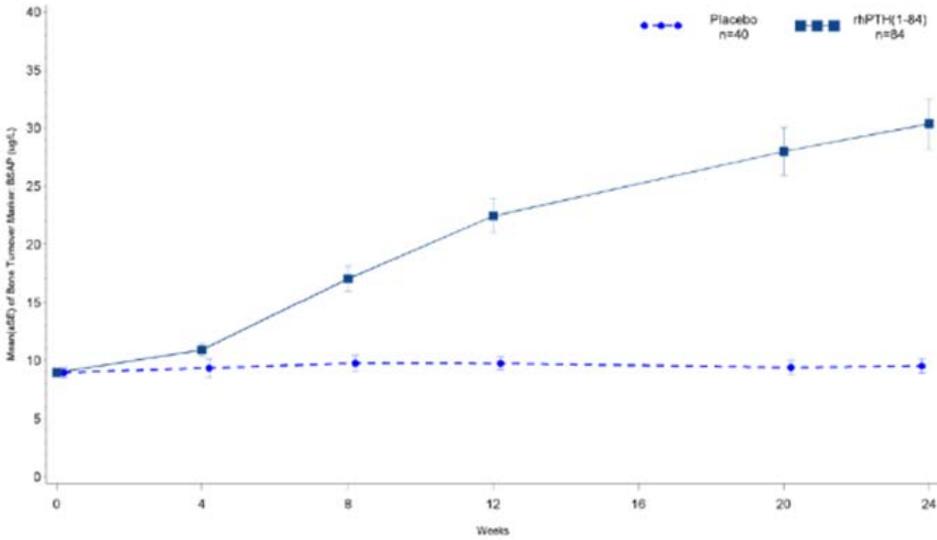
**A. Percent Change (Mean  $\pm$ SE) from Baseline in Dose of Calcium—ITT Population**



**B. Change from Baseline in Dose of Active Vitamin Metabolite/Analog—ITT Population**



**C. Mean ( $\pm$ SE) of Bone Specific Alkaline Phosphatase (ug/L) by Trial Week—**



I will let you know for sure if the graphs you sent me yesterday need to be submitted formally to the BLA once I have conferred with the team.

Regards,  
Elizabeth

---

**From:** Jehan D. Rowlands [mailto:JRowlands@nps.com]  
**Sent:** Monday, August 11, 2014 12:23 PM  
**To:** Chen, Elizabeth  
**Subject:** RE: BLA 125511 - more IRs

Dear Elizabeth,

Please find the requested graph(s) for mean serum phosphorus attached:

- A. Total
- B. Excluding Site 1002
- C. Site 1002 only

Please let me know if these graphs should be submitted formally to the BLA as a Response to "IR 39"?

Please confirm receipt.

Thank you.

Kind regards,

Jehan

Jehan Rowlands, PharmD | Director, Regulatory Affairs | NPS Pharma | Phone: 908.450.5537 | [jrowlands@nps.com](mailto:jrowlands@nps.com)




---

**From:** Chen, Elizabeth [mailto:Elizabeth.Chen@fda.hhs.gov]  
**Sent:** Thursday, August 07, 2014 9:40 AM  
**To:** Jehan D. Rowlands  
**Subject:** RE: BLA 125511 - more IRs

Dear Jehan,

(Another informal IR): Could you please provide the location of the graph for mean phosphorus levels during the trail in both groups?

Regards,  
Elizabeth

---

**From:** Chen, Elizabeth  
**Sent:** Monday, August 04, 2014 9:44 AM  
**To:** 'Jehan D. Rowlands'  
**Subject:** RE: BLA 125511 - more IRs

Dear Jehan,

Thank you very much, I confirm receipt.

Regards,  
Elizabeth

---

**From:** Jehan D. Rowlands [<mailto:JRowlands@npsp.com>]  
**Sent:** Monday, August 04, 2014 9:36 AM  
**To:** Chen, Elizabeth  
**Subject:** FW: BLA 125511 - more IRs

Dear Elizabeth,

Attached are the requested table and graphs. These have been previously submitted to the FDA.

Please confirm receipt. Please let me know if you have any questions.

Kind regards,

Jehan

Jehan Rowlands, PharmD | Director, Regulatory Affairs | NPS Pharma | Phone: 908.450.5537 | [jrowlands@npsp.com](mailto:jrowlands@npsp.com)



---

**From:** Chen, Elizabeth [<mailto:Elizabeth.Chen@fda.hhs.gov>]  
**Sent:** Thursday, July 31, 2014 10:18 AM  
**To:** Jehan D. Rowlands  
**Subject:** BLA 125511 - more IRs

Dear Jehan,

Please provide the following:

- 1) For the pivotal trial: a table (or provide the location if previously sent) with the following data (excluding Site 1002): statistics for mean serum calcium for baseline through EOT, including all available intermediate timepoints. This should include actual values, not change from baseline.
- 2) For REPLACE: a graph (this was previously sent, but the link has since expired) with the scatterplot of serum phosphorus by study visit.

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

---

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**From:** Chen, Elizabeth  
**To:** "[Jehan D. Rowlands](mailto:Jehan.D.Rowlands)"  
**Subject:** RE: BLA 125511 - more IRs  
**Date:** Thursday, August 14, 2014 11:44:00 AM  
**Attachments:** [image002.png](#)  
[image003.png](#)  
[image004.png](#)

---

Dear Jehan,

Please see the questions below from the clinical reviewer:

1. In the pivotal trial, please confirm that the doses of oral calcium used refer to the total dose (not elemental calcium). Also, please specify what dose(s) of tablets were used in the trial.
2. For trial 040, beside the one SAE of hypercalcemia that required hospitalization, were there any other events of hypercalcemia that required an ER visit?
3. For Trial 008, how many of the baseline DXA scans for this trial actually came from Trial 040? Were any of the baseline scans for 040 used as the baseline scans for 040?
4. For Trial 008 in the CSR, it states on p. 48 that final REPLAY/REPLACE parameters were used as baseline parameters for this study. Does that refer to final on-treatment or post-observation period for REPLACE? Also, on p. 64 it states that baseline values from REPLACE would be used as baseline values for Trial 008. Please clarify this apparent discrepancy.

Regards,  
Elizabeth

---

**From:** Jehan D. Rowlands [<mailto:JRowlands@npsp.com>]  
**Sent:** Thursday, August 14, 2014 8:47 AM  
**To:** Chen, Elizabeth  
**Subject:** RE: BLA 125511 - more IRs

Dear Elizabeth,

I confirm receipt. We plan to get the requested graph to you by COB today.

Kind regards,

Jehan

---

**From:** Chen, Elizabeth [<mailto:Elizabeth.Chen@fda.hhs.gov>]  
**Sent:** Thursday, August 14, 2014 7:55 AM  
**To:** Jehan D. Rowlands  
**Subject:** RE: BLA 125511 - more IRs

Dear Jehan,

Thank you for this response. For the first request, would it be possible to provide a graph of 24 hr urine calcium (no serum) for both groups (both groups on one graph) before COB today? If this has not been previously submitted, then it might need to be submitted separately to the BLA. I will get back to you on the other IR responses.

Regards,  
Elizabeth

---

**From:** Jehan D. Rowlands [<mailto:JRowlands@npsp.com>]  
**Sent:** Tuesday, August 12, 2014 12:54 PM  
**To:** Chen, Elizabeth  
**Subject:** FW: BLA 125511 - more IRs

Dear Elizabeth,

For Request 1 (below), I have attached two graph which depict the actual mean values of 24-hour urine calcium for the pivotal trial (excluding Site 1002). These graphs were previously provided as part of the NPS Response to IR 30. Please confirm if these graphs satisfy the reviewer's request.

For Request 2, all three graphs (below) are for the ITT population. In addition, graphs A and B are based on the physician-prescribed data.

Please confirm receipt.

Please let me know if you have any questions.

Thank you.

Kind regards,

Jehan

Jehan Rowlands, PharmD | Director, Regulatory Affairs | NPS Pharma | Phone: 908.450.5537 | [jrowlands@npsp.com](mailto:jrowlands@npsp.com)



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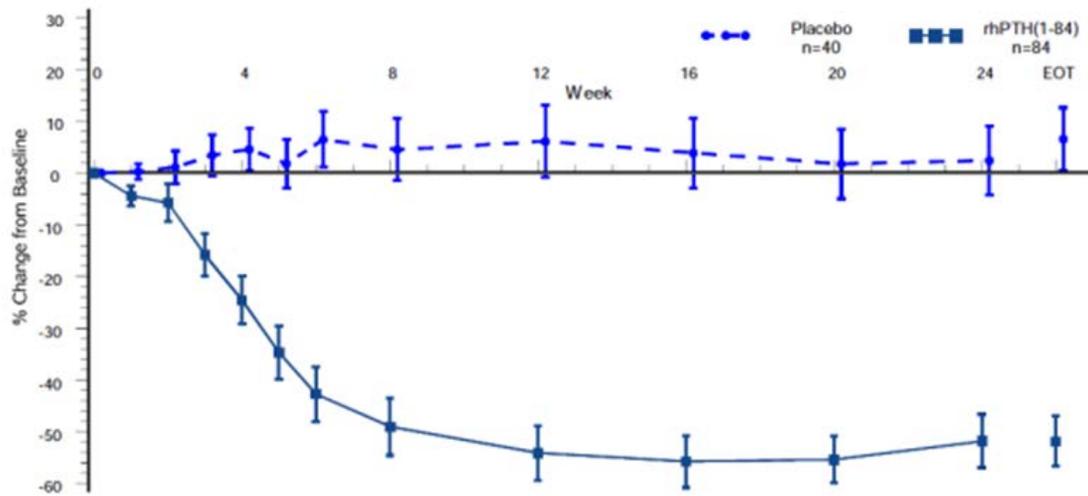
**From:** Chen, Elizabeth [<mailto:Elizabeth.Chen@fda.hhs.gov>]  
**Sent:** Tuesday, August 12, 2014 9:18 AM  
**To:** Jehan D. Rowlands  
**Subject:** RE: BLA 125511 - more IRs

Dear Jehan,

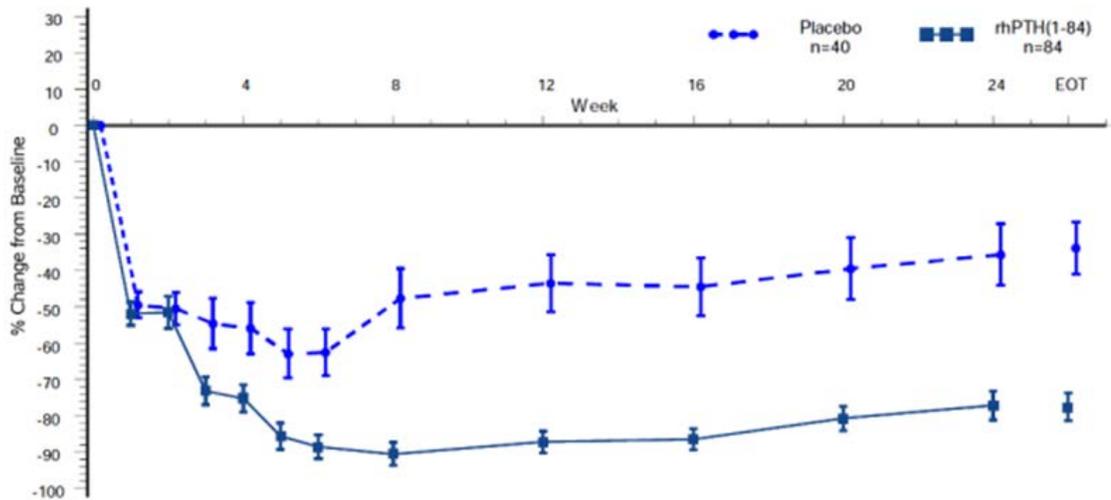
I have another request from the reviewer:

1. Can you please provide the location for the updated figure (excluding Site 1002) with the actual mean values of 24-hour urine calcium over time (not just the changes from baseline) for the pivotal trial?
2. Please confirm if the following figures are for the ITT population:

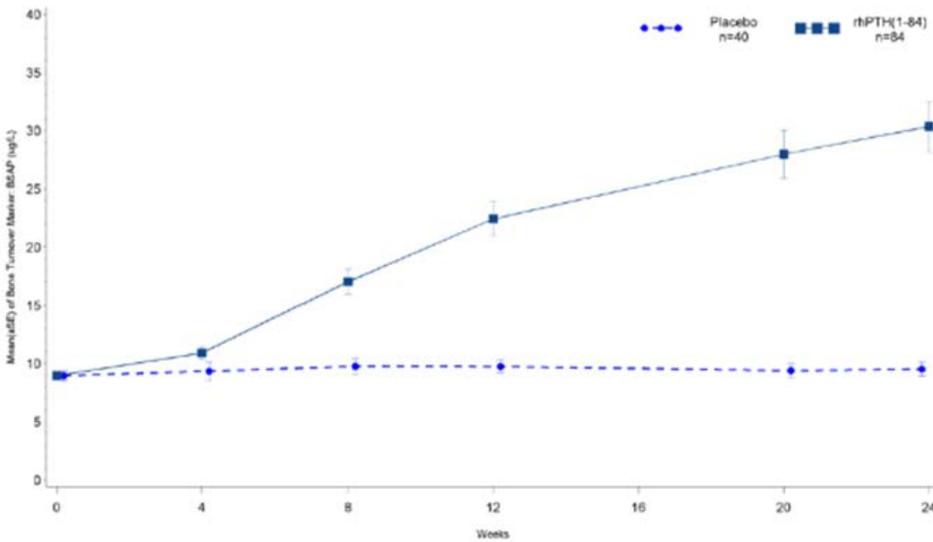
**A. Percent Change (Mean  $\pm$ SE) from Baseline in Dose of Calcium—ITT Population**



**B. Change from Baseline in Dose of Active Vitamin Metabolite/Analog—ITT Population**



C. Mean ( $\pm$ SE) of Bone Specific Alkaline Phosphatase (ug/L) by Trial Week—



I will let you know for sure if the graphs you sent me yesterday need to be submitted formally to the BLA once I have conferred with the team.

Regards,  
Elizabeth

---

**From:** Jehan D. Rowlands [mailto:JRowlands@npsp.com]  
**Sent:** Monday, August 11, 2014 12:23 PM  
**To:** Chen, Elizabeth  
**Subject:** RE: BLA 125511 - more IRs

Dear Elizabeth,

Please find the requested graph(s) for mean serum phosphorus attached:

- A. Total
- B. Excluding Site 1002
- C. Site 1002 only

Please let me know if these graphs should be submitted formally to the BLA as a Response to "IR 39"?

Please confirm receipt.

Thank you.

Kind regards,

Jehan

Jehan Rowlands, PharmD | Director, Regulatory Affairs | NPS Pharma | Phone: 908.450.5537 | [jrowlands@npsp.com](mailto:jrowlands@npsp.com)



---

**From:** Chen, Elizabeth [<mailto:Elizabeth.Chen@fda.hhs.gov>]  
**Sent:** Thursday, August 07, 2014 9:40 AM  
**To:** Jehan D. Rowlands  
**Subject:** RE: BLA 125511 - more IRs

Dear Jehan,

(Another informal IR): Could you please provide the location of the graph for mean phosphorus levels during the trail in both groups?

Regards,  
Elizabeth

---

**From:** Chen, Elizabeth  
**Sent:** Monday, August 04, 2014 9:44 AM  
**To:** 'Jehan D. Rowlands'  
**Subject:** RE: BLA 125511 - more IRs

Dear Jehan,

Thank you very much, I confirm receipt.

Regards,  
Elizabeth

---

**From:** Jehan D. Rowlands [<mailto:JRowlands@npsp.com>]  
**Sent:** Monday, August 04, 2014 9:36 AM  
**To:** Chen, Elizabeth  
**Subject:** FW: BLA 125511 - more IRs

Dear Elizabeth,

Attached are the requested table and graphs. These have been previously submitted to the FDA.

Please confirm receipt. Please let me know if you have any questions.

Kind regards,

Jehan

Jehan Rowlands, PharmD | Director, Regulatory Affairs | NPS Pharma | Phone: 908.450.5537 | [jrowlands@npsp.com](mailto:jrowlands@npsp.com)



---

**From:** Chen, Elizabeth [<mailto:Elizabeth.Chen@fda.hhs.gov>]  
**Sent:** Thursday, July 31, 2014 10:18 AM  
**To:** Jehan D. Rowlands

**Subject:** BLA 125511 - more IRs

Dear Jehan,

Please provide the following:

- 1) For the pivotal trial: a table (or provide the location if previously sent) with the following data (excluding Site 1002): statistics for mean serum calcium for baseline through EOT, including all available intermediate timepoints. This should include actual values, not change from baseline.
- 2) For REPLACE: a graph (this was previously sent, but the link has since expired) with the scatterplot of serum phosphorus by study visit.

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
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PH: 240-402-3729

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**From:** Chen, Elizabeth  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Subject:** BLA 125511 - IR  
**Date:** Wednesday, August 27, 2014 11:21:00 AM

---

Dear Jehan,

See the following request from the clinical reviewer for Natpara (BLA 125511) and respond as soon as possible:

Please fill in the following table for the Natpara arm. List subjects in the table by type of underlying diagnosis (e.g postsurgical, autoimmune, idiopathic, Di George Syndrome, etc.).

Patient ID	Cause of hypoparathyroidism	Responder (yes) or not (no)

If there is anything I have missed since I have been away, please let me know. I am working to catch up on everything.

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

**From:** Chen, Elizabeth  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Subject:** BLA 125511 - IR  
**Date:** Friday, September 05, 2014 11:10:00 AM

---

Dear Jehan,

This may have already been submitted, but we are having some difficulty locating it:

Please provide one figure with the actual mean 24-hour urinary calcium values over time (not the change from baseline) for both groups (2 curves in one figure) with Site 1002 excluded. Please also include a dotted horizontal line across the graph representing the 300 mg/24 hour "cut-off".

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

**From:** Chen, Elizabeth  
**To:** ["Jehan D. Rowlands"](mailto:Jehan.D.Rowlands)  
**Subject:** RE: BLA 125511 - IR - baseline serum PTH levels  
**Date:** Tuesday, September 09, 2014 10:52:00 AM

---

Dear Jehan,

As a follow up, what was the central lab assay normal range for PTH?

Regards,  
Elizabeth

---

**From:** Jehan D. Rowlands [<mailto:JRowlands@npsp.com>]  
**Sent:** Monday, September 08, 2014 1:51 PM  
**To:** Chen, Elizabeth  
**Subject:** RE: BLA 125511 - IR - baseline serum PTH levels

Dear Elizabeth,

Please find attached the requested information (table). This information was submitted previously as part of NPS Response to IR 29.

Please let me know if you have any questions.

Kind regards,

Jehan

---

**From:** Chen, Elizabeth [<mailto:Elizabeth.Chen@fda.hhs.gov>]  
**Sent:** Monday, September 08, 2014 12:22 PM  
**To:** Jehan D. Rowlands  
**Subject:** BLA 125511 - IR - baseline serum PTH levels

Dear Jehan,

I have a question from the clinical reviewer. Is there any data regarding baseline serum PTH levels in the pivotal trial? If so, where can this data be found?

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)

PH: 240-402-3729

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**From:** Chen, Elizabeth  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Subject:** BLA 125511 - Information Request (Device Related)  
**Date:** Thursday, September 18, 2014 2:14:00 PM

---

Dear Jehan,

I have a request for additional information from the clinical reviewer. I believe something very similar to this may have been asked previously by the device reviewer, so if you have sent this to me previously, I apologize.

Were there any ADVERSE EVENTS of device/pen malfunction associated with either the Ypsomed or Haselmeier pens during the clinical trials? Specifically, were there any malfunctions that were ALSO reported as adverse events? If so, please provide a list.

Please let me know if you have any questions regarding this request.

Thanks,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

**From:** Chen, Elizabeth  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Subject:** BLA 125511 - Inspection Inquiry  
**Date:** Thursday, September 18, 2014 6:05:00 PM

---

Dear Jehan,

I have a question related to inspections.

In the application (submission section 3.2.P.3.1-1), NPS (Bedminster, NJ address) is listed as being responsible for QA and final release of drug product. Is there a laboratory at this facility, and is actual testing performed here?

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

**From:** [Chen, Elizabeth](#)  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Subject:** BLA 125511 - Natpara USPI (1)  
**Date:** Thursday, October 30, 2014 1:06:00 PM  
**Attachments:** [Natpara USPI with FDA edits 10-30-2014.docx](#)

---

Dear Jehan,

Thank you for your patience. As discussed on the phone earlier this morning, I am attaching the Natpara label with edits from the Agency.

Please note that we have focused on the items pertaining to the REMS and osteosarcoma, and that these sections have been vetted extensively by all involved groups here at the Agency. Please prioritize review of these sections in order to expedite development of the REMS.

The rest of the label remains under review, and we may have additional feedback in the future.

Please let me know if you have any questions.

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

**From:** Chen, Elizabeth  
**To:** ["Jehan D. Rowlands"](mailto:JRowlands@npsp.com)  
**Subject:** RE: BLA 125511 - General Updates  
**Date:** Wednesday, December 31, 2014 7:53:00 AM

---

Dear Jehan,

The answer to both of your questions is 'yes'. The final name listed on the labels should be:  
**Natpara (parathyroid hormone) for Injection**

Please let me know if you have any additional questions.

Happy new year!  
Elizabeth

---

**From:** Jehan D. Rowlands [mailto:JRowlands@npsp.com]  
**Sent:** Tuesday, December 30, 2014 2:56 PM  
**To:** Chen, Elizabeth  
**Subject:** RE: BLA 125511 - General Updates

Dear Elizabeth,

Thank for you for the below information. I would like to get some additional clarification about the final established name as it relates to the carton/container labeling.

In the DMEPA comments that we received on August 11, 2014 (via email), DMEPA requested that for all carton and container labeling, "NATPARA" be changed to "Natpara". On September 24, 2014 NPS submitted revised carton/container labeling to the BLA incorporating DMEPA comments (BLA Sequence No. 0046). (example attached)

- Could you please confirm if we can still retain "Natpara" for the carton and container labeling, as per DMEPA recommendation?

In addition, in our September 24, 2014 response to DMEPA comments, we capitalized the "I" in the word "injection":

- Could you please confirm if we can still retain the upper case "I" in the word "Injection" for the carton and container labeling: "Natpara® (parathyroid hormone) for Injection"?

Thank you.

Happy Holidays,

Jehan

Jehan Rowlands, PharmD | Director, Regulatory Affairs | NPS Pharma | Phone: 908.450.5537 | [jrowlands@npsp.com](mailto:jrowlands@npsp.com)



---

**From:** Chen, Elizabeth [<mailto:Elizabeth.Chen@fda.hhs.gov>]  
**Sent:** Wednesday, December 24, 2014 4:37 PM  
**To:** Jehan D. Rowlands  
**Subject:** BLA 125511 - General Updates

Dear Jehan,

I am attaching a copy PMR form you submitted; we have accepted your minor revision. We now consider this final. Please submit this officially to the application.

I also have an update regarding the established name for Natpara. We consider the final established name for the product to be "NATPARA® (parathyroid hormone) for injection". (b) (4)

(b) (4)

Please let me know if you have any additional questions. I will be working December 29-31, 2014.

Happy holidays,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
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**From:** Chen, Elizabeth  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Subject:** BLA 125511 - Patient Labeling (Medication Guide and Instructions for Use)  
**Date:** Monday, January 05, 2015 4:10:00 PM  
**Attachments:** [\(final\\_marked\) DMPP OPDP Natpara MG.docx](#)  
[\(final\\_clean\) DMPP OPDP Natpara MG.docx](#)  
[\(final\\_marked\) DMPP OPDP Natpara IFU.docx](#)  
[\(final\\_clean\) DMPP OPDP Natpara IFU.docx](#)

---

Dear Jehan,

Please see the attached with our comments on the Medication Guide and Instructions for Use for Natpara. I have attached both clean and tracked-changes copies of the documents for ease of reference.

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

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

**From:** Chen, Elizabeth  
**To:** ["Jehan D. Rowlands"](#)  
**Subject:** RE: BLA 125511 - Patient Labeling (Medication Guide and Instructions for Use)  
**Date:** Wednesday, January 14, 2015 4:17:00 PM  
**Attachments:** [\(DMPP OPDP comments 1-13-15\) DMPP OPDP Natpara MG NPS changes tracked FI....docx](#)  
[\(DMPP OPDP Natpara IFU \(track changes\) NPS changes tracked 09 JAN 2015 F....docx](#)

---

Dear Jehan,

I'm attaching some additional comments to the documents submitted with this e-mail from the Patient Labeling reviewers.

Regards,  
Elizabeth

---

**From:** Jehan D. Rowlands [mailto:[JRowlands@npsp.com](mailto:JRowlands@npsp.com)]  
**Sent:** Friday, January 09, 2015 4:03 PM  
**To:** Chen, Elizabeth  
**Subject:** RE: BLA 125511 - Patient Labeling (Medication Guide and Instructions for Use)

Dear Elizabeth,

Thank you for providing the FDA comments on the Natpara Medication Guide and Instructions for Use.

We have revised the Medication Guide and Instructions for Use incorporating FDA's comments. We used the "clean" versions of the documents provided by the FDA and then added in NPS-proposed changes/comments (which are tracked).

The following documents are attached:

- NPS-proposed Medication Guide (changes tracked, MS Word)
- NPS-proposed Instructions for Use (changes tracked, MS Word)
- NPS-proposed Instructions for Use (clean, PDF) – this PDF better represents what the Instructions for Use booklet will look like once printed

Please confirm if the NPS-proposed Medication Guide and Instructions for Use are acceptable to the FDA or please let us know if there are any additional FDA comments.

Thank you.

Kind regards,

Jehan

**Jehan Rowlands, PharmD** | Director, Regulatory Affairs | NPS Pharma | Phone: 908.450.5537 |

[jrowlands@npsp.com](mailto:jrowlands@npsp.com)



---

**From:** Chen, Elizabeth [<mailto:Elizabeth.Chen@fda.hhs.gov>]  
**Sent:** Monday, January 05, 2015 4:11 PM  
**To:** Jehan D. Rowlands  
**Subject:** BLA 125511 - Patient Labeling (Medication Guide and Instructions for Use)

Dear Jehan,

Please see the attached with our comments on the Medication Guide and Instructions for Use for Natpara. I have attached both clean and tracked-changes copies of the documents for ease of reference.

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

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

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**From:** Chen, Elizabeth  
**To:** "[Jehan D. Rowlands](#)"  
**Subject:** RE: BLA 125511 - Natpara REMS Documents  
**Date:** Friday, January 16, 2015 11:40:00 PM  
**Attachments:** [BLA 125511 - REMS Comments 3.docx](#)  
[2015 01 16 Appendix 01 NATPARA REMS Document.docx](#)  
[2015 01 16 Appendix 02 Natpara Training Module Prescriber.ppt](#)  
[2015 01 16 Appendix 03 Natpara Prescriber Enrollment Form.doc](#)  
[2015 01 16 Appendix 04 Natpara REMS Program An Introduction.doc](#)  
[2015 01 16 Appendix 05 Natpara Pharmacy Reps training module.ppt](#)  
[2015 01 16 Appendix 06 Natpara Pharmacy Enrollment Form.doc](#)  
[2015 01 16 Appendix 07 Natpara Patient Brochure.docx](#)  
[2015 01 16 Appendix 08 Natpara REMS Patient Prescriber Acknowledgment Form.docx](#)  
[2015 01 16 Appendix 09 NATPARA REMS Program Prescriber Certification Web Page.docx](#)  
[2015 01 16 Appendix 10 NATPARA REMS Program Pharmacy Certification Web Page.docx](#)  
[2015 01 16 Appendix 11 Natpara REMS Webpage.docm](#)  
[2015 01 16 Appendix 12 Natpara REMS Supporting Document.docx](#)

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Dear Jehan,

I apologize for the lateness of this message. I have attached a file with comments that also documents all changes, as well as all the REMS Documents:

- Appendix 1 – Natpara REMS Document
- Appendix 2 – Natpara REMS Training Module for Prescribers
- Appendix 3 – Natpara REMS Prescriber Enrollment Form
- Appendix 4 – Natpara REMS Program: An Introduction
- Appendix 5 – Natpara REMS Training Module for Pharmacy Representatives
- Appendix 6 – Natpara REMS Pharmacy Enrollment Form
- Appendix 7 – Natpara Patient Brochure
- Appendix 8 – Natpara REMS Patient-Prescriber Acknowledgement Form
- Appendix 9 – Natpara REMS Website – Prescriber Certification Webpage
- Appendix 10 – Natpara REMS Website – Pharmacy Certification Webpage
- Appendix 11 – Natpara REMS Website – Home
- Appendix 12 – REMS Supporting Document

Please let me know if you have any questions.

Regards,  
Elizabeth

---

**From:** Jehan D. Rowlands [mailto:[JRowlands@npsp.com](mailto:JRowlands@npsp.com)]  
**Sent:** Thursday, January 08, 2015 3:32 PM  
**To:** Chen, Elizabeth  
**Subject:** BLA 125511 - Natpara REMS Documents

Dear Elizabeth,

Please find attached all of the REMS Documents (14 attachments). Each document is listed in the table below with a description of the types of revisions/changes made to each. For the most part, updates to each document have been made to be consistent with the most current version of the Proposed REMS Document, and current Label.

In addition, we have provided a REMS Supporting Document and Prescriber/Pharmacy Certification web pages.

Please confirm if these REMS documents are acceptable to the FDA or please let us know if there are any additional FDA comments.

<b>Natpara REMS: Summary of Changes</b>	
<b>NPS revisions/comments</b>	
<b>01/08/2015</b>	
<i>Global/General comments</i>	
<i>Comment</i>	NPS has updated all of the REMS documents to be consistent with most current versions of the Proposed REMS Document, current Label. NPS-proposed changes are tracked vs. the most recent FDA version/template, except for the training module slides (ppt format).
NATPARA REMS Document	
<i>Comment</i>	Updated to reflect FDA comments provided on 05 Jan 2015. NPS responses to FDA questions/requests are provided in comment fields. All changes in this document are tracked.
Appendix 1 NATPARA REMS Message Maps	
<i>Comment</i>	Updated to be consistent with most current version of the Proposed REMS Document, and current Label. NPS-proposed changes are tracked vs. the most recent FDA version/template.
Appendix 2_2 NATPARA Letter to Prescribers	
<i>Comment</i>	Updated to be consistent with most current version of the Proposed REMS Document, and current Label. NPS-proposed changes are tracked vs. the most recent FDA version/template.
Appendix 3 NATPARA Training Module Prescriber	
<i>Comment</i>	Updated to be consistent with most current version of the Proposed REMS Document, and current Label. This document is a CLEAN version.
Appendix 4 NATPARA Prescriber Enrollment Form	
<i>Comment</i>	Updated to be consistent with most current version of the Proposed REMS Document, and current Label. NPS-proposed changes are tracked vs. the most recent FDA version/template.
Appendix 5 NATPARA REMS Program – An Introduction	
<i>Comment</i>	Updated to be consistent with most current

	version of the Proposed REMS Document, and current Label. NPS-proposed changes are tracked vs. the most recent FDA version/template.
Appendix 6 NATPARA Pharmacy Reps. Training Module	
<i>Comment</i>	Updated to be consistent with most current version of the Proposed REMS Document, and current Label. This document is a CLEAN version.
Appendix 7 NATPARA Pharmacy Enrollment Form	
<i>Comment</i>	Updated to be consistent with most current version of the Proposed REMS Document, and current Label. NPS-proposed changes are tracked vs. the most recent FDA version/template.
Appendix 8 NATPARA Patient Brochure	
<i>Comment</i>	Updated to be consistent with most current version of the Proposed REMS Document, and current Label. NPS-proposed changes are tracked vs. the most recent FDA version/template.
Appendix 9 NATPARA Patient-Prescriber Acknowledgement Form	
<i>Comment</i>	Updated to be consistent with most current version of the Proposed REMS Document, and current Label. NPS-proposed changes are tracked vs. the most recent FDA version/template.
Appendix 10 NATPARA REMS Web Page	
<i>Comment</i>	Updated to be consistent with most current version of the Proposed REMS Document, and current Label. NPS-proposed changes are tracked vs. the most recent FDA version/template.
NATPARA REMS Prescriber Certification Web Page	
<i>Comment</i>	Updated to be consistent with most current version of the Proposed REMS Document, and current Label.
NATPARA REMS Pharmacy Certification Web Page	
<i>Comment</i>	Updated to be consistent with most current version of the Proposed REMS Document, and current Label.
NPS NATPARA REMS Supporting Document (SD)	
<i>Comment</i>	This SD reflects the most current version of the Proposed REMS Document, and current Label. It

includes the REMS Assessment Plan provided by the FDA.

Thank you.

Kind regards,

Jehan

**Jehan Rowlands, PharmD** | Director, Regulatory Affairs | NPS Pharma | Phone: 908.450.5537 | [jrowlands@npsp.com](mailto:jrowlands@npsp.com)



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**From:** Chen, Elizabeth  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Subject:** BLA 125511 - Natpara label  
**Date:** Sunday, January 18, 2015 2:40:00 PM  
**Attachments:** [Final Natpara proposed-clean.docx](#)  
[Natpara PI - proposed - tracked - FDA edits 01-18-2015.docx](#)

---

Dear Jehan,

I am attaching a tracked changes version of the Natpara label, as well as a clean version (we consider this substantially complete at this point). Please let me know if you have any questions. I will be checking e-mail periodically through today and tomorrow.

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

**From:** Chen, Elizabeth  
**To:** ["Jehan D. Rowlands"](#)  
**Subject:** RE: Revised carton and container labels have been submitted to the NATPARA BLA today  
**Date:** Tuesday, January 20, 2015 5:56:00 PM  
**Attachments:** [\(DMPP comment for signs of osteosarcoma 1-20-15\) Natpara MG \(clean\) FINA...docx](#)

---

Hi Jehan,

I am sending one additional statement to be added to the Medication Guide (see attachment), but I am still waiting on the edits to the REMS documents. I will log on again from home to check on the status, and might be able to pass it on this evening.

Regards,  
Elizabeth

---

**From:** Jehan D. Rowlands [<mailto:JRowlands@npsp.com>]  
**Sent:** Tuesday, January 20, 2015 3:30 PM  
**To:** Chen, Elizabeth  
**Subject:** RE: Revised carton and container labels have been submitted to the NATPARA BLA today

Thanks for the confirmation Elizabeth!

Kind regards,

Jehan

---

**From:** Chen, Elizabeth [<mailto:Elizabeth.Chen@fda.hhs.gov>]  
**Sent:** Tuesday, January 20, 2015 3:29 PM  
**To:** Jehan D. Rowlands  
**Subject:** RE: Revised carton and container labels have been submitted to the NATPARA BLA today

Hi Jehan,

We've received the submission of the carton and container labeling for Natpara. I am awaiting final approval on the additional REMS language before getting back to you, but it should be before COB today.

Regards,  
Elizabeth

---

**From:** Jehan D. Rowlands [<mailto:JRowlands@npsp.com>]  
**Sent:** Tuesday, January 20, 2015 3:28 PM  
**To:** Chen, Elizabeth  
**Subject:** Revised carton and container labels have been submitted to the NATPARA BLA today

Dear Elizabeth,

Just wanted to confirm that the revised carton and container labels for NATPARA have been

formally submitted to the BLA earlier today.

Please let me know if you have any questions.

Kind regards,

Jehan

**Jehan Rowlands, PharmD** | Director, Regulatory Affairs | NPS Pharma | Phone: 908.450.5537 |  
[jrowlands@npsp.com](mailto:jrowlands@npsp.com)



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**From:** Chen, Elizabeth  
**To:** "[Jehan D. Rowlands](#)"  
**Subject:** RE: Revised carton and container labels have been submitted to the NATPARA BLA today  
**Date:** Wednesday, January 21, 2015 8:46:00 AM

---

Dear Jehan,

I am now sending comments to be added to the label and to the REMS documents.

To Section 5.1 of the label (Warnings and Precautions), please add the following statement: "Instruct patients to promptly report clinical symptoms (e.g., persistent localized pain) and signs (e.g., soft tissue mass tender to palpation) that could be consistent with osteosarcoma."

In order to be consistent with the change in the label and medication guide, please add the following comments to the REMS documents:

\*\*\*\*\*

**A. Message for Patients: (add to REMS Message Map for Patients, PPAF, and Patient Brochure)**

[Redacted content] (b) (4)

For the PPAF - Put a third bullet under the patient acknowledgement:

- [Redacted content] (b) (4)  
[Redacted content] :
  - o pain in any areas of (b) (4) body that does not go away
  - o any new or unusual lumps or swelling under (b) (4) skin that is tender to touch.

For the patient brochure, make it a separate question:

**What are the signs and symptoms of bone cancer?**

- o pain in any areas of your body that does not go away
- o any new or unusual lumps or swelling under your skin that is tender to touch.

Tell your doctor right away if you have any of these signs or symptoms.

**B. Message for Prescribers: (add to REMS Message Map for Prescribers and to all materials for prescribers)**

[Redacted content] (b) (4)

\*\*\*\*\*

Please call me if you have any questions.

Regards,  
Elizabeth

---

**From:** Jehan D. Rowlands [mailto:JRowlands@npsp.com]  
**Sent:** Tuesday, January 20, 2015 7:25 PM  
**To:** Chen, Elizabeth  
**Subject:** RE: Revised carton and container labels have been submitted to the NATPARA BLA today

Thank you Elizabeth. I have forwarded it to our team for review and I expect to send you the final clean version of the medication guide early Wednesday morning.

Your update on the status of the FDA edits to the REMS documents is noted.

Kind regards,

Jehan

---

**From:** Chen, Elizabeth [mailto:Elizabeth.Chen@fda.hhs.gov]  
**Sent:** Tuesday, January 20, 2015 5:56 PM  
**To:** Jehan D. Rowlands  
**Subject:** RE: Revised carton and container labels have been submitted to the NATPARA BLA today

Hi Jehan,

I am sending one additional statement to be added to the Medication Guide (see attachment), but I am still waiting on the edits to the REMS documents. I will log on again from home to check on the status, and might be able to pass it on this evening.

Regards,  
Elizabeth

---

**From:** Jehan D. Rowlands [mailto:JRowlands@npsp.com]  
**Sent:** Tuesday, January 20, 2015 3:30 PM  
**To:** Chen, Elizabeth  
**Subject:** RE: Revised carton and container labels have been submitted to the NATPARA BLA today

Thanks for the confirmation Elizabeth!

Kind regards,

Jehan

---

**From:** Chen, Elizabeth [mailto:Elizabeth.Chen@fda.hhs.gov]  
**Sent:** Tuesday, January 20, 2015 3:29 PM  
**To:** Jehan D. Rowlands  
**Subject:** RE: Revised carton and container labels have been submitted to the NATPARA BLA today

Hi Jehan,

We've received the submission of the carton and container labeling for Natpara. I am awaiting final approval on the additional REMS language before getting back to you, but it should be before COB

today.

Regards,  
Elizabeth

---

**From:** Jehan D. Rowlands [<mailto:JRowlands@npsp.com>]  
**Sent:** Tuesday, January 20, 2015 3:28 PM  
**To:** Chen, Elizabeth  
**Subject:** Revised carton and container labels have been submitted to the NATPARA BLA today

Dear Elizabeth,

Just wanted to confirm that the revised carton and container labels for NATPARA have been formally submitted to the BLA earlier today.

Please let me know if you have any questions.

Kind regards,

Jehan

Jehan Rowlands, PharmD | Director, Regulatory Affairs | NPS Pharma | Phone: 908.450.5537 | [jrowlands@npsp.com](mailto:jrowlands@npsp.com)



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**From:** Chen, Elizabeth  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Subject:** BLA 125511 - Final Label (PI)  
**Date:** Wednesday, January 21, 2015 1:51:00 PM  
**Attachments:** [Final Natpara proposed FDA \(Clean\) 21 JAN 2015.docx](#)  
[Final Natpara proposed FDA \(changes tracked\) 21 JAN 2015.docx](#)

---

Dear Jehan,

I am attaching what we consider to be a finalized label (package insert only), with both a clean and tracked-changes version (minor edits only). If you agree with all changes, please return the clean version.

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

**From:** Chen, Elizabeth  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Subject:** BLA 125511 - Updated PMR Descriptions  
**Date:** Thursday, January 22, 2015 10:07:00 AM  
**Attachments:** [2014\\_1\\_21\\_Natpara PMRs\\_status post SRT.doc](#)

---

Dear Jehan,

Based on suggestions and feedback from upper management, we have made revisions to the PMRs for Natpara (see tracked changes in attached file). Please confirm receipt and concurrence.

As always, feel free to contact me with any questions you may have.

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

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/s/  
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ELIZABETH R CHEN  
01/22/2015

## Voqui, Jessica

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**From:** Voqui, Jessica  
**Sent:** Monday, June 02, 2014 5:24 PM  
**To:** Lowy, Naomi; Jairath, Meghna  
**Cc:** Papadopoulos, Elektra; CDER SEALD Endpoints  
**Subject:** SEALD Consult for BLA 125511 (SF-36)

Dear Naomi and Meghna,

This is a follow-up to the a SEALD consult request made by the Division of Metabolism and Endocrinology Products (DMEP) for BLA 125511 for parathyroidismhormone for injection as treatment for hypoparathyroidism, submitted by NPS Pharmaceuticals, Inc. DMEP requested that we provide advice regarding the relevance of the SF-36 in assessing hypoparathyroidism [REDACTED] (b) (4) The SF-36 was one of several exploratory endpoints used in the clinical trial study (CL1-11-040).

Suggested comments to sponsor, if needed:

[REDACTED] (b) (4)

Please be advised that the SEALD Endpoints Team reviews the methodological adequacy of clinical outcome assessments for primary and key secondary endpoints (i.e., those that have appropriate multiplicity adjustment in the statistical analysis plan) that are intended to measure treatment benefit. A SEALD endpoint review is not necessary for exploratory endpoints because these are generally inadequate to support labeling claims due to their exploratory status. Therefore, at this time, we do not intend to provide a written review and will close out the consult request with this email.

Please let us know if you have any additional questions. Thank you!

Best regards,  
Jessica

LT Jessica Voqui, PharmD, MS  
Regulatory Review Officer  
Study Endpoints and Labeling Development (SEALD)  
Office: (301) 796-2915  
Fax: (301) 796-9855

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/s/  
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JESSICA VOQUI  
06/03/2014

ELEKTRA J PAPADOPOULOS  
06/03/2014

**From:** [Jehan D. Rowlands](#)  
**To:** [Chen, Elizabeth](#)  
**Subject:** RE: Proposal and Timing of Information Requested in IR 29  
**Date:** Friday, May 30, 2014 11:06:32 AM

---

Dear Elizabeth,

Here is the Subject ID (with positive Ab):

Site ID	Unique Subject ID	CL1-11-040 Subject ID	PAR-C10-008 Subject ID
1008	<a href="#">CL1-11-040-1008-0004</a>	<a href="#">1008-0004</a>	
1002	<a href="#">CL1-11-040-1008-0004</a>		<a href="#">1008-0004</a>

The unique subject ID was created for the convenience of identifying the same subject who participated in multiple studies. The study ID as the prefix in the unique subject ID represents the first study that the subject was enrolled in.

Please let me know if you have any questions.

Kind regards,

Jehan

---

**From:** Chen, Elizabeth [mailto:[Elizabeth.Chen@fda.hhs.gov](mailto:Elizabeth.Chen@fda.hhs.gov)]  
**Sent:** Friday, May 30, 2014 10:43 AM  
**To:** Jehan D. Rowlands  
**Subject:** RE: Proposal and Timing of Information Requested in IR 29

Dear Jehan,

Please provide the subject ID of the specific patient mentioned below (with positive Ab).

Regards,  
Elizabeth

---

**From:** Jehan D. Rowlands [mailto:[JRowlands@npsp.com](mailto:JRowlands@npsp.com)]  
**Sent:** Thursday, May 29, 2014 11:16 AM  
**To:** Chen, Elizabeth  
**Subject:** RE: Proposal and Timing of Information Requested in IR 29

Dear Elizabeth,

Thank you very much for providing these responses so quickly!

Kind regards,

Jehan

---

**From:** Chen, Elizabeth [<mailto:Elizabeth.Chen@fda.hhs.gov>]  
**Sent:** Thursday, May 29, 2014 9:38 AM  
**To:** Jehan D. Rowlands  
**Subject:** RE: Proposal and Timing of Information Requested in IR 29

Dear Jehan,

Please see responses to your questions below. A teleconference will not be scheduled. Please let me know if additional clarification is needed.

Regards,  
Elizabeth

---

**From:** Jehan D. Rowlands [<mailto:JRowlands@npsp.com>]  
**Sent:** Wednesday, May 28, 2014 4:28 AM  
**To:** Chen, Elizabeth  
**Subject:** Proposal and Timing of Information Requested in IR 29

Dear Elizabeth,

I am following up to confirm whether the format of the tables for the REPLACE Trial (Study CL1-11-040), (full data included, minus Columbia - site 1002, site 1002) provided to you on Monday, May 26, 2014 was acceptable for the reviewers. Could you please confirm?

In addition, our proposal for the timing for providing the additional requested information is as follows:

- Study CL1-11-040 (REPLACE) – efficacy and safety tables, figures and listings to be provided to FDA by Wednesday, May 28
- Study PAR-C10-008 (RACE) long term study - all tables to be provided by Friday, May 30<sup>th</sup>; figures and listings by Sunday, June 1<sup>st</sup>
- All requested IR's re-analyzed (up to and including IR 23) to be provided by Friday, May 30<sup>th</sup>
- Population PK analysis – we have contacted (b) (4) (vendor who did analysis) and they tentatively promised this to be provided by the end of this week (May 30)

Please confirm if this above proposal for delivery dates is acceptable for FDA.

We also have the following questions for which we are seeking feedback/clarification and would appreciate the opportunity to discuss with FDA as soon as possible during an informal teleconference:

- There have been no new datasets generated. The tables and listings that are provided are an analysis of a subset of data without the Columbia site (1002) and the Columbia site alone.

Does the FDA agree that we do not need to provide any new datasets?:

**not at this time**

- Are there any specific tables from the ISS and ISE that the FDA would like to receive? If yes, will these tables take priority over those of the individual studies?

**not at this time**

We will re-calculate the overall exposure removing the Columbia site and propose to provide this information to FDA early next week.

- Are there any other integrated tables that the FDA would like to see removing the Columbia site?

**not at this time**

- For the Advisory Committee meeting, we will not present any information from the Bilezikian IIT and will remove his patients from analysis of data from any NPS-sponsored studies. All exposure data will be calculated without Columbia patients. We will only reference Dr. Bilezikian's published data in the briefing book. Any data presented in either the briefing book or at the advisory committee meeting will be minus Columbia data. Does the FDA agree that this is acceptable?

**yes**

- There was one SAE (hypocalcemia in the withdrawal phase which occurred 27 days after treatment) and one TEAE leading to discontinuation (hypertension) at the Columbia site. How would FDA like for us to handle this SAE and TEAE leading to discontinuation?

**They can be excluded**

- One subject in RACE from the Columbia site (1002) had positive/non-specific antibodies at Week 40 and Month 24. The same subject was enrolled in REPLACE at Site 1008 and experienced positive/non-specific antibodies at Weeks 24 and 28. Does the FDA agree that we do not need to re-analyze antibody data excluding the Columbia site since this subject was positive/non-specific in REPLACE at a different site?

**Yes. Please provide the subject ID.**

- We would like to be consistent with FDA with respect to the removal of the Columbia patients in REPLACE. For the Advisory committee meeting, in terms of the REPLACE data analysis including 124 patients instead of the original 134, what is the message that the FDA would like for us to communicate regarding the removal of the Columbia site?

**Comments regarding this are preliminary. However, the committee should be informed that there was a problematic site that required removal of data from that site and that all data presented exclude subjects from that site.**

We would appreciate the opportunity to discuss these questions with the FDA during an informal teleconference. Please confirm the timing of the call.

Thank you.

Kind regards,

Jehan

**Jehan Rowlands, PharmD** | Director, Regulatory Affairs | NPS Pharma | Phone: 908.450.5537 | [jrowlands@npsp.com](mailto:jrowlands@npsp.com)



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/s/  
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ELIZABETH R CHEN  
06/03/2014



BLA 125511/0

## INFORMATION REQUEST

NPS Pharmaceuticals Inc.  
Attention: Jehan Rowlands, Pharm.D.  
Director, Regulatory Affairs  
550 Hills Drive, 3rd Floor  
Bedminster, NJ 07921

Dear Dr. Rowlands:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for Natpara (parathyroid Hormone (1-84) Human Recombinant injection).

We also refer you to the teleconference held on May 23, 2014, at 10 AM to discuss re-analysis of data from the pivotal trial supporting your BLA to exclude data from the Columbia site. We request a prompt written response in order to continue our evaluation of your BLA.

Provide updated analyses of the efficacy and safety data in the clinical study report for the pivotal clinical trial REPLACE excluding the Columbia site and provide the following:

1. Present original tables, figures, and lists from the original report and contrast these to:
  - identical tables, figures, or lists derived from data that *excludes* the Columbia site, and
  - identical tables, figures, or lists derived from data that includes *only* the Columbia site.

The number of patients included in each of these re-analyses should be included in the tables and numerical discrepancies should be clearly explained. Analysis datasets used to generate this updated information should be submitted along with the report.

2. This format should be used for all the data important to benefit risk determination (i.e., demographic, exposure, efficacy and safety, pharmacokinetics/pharmacodynamics, and immunogenicity data).
3. Present data for both the controlled phase of the trial as well as for the trial extension.

4. Re-analyze data for all the clinical information requests received from the Agency (see list of dates attached) using the same data presentation format as described in bullet (1). Label each of these analyses according to the date on the provided list.

If you have any questions, contact Elizabeth Chen, Regulatory Project Manager, at (240) 402-3729.

Sincerely,

*{See appended electronic signature page}*

Jean-Marc Guettier, M.D.  
Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure:  
Dates of clinical information requests

**Dates of Information Requests (Clinical)**

01/16/2014 – IR 1  
01/23/2014 – IR 2  
01/24/2014 – IR 3  
01/28/2014 – IR 4  
02/10/2014 – IR 5  
02/11/2014 – IR 6 (Clinical and CMC)  
02/26/2014 – IR 8 (Immunogenicity and Clinical)  
02/28/2014 – IR 9 (Clinical and Device)  
03/21/2014 – IR 12  
03/24/2014 – IR 13  
03/25/2014 – IR 14 (Clinical Pharmacology)  
03/31/2014 – IR 15  
04/01/2014 – IR 16 (Drug substance/product and Clinical)  
04/04/2014 – IR 17  
04/10/2014 – IR 18  
04/28/2014 – IR 20  
05/06/2014 – IR 21  
05/16/2014 – IR 23  
05/22/2014 – IR 27  
05/22/2014 – IR 28

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/s/  
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JEAN-MARC P GUETTIER  
05/27/2014

**From:** Chen, Elizabeth  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Subject:** BLA 125511 - IR 28  
**Date:** Thursday, May 22, 2014 5:06:00 PM  
**Attachments:** [BLA 125511 IR 28.doc](#)

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Dear Jehan,

Please see the attached information request. The Agency would also like to request an informal teleconference with NPS Pharmaceuticals *as soon as possible* (Friday, May 23 in the morning or early during the week of the 26<sup>th</sup>).

Regards,  
Elizabeth

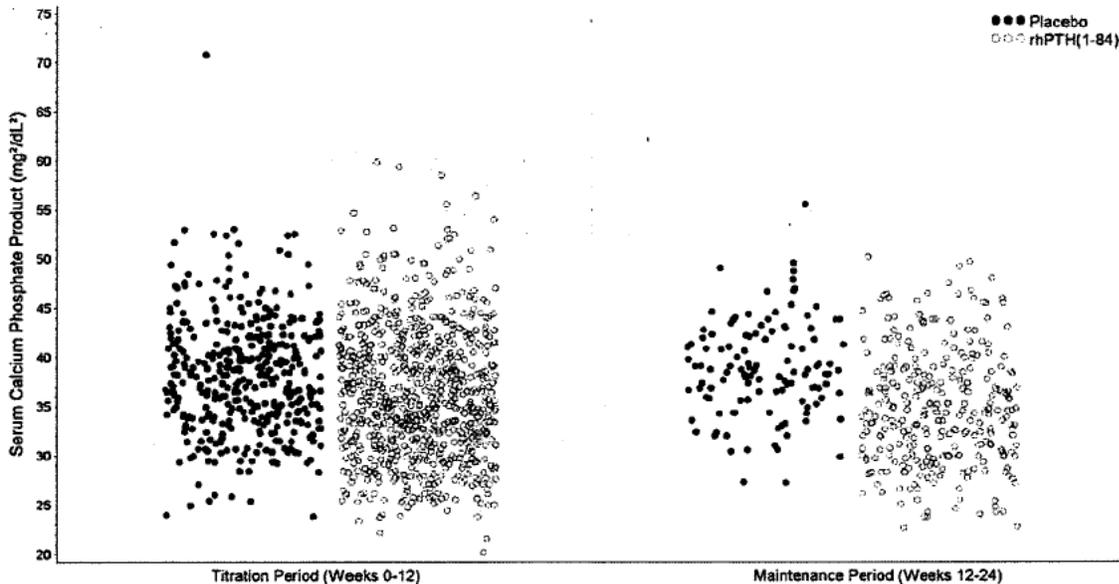
Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

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/s/  
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ELIZABETH R CHEN  
05/29/2014

- 1) While you submitted the Form 3455 for (b) (6) you did not submit any supporting information. The form states "Details of the individual's disclosable financial arrangement and interest are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests." Please provide this information.
- 2) Re: Trial 040, aside from the SAEs for hypocalcemia and hypercalcemia, how many subjects required ER visits that would not have been coded as SAEs?
- 3) In your response to our IR from March 12, 2014, you provided a scatterplot of serum calcium-phosphate product by study period (shown below). It appears that there were at least 5 abnormal measurements for the study drug group during the titration period. The CSR also states that at Week 4, there were 2 subjects in the NPSP558 group with high levels and from Week 5 on, and no subject had a high level (until Week 24). Please clarify if the abnormal data points below reflect these subjects.



- 4) In the CSR for Trial 040, confirm that Table 12-7 includes the post-treatment phase.
- 5) For Trial 040, provide more information for the subject who discontinued due to rash. Describe the rash and the time course in greater detail.

- 6) Re: the scatterplot below that you provided as a Response to Information Request: There are 5 data points that are markedly lower (Week 0, Week 1, Week 20, and 2 at Week 24). Were these data points associated with hypocalcemia AEs? Who were these subjects? Please provide more information about the circumstances surrounding these points.



- 7) Re: the table that you provided in a Response to IR from February 18, 2014 including AEs > 4% and greater in NPSP558: does this include post-treatment phase? Could you provide the same information split into 2 tables, one for titration phase and one for maintenance phase?

Please respond by June 6, 2014.

Regards,  
Elizabeth

**From:** Chen, Elizabeth  
**To:** "[Jehan D. Rowlands](#)"  
**Subject:** BLA 125511 - IR 27  
**Date:** Thursday, May 22, 2014 4:58:00 PM

---

Dear Jehan,

Please see the additional follow-up question regarding your response to IR 21:

The CSR for 009 stated that there were five subjects with a total of 7 hypercalcemia events. Tables 2.1 and 2.2 suggest that there were more than this (10 subjects). Please clarify.

Please also see the two following requests for information related to Trial 040:

1. RE: Trial 040, it states that there was a DSMB comprised of 3 physicians and an independent statistician and they were free of "significant" conflicts of interest. Please more explicitly describe who were these physicians—were they NPS employees, etc.?
2. Re: Trial 040 and baseline medical conditions, why were not all subjects coded as having hypoparathyroidism?

This can be considered as IR 27. Please provide responses by June 6, 2014.

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

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**From:** Jehan D. Rowlands [mailto:[JRowlands@npsp.com](mailto:JRowlands@npsp.com)]  
**Sent:** Tuesday, May 20, 2014 11:14 PM  
**To:** Chen, Elizabeth  
**Subject:** NPS Response to IR 21

Dear Elizabeth,

Attached is the NPS Response to IR 21. The formal response will be submitted to the BLA via the Gateway within a few days.

Please let me know if you have any questions.

Kind regards,

Jehan

**Jehan Rowlands, PharmD** | Director, Regulatory Affairs | NPS Pharma | Phone: 908.450.5537 |  
[jrowlands@npsp.com](mailto:jrowlands@npsp.com)



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ELIZABETH R CHEN  
05/29/2014

**From:** [Jehan D. Rowlands](#)  
**To:** [Chen, Elizabeth](#)  
**Subject:** RE: BLA 125511 - IR 26 (Urgent)  
**Date:** Tuesday, May 20, 2014 4:40:46 PM  
**Attachments:** [Study CL1-11-040 ACM Lab Reference Ranges.pdf](#)  
[Study PAR C10-009 Reference Ranges.pdf](#)  
[Study PAR-C10-007 Reference Ranges 19April2011.pdf](#)  
[Study PAR-C10-008 Reference Ranges V4 07 03Apr2012.pdf](#)

---

Dear Elizabeth,

Attached are the Reference Ranges for Studies:

- CL1-11-040
- PAR-C10-007
- PAR-C10-008
- PAR-C10-009

Please let me know if you have any questions.

Kind regards,

Jehan

---

**From:** Chen, Elizabeth [mailto:[Elizabeth.Chen@fda.hhs.gov](mailto:Elizabeth.Chen@fda.hhs.gov)]  
**Sent:** Tuesday, May 20, 2014 10:45 AM  
**To:** Jehan D. Rowlands  
**Subject:** BLA 125511 - IR 26 (Urgent)

Dear Jehan,

Please see the below information request and provide a response by COB today (response can be provided by e-mail only):

Provide the location of the normal ranges used for all laboratory values.

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

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ELIZABETH R CHEN  
05/29/2014

**From:** Chen, Elizabeth  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Subject:** BLA 125511 - IR 25  
**Date:** Monday, May 19, 2014 6:17:00 PM

---

Dear Jehan,

I have the following information request from both the clinical reviewer and one of the device reviewers from CDRH:

Please provide detailed descriptions/narratives of the circumstances surrounding the 15 device complaints for the Ypsomed and the 13 complaints for the Haselmeier pen summarized in CSR 008, Table 14.3.9.1.

Please respond by June 2, 2014.

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

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ELIZABETH R CHEN  
05/22/2014

**From:** Chen, Elizabeth  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Subject:** BLA 125511 - IR 24  
**Date:** Friday, May 16, 2014 10:28:00 AM  
**Attachments:** [BLA 125511 IR 24.doc](#)

---

Dear Jehan,

Please see the following information request from one of the device reviewers at CDRH.

Regards,  
Elizabeth Chen

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

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ELIZABETH R CHEN  
05/19/2014

**IR 24**

**BLA 125511**

1. The Halsemier reusable pen-injector performance testing you have provided as the 8 page document in 3.2.R (TR-1031-0049-00) is devoid of basic device specification details (for example, activation force, dispensing time and etc.) which is unacceptable to the Agency. For dose accuracy of a biologic-device combination product, the testing should be performed using final-finished product (device with needle fully assembled with the biologic) actually dispensing the subject biologic. Please provide the actual test reports and accompanying clear concise write-up to include test objective, protocol, actual sample size, pass/fail criteria, results and conclusion for each of the test performed (9.2.2 to 9.2.5 and 10.1).
2. We are unable to locate the reports of TP-10206, TP-1030, Protocol B87000-00, DE\_Form 3.3.4NPS-00 and DE\_Form 3.3.5NPS-02 mentioned on Page 8 of TR-1031-0049-00 to assess the performance details. Please provide all of these reports.
3. Your re-usable pen is intended for 2 years of daily injection use. During the 2 years, the pen assembled with the biologic cartridge is refrigerated except for the few minutes each day when the injector takes place. Please provide realistic pen-injector device lifetime testing simulating long term refrigerator (96 hours is inadequate) using devices near the end-of-shelf-life that your device can accurately dispense the prescribed biologic dose daily for 3 years (1.5 times of the intended 2 years) without medication error, device malfunction /breakage or adverse events.
4. Many users use alcohol pads to clean their medical devices and alcohol has been known to degrade plastic leading to cracking. Your re-usable pen-injector is intended for daily use over 2 years of time. Will your pen-injector withstand 730 days of alcohol wiping or will there be a warning statement in your labeling to advise them otherwise?
5. Figure 3.2.R.2-18 Injection Time to Deliver Dose (page 25 of 27) is a blank. Please re-submit the appropriate graph.
6. Warning to the patients in the labeling that if the needle is removed before counting to 10 seconds after the counter is reset to zero, then under-dosing will occur and may require additional or increased parathyroid administration.

Please respond by May 30, 2014.

Regards,  
Elizabeth

**From:** Chen, Elizabeth  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Subject:** BLA 125511 - IR 23  
**Date:** Friday, May 16, 2014 6:10:00 AM  
**Attachments:** [BLA 125511 IR 23.doc](#)

---

Dear Jehan,

Please see the attached information request.

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

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ELIZABETH R CHEN

05/19/2014

**IR 23**

**BLA 125511**

1. For CSR for Trial 008, the reference lines on figures 11-8 through 11-11 seemingly refer to the normal reference ranges previously provided by you. However, for at least one of the figures (P1NP) the dotted line does not correlate with the reference range. Also, there are multiple reference ranges for s-CTx. What value is represented in the dotted line in Figure 11-9?
2. Re: changes in s-CTx in all the trials, since there is only a reference range high that you have provided, how is one to understand whether this parameter is improving? Do you consider the baseline s-cTx levels in 040 abnormal?

Information requests related to the teleconference on May 14, 2014:

3. For the pivotal trial, please re-analyze the primary endpoint data using the original 3<sup>rd</sup> component of the primary endpoint.
4. For Study 008, please provide a) a scatterplot (as requested previously) for serum calcium, serum phosphorus, and 24 hour urinary calcium data at baseline (for Study 008) and Months 6, 12, 24, and 52. Please include 'n' and the reference ranges in the plots.
5. For 008, please provide a table as shown below showing the number and percentage of patients at each timepoint with urine calcium in the normal range (i.e. < 300 mg/dl) and abnormal range of the total number of patients with data for each particular timepoint (Months 6, 12, 24, and 52). (see sample table on next page)

Please respond by May 30, 2014.

Regards,  
Elizabeth

**From:** Chen, Elizabeth  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Subject:** BLA 125511 - IR 22  
**Date:** Wednesday, May 07, 2014 2:29:00 PM  
**Attachments:** [BLA 125511 IR 22.doc](#)

---

Dear Jehan,

Please see the attached information request from one of the device reviewers within CDRH.

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

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ELIZABETH R CHEN  
05/07/2014

**IR 22**  
**BLA 125511**

1. We are unable to conclude that the Human Factors (HF) validation study demonstrates that the device can be used safely and effectively by intended users. There were multiple reports of critical use errors which may lead to single and multiple missed-doses, and underdose and needle stick injuries that could lead to patient harm.

You stated that the severity of harm associated with the instances are "slight" meaning that the hazard may cause temporary impairment of a body function or temporary damage to a body structure and does not require medical/surgical intervention to prevent permanent damage. However, we believe that the clinical harm associated with a single missed-dose or underdose could lead to clinically important hypocalcemia, and consequently, multiple missed-dose (s) and underdose(s) can exacerbate the patient conditions. In addition, needle stick injuries represent a known risk with needle-based devices that should be adequately mitigated. There are three specific areas of concern:

- a. We note that the use of the device requires manual assembly of different components prior to priming and administration of the drug i.e. attaching the needle, attaching the medication cartridge onto the pen, turning the wheel on the mixing device, turning the blue dosage knob so that the dose window shows the word "GO", etc. Consequently, the HF study showed that use errors largely occurred while users performed these preparatory steps. And comments from study participants indicated some notable concerns regarding the tactile/auditory feedback when attaching the needle, confusion regarding the stoppers stop moving versus the wheel stop moving, visual feedback from the stoppers, the needle to keep the needle in place while priming, holding the device in the up-right orientation when tapping when some users may be accustomed to holding it downwards, etc. We recommend that you further optimize your Instructions for Use (IFU) and training to successfully communicate to users the critical information, and to clearly communicate the specific device (tactile/auditory/visual) feedback in each of the preparatory steps. There is also a need to provide clear instructions to users that they need to verify that the device components have been properly assembled prior to performing the priming and administration steps, and if they need additional assistance, then they should be directed to call the 1-800-number.
- b. There were two use errors observed with the step of holding the device at the injection site for 10 seconds. The 10 seconds duration and the clinical consequence of underdose should be further emphasized in your IFU.
- c. There were two use errors observed when two participants discarded the large needle cap prior to recapping. The importance of placing the cap onto the needle prior to discarding should be emphasized in your IFU.

Please make the necessary modifications and provide data demonstrating that the additional mitigations are effective with 15 healthcare providers and lay patients combined.

Please respond by May 21, 2014.

Regards,  
Elizabeth

**IR 21**

**BLA 125511**

Regarding Trial 009 (REPEAT):

1. The CSR states that the composite endpoint for Trial 009 was chosen to match that of the pivotal trial. Please re-analyze the primary endpoint using the identical criteria from the pivotal trial (eliminating the additional criteria re: the maximum allowed calcium and calcitriol doses).
  
2. Regarding changes in calcium levels:
  - Confirm that the values you provide are not albumin-corrected.
  - Similar to previous requests, provide a scatterplot of calcium levels during the trial by study visit, with the LLN and ULN clearly delineated. Provide the same for phosphorus levels and 24-hour urine calcium.
  - Similar to tables you provided in previous information requests for Trial 009, provide tables with incidences of hypercalcemia and hypocalcemia by calcium category for the each trial period and total trial duration.
  
3. For bone markers, please provide new figures showing the actual mean values by Week. Provide your list of normal values for these markers.

Please respond by May 20, 2014.

Regards,  
Elizabeth

**From:** Chen, Elizabeth  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Subject:** BLA 125511 - IR 22  
**Date:** Wednesday, May 07, 2014 2:29:00 PM  
**Attachments:** [BLA 125511 IR 22.doc](#)

---

Dear Jehan,

Please see the attached information request from one of the device reviewers within CDRH.

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

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/s/  
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ELIZABETH R CHEN  
05/07/2014



BLA125511/0

**MID-CYCLE COMMUNICATION**

NPS Pharmaceuticals Inc.  
Attention: Jehan Rowlands, Pharm.D.  
Director, Regulatory Affairs  
550 Hills Drive, 3rd Floor  
Bedminster, NJ 07921

Dear Dr. Rowlands:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for Natpara (parathyroid Hormone (1-84) Human Recombinant injection).

We also refer to the teleconference between representatives of your firm and the FDA on April 2, 2014. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, contact Elizabeth Chen, Regulatory Project Manager, at (240) 402-3729.

Sincerely,

*{See appended electronic signature page}*

Jean-Marc Guettier, M.D.  
Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure:  
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

**MID-CYCLE COMMUNICATION**

**Meeting Date and Time:** April 2, 2014, 2:00 PM to 3:00 PM

**Application Number:** BLA 125511/0

**Product Name:** Natpara (parathyroid Hormone (1-84) Human Recombinant injection)

**Indication:** Replacement for endogenous parathyroid hormone (1-84) for the long-term treatment of hypoparathyroidism

**Applicant Name:** NPS Pharmaceuticals Inc.

**Meeting Chair:** Dragos Roman, M.D.

**Meeting Recorder:** Elizabeth Chen, Pharm.D.

**FDA ATTENDEES**

Division of Metabolism and Endocrinology Products

Jean-Marc Guettier, M.D., Director  
Dragos Roman, M.D., Clinical Team Leader  
Naomi Lowy, M.D., Clinical Reviewer  
Robert Maher, Ph.D., DABT, Nonclinical Reviewer  
Karen Davis Bruno, Ph.D., Supervisory Pharmacologist  
Elizabeth Chen, Pharm.D., Regulatory Project Manager  
Pamela Lucarelli, Chief, Project Management Staff

Office of Clinical Pharmacology

Manoj Khurana, Ph.D., Clinical Pharmacology Reviewer  
Nitin Mehotra, Ph.D., Clinical Pharmacology Reviewer  
Immo Zadezensky, Ph.D., Clinical Pharmacology Team Leader

Division of Biometrics II

Jennifer Clark, Ph.D., Statistician

Office of Pharmaceutical Science

Jessica Cole, Ph.D., Product Quality Microbiology Reviewer

Office of Manufacturing and Product Quality

Colleen Thomas, Ph.D., Product Quality Microbiology Reviewer  
Patricia Hughes, Ph.D., Microbiologist

Office of Biologic Products

Montserrat Puig, Ph.D., Laboratory of Immunology

Daniela Verthelyi, M.D., Ph.D., Team Leader, Laboratory of Immunology

Center for Devices and Radiological Health

Lana Shiu, M.D., Senior Medical Advisor

Office of Strategic Programs

Kimberly Taylor, Operations Research Analyst

## **OTHER ATTENDEES**

Eastern Research Group, Inc.

(b) (6)

## **APPLICANT ATTENDEES**

Elizabeth Delmaestro, RPh, Ph.D., Senior Director, Pharmacovigilance

Xin Du, Ph.D., Senior Director, Regulatory Affairs CMC

Roger Garceau, M.D., Executive Vice President, R&D and Chief Medical Officer

Michael Grace, Ph.D., Senior Director, Analytical Development

Hjalmar Lagast, M.D., Vice President, Clinical Development

Joseph Rogus, Senior Vice President, Technical Operations & Supply Chain Management

Ralf Rosskamp, M.D., Vice President, Global Clinical Development

Jehan Rowlands, Pharm.D., Director, Regulatory Affairs

Anthony Sileno, M.S., Vice President, Pre-Clinical and Clinical Operations

Ella Stamler, Director, Quality Assurance – Medical Device

Peter Valentinsson, Vice President, Global Pharmaceutical Sciences

Paul Vandenberg, Ph.D., Head, Global Quality control

Richard Wilcocks, Senior Director, Technical Services

Caesar Snodgrass-Pilla, Director, Analytical Development

## **1.0 INTRODUCTION**

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

## **2.0 SIGNIFICANT ISSUES**

Nonclinical

We acknowledge that your proposed product labeling does not include (b) (4)  
Based on the data available, this is a concern and will be a review issue.

### Microbiology

#### Drug substance:

1. The drug substance should have a bioburden specification that is reported on the Certificate of Analysis. Change the in-process limit for drug substance bioburden to a release specification.
2. Because method qualification data for the bioburden and endotoxin tests was not provided, it is not clear whether the test methods are suitable for drug substance testing.

#### Drug product:

The (b) (4) validation studies for the active drug product solution do not appear to be conducted with the proposed commercial formulation but were conducted using a formulation previously under development for a different indication.

## **3.0 INFORMATION REQUESTS**

### Microbiology

A product quality microbiology request for the drug substance was sent prior to the mid-cycle meeting.

A response is requested by April 29, 2014.

### Immunogenicity:

1. Regarding the ADA incidence on subjects with hypoparathyroidism:
  - a. You calculated the % of ADA+ subjects based on 132 drug-naïve treated patients that received rhPTH therapy in the NSP-sponsored studies, including 90 subjects from study CL1-11-040. However, only approximately 1/3 of these 90 subjects' samples were tested using the validated MSD-ECL assay. Since the anti-rhPTH antibody incidence reported is based on the MSD-ECL results, please recalculate the percent of ADA+ samples considering the total number of subjects tested instead of the number of subjects treated with rhPTH.
  - b. The results from the Bilizekian study samples (n=8) should not be combined with those from the NSP-sponsored studies, since the tested samples were collected 1-3 years after the end of treatment, and the short term assessment for the development of ADA is lacking.
  - c. The incidence of ADA in the hypoparathyroidism study appears to be higher than that reported for the osteoporosis patients. Differences in the sensitivity of the assay as well as differences in the patient populations may have contributed to the distinct rates of ADA. Therefore immunogenicity data obtained from hypoparathyroidism and osteoporosis studies should not be pooled together but could be reported separately, indicating that the serum ADA levels were evaluated with different methods and acknowledging potential differences in the susceptibility of the two populations to develop Ab against rhPTH.

2. Regarding the immunogenicity assays and their validation:
  - a. You report the Ab titer from ADA+ confirmed samples as the log10 of the reciprocal dilution in which the result is above the CP of the assay. Confirm that the initial dilution of the serum (b) (4) is considered in the titer determination or recalculate and resubmit the data as needed.
  - b. (b) (4)
  - c. The information regarding full validation for the updated (modified) NAb assay requested in an IR letter from February 26th, 2014 is still pending, since the table referenced in your response includes validation parameters from the original assay validation report (drug tolerance and sensitivity) that were not confirmed using the method used to test the clinical samples. As per your statement in the TNJR11-174 report saying "Drug tolerance and sensitivity will be conducted with the revised method and reported as an addendum (with additional long term stability [at -70°C]) to the validation report", please provide these updates or clarify your response to our IR letter.
3. We are concerned that proposed the endotoxin specifications allow for up to (b) (4). Low levels of endotoxin can contribute to product immunogenicity. Revise your product release specifications to reflect your manufacturing experience and reduce the immunogenicity risk.

A response is requested by April 15, 2014.

#### **4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT**

There are no major safety concerns identified at this time, and there is currently no need for a REMS.

#### **5.0 ADVISORY COMMITTEE MEETING**

The Endocrine and Metabolic Drugs Advisory Committee meeting is tentatively planned to take place at on July 24, 2014.

#### **6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES**

The late-cycle meeting is planned to take place on Tuesday, July 8, 2014, from 12:00 PM to 1:00 PM.

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JEAN-MARC P GUETTIER  
04/28/2014

**From:** Chen, Elizabeth  
**To:** "[Jehan D. Rowlands](mailto:JRowlands@npsp.com)"  
**Subject:** BLA 125511 - IR 20  
**Date:** Monday, April 28, 2014 4:32:00 PM

---

Dear Jehan,

I have the follow related clarification for this IR from a reviewer here at FDA:

Subject 2001-0001 is listed has as having a pre-treatment SAE, but the narrative states that she was hospitalized for hypocalcemia around Week 20. Please clarify.

This will be considered IR 20.

Regards,  
Elizabeth

---

**From:** Jehan D. Rowlands [<mailto:JRowlands@npsp.com>]  
**Sent:** Wednesday, April 16, 2014 2:57 PM  
**To:** Chen, Elizabeth  
**Subject:** RE: NPS Response to IR 15

Dear Elizabeth,

Thank you for the confirmation on IR 14 and IR 15!

Kind regards,

Jehan

---

**From:** Chen, Elizabeth [<mailto:Elizabeth.Chen@fda.hhs.gov>]  
**Sent:** Wednesday, April 16, 2014 2:56 PM  
**To:** Jehan D. Rowlands  
**Subject:** RE: NPS Response to IR 15

Dear Jehan,

Thank you very much, the information has been forwarded on to the reviewers.

Regards,  
Elizabeth

---

**From:** Jehan D. Rowlands [<mailto:JRowlands@npsp.com>]  
**Sent:** Tuesday, April 15, 2014 10:22 PM  
**To:** Chen, Elizabeth  
**Subject:** NPS Response to IR 15

Dear Elizabeth,

Attached is the NPS response to IR 15 (contained in FDA email dated 31 March 2014).

The formal response to the BLA will be submitted within a couple of days via the Gateway.

Please confirm receipt of IR 14 and IR15 both submitted separately today via email.

Please let me know if you have any questions.

Kind regards,

Jehan

Jehan Rowlands, PharmD  
Director, Regulatory Affairs  
NPS Pharmaceuticals  
Office: 908-450-5537  
Mobile: (b) (6)  
[jrowlands@npsp.com](mailto:jrowlands@npsp.com)

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ELIZABETH R CHEN  
05/07/2014

**From:** Chen, Elizabeth  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Subject:** BLA 125511 - IR19  
**Date:** Thursday, April 24, 2014 11:56:00 AM  
**Attachments:** [BLA 125511 IR 19.doc](#)

---

Dear Jehan,

Please see the attached information request from our microbiology reviewer.

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

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/s/  
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ELIZABETH R CHEN  
04/28/2014

IR 19

BLA 125511

Please provide the following information or a reference to its location in the subject submission.

1. Please provide rabbit pyrogen test data for three different lots of the drug product to demonstrate that the drug product does not contain pyrogenic substances other than bacterial endotoxin. Alternately, you may request a waiver if you demonstrate equivalent pyrogen detection consistent with the recommendations in Question 9 from the Guidance for Industry Pyrogens and Endotoxins Testing: Questions and Answers (<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm310098.pdf>)
2. Provide a description of the acceptance criteria for, and the planned completion date for the transport validation studies for the drug product described in Module 3.2.P.3.5. Specifically, describe the transport studies to support shipping (b) (4) to the secondary packaging facilities.
3. Confirm that the set points used for the sterilization validation studies for the (b) (4) are equivalent (or worst case) to the production set points.
4. Describe the duration of the (b) (4) (b) (4) (b) (4) validation (media fill) studies.

Please respond by May 8, 2014.

Regards,  
Elizabeth

**From:** Chen, Elizabeth  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Subject:** BLA 125511 - IR 18  
**Date:** Thursday, April 10, 2014 4:42:00 PM  
**Attachments:** [BLA 125511 IR 18.doc](#)

---

Dear Jehan,

Please see the attached request for information from the clinical reviewer.

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

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ELIZABETH R CHEN  
04/16/2014

**IR 18**

**BLA 125511**

For RELAY, could you please provide the following:

1. A figure of mean calcium values over time for both groups, with the limits of normal clearly delineated
2. A scatterplot of albumin-corrected serum calcium values over time for both groups, again with ULN and LLN delineated

For REPLACE, regarding urinary calcium, provide a table that gives the percentages of normal and abnormal values for 24-hour urinary calcium for each group, at each available timepoint; provide an N for each timepoint

Please use the sample table on the next page to give your response.

Please respond by April 24, 2014.

Regards,  
Elizabeth

**From:** [Jehan D. Rowlands](#)  
**To:** [Lucarelli, Pamela K](#)  
**Cc:** [Chen, Elizabeth](#); [Jairath, Meghna](#)  
**Subject:** RE: BLA 125511 (Natpara) Clinical Pharmacology Information Request  
**Date:** Tuesday, March 25, 2014 2:36:38 PM

---

Hi Pam,

I confirm receipt. According to the sequence of information requests (IRs) received thus far, this request should be considered "IR14". Could you please confirm.

I will give you a call shortly to discuss a separate important issue.

Thank you.

Kind regards,

Jehan

---

**From:** Lucarelli, Pamela K [mailto:Pamela.Lucarelli@fda.hhs.gov]  
**Sent:** Tuesday, March 25, 2014 2:03 PM  
**To:** Jehan D. Rowlands  
**Cc:** Chen, Elizabeth  
**Subject:** BLA 125511 (Natpara) Clinical Pharmacology Information Request

Hi Jehan,

Elizabeth Chen is out of the office and I am covering her applications until Thursday. Please find below an information request from our clinical pharmacology review team.

1. Please clarify what criteria was used for classification of an adverse reaction of hypercalcaemia as well as hypocalcaemia in the clinical trials. In general what numerical cut-offs were used to characterize hypercalcaemia, hypocalcaemia, and hypercalciurea?
2. We are looking for individual level data on Natpara dose by visit. Considering your response to information request dated 02/06/2014, it appears that this data is not readily available in any single data-set. Therefore, please provide us the SAS program code that was used for generating mean dose of Natapara by visit graph (Page 3 of the Response dated 02/06/2014) and confirm if this code also outputs individual level data for dose by visit.

Acknowledge receipt of this email. If you have any questions, let me or Elizabeth know.

Thanks,  
Pam  
Pamela Lucarelli

Chief, Project Management Staff  
FDA/Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
WO22 - Room 3364  
10903 New Hampshire Avenue  
Silver Spring, MD 20903  
Phone 301.796.3961  
Fax 301.796.9712  
[pamela.lucarelli@fda.hhs.gov](mailto:pamela.lucarelli@fda.hhs.gov)

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ELIZABETH R CHEN  
04/01/2014

**From:** [Jehan D. Rowlands](#)  
**To:** [Chiang, Raymond](#)  
**Cc:** [Chen, Elizabeth](#); [Jairath, Meghna](#)  
**Subject:** RE: Natpara -- BLA 125511  
**Date:** Monday, March 24, 2014 4:43:18 PM

---

Hi Raymond,

Thanks for your call. This is to confirm that I've received your email.

Should we consider this request as "IR13"?

FYI, the previous request was IR12.

Kind regards,

Jehan

Jehan Rowlands, PharmD  
Director, Regulatory Affairs  
NPS Pharmaceuticals  
Office: 908-450-5537  
Mobile: (b) (6)  
[jrowlands@npsp.com](mailto:jrowlands@npsp.com)

---

**From:** Chiang, Raymond [mailto:Raymond.Chiang@fda.hhs.gov]  
**Sent:** Monday, March 24, 2014 4:37 PM  
**To:** Jehan D. Rowlands  
**Cc:** Chen, Elizabeth  
**Subject:** Re: Natpara -- BLA 125511

Hi Jehan,

Thanks for talking with me on the phone. I'm covering for Liz for the next couple days. Please see information request from the FDA medical officer and CMC reviewer.

Please respond to the FDA medical officer's request as soon as possible. Please also confirm receipt of email.

Thanks,

Ray

Raymond S. Chiang, MPT, MS, MS  
Division of Metabolism & Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

Email: [Raymond.Chiang@fda.hhs.gov](mailto:Raymond.Chiang@fda.hhs.gov)

*From FDA medical officer:*

*On p. 56 of the CSR for Trial 040, it states that the database was unlocked. Please provide the date that this occurred.*

*From FDA CMC reviewer:*

*We acknowledge receipt of your amendment dated 18-FEB-2014 and require further clarification regarding the (b) (4) that arise following reconstitution of the Natpara drug product:*

(b) (4) (b) (4)





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ELIZABETH R CHEN  
04/01/2014

**From:** Chen, Elizabeth  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Subject:** BLA 125511 - IR 12  
**Date:** Friday, March 21, 2014 3:15:00 PM  
**Attachments:** [Hyper\\_Hypo-Calcemia\\_Events\\_Incidence.doc](#)  
[BLA 125511 IR 12.doc](#)

---

Dear Jehan,

Please see the following information request from our reviewers, along with an additional attachment for reference.

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

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ELIZABETH R CHEN  
03/21/2014

**IR 12**

**BLA 125511**

Clinical

You have previously provided tables that reflect both numbers of events of and numbers (%) patients with hypercalcemia/hypocalcemia. When comparing the 2 sets of tables (events vs. subjects), in some instances there appear to be fewer events than number of patients with events. For example, in Table 1 in the attached document, it lists 19 events of calcium > 10.6 for the trial duration in the Natpara group, yet in Table 1.1 it says that 32 subjects had such a value during the entire trial. How can there be fewer events than subjects with that value? Similar apparent discrepancies exist in the remainder of the hypercalcemia tables as well as the hypocalcemia tables. Please explain this apparent discrepancy.

Please respond by April 4, 2014.

Regards,  
Elizabeth

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

**From:** Chen, Elizabeth  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Cc:** [Jairath, Meghna](#); [Lucarelli, Pamela K](#)  
**Subject:** BLA 125511 - IR 11  
**Date:** Monday, March 17, 2014 2:54:00 PM  
**Attachments:** [BLA 125511 IR 11.doc](#)

---

Dear Jehan,

Please see the attachment containing IR 11.

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

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ELIZABETH R CHEN  
03/18/2014

**IR 11**

**BLA 125511**

Microbiology

Please provide the following information or a reference to its location in the subject submission.

1. We refer to the bacterial challenge (b) (4) validation studies. Table 3.2.P.3.5-2 indicates that the proposed Natpara commercial formulation was not utilized in the bacterial retention studies. Please submit the results from bacterial challenge studies using the proposed commercial formulation and manufacturing conditions
2. The sterility test method verification studies (MB110208/0) refer to tests conducted in 2008 with formulation PTH (b) (4). The proposed commercial formulations for Natpara range from (b) (4). Provide a justification for how the submitted validation report supports the proposed commercial formulations.
3. Confirm that the endotoxin test method verification studies described in QC-AVR-PTH-007 version 2 utilized the proposed commercial formulations. Indicate whether these tests were conducted on the reconstituted drug product.

Please respond by April 17, 2014.

Regards,  
Elizabeth

**From:** [Jairath, Meghna](#)  
**To:** [Jehan D. Rowlands \(JRowlands@npsp.com\)](mailto:JRowlands@npsp.com)  
**Cc:** [Chen, Elizabeth](#)  
**Subject:** clarification\_ BLA 125511 Sponsor response to IR 9  
**Date:** Friday, March 14, 2014 3:56:11 PM

---

Hey Jehan,

We have the following clarification on the your responses to IR9.

**FDA Clarification Comment: After looking at the 12 page document that you submitted, it still references back to the BLA sections 3.2.R.2 which we previously informed you contained many blank pages where the device information should be. Has that section been updated or fixed?**

Thanks,  
Meghna

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ELIZABETH R CHEN  
03/18/2014

**From:** [Jairath, Meghna](#)  
**To:** [Jehan D. Rowlands \(JRowlands@npsp.com\)](mailto:JRowlands@npsp.com)  
**Cc:** [Chen, Elizabeth](#)  
**Subject:** IR 10 Follow up to Applicant's Response to IR6 BLA 125511  
**Date:** Tuesday, March 11, 2014 1:03:52 PM

---

## IR 10

### BLA 125511

Hello,

We refer to your amendment dated February 18, 2014, containing a response to our IR 6 dated February 11, 2014 sent via email.

Repeating our question and your response below. Followed by our follow-up comment.

### CMC

**FDA Request 7:** Revise the proposed acceptance criteria for Appearance as part of the drug product specifications for a) Tests Performed on Chamber 2 (Diluent for Reconstitution), and b) Tests Performed on Reconstituted Drug Product for Natpara. The proposed acceptance criteria for Appearance (b) (4)

(b) (4) is not appropriate for an injectable product. The acceptance criteria for Appearance should be consistent with that proposed during the clinical development for the hypoparathyroidism indication (“Colourless solution free of foreign particles”).

**NPS Response 7:** The Sponsor will revise the acceptance criteria for Appearance for Tests Performed on Chamber 2 (Diluent for Reconstitution) and Tests Performed on Reconstituted Drug Product for Natpara to “Colorless solution free of foreign particles”.

**FDA Follow-Up Comment:** Please submit a revised Natpara Drug Product Specifications to the BLA incorporating the revisions you agreed upon in your amendment dated February 18, 2014 (see above).

Please respond by 3/18/14.

Thanks,  
Meghna and Elizabeth

---

**From:** Jairath, Meghna [<mailto:Meghna.Jairath@fda.hhs.gov>]  
**Sent:** Tuesday, February 11, 2014 3:10 PM  
**To:** Jehan D. Rowlands  
**Subject:** IR6 BLA 125511

Hello,  
Please see attachment for additional comments.

Thanks,  
Meghna

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MEGHNA M JAIRATH  
03/16/2014

**From:** Chen, Elizabeth  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Cc:** [Jairath, Meghna](#)  
**Subject:** IR9 BLA 125511  
**Date:** Friday, February 28, 2014 4:55:00 PM  
**Attachments:** [BLA 125511 IR 9.doc](#)

---

Dear Jehan,

I have some additional questions from our clinical and device review teams.

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

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/s/  
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ELIZABETH R CHEN  
03/18/2014

IR 9

BLA 125511

Device Evaluation

1. Please re-submit all relevant device constituent information to include all device drawings, including the needle, materials of construction, biocompatibility, sterility, shelf life test, as well as all testing in the final finished product configuration (drug filled into the device assembled with the needle delivering actual medication). You will also need to track/categorize/analyze and submit all device-related medication errors, injuries and malfunctions.

Clinical

2. Please provide a plot for calcium phosphate product in Study CL1-11-040 similar to the following example reproduced from **D Mitchell et al *J Clin Endocrinol Metab* 97: 4507–4514, 2012**. Include only individual pairs of calcium and phosphate measurements that were measured on the same day. Provide the total number of available such datapoints. Present the data by treatment group (Natpara and placebo) for the titration and maintenance periods within each treatment group.

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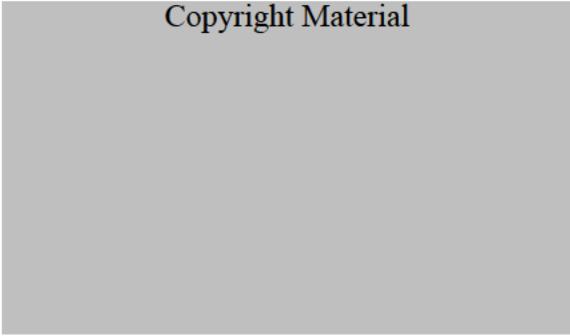
3. Please provide a distribution plot of the 24-hour urine calcium measurements during Study CL1-11-040 similar to the following example reproduced from **D Mitchell et al** *J Clin Endocrinol Metab* **97: 4507–4514, 2012**. Present the data by treatment arm (Natpara vs. placebo) and study period for each treatment arm (titration vs. maintenance vs. both periods combined). Provide the total number of available datapoints in each graph.

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4. Please provide a scatterplot of all 24-h urine calcium levels with serum calcium levels recorded the same day during Study CL1-11-040 similar to the following example reproduced from **D Mitchell et al** *J Clin Endocrinol Metab* **97: 4507–4514, 2012**. Present the data by treatment arm (Natpara vs. placebo) and study period for each treatment arm (titration vs. maintenance vs. both periods combined). Provide the total number of available datapoints in each graph.

Copyright Material



Please respond by March 14, 2014.

Regards,  
Elizabeth

**From:** Chen, Elizabeth  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Cc:** [Jairath, Meghna](#)  
**Subject:** IR8 BLA 125511  
**Date:** Monday, February 24, 2014 7:02:00 PM  
**Attachments:** [BLA 125511 IR 8.doc](#)

---

Dear Jehan,

Please see the attached document with some additional questions.

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

**From:** Chen, Elizabeth  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Cc:** [Jairath, Meghna](#)  
**Subject:** RE: IR8 BLA 125511  
**Date:** Wednesday, February 26, 2014 5:06:00 PM  
**Attachments:** [BLA 125511 IR 8 NEW.doc](#)

---

Dear Jehan,

I have a revision to the immunogenicity questions sent in IR8, as well as some additional clinical questions. Please use this file instead of the file that was sent to you on Monday.

Regards,  
Elizabeth Chen

---

**From:** Chen, Elizabeth  
**Sent:** Monday, February 24, 2014 7:03 PM  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Cc:** [Jairath, Meghna](#)  
**Subject:** IR8 BLA 125511

Dear Jehan,

Please see the attached document with some additional questions.

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

**From:** [Jehan D. Rowlands](#)  
**To:** [Jairath, Meghna](#); [Chen, Elizabeth](#)  
**Subject:** RE: IR8 BLA 125511  
**Date:** Thursday, February 27, 2014 8:59:14 AM

---

Hi Meghna,

Yes, we will combine IR7 and IR8 when we send the formal submission, but will email you the responses sooner as requested.

Kind regards,

Jehan

---

**From:** Jairath, Meghna [<mailto:Meghna.Jairath@fda.hhs.gov>]  
**Sent:** Wednesday, February 26, 2014 6:10 PM  
**To:** Jehan D. Rowlands; Chen, Elizabeth  
**Subject:** RE: IR8 BLA 125511

Hey Jehan,

If possible please submit the responses to IR 7 and 8 to the BLA together. You can always send us an email responses much sooner as you have been doing. Trying to avoid too many amendments.

Thx  
Meghna

---

**From:** Jehan D. Rowlands [<mailto:JRowlands@npsp.com>]  
**Sent:** Wednesday, February 26, 2014 6:07 PM  
**To:** Chen, Elizabeth  
**Cc:** Jairath, Meghna  
**Subject:** RE: IR8 BLA 125511

Thank you Elizabeth.

I confirm receipt of the new IR8.

Kind regards,

Jehan Rowlands

---

**From:** Chen, Elizabeth [<mailto:Elizabeth.Chen@fda.hhs.gov>]  
**Sent:** Wednesday, February 26, 2014 5:07 PM  
**To:** Jehan D. Rowlands  
**Cc:** Jairath, Meghna  
**Subject:** RE: IR8 BLA 125511

Dear Jehan,

I have a revision to the immunogenicity questions sent in IR8, as well as some additional clinical

questions. Please use this file instead of the file that was sent to you on Monday.

Regards,  
Elizabeth Chen

---

**From:** Chen, Elizabeth  
**Sent:** Monday, February 24, 2014 7:03 PM  
**To:** [JRowlands@npsp.com](mailto:JRowlands@npsp.com)  
**Cc:** Jairath, Meghna  
**Subject:** IR8 BLA 125511

Dear Jehan,

Please see the attached document with some additional questions.

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

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ELIZABETH R CHEN  
02/28/2014

**IR 8**

**BLA 125511**

Immunogenicity

1. Screening assay:
  - 1.1. Provide the validation of the (b) (4) RIA assay (b) (4) that was used to test the serum samples from study CL1-11-040.
  - 1.2. Clarify the criteria used to re-test the patient samples for ADA using the (b) (4) MSD-ECL assay.
  - 1.3. Clarify whether the baseline time point for patients in study CL1-11-040 was confirmed by the (b) (4) MSD-ECL assay and provide the corresponding data.
  - 1.4. You state in the integrated summary of immunogenicity (page 62) that 4/132 patients were positive at baseline, however Tables 2-1 and 2-2 of the same summary document (pages 19-20) show that all patients were negative at baseline by the RIA assay and no baseline data is provided in the MSD-ECL table. Please clarify this discrepancy.
  - 1.5. Provide the complete MSD-ECL dataset for studies PAR-C10-007, 008 and 009.
  
2. Neutralizing antibodies: We understand that you evaluated Nabs in samples of study PAR-C10-007 using the validated original assay (report TNJR11-194) and in the samples of study PAR-C10-008 and 009 with an updated protocol (validation report TNJR11-174). Please provide:
  - a complete validation report for the updated Nab assay
  - The Nab results for study CL1-11-040
  - If these data were already submitted, please identify the section of the BLA where they can be found.
  
3. In the integrated summary of immunogenicity section you report that 12 subjects (14 subjects in addendum) developed antibodies out of 132 (140 subjects in addendum) newly treated subjects in the 4 NPS-sponsored studies (including the Bilizekian study in addendum). Figure 2.1 in the integrated summary of immunogenicity document suggests that there are only 129 (instead of 132) drug-naïve subjects. Please clarify.

Please respond by March 10, 2014.

Regards,  
Elizabeth

**From:** Chen, Elizabeth  
**To:** ["JRowlands@npsp.com"](mailto:JRowlands@npsp.com)  
**Cc:** [Jairath, Meghna](#)  
**Subject:** IR7 BLA 125511  
**Date:** Monday, February 24, 2014 3:12:00 PM  
**Attachments:** [BLA 125511 IR 7.doc](#)

---

Dear Jehan,

Please see the attached document with some questions.

Regards,  
Elizabeth

Elizabeth Chen, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[elizabeth.chen@fda.hhs.gov](mailto:elizabeth.chen@fda.hhs.gov)  
PH: 240-402-3729

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/s/  
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ELIZABETH R CHEN  
02/28/2014

**IR 7**

**BLA 125511**

Safety Evaluation

1. In the Pre-BLA meeting on May 15, 2012 (followed by FDA minutes on June 14, 2012 and Sponsor's Letter on June 22, 2012), you agreed to collect medication errors related to both the Ypsomed Pen and the Haselmeier Pen & (b)(4) mixing device (the planned commercial Natpara Pen and Natpara Mixing Device) in the RACE trial (PAR-C10-008).

We are unable to find the document containing information about these medication errors in EDR. Please direct us to where to find this information.

2. Additionally, you previously stated that the Haselmeier Pen & (b)(4) mixing device is currently being marketed overseas, and that no medication errors have occurred with this device. Please confirm this statement and provide information on which countries this particular device is being marketed in, as well as distribution data/drug usage data, if possible.

Risk Evaluation

3. We acknowledge your submission of a proposed risk management plan. Your response to questions 14 and 15 included in the 74-day letter provided sufficient information to clarify the intent of your proposal and address FDA's preliminary questions about the proposed risk management plan.

At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the Natpara outweigh the risks of medication error, hypocalcemia, hypercalcemia, or any other risk to be identified during the review process and, if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application. We remind you that your proposed risk management plan will not be approved as a REMS unless and until the FDA determines that it is required to ensure that the benefits of the drug outweigh the risks and that it meets the FDAAA criteria.

Please respond by March 10, 2014.

Regards,  
Elizabeth

**From:** [Jairath, Meghna](#)  
**To:** [Jehan D. Rowlands \(JRowlands@npsp.com\)](mailto:JRowlands@npsp.com)  
**Subject:** IR6 BLA 125511  
**Date:** Tuesday, February 11, 2014 3:10:04 PM  
**Attachments:** [BLA IR 6.doc](#)

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Hello,  
Please see attachment for additional comments.

Thanks,  
Meghna

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/s/  
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MEGHNA M JAIRATH  
02/11/2014

## IR 6

BLA 125511

### Clinical

1. Please clarify the approach to using investigator vs. patient diary data. Were all analyses conducted on both data? Is one specific analysis only mentioned in the CSR if there were discrepant data/results from the two sources? Explain how discrepant results were otherwise handled.
2. Please provide the location for individual final doses of calcium and vitamin D supplements.
3. Provide a table of baseline medical conditions by PT (regardless of SOC) in decreasing order of frequency.
4. Re: the list of hypocalcemia symptoms discussed in CSR for Trial 040, 11.4.1.2.3, was this list defined *a priori*?
5. For the summary of treatment-emergent AEs, please provide another table using >2% as a cut-off. Please include the n (%) for the SOCs in addition to the PTs.
6. Re: one of your methods used for analysis of calcium events (as discussed in 12.2.3): it states that "individual PTs were combined with the associated laboratory PT". Does this mean that for any calcium-related PT, you attempted to link a laboratory PT to the first event? Please explain in more detail.

### CMC

7. Revise the proposed acceptance criteria for Appearance as part of the drug product specifications for a) Tests Performed on Chamber 2 (Diluent for Reconstitution), and b) Tests Performed on Reconstituted Drug Product for Natpara. The proposed acceptance criteria for Appearance (b) (4)  
 is not appropriate for an injectable product. The acceptance criteria for Appearance should be consistent with that proposed during the clinical development for the hypoparathyroidism indication ("Colourless solution free of foreign particles").

8. In addition, provide further clarification for the following items:

- a. Provide a detailed description of the analytical method(s) used in assessing Appearance of the reconstituted drug product. Describe (b) (4) the analytical method used for Appearance (Method QC-ANP-PTH-5015R) (b) (4).  
[REDACTED]  
[REDACTED] Describe the “reference library” that has been established to assess Appearance. Describe how the “appearance method was optimized (b) (4) [REDACTED] (as stated in 3.2.P.5.6.1.1).
- b. [REDACTED] (b) (4)
- c. How frequently do particles occur in the reconstituted drug product? What are the determining factors that cause particles to form in some samples but not others? Describe how these particles can be controlled in the reconstituted drug product.
- d. Explain how visible (b) (4) particles may develop in the reconstituted drug product over the 14 day use period but no changes were observed in 1) Opalescence, and 2) Particulate Matter with samples that may contain visible particles (as stated in 3.2.P.8.1.15).
- e. Provide details of the nonclinical and clinical evaluations conducted using drug product batches that contain visible (b) (4) particles showing that “these batches have been demonstrated to be safe, effective and of acceptable product quality by clinical evaluation” (as stated in 3.2.P.5.6.1.1).

Please respond by February 18, 2014.

Thanks,  
Meghna

**From:** [Jairath, Meghna](mailto:Jairath.Meghna)  
**To:** [Jehan D. Rowlands \(JRowlands@npsp.com\)](mailto:JRowlands@npsp.com)  
**Subject:** IR5 Natpara BLA 125511  
**Date:** Monday, February 10, 2014 7:58:45 AM  
**Attachments:** [image001.png](#)  
[Hypocalcemia incidence.doc](#)

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**IR 5**  
**BLA 125511**

Hello,

Please add standard deviations to the graph that depicts the mean Natpara dose over time (please refer to graph submitted via email dated February 67, 2014 to our response to IR4).

- 1) Please populate the following tables (see attached Word document). Indicate the source of information for each table.
- 2) Submit in the form of a graph a) the incidence and b) the number of events of hypocalcemia, hypercalcemia, and hypercalciuria for the periods of optimization, titration (weeks 0-12) and maintenance (weeks 12-24). The graph can use groups of columns (each group containing separate columns for hypocalcemia, hypercalcemia, and hypercalciuria, with three groups overall: one for optimization, one for titration and one for maintenance).

Thanks,  
Meghna

---

**From:** Jehan D. Rowlands [<mailto:JRowlands@npsp.com>]  
**Sent:** Thursday, February 06, 2014 11:08 AM  
**To:** Jairath, Meghna  
**Subject:** Natpara BLA 125511: Response to IR4 (Sequence No. 0007)

Hi Meghna,

For your convenience, attached is the Response to IR4 (Sequence No 0007). I've attached the cover letter, Form 356h, and the Response document. All these will be formally submitted through the gateway either today or tomorrow.

Please let me know if you have any questions.

Kind regards,

Jehan

---

**From:** Jairath, Meghna [<mailto:Meghna.Jairath@fda.hhs.gov>]  
**Sent:** Tuesday, January 28, 2014 3:13 PM  
**To:** Jehan D. Rowlands

**Subject:** IR 4 Natpara  
**Importance:** High

**IR 4**  
**BLA 125511**

Hello,  
Thank you for responding to our IR2 request so quickly.

We have additional clarification on the graph and requests below.

**Regarding the Graph:**

1. Please confirm that the bars around the mean represent standard errors. **YES**
2. Since the graph does not include a specific “n” of patients for each time point represented, are we correct in assuming that the “n” for each time point is the same as the in Figure 11-9 on page 134 of the Clinical Study Report CL1-11-040 ? **YES**
3. For future similar graphs please keep the same colors as in the study report for consistency.

**Additional request:**

4. Please indicate if you have in the NDA a graph depicting the mean dose of Natpara by study visit in the Natpara arm (ITT population). If not, please provide such a graph and reference the source in the NDA for the information used to construct the graph.
5. Provide a scatterplot of albumin-corrected serum calcium values in each treatment arm for the duration of the CL1-11-040 trial in the ITT population (calcium levels on the “Y” axis and time on the “x” axis). Indicate the upper limit and lower limit of the normal range on the graph. You may present two such graphs (one for the Natpara arm and one for the placebo arm) or, if the graph is not too crowded, you may present a single graph with both arms; please make sure that the two arms are represented by distinct colors to ensure readability.
6. Provide a scatterplot for serum phosphate values (ITT population) following the same recommendations made above for albumin-corrected serum calcium.

Thx  
Meghna

---

**From:** Jehan D. Rowlands [<mailto:JRowlands@npsp.com>]  
**Sent:** Friday, January 24, 2014 12:05 PM  
**To:** Jairath, Meghna  
**Subject:** RE: IR 2 Natpara question

Hi Meghna,

Please see attached. Please check with your reviewer whether the attached graph satisfies the request. If so, we will send it formally as an amendment to the BLA as a response to IR 2.

Thank you.

Kind regards,

Jehan

Jehan Rowlands, PharmD  
Director, Regulatory Affairs  
NPS Pharmaceuticals  
Office: 908-450-5537  
Mobile: (b) (6)  
[jrowlands@npsp.com](mailto:jrowlands@npsp.com)

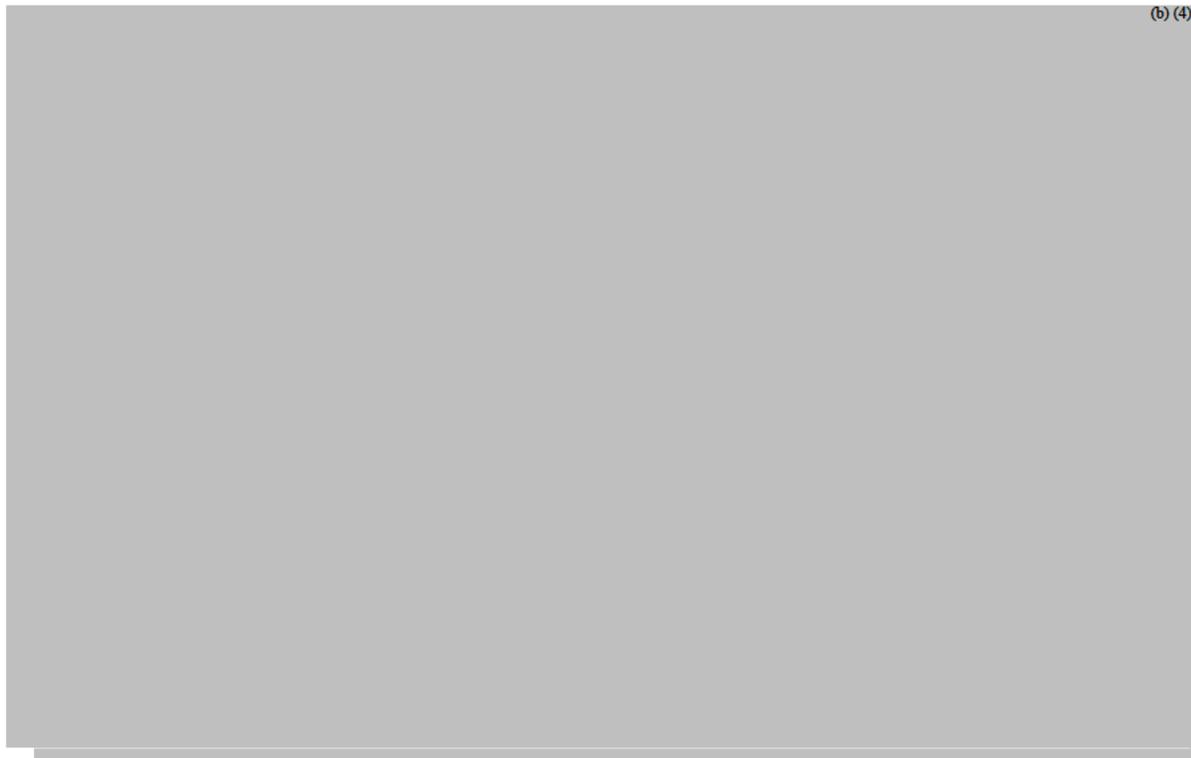
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**From:** Jairath, Meghna [<mailto:Meghna.Jairath@fda.hhs.gov>]  
**Sent:** Thursday, January 23, 2014 11:23 AM  
**To:** Jehan D. Rowlands  
**Subject:** IR 2 Natpara question

Hello,

Please send us the location of the following in blue text below in the BLA submission.

A graph describing the mean albumin-corrected total serum calcium for the ITT population similar to the one copied below for the change from baseline? If not, please send such graph that would include the calcium values in mg units on the vertical axis.



**Thx**  
**Meghna**

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This message may contain confidential information. It is intended only for the use of the addressee(s) named above and may contain information that is legally privileged. If you are not the addressee, you are hereby notified that reading, disseminating, distributing or copying this message is strictly prohibited. If you have received this message by mistake, please notify us by replying to the message and delete the original message immediately thereafter.

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MEGHNA M JAIRATH  
02/11/2014



BLA 125511/0

## INFORMATION REQUEST

NPS Pharmaceuticals Inc.  
Attention: Jehan Rowlands, Pharm.D.  
Director, Regulatory Affairs  
550 Hills Drive, 3rd Floor  
Bedminster, NJ 07921

Dear Dr. Rowlands:

Please refer to your Biologics License Application (BLA) dated October 23, 2013, received October 24, 2013, submitted under section 351(a) of the Public Health Service Act for Parathyroid Hormone (1-84) Human Recombinant injection.

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

All the changes, addition and deletion are in *italics*.

### Highlights

#### 1. Highlights Limitation Statement

Change the name of the drug product to UPPER CASE letters.

### Highlights Details

#### 2. Initial U.S. Approval in Highlights

Change [year] to xxxx.

#### 3. Patient Counseling Information Statement in Highlights

Delete "See 17 for PATIENT COUNSELING INFORMATION and [REDACTED] (b) (4) [REDACTED]" and add "See 17 for PATIENT COUNSELING INFORMATION and Medication Guide".

We request that you resubmit labeling (Microsoft Word format) that addresses these issues by January 31, 2014. The resubmitted labeling will be used for further labeling discussions

Submit revised content of labeling 21 CFR 201.100(d)(3) in structured product labeling (SPL) format as described at: <http://www.fda.gov/oc/datacouncil/spl.html>.

If you have any questions, please contact Meghna M. Jairath, Pharm.D., Regulatory Project Manager, at (301) 796-4267.

Sincerely,

*{See appended electronic signature page}*

Jean-Marc Guettier, M.D.  
Director (Acting)  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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JEAN-MARC P GUETTIER  
01/28/2014

**From:** [Jairath, Meghna](#)  
**To:** [Jehan D. Rowlands \(JRowlands@npsp.com\)](mailto:Jehan.D.Rowlands@npsp.com)  
**Subject:** IR 3\_ BLA 125511 Clinical Inspections  
**Date:** Friday, January 24, 2014 3:37:58 PM  
**Importance:** High

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**Information Request 3**  
**BLA 125511**

**Respond by: January 31, 2014**

Hello,

We have the following information requests in regards with clinical inspections..

1. In the CL1-11-040 clinical study report (Section 9.1, page 56), it states:

“Subsequent to the database lock, NPS clinical operations made the decision to unlock the CL1-11-040 Inform database based on the following observation/actions. Additional adverse events were discovered and reported to NPS post data lock **by 5 sites**. Upon review, discrepancies were also noted between source records versus Inform involving start and stop dates, frequency, severity, relationship, and action taken for these adverse events, requiring correction to the Inform data collection module **at the 5 sites**. The discrepancies were mainly due to the overlap between most of these events and the signs and symptoms associated with the subject’s underlying disease or disorder (ie, the condition present at baseline vs a worsening of the disease or disorder) (Appendix 16.1.1, CL1-11-040 Protocol Section 6.2.2.1, Adverse Event Definition).”

We are unable to locate any mention of the actual sites. Please send the actual site numbers?

2. The clinical study report (Section 9.1 page 58) mentions pen complaints and that a complaint reporting system was established to track and analyze all product complaints. Can you send us the location in the application where this report resides? If it is not in the application, please submit for review.

3. Have the DSMB meeting minutes been submitted? If not, please have them submit for review.

Thanks,  
Meghna

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/s/  
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MEGHNA M JAIRATH  
02/03/2014

**From:** [Jairath, Meghna](#)  
**To:** [Jehan D. Rowlands \(JRowlands@npsp.com\)](mailto:JRowlands@npsp.com)  
**Subject:** IR 2 Natpara question  
**Date:** Thursday, January 23, 2014 11:23:26 AM  
**Attachments:** [image001.png](#)

---

Hello,

Please send us the location of the following in blue text below in the BLA submission.

A graph describing the mean albumin-corrected total serum calcium for the ITT population similar to the one copied below for the change from baseline? If not, please send such graph that would include the calcium values in mg units on the vertical axis.



**Thx**  
**Meghna**

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/s/  
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MEGHNA M JAIRATH  
02/03/2014



BLA 125511/0

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

NPS Pharmaceuticals, Inc.  
550 Hills Drive, 3rd Floor  
Bedminster, New Jersey 07921

Attention: Jehan Rowlands, PharmD  
Director, Regulatory Affairs

Dear Dr. Rowlands:

Please refer to your Biologics License Application (BLA) dated October 23, 2013, received October 24, 2013, submitted under section 351(a) of the Public Health Service Act, for Recombinant Human Parathyroid Hormone, 25 mcg/dose, 50 mcg/dose, 75 mcg/dose, and 100 mcg/dose.

We also refer to your October 23, 2013, correspondence, received October 24, 2013, requesting review of your proposed proprietary name, Natpara. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your October 23, 2013 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Terrolyn Thomas, M.S., M.B.A., Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3981. For any other information regarding this application, contact Meghna Jairath, Regulatory Project Manager, in the Office of New Drugs at (301) 796-4267.

Sincerely,

*{See appended electronic signature page}*

Kellie A. Taylor, Pharm.D., MPH  
Deputy Director  
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 on behalf of KELLIE A TAYLOR  
01/19/2014

**From:** [Jairath, Meghna](#)  
**To:** [Jehan D. Rowlands](#)  
**Subject:** BLA 125511 IR1 clinical  
**Date:** Thursday, January 16, 2014 12:21:09 PM  
**Attachments:** [BLA IR1 clinical.doc](#)

---

Hello,  
Please see the attachment with the IR.

Thx  
Meghna

**IR1 Clinical**

**BLA 125511**

**Response: January 30, 2014**

Hello,

Please respond to the questions listed below.

1. Please provide a table with the breakdown of etiologies of hypoparathyroidism for both groups (should include etiology as well as childhood vs. adult onset).
2. On p. 5 of the CSR for CL1-11-040, it states that “in some cases” subjects were optimized on calcium carbonate rather than citrate. Please explain the reason for the different treatment in some patients and specify how many received citrate vs. carbonate.
3. On p. 6 of the CSR for CL1-11-040, it states that up-titration of study drug occurred over a 6- to 8-week period. However, on p. 54 it states that a final dose escalation occurred at Week 4 (plus an additional week). Explain this apparent discrepancy—how could the titration period last up to 8 weeks?
4. Explain why Amendment 7 (specifically, an albumin-corrected total serum calcium goal) is listed as a ‘minor change’, rather than a substantive change, in Table 9-2.

Thanks,  
Meghna

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/s/  
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MEGHNA M JAIRATH  
01/17/2014



BLA 125511/0

**FILING COMMUNICATION –  
FILING REVIEW ISSUES IDENTIFIED**

NPS Pharmaceuticals Inc.  
Attention: Jehan Rowlands, Pharm.D.  
Director, Regulatory Affairs  
550 Hills Drive, 3rd Floor  
Bedminster, NJ 07921

Dear Dr. Rowlands:

Please refer to your Biologics License Application (BLA) dated and received October 23, 2013, submitted under section 351(a) of the Public Health Service Act for Parathyroid Hormone (1-84) Human Recombinant injection.

We also refer to your amendment dated November 11, 2013, containing Case Report Forms (CRFs).

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 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm> . Therefore, the user fee goal date is **October 24, 2014**.

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 **July 6, 2014**. In addition, the planned date for our internal mid-cycle review meeting is **March 19, 2014**. We are currently planning to hold an advisory committee meeting to discuss this application.

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

**Microbiology**

Please provide the following information or a reference to its location in the BLA.

1. The proposed manufacturing process includes [REDACTED] (b) (4)  
[REDACTED]
2. Provide the results from three recent sterilization validation studies for the [REDACTED] (b) (4). Include a description of any bracketing programs and a justification for inclusion of the components within the bracketing program. Include a detailed discussion of the use of validation loads that are not identical to the proposed commercial load(s). Please refer to the following Guidance for more information: Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072171.pdf>)
3. Provide the results from three recent validation studies for the [REDACTED] (b) (4). Include a description of any bracketing programs and a justification for inclusion of the components within the bracketing program.
4. Module 3.2.A.1.9 described the environmental monitoring program acceptance criteria. Provide a description of the media and incubation conditions used in the environmental monitoring program.
5. We note the claim that maximum hold times have not been established and will be developed during the process validation studies. Provide maximum hold times for the proposed manufacturing process. Sterile hold times should be supported by [REDACTED] (b) (4) validation (media fill) data.
6. Insufficient information has been provided on the [REDACTED] (b) (4) simulations. Provide a detailed description of the [REDACTED] (b) (4) simulations to include a description of the process and the routine and non-routine interventions. Include information on the process for both chambers 1 and 2. For more information please refer to the following Guidance: [REDACTED] (b) (4)  
[REDACTED]
7. Provide the following information for the three most recent media fills used to support the proposed manufacturing process. Include the detailed information for filling of chambers 1 and 2 and, if a bracketing program is utilized, provide a detailed description and justification for the bracketing approach.
  - a. The date(s) of filling and the media fill identification number
  - b. The total fill duration
  - c. The number of units filled

- d. The number of units rejected, with a brief explanation of the reason for the rejection
  - e. The number of units incubated
  - f. The number of positive units
  - g. The line speed
  - h. The container closure system used
  - i. The incubation conditions
  - j. A summary of growth promotion studies
  - k. Any relevant deviations or excursions
8. Provide a summary of, or the results from, the sterility and endotoxin method verification studies.

### **Statistics**

9. An additional dataset containing all primary and secondary efficacy endpoints for the placebo controlled study CL1-11-040 is needed. There should be one observation per subject with a separate variable for each endpoint indicating whether the endpoint was achieved.

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

10. Provide samples of the pen-injector system including the disposable multiple dose glass dual-chamber cartridge, Natpara Mixing Device and Natpara Reusable Pen.

### **Clinical Pharmacology**

11. Please submit the NONMEM data sets and model files associated with the Population PK reports ALX1-11-93001-POP-PK, NPSP-PCS-101-POP-PK, and NPSP-PCS-101-Exploratory PKPD Analysis. All datasets used for model development and validation should be submitted as a SAS transport files (\*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with \*.txt extension (e.g.: myfile\_ctl.txt, myfile\_out.txt). In addition, include a model development decision tree and/or table which gives an overview of modeling steps or indicate the location, in case you have included such information in the existing reports. In case you have submitted these data sets in the requested format, indicate its location.

### **Office of Surveillance and Epidemiology(OSE)**

#### *Division of Medication Error Prevention and Analysis*

12. In your Simulated Use Validation Testing of Natpara, Version 1.0, submitted on October 23, 2013, the Human Factor Study results for each testing session were combined together in Appendix 4.1, Analysis of Use Events. Please provide a breakdown of the user tasks

observed at the end of each training session for each user group (e.g. HCP, Day 1 LPs, Day 15 LPs, and Day 29 LPs) that were scored as resolved or incorrect. For example, please provide detailed results of each testing session to explain why 5 health care providers (HCP) were given an incorrect score and why 2 health care providers were given a resolved score after 1 training session.

13. We note that two lay people (LP) were determined at their end of second training session not to be proficient, and thus were excluded from the study due to scheduling limitations. Please provide a detailed description of the user tasks that they were determined not proficient at and a root cause analysis of their incompetence.

#### *Division of Risk Management*

FDA is seeking clarification of your proposed risk management activities. At this time, FDA is not requesting you submit a risk evaluation and mitigation strategy (REMS).

14. The submitted Risk Management Plan provides a high level description of NPS Pharmaceuticals' commercial support plan describing how the mitigation strategy tested in the Human Factor Study will be implemented post-approval. The proposed plan includes:
  - a. distribution of Natpara via a restricted specialty pharmacy network;
  - b. healthcare professional and patient training before the product is shipped to the patient;
  - c. healthcare provider and patient support provided by NPS Advantage; and
  - d. a requirement for completion of a referral form to document the patient and physician office staff have been properly trained on the use of Natpara and the delivery device.

Please submit a fully developed risk mitigation strategy proposal including all planned materials necessary to implement your proposal (e.g., proposed communication and education materials and forms) and program process flow chart including but not limited to healthcare professionals, patients, and specialty pharmacy staff training approach and program built-in safeguards (e.g., specialty pharmacy role in product distribution, role of NPS Advantage).

15. The clinical development program for Natpara showed that inappropriate use of Natpara's complex delivery system (medication error) may result in serious adverse events (i.e., hypo/hypercalcemia). Please provide your rationale for why a risk evaluation and mitigation strategy (REMS) is not required for this product

#### **Center for Devices and Radiological Health(CDRH)/Compliance**

16. The information provided by your firm has inadequately addressed the requirements of 21 CFR 820.30. In the submission, you described and provided summarized results of the different tests conducted for the design verification and validation. However your firm did not provide its design control procedure covering the Design Input, Design output and

Design Validation/Verification, including design changes, for the overall finished combination product in order to ensure that specified design requirements are met.

17. The information provided by your firm has inadequately addressed the requirements of 21 CFR 820.50. In the submission, you provided a table of your firms involved in the manufacturing of the combination product and the different device components, as well as their responsibilities. However, you did not provide a copy of the procedures for purchasing controls or supplier qualification. Also, your firm explained that the cartridge holders, Natpara Mixing Devices, and Natpara Reusable Pens are tested upon receipt at a secondary packaging site. However your firm did not provide the name and location of the secondary packaging site. The controls applicable to suppliers should be specified, and should include the requirement that your firm be notified of any changes made to the product supplied that may impact the safety and effectiveness of the finished product. The procedures should describe your firm's supplier evaluation process and describe how it will determine type of and extent of control it will exercise over suppliers.
18. There was no information available for review regarding the establishment of a CAPA system compliant with 21 CFR 820.100.

The description of the manufacturing activities of the finished combination product was inadequate and a proper review of the manufacturing, including packaging of the finished product could not be conducted.

You may find useful information regarding the types of documents to provide in the document called 'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003). This document may be found at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm>

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.

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) and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

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

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

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

If you have any questions, call Meghna M. Jairath, Pharm.D., Regulatory Project Manager, at (301) 796-4267.

Sincerely,

*{See appended electronic signature page}*

Jean-Marc Guettier, M.D.  
Director (Acting)  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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JEAN-MARC P GUETTIER  
01/06/2014



BLA 125511

**BLA ACKNOWLEDGEMENT**

NPS Pharmaceuticals Inc.  
Attention: Jehan Rowlands, Pharm.D.  
Director, Regulatory Affairs  
550 Hills Drive, 3<sup>rd</sup> Floor  
Bedminster, NJ 07921

Dear Dr. Rowlands:

We have received your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for the following:

<b>Name of Biological Product:</b>	Parathyroid Hormone (1-84) Human Recombinant
<b>Date of Application:</b>	October 23, 2013
<b>Date of Receipt:</b>	October 23, 2013
<b>Our Secondary Tracking Number (STN):</b>	BLA 125511
<b>Proposed Use:</b>	Treatment of hypoparathyroidism

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the format and content requirements of 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 BLA Submission Tracking 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 Metabolism and Endocrinology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

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

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

If you have any questions, call me, at (301) 796-4267.

Sincerely,

*{See appended electronic signature page}*

Meghna Jairath, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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MEGHNA M JAIRATH  
12/04/2013



IND 76514

**MEETING MINUTES**

NPS Pharmaceuticals, Inc.  
Attention: Sandra C. Cottrell, M.A., Ph.D.  
Vice President, Regulatory Affairs & Drug Safety  
550 Hills Drive, 3rd Floor  
Bedminster, NJ 07921

Dear Dr. Cottrell:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for NPSP558; ALX1-11 (recombinant parathyroid hormone [rDNA origin] for injection, rhPTH (1-84).

We also refer to the presubmission meeting between representatives of your firm and the FDA on May 15, 2012. The purpose of the meeting was to discuss your upcoming submission of a Biologics License Application for rhPTH [1-84] powder for subcutaneous injection for the treatment of hypoparathyroidism.

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

If you have any questions, call me at (301) 796-4267.

Sincerely,

*{See appended electronic signature page}*

Meghna Jairath, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** B  
**Meeting Category:** Pre-BLA

**Meeting Date and Time:** March 15, 2012  
**Meeting Location:** 10903 New Hampshire Avenue, White Oak Building 22,  
Conference Room 1313, Silver Spring, Maryland 20903

**Application Number:** IND 76514  
**Product Name:** NPSP558; ALX1-11(recombinant parathyroid hormone [rDNA  
origin] for injection, rhPTH(1-84)  
**Indication:** Treatment of hypoparathyroidism  
**Sponsor/Applicant Name:** NPS Pharmaceuticals, Inc.

**Meeting Chair:** Mary Parks, M.D.  
**Meeting Recorder:** Meghna M. Jairath, Pharm.D.

**FDA ATTENDEES**

**Office of New Drugs**

Beth Duvall, M.S., Associate Directors for Regulatory Affairs

**Office of Drug Evaluation II (ODE II)**

Leah W. Ripper, Associate Director for Regulatory Affairs

**Division of Metabolism and Endocrinology Products (DMEP)**

Mary Parks, M.D., Division Director  
Meghna M. Jairath, Pharm.D., Regulatory Project Manager  
Julie Marchick, Chief, Project Management Staff  
Naomi Lowy, M.D., Clinical Reviewer  
Dragos Roman, M.D., Medical Team Leader  
Karen Davis-Bruno, Ph.D., Pharmacology/Toxicology Team Leader  
Ronald Wange, Ph.D., Pharmacology/Toxicology reviewer

**Division of Clinical Pharmacology II (DCP II), Office of Clinical Pharmacology (OCP),  
Office of Translational Sciences (OTS)**

Jaya Vaidyanathan, Ph.D., Clinical Pharmacology Team leader  
Zhihong Li, Ph.D., Clinical Pharmacology Reviewer

**Division of New Drug Assessment III, Office of New Drug Quality Assessment (ONDQA)**

Suong (Su) Tran, Ph.D., Chemistry, Manufacturing and Control Lead, Division III

**Office of Pharmaceutical Science, New Drug Microbiology Staff**

Jessica Cole, Ph.D. Microbiology Reviewer

**Division of Biometrics II (DB II), Office of Biometric (OB)**

Jon (Todd) Sahlroot, Ph.D., Deputy Division Director and Statistics Team Leader

Japo Chaudhary, Ph.D., Biometrics reviewer

**Office of Surveillance and Epidemiology**

Yelena Maslov, Pharm.D., Acting Team Leader, Division of Medication Error Prevention and Analysis (DMEPA)

Reasol S. Agustin, Pharm.D., LCDR, Safety Evaluator, DMEPA

**Office of Medical Policy Initiatives/Division of Medical Policy Programs**

Shawna Hutchins, MPH, BSN, RN, Patent Labeling Reviewer

**Center for Devices and Radiologic Health Devices**

Quynh Nhu Nguyen, Lieutenant, U.S. Public Health Service, Biomedical Engineer/Injection Systems Human Factors Specialist

Alan Stevens, LCDR, Infusion Pump Team Leader, General Hospital Devices Branch

**Office of Compliance, Office of Manufacturing and Product Quality, Division of Good Manufacturing Practice Assessment, Biotech Manufacturing Assessment Branch**

Patricia Hughes, Lead Consumer Safety Officer

Reyes Candau-Chacon, Biologist

Colleen Thomas, Consumer Safety Officer

**Office of Compliance, Office of Manufacturing and Product Quality, Division of Good Manufacturing Practice Assessment**

Steve Hertz, Consumer Safety Officer

**Office of Orphan Products**

Jeff Fritsch, R.Ph., Drug Designation Team

**Office of Compliance/Office of Scientific Investigations/Division of Good Clinical Practice Compliance/Good Clinical Practice Assessment Branch**

Susan Leibenhaut, M.D., Medical Officer

**Office of Planning and Informatics (OPI)/ Office of Planning and Analysis (OPA)**

Patrick Frey, Director

**SPONSOR ATTENDEES**

Zane Bai, M.S., M.B.A., Director, Biostatistics  
Sandra Cottrell, M.S., Ph.D., V.P. Regulatory Affairs & Pharmacovigilance  
Roger Garceau, M.D., Senior V.P., R&D and Chief Medical Officer  
Ali Kandil, Ph.D., Head of Manufacturing  
Hjalmar Lagast, M.D., V.P. Clinical Development and Medical Affairs  
Joseph Rogus, M.S., V.P. Technical Operations & Supply Chain Management  
Anthony Sileno, M.S., Head of R&D Operations  
Lisa Suttner, M.S., Senior Director, Regulatory Affairs Product Development  
Paul Vandenberg, Ph.D., Head of Analytical Development and Quality Control  
Rick Wilcocks, M.S., Senior Director, Technical Services

## **BACKGROUND**

The following background was extrapolated from NPS Pharmaceuticals briefing package.

NPSP558 is manufactured using a strain of *Escherichia coli* modified by recombinant deoxyribonucleic acid (rDNA) technology. The amino acid sequence of this synthesized rhPTH(1-84) is identical to that of native (endogenous) human parathyroid hormone. NPSP558 has not been granted marketing authorization anywhere for the indication in treatment of hypoparathyroidism.

In 2007, FDA granted Orphan Drug Designation for NPSP558 (rhPTH [1-84]) for the treatment of hypoparathyroidism. On December 17, 2007, a pre-IND meeting was held with the Division of Metabolism and Endocrinology Products (DMEP). Subsequently, NPS submitted the IND on September 19, 2008.

On July 6, 2010, a Type C advice meeting was held. An agreement was reached on a bridging strategy for the transition from the pen injector device used in the clinical trials to the intended commercial pen injector.

Recently, NPS Pharmaceuticals completed their Phase 3 pivotal study, designated CL1-11-040. The proposed clinical data were discussed at a Type C advice meeting held on September 26, 2011. NPS Pharmaceuticals will rely on their sponsored global efficacy and safety studies in hypoparathyroidism, data from four Investigator-Initiated Trials (IITs) in hypoparathyroidism, safety data from clinical trials, and postmarketing experience in patients with osteoporosis when submitting the BLA application.

On November 7, 2011, a proprietary name, Natpara, was conditionally accepted.

FDA confirmed NPS Pharmaceuticals' Request for Designation, that rhPTH(1-84) should be designated as a biologic in an correspondence dated December 23, 2011. Accordingly, a BLA application will be submitted for this biologic-device combination for the orphan disease indication for the treatment of hypoparathyroidism.

NPS Pharmaceuticals requested this pre-BLA meeting in a letter dated February 29, 2012, and FDA granted the meeting scheduled for May 15, 2012.

Repeated below in regular text are NPS Pharmaceutical's questions followed by FDA's preliminary responses written in **bold** text. The meeting discussion appears in *italic*.

## **DISCUSSION**

### **1.1 Quality**

**Sponsor Question 1:** Is it appropriate to include the mixing device and pen injector device information in the BLA under Section 3.2.R or should the information be provided in a newly created Section 3.2.D, or does the Division recommend that we use another approach?

**FDA Preliminary Comment:** We agree that all information related to the device constituents should be located in the same module regardless of which specific section you prefer to place it in (e.g. Section 3.2.R vs. Section 3.2.D).

*Meeting Discussion: No further Discussion*

### **1.1.2 Drug Product Process Validation**

**Sponsor Question 2:** Does the Agency agree with the Sponsor's clarified drug product process validation approach and timing as described in Section 10.1 of this briefing document regarding what information will be (i) included in the BLA submission, (ii) available at the time of the Pre-Approval Inspection, and (iii) completed prior to commercial distribution of product?

**FDA Preliminary Comment:** In general, we agree with your approach. However, we need some clarifications listed below:

- a. Please confirm that the target volume of diluent will be <sup>(b) (4)</sup> mL filled in the cartridges with four different DP concentrations, to achieve four different DP strengths.
- b. It is not clear whether lyophilization studies will be performed for all dosage strengths.
- c. Endotoxin and bioburden tests and criteria should be part of your critical process controls.
- d.  <sup>(b) (4)</sup>
- e. In-process holding times should be validated at scale for microbial quality (bioburden and endotoxin). If hold time validation is not complete at the time of submission, interim strategies for monitoring in-process material for microbial quality should be in place.

- f. Container closure integrity testing of cartridges should include shipping validation studies. The study should include worst-case conditions for mechanical stress studies (impact, airfreight barometric simulation, etc.) and ambient temperatures.**

*Meeting Discussion: Sponsor had responses for points (a) and (b) above but no further comments on points (c) to (f) (please see attached slide number three below).*

*Sponsor's response repeated from slide three for points (a) and (b).*

*(a) Target fill for the diluent for all 4 strengths is the same - this fill is 1.13 mL (not (b) (4) mL, which is the fill for the active chamber #1 for all 4 strengths prior to lyophilization. FDA had no further comment.*

*(b) Yes. Validation of the lyophilization process at production scale will be performed for all 4 strengths. In addition, DSC studies have been performed and have demonstrated that for all 4 strengths (as well as the placebo) the thermal characteristics are the same. A copy of the formal report will be provided in the BLA. (b) (4)*

(b) (4)

## **1.2 Nonclinical**

**Sponsor Question 3:** Does the Division agree that the identified preclinical studies conducted in this program are adequate and sufficient to support the planned marketing application?

**FDA Preliminary Comment: Yes, this is acceptable.**

*Meeting Discussion: No further Discussion*

**Sponsor Question 4:** Does the Division agree with the locations of the nonclinical reports within the structure of Module 4?

**FDA Preliminary Comment: Yes, this is acceptable.**

*Meeting Discussion: No further Discussion*

## **1.3 Clinical**

**Sponsor Question 5:** Does the Division agree with the proposed presentation of efficacy results?

**FDA Preliminary Comment: Yes, this is acceptable.**

*Meeting Discussion: No further Discussion*

**Sponsor Question 6:** Does the Division agree with the proposed approach to the integrated summary of efficacy?

**FDA Preliminary Comment: Yes. For the meeting, please specify which parameters you intend to compare across studies.**

*Meeting Discussion: Refer to sponsor's slide four below which list the parameters. FDA stated that the sponsor should compare and contrast selected efficacy variables in a side-by-side comparison of efficacy results across studies as applicable, along with an explanation regarding why pooling is not appropriate. Sponsor agreed to this.*

### **1.3.2 Strategy for Presenting Clinical Datasets**

**Sponsor Question 7:** Does the Division agree with the overall data format and content for individual studies?

**FDA Preliminary Comment: Overall, it appears that the data formatting is adequate. Refer to Preliminary Comment to Question 8 for issues regarding osteoporosis trial data content.**

*Meeting Discussion: No further Discussion*

**Sponsor Question 8:** With regard to legacy data sets for the osteoporosis studies, does the Division also wish to receive the full data sets in their original format or is the presentation of the CDISC formatted safety and partial efficacy parameters sufficient?

**FDA Preliminary Comment: We are primarily interested in the safety data generated from the osteoporosis program. Therefore, it is not necessary to submit datasets for efficacy from the osteoporosis program. While you may submit the safety datasets as proposed, presentation of safety of rhPTH(1-84) from the osteoporosis program should be primarily in summary form. Emphasis should be placed on serious adverse events in the placebo-controlled trials. Should you choose to not submit the complete osteoporosis safety datasets in the BLA, we may request some data during the review. Depending on the amount of data submitted during the review and for what purpose, this submission may result in a review extension if it is considered to be a major amendment.**

*Meeting Discussion: Refer to sponsor's slide five below.*

*Sponsor's response repeated from slide five: NPS will provide ISS combined analysis data sets for all studies and individual study safety data sets for osteoporosis in SDTM (Please see Table 3 [submission page 16 of 294]).*

*FDA stated that they can submit them and had no further comments.*

### 1.3.3 ISS Data Integration and Presentation Strategy

**Sponsor Question 9:** Upon review of the tables provided, does the Division find the approaches for pooling adequate and sufficient to support a thorough review of the data? (Meaning, is the ISS Data Integration and Presentation Strategy acceptable?)

**FDA Preliminary Comment: Yes. See response to Question 8 regarding inclusion of osteoporosis data.**

*Meeting Discussion: No further Discussion*

### 1.3.4 QTc Assessment

During the original development program for the use of rhPTH(1-84) in treating postmenopausal women with osteoporosis there was a discussion with the Agency at a Type C Advice meeting on December 16, 2003 regarding the evaluation of the effect of rhPTH(1-84) on cardiovascular function. At that time NPS Pharmaceuticals and the Division agreed on the sufficiency of evaluation of cardiac function in ~600 participants treated at the 100 µg dose in the two Phase III studies for the original indication rather than doing a specific QTc Safety Pharmacology study.

For the current BLA for the use of Natpara in the treatment of hypoparathyroidism, NPS Pharmaceuticals will have performed centrally-read ECGs at baseline and Tmax post-dose in Studies C09-002 and CL1-011-040 and will report PR, QRS, QTcB and QTcF intervals. Both studies also included blood draws for levels of PTH and serum calcium. These data will also be included in a separate study report along with centrally read ECG data from the PAR-C10-007, PAR-C10-008, PAR-C10-009 and Mosekilde PK/PD substudy. The Sponsor believes these data, combined with the safety database from the original NDA and the extensive exposure through European marketing since 2006 in osteoporosis would continue to support the established lack of impact of rhPTH(1-84) on QTc.

**Sponsor Question 10:** Does the Agency agree with this approach?

**FDA Preliminary Comment: Yes, this is acceptable. The BLA should specifically include a summary of the QT interval data analysis from the original osteoporosis NDA.**

*Meeting Discussion: No further Discussion*

### 1.3.5 Strategy for 4 month Safety Update

In the Original BLA submission, NPS Pharmaceuticals plans to provide an interim Clinical Study Report for the only on-going, 12 month, NPS-sponsored US study (PAR-C10-008) in hypoparathyroidism. In the 4-month safety update NPS Pharmaceuticals will provide updated safety data from this study. Since the enrollment into this study has been stopped in February 2012, the additional data from study PAR-C10-008 will consist of approximately 4 months of

observation (2 bimonthly visits) on the ongoing subjects (approximately 51) based on the September 30 planned cut-off for the 4 month safety update. Given this relatively small amount of additional data from the ongoing clinical program, NPS Pharmaceuticals proposes to provide an addendum to the ISS containing data listings for these subjects rather than pooling these data and re-running the extensive number of tables in the ISS that contain Study PAR-C10-008 data. The addendum will summarize any AEs or safety observations that were unusual or unexpected based on the original ISS, and NPS will identify and include CRFs and case narratives for any subjects who died, had another SAE, or discontinued due to an adverse event or reason "Other".

**Sponsor Question 11:** Is this approach reasonable?

**FDA Preliminary Comment: Yes. Beyond the unusual and unexpected AEs, the addendum should detail any hypocalcemic and hypercalcemic events.**

*Meeting Discussion: No further Discussion*

## **1.4 Regulatory**

### **1.4.1 Pediatric Development**

According to the requirements of the Pediatric Research Equity Act (PREA) of 2003 and its subsequent renewal within the FDA Amendments Acts of 2007, and with reference to FDA's *Procedural Guidance from September, 1999, Guidance for Industry Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act*, there is no obligation under PREA for sponsors of drugs or biologics with Orphan Designation (OD) to provide pediatric data, as defined by PREA, at the time of submitting an initial marketing application. Further, as per this Guidance, PREA states, "Unless the Secretary requires otherwise by regulation, this section does not apply to any drug for an indication for which orphan designation has been granted under section 526... [and] a pediatric assessment is not required for an application to market a product for an orphan-designated indication, and **waivers are not needed** at this time" (bolding here for emphasis). rhPTH(1-84) received Orphan Designation from the U.S. Food and Drug Administration for hypoparathyroidism on August 31, 2007. Accordingly, NPS Pharmaceuticals does not intend to provide a request for Waiver in Module 1.9.1.

**Sponsor Question 12:** Does the Agency agree that a waiver request, relative to pediatric development as otherwise required under PREA, is not required for Natpara™ (rhPTH[1-84]) based on its Orphan Designation for hypoparathyroidism?

**FDA Preliminary Comment: Yes.**

*Meeting Discussion: No further Discussion*

### **1.4.2 Priority Review**

In 1992, under the Prescription Drug User Act (PDUFA), FDA agreed to specific goals for improving the drug review time and created a two-tiered system of review times – *Standard Review* and *Priority Review*. To qualify for *Priority Review*, drugs should have the potential to provide significant advances in treatment, including, for example:

- Evidence of increased effectiveness in treatment, prevention, or diagnosis of disease;
- Elimination or substantial reduction of a treatment-limiting drug reaction;
- Documented enhancement of patient willingness or ability to take the drug according to the required schedule and dose; or
- Evidence of safety and effectiveness in a new subpopulation, such as children.

**Sponsor Question 13:** While data review will be needed to support a comprehensive benefit-risk assessment, would the Agency please comment on the general strategy for priority review?

**FDA Preliminary Comment:** It is premature to comment on priority review designation. This is decided at the Filing Meeting. The criteria you mention are used in this decision.

*Meeting Discussion:* No further discussion.

### 1.4.3 Labeling

A boxed warning regarding nonclinical observations of osteosarcoma currently exists on the label for a different product in a similar class (Forteo® (PTH[1-34])). NPS Pharmaceuticals is proposing [REDACTED] (b) (4)

[REDACTED] (b) (4)

**Sponsor Question 14:** Will the Division comment on the proposed strategy [REDACTED] (b) (4) in the Natpara label for hypoparathyroidism?

**FDA Preliminary Comment: Comments regarding a boxed warning will be made following a complete review of the safety data.**

*Meeting Discussion: No further Discussion*

#### **1.4.4 Advisory Committee Planning**

Natpara will be reviewed by FDA as treatment for hypoparathyroidism, for which there is no approved replacement therapy. However, it is a recombinant version of the naturally occurring hormone which these patients lack and has not been associated with a significant safety risk. While NPS Pharmaceuticals appreciates that a final decision is contingent on the BLA review, for planning purposes NPS Pharmaceuticals wishes to have the benefit of any preliminary comments that the Division could provide regarding whether this product will likely be presented to the Endocrinologic and Metabolic Drugs Advisory Committee.

**Sponsor Question 15:** Does the Division anticipate that they will refer Natpara to the Endocrinologic and Metabolic Drugs Advisory Committee [EMDAC] during their review of the BLA?

**FDA Preliminary Comment: It is premature to comment on this. Many factors, which are analyzed upon receipt of the BLA submission, contribute to the decision of taking a biologic to the EMDAC. We will inform you of such a decision as early as possible in the review cycle.**

*Meeting Discussion: No further Discussion*

#### **Additional Comments:**

##### *Clinical*

1. In the BLA submission, in which location do you plan to include the pre-specified analysis of events associated with hypocalcemia, hypercalcemia, and hypercalciuria.

*Meeting Discussion: Refer to sponsor's slide six below.*

*Sponsor's response repeated from slide six: These data will be provided in the ISS and defined in the ISS SAP. Individual osteo study reports contain analyses of hypercalcemia and hypercalciuria. Within each study report for hypoparathyroidism, all 3 parameters (hypocalcemia, hypercalcemia, and hypercalciuria) are discussed.*

*FDA further asked if the sponsor plans to present these safety data by dose. Sponsor stated that because titration is an inherent part of this therapy, these adverse events should be considered in the global context of titration rather than in relation to a specific dose at a specific time. FDA had no further comment regarding this.*

2. In Study CL1-11-040, 10 out of 90 subjects had an SAE in the NPSP558 treatment group, and one was related to hypercalcemia. At the meeting, please discuss this SAE of hypercalcemia, and describe how many other hypercalcemic (non-SAE) events were noted.

*Meeting Discussion: Refer to sponsor's slide six below.*

*Sponsor's response repeated from slide 6: A summary of all hypercalcemia AEs and individual SAE subject data for subjects 1007-0003 and 0002-0002 are provided on the following slides: 7 to 11.*

*FDA requested that in the BLA the sponsor should include tables for all subjects with any hypercalcemia (not just SAEs) similar to those provided on Slides 7-11. These allow the Division to better understand the development and resolution of such events.*

*In addition, FDA requested the sponsor to include in the BLA individual patient graphs of all hypercalcemia events in study CL1-11-040 (REPLACE). FDA stated that we will provide further guidance for such graphs.*

*Post-meeting comments: For the graphs requested, the x-axis should be days in the trial and y-axis calcium level. For each abnormal timepoint (as well as timepoint preceding or following an abnormal level, as relevant)), you should superimpose on the graph (with an arrow) an explanation or relevant background (e.g., drug was titrated to a certain dose, doses of calcium and vitamin D were adjusted, etc.) to help understand the changes at each timepoint.*

3. At the meeting, please comment on any immunogenicity data generated during the development programs of rh(PTH)1-84.

*Meeting Discussion: Refer to sponsor's slides 12-15 below. FDA had no additional comments.*

*Center for Devices and Radiological Health (CDRH)*

#### *Human Factors*

4. You did not submit any questions regarding Human Factors for this meeting request. However, we note that at the Type C meeting on July 6, 2010, there were several issues related to your revised Human Factors protocol that should be addressed. If necessary, please submit a revised Human Factors/usability validation study protocol for review before implementation.
5. In addition, please note the following expectation for the Human Factors/usability validation study report: The report should begin with a conclusion that the device is reasonably safe and effective for the intended users, uses and use conditions. A summary of relevant portions of preliminary analyses, evaluations, the validation testing should be used as support of this conclusion. **Your data analysis should be prioritized based on identified risk and task**

**priority (from highest to lowest) to determine the magnitude and significance of the use errors, failures and difficulties that occurred during the testing.** The test results, and particularly failures or patterns of subjective reports of difficulty with the use of the device should be discussed with respect to identified risks and whether they were caused by aspects of the design of the device, its labeling, the content or proximity of training and whether modifications are required. Residual risk associated with use that cannot be further reduced through modifications of training, labeling, or modifications to the design of the UI should be discussed and rationale provided for why it cannot be further reduced. Note that stated plans to modify design flaws that could result in clinical impact on patients in future versions of the device are generally unacceptable.

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 recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and is available online at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>.

*Meeting Discussion: Refer to sponsor's slide 16 below.*

*Repeated sponsor's response from slide 16: NPS conducted the full Human factors protocol for the pen injector & mixing device in both trained and untrained healthy volunteers. This protocol (PAR-C10-006) was discussed with the Agency (meeting & several IND Serial submission responses). The study report for PAR-C10-006 was submitted to the IND Serial 079. The pen injector and mixing devices and the IFU are now being used in a hypo clinical study (RACE, PAR-C10-008), which should address the outstanding issues which could not be addressed in a simulated environment (infections, injection site reactions etc.)*

*FDA asked to provide any medication error data collected in these trials. Sponsor agreed to this. FDA asked if the device used in RACE trial (PAR-C10-008) is the same that will be used commercially. Sponsor stated it is different, but they will submit medication error data related to both devices: the one used in RACE trial and the one that they plan to market.*

#### *Devices*

6. The submission does not refer to any studies regarding safety of the final device design presentation. Therefore, we are unable to agree that the studies are adequate and sufficient.
7. The sponsor should provide documentation demonstrating that device hazards have been identified and mitigated. Evidence of successful implementation of safety requirements into the final design should be provided and traced to the respective hazard mitigations

*Meeting Discussion: Refer to sponsor's slide 17 below.*

*Sponsor stated that based on the prior meetings held with FDA July 2010, and December 2011 (chemistry, manufacturing, and controls) and the good advice they received so far, they have no further questions for us. This is why sponsor did not submit any additional information in this pre-submission meeting request. Sponsor stated they will submit all the required information in the BLA.*

*FDA stated that the sponsor should provide a manufacturing schedule in the BLA and to make sure the site is in operation. Once FDA receives the BLA, the inspection will take place within 2 to 4 months. Sponsor acknowledged this.*

#### *Chemistry, Manufacturing, and Controls (CMC)*

8. All facilities should be registered with FDA at the time of the BLA submission and be ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). The facilities should be in operation and manufacturing the drug substance/drug product named in the BLA during the pre-license inspection. Please include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers. A preliminary manufacturing schedule for both the drug substance and drug product should be provided in the BLA submission to facilitate the planning of the pre-license inspections. Manufacture facility information should be included in the BLA as background information for the pre-license inspections.

*Meeting Discussion: Refer to sponsor's slide 17 below. FDA had no further comment.*

9. The CMC Drug Substance section of the BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control. The provided information should include, but not be limited to the following:
  - Monitoring of bioburden and endotoxin levels at critical manufacturing steps using validated bioburden and endotoxin tests. The pre-determined bioburden and endotoxin limits should be provided (3.2.S.2.4).
  - Three successful consecutive product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).
  - Column resin sanitization and storage validation (3.2.S.2.5).
  - Bioburden and endotoxin data obtained during manufacture of the three conformance lots (3.2.S.2.5).
  - Data summaries of shipping validation studies (3.2.S.2.5).
  - Drug substance bioburden and endotoxin release specifications. The bioburden limit should be < 1 CFU/10 mL for bulk materials allowed to be stored for extended periods of time at refrigerated temperatures (3.2.S.4).

*Meeting Discussion: Refer to sponsor's slides 19 and 20 below. FDA stated that they can submit this data with the BLA or as an amendment.*

10. The CMC Drug Product section of the BLA (Section 3.2.P) should contain validation data summaries to support the (b) (4) operations. For guidance on the type of data and information that should be submitted, refer to the 1994 (b) (4)

- Test methods and validation data summaries for the container closure integrity test and preservative effectiveness test should be submitted in Section 3.2.P.2.5 of the submission.
- Provide the study protocols and validation data summaries in Section 3.2.P.3.5 for the following:
  - Bacterial retention study for the (b) (4).
  - (b) (4) equipment and components, and the equipment requalification program.
  - In-process controls and hold times.
  - Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs.
  - A description of the routine environmental monitoring program.
  - The lyophilization process.
- We recommend that the container closure integrity test be performed in lieu of the sterility test for stability samples at initial time and every 12 months (annually) until expiry (3.2.P.8.2).

*Meeting Discussion: Refer to sponsor's slides 19 to 21 below.*

*FDA stated that data is required for any hold times (b) (4) for bioburden and endotoxin level due to potential for microbial growth promotion. Sponsor stated that they have only (b) (4)*

*(b) (4) FDA stated that if this solution is bactericidal, hold time data for bioburden and endotoxin would not be required. FDA clarified that this would not apply to in-process pools stored at or below -20°C, for which no data would be required since frozen product would not support growth.*

*FDA requested confirmation that the validated method and validation report would be included in the BLA. Sponsor stated it would.*

We also refer to your submission dated, January 25, 2012, which contained Instructions For Use (IFU) for the (b) (4) reconstitution device and the Haselmeier Pen Injector. We have the following comments and requests.

1. You should submit either a Medication Guide (MG) or a Patient Package Insert (PPI) in addition to the Instructions for Use (IFU).

2. The standard header and introductory paragraph in the IFU should be the same as the drug product's MG or PPI. Instead of saying "Medication Guide" or "Patient Information," the header should say "Instructions for Use".
3. Following the introductory paragraph, the first information to appear should be a bulleted list of all the supplies needed when applicable.
4. Patient instructions that are not sequential should be bulleted.
5. Patient instructions that are sequential should be noted as "**Step 1, Step 2**" etc.
6. If instructions should be repeated more than once, do not repeat steps. Refer patient back to listed steps. **For example** "Repeat steps 3 to 5".
7. Figures (diagrams or photos) should accompany all numbered steps as appropriate and should be placed immediately adjacent to the related step. The diagrams or photos should be labeled as "**Figure A, Figure B**" etc.
8. For devices there should be a figure which includes detailed labeling for each part of the device that the patient is expected to become familiar with. **For example**, a syringe should have the plunger labeled, and also the numbering and markings on the barrel of the syringe. The numbering and markings should be clearly visible and easy for the patient to read.
9. Refer to each figure at the end of each numbered step. **For example**, at the end of Step 1, say **(See Figure A)**.
10. If the IFU **will not** be attached to the MG or PPI, include the following at the end of the IFU:
  - storage instructions exactly as written in the MG or PPI
  - "This Instructions for Use has been approved by the U.S. Food and Drug Administration."
  - manufacturer's name and address
  - Revised (or Approved for new NDAs or BLAs) Month Year
11. If the IFU **will** be attached to the MG or PPI, include the following at the end of the IFU:
  - "This Medication Guide and Instructions for Use has been approved by the U.S. Food and Drug Administration."
  - manufacturer's name and address Revised (or Approved for new NDAs or BLAs) Month Year

*Meeting Discussion: Refer to sponsor's slide 22 below.*

*Sponsor inquired if we had any comments on a Risk Evaluation and Mitigation Strategy (REMS). FDA also stated that the sponsor should do analysis of safety with respect to calcemic changes and propose a safe starting dose and drug regimen in the BLA. Sponsor stated that the patient is dosed based on calcemic response and not on other parameters. Sponsor stated they can present this as a titration phase. FDA stated that the titration phase should be clearly articulated and easily understandable for the purpose of labeling. Sponsor stated that they are not planning on*

*submitting a REMS but a Medication Guide (MG) and IFU for patients. Sponsor will include the titration in both the MG and IFU in ways which can be easily understood.*

*FDA asked which medical disciplines would be prescribing the product and managing the dosing and titration, endocrinologists or general practitioners. Sponsor stated that endocrinologists will initiate the treatment and then transfer them to general practitioners once patients are stabilized.*

*Post meeting note: Please note that DMEPA and CDRH have not completed the review of all the materials for Human Factors Engineering and Usability Engineering Report entitled "A Usability Testing Study of (b) (4) Mixing Device and Haselmeier Pen Injector" in light of additional materials submitted to FDA on April 26, 2012. However, FDA has identified some preliminary deficiencies and final comments from DMEPA and CDRH will be forthcoming in July 2012. If needed, upon receiving the DMEPA and CDRH comments, which are anticipated to be completed in July, you can request a meeting with DMEPA and CDRH to discuss further any potential deficiencies. We like to ensure that you submit a "complete" BLA application under PDUFA V and recommend that the concerns identified by DMEPA and CDRH be resolved prior to your BLA submission.*

#### *OSI*

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

The dataset that is requested as per Item III below, is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

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

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

1. Please include the following information in a tabular format in the original NDA for each of the completed Phase 3 NPS-sponsored clinical trials, Study C11-11-040 (REPLACE) and Study PAR C-10-007 (RELAY):
  - a. Site number
  - b. Principal investigator

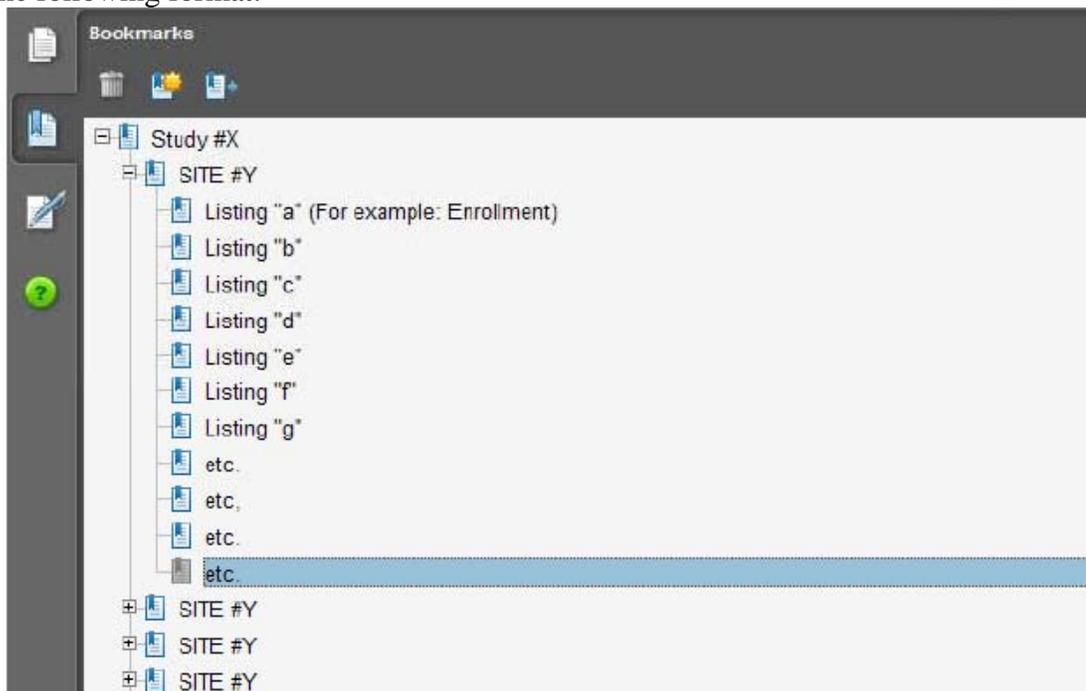
- c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
  - d. Current Location of Principal Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
2. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 3 NPS-sponsored clinical trials:
  - a. Number of subjects screened for each site by site
  - b. Number of subjects randomized for each site by site
  - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed Phase 3 NPS-sponsored clinical trials:
  - a. Location of Trial Master File (actual physical sites where documents are maintained and would be available for inspection)
  - b. Name, address and contact information of all CROs used in the conduct of the clinical trials
  - c. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
  - d. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)
4. For each pivotal trial provide a sample annotated Case Report Form (if items are provided elsewhere in submission, please describe location or provide a link to requested information).
5. For each pivotal trial provide original protocol and all amendments (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

*Meeting Discussion: Refer to sponsor's slide 23 below. No further comments.*

**B. Request for Subject Level Data Listings by Site**

1. For each pivotal trial: Site-specific individual subject data ("line") listings. For each site provide line listings for:
  - a. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
  - b. Subject listing for treatment assignment (randomization)
  - c. Subject listing of drop-outs and subjects that discontinued with date and reason
  - d. Evaluable subjects/ non-evaluable subjects and reason not evaluable
  - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
  - f. By subject listing, of AEs, SAEs, deaths and dates

- g. By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
  - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint. For example, in Study C11-11-040, for the determination of a “responder” status for each subject, the dose of oral calcium, dose of active Vitamin D metabolite/drug and the serum calcium value and albumin value should be provided. In addition, provide the secondary endpoint of the frequency of clinical symptoms of hypocalcemia.
  - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
  - j. By subject listing, of laboratory tests performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



*Meeting Discussion: Refer to sponsor’s slide 24 below. No further comments.*

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

OSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to Attachment 1, “Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA

Submissions” for further information. We request that you provide a dataset, as outlined, which includes requested data for each pivotal study submitted in your application.

*Meeting Discussion: Refer to sponsor’s slide 25 below.*

*Sponsor response repeated from slide 25: In this orphan disease the largest enrollment at any site was 10 subjects (at a US site) and 9 (at an ex-US site) across the 33 global sites for the 134 randomized hypo patients in the pivotal study CL1-11-040.*

*Given NPS’ interpretation of the pilot program’s intended use and objectives, the Sponsor believed that this labor intense analysis would not provide meaningful data for OSI given the limited number of subjects involved. NPS respectfully requested that the Agency consider NPS not participating in this pilot, since it could cause an undue financial and operational burden on our small company with the likely consequence of delaying the submission.*

*FDA stated that the sponsor is not required to participate in the optional OSI site level dataset pilot program. FDA also stated that other Orphan drug products have participated in this program in the past.*

## **DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

- The content of a complete application was discussed.

All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion on the need for a REMS was held and it was concluded that the sponsor is not planning on submitting one.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission: You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

## **PRESCRIBING INFORMATION**

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

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

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm>

[084159.htm](#). We encourage you to review the information at this website and use it as you draft prescribing information for your application.

### **MANUFACTURING FACILITIES**

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

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

Consider using tables similar to the ones below as attachments to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA #####, Establishment Information for Form 356h."

Product name, BLA #####, Establishment Information for Form 356h

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

Corresponding names and titles of onsite contact:

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

**2.0 ATTACHMENTS AND HANDOUTS**

## **Attachment 1**

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

#### INTRODUCTION

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

#### 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 to facilitate the evaluation of the application. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

#### **Site-Specific Efficacy Results**

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- Treatment Efficacy Result Standard Deviation (TRTEFFS) – the standard deviation of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis

- Site-specific Efficacy Effect Size Standard Deviation (SITEEFFS) – the standard deviation of the site-specific efficacy effect size (SITEEFFE)
- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.
- Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report.

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) –the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, “TRTEFFR.”

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.
- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.
- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).
- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the “endpoint” plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1: *Table 1 Clinical Site Data Elements Summary Listing (DE)*. A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (\*.xpt).

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

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter "1".	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters).	Active (e.g., 25mg), Comparator drug product name (e.g., Drug x), or Placebo
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20

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

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount (\$USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parties. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	25000.00
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	INITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

Exhibit 2: Example for Clinical Site Data Elements Summary Listing (Table 1)

STUDY	STUDYT	DOM	SPON	SPONN	IND	UNDER	NDA	BL	SUPPN	SIT	ARM	ENR	SCREE	DISCO
Y	L	AIN	NO	AME		IND		A	UM	EID		OLL	N	NT
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	27	60	1

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FINLDISC	LAS
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	-1	
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	-1	
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	45000.00	Was
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45000.00	Was
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	25000.00	Jef
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	25000.00	Jef
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	0.00	Li
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	0.00	Li

IND 076514  
 Minutes of Pre-BLA Meeting  
 May 15, 2012

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

Attachment 2

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

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

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

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



<sup>1</sup> Please see the OSI Pre-NDA Request document for a full description of requested data files

IND 076514  
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May 15, 2012

- C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1  
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

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

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

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/s/  
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MEGHNA M JAIRATH  
06/14/2012

**LATE-CYCLE COMMUNICATION**  
**DOCUMENTS**



BLA 125511

**LATE-CYCLE MEETING MINUTES**

NPS Pharmaceuticals Inc.  
Attention: Jehan Rowlands, Pharm.D.  
Director, Regulatory Affairs  
550 Hills Drive, 3rd Floor  
Bedminster, NJ 07921

Dear Dr. Rowlands:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for Natpara (parathyroid Hormone (1-84) Human Recombinant injection).

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on July 31, 2014.

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

If you have any questions, contact Elizabeth Chen, Regulatory Project Manager, at (240) 402-3729.

Sincerely,

*{See appended electronic signature page}*

Jean-Marc Guettier, M.D.  
Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure:  
Late Cycle Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

**MEMORANDUM OF LATE-CYCLE MEETING MINUTES**

**Meeting Date and Time:** July 31, 2014, 2:00 PM to 3:00 PM  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1421  
Silver Spring, Maryland 20903

**Application Number:** BLA 125511  
**Product Name:** Natpara (parathyroid Hormone (1-84) Human Recombinant injection)  
**Indication:** Replacement for endogenous parathyroid hormone (1-84) for the long-term treatment of hypoparathyroidism  
**Applicant Name:** NPS Pharmaceuticals Inc.

**FDA ATTENDEES**

Office of Drug Evaluation II

Curtis Rosebraugh, M.D., M.P.H., Director

Division of Metabolism and Endocrinology Products

Jean-Marc Guettier, M.D., Director  
Dragos Roman, M.D., Clinical Team Leader  
Naomi Lowy, M.D., Clinical Reviewer  
Andreea Lungu, M.D., Clinical Reviewer  
Karen Davis Bruno, Ph.D., Nonclinical Team Leader  
Robert Maher, Ph.D., Nonclinical Reviewer  
Pamela Lucarelli, Chief, Project Management Staff  
Elizabeth Chen, Pharm.D., Regulatory Project Manager

Office of Biostatistics

Mark Rothmann, Ph.D., Team Leader  
Jennifer Clark, Ph.D., Statistical Reviewer

Office of Clinical Pharmacology

Chandra Sahajwalla, Ph.D., Director, Division of Pharmacology II  
Nitin Mehotra, Ph.D., Clinical Pharmacology Reviewer  
Manoj Khurana, Ph.D., Clinical Pharmacology Reviewer

Office of Combination Products

Bindi Nikhar, M.D., Associate Clinical Director

Office of Scientific Investigations, Good Clinical Practice Assessment Branch

Cynthia Kleppinger, M.D., Senior Medical Officer

Office of Surveillance and Epidemiology

Amarilys Vega, Medical Officer, Division of Risk Management

Office of Manufacturing and Product Quality

Colleen Thomas, Ph.D., Product Quality Microbiology Reviewer

**EASTERN RESEARCH GROUP ATTENDEES**

 <sup>(b) (6)</sup>, Independent Assessor

**APPLICANT ATTENDEES**

Robert Ashworth, Ph.D., Vice President, Global Regulatory Affairs  
Xin Du, Ph.D., Senior Director, Regulatory Affairs CMC  
Roger Garceau, M.D., Executive Vice President & Chief Medical Officer  
Michael Grace, Ph.D., Senior Director, Analytical Development  
Hjalmar Lagast, M.D., Vice President, Clinical Development  
Theresa Matkovits, Ph.D., Research and Development Program Leader  
Ralf Rosskamp, M.D., Vice President, Global Clinical Development  
Jehan Rowlands, Pharm.D., Director, Regulatory Affairs

**1.0 BACKGROUND**

BLA 125511 was submitted on October 24, 2013, for Natpara (parathyroid Hormone (1-84) Human Recombinant injection).

Proposed indication: Replacement for endogenous parathyroid hormone (1-84) for the long-term treatment of hypoparathyroidism

PDUFA goal date: October 25, 2014 (Note: since the time of the LCM, the goal date has been extended to January 25, 2014).

FDA issued a Background Package in preparation for this meeting on July 24, 2014.

**2.0 DISCUSSION**

1. Introductory Comments

Welcome, Introductions, Ground rules, Objectives of the meeting

**Discussion:** None

2. Discussion of Substantive Review Issues

- Data Reliability/Integrity
- Clinical Pharmacology

**Discussion:** Since no adequate dose ranging studies were performed for this indication, alternative dosing regimens should be considered in order to improve outcomes from administration of the drug.

3. Discussion of Minor Review Issues

- Clinical Benefit
- Protocol Amendment 7
- Safety
- Titration

**Discussion:**

The Agency discussed reservations it had regarding the demonstration of a clinical benefit of Natpara that goes beyond treating hypocalcemia in the patients with hypoparathyroidism.

The applicant clarified the protocol changes that were implemented with amendment 7 (submitted December 16, 2009) of the pivotal trial, and indicated that the purpose of the amendment was to improve investigators' understanding of what was meant by normal serum calcium range. The FDA discussed the - impact that the amendment had on efficacy data analysis.

The Agency requested clarification on how safety data for adverse events of hypocalcemia and hypercalcemia were collected during the trials. The applicant explained that events were recorded by both symptoms and lab definitions.

The complexity of the titration regimen in the pivotal trial was discussed. NPS informed the Agency that changes were made to the titration protocol based on feedback from investigators and that the simplified titration was used in another trial. The applicant plans to use the updated titration plan for labeling.

4. Information Requests from Product Quality Microbiology (Drug Substance)

**Discussion:** Request has been sent and responded to by the sponsor.

5. Discussion of Upcoming Advisory Committee Meeting

**Discussion:** Alignment was reached on how to present information related to the problematic site and unreliable data originating from this site.

There will be no extensive presentation on osteosarcoma during the advisory committee meeting, but osteosarcoma-related issues will be presented and discussed as part of the overall risk-benefit analysis.

6. Postmarketing Requirements/Postmarketing Commitments from Product Quality Microbiology (Drug Substance)

**Discussion:** Request has been sent and responded to by the sponsor.

7. Major Labeling Issues

**Discussion:** None

8. Review Plans

**Discussion:** None

9. Wrap-up and Action Items

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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/s/  
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JEAN-MARC P GUETTIER  
01/06/2015



BLA 125511

**LATE CYCLE MEETING  
BACKGROUND PACKAGE**

NPS Pharmaceuticals Inc.  
Attention: Jehan Rowlands, Pharm.D.  
Director, Regulatory Affairs  
550 Hills Drive, 3rd Floor  
Bedminster, NJ 07921

Dear Dr. Rowlands:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for Natpara (parathyroid Hormone (1-84) Human Recombinant injection).

We also refer to the Late-Cycle Meeting (LCM) scheduled for July 31, 2014. Attached is our background package, including our agenda, for this meeting.

If you have any questions, contact Elizabeth Chen, Regulatory Project Manager, at (240) 402-3729.

Sincerely,

*{See appended electronic signature page}*

Jean-Marc Guettier, M.D.  
Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

ENCLOSURE:  
Late-Cycle Meeting Background Package

## LATE-CYCLE MEETING BACKGROUND PACKAGE

**Meeting Date and Time:** July 31, 2014, 2:00 PM to 3:00 PM  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1421  
Silver Spring, Maryland 20903

**Application Number:** BLA 125511  
**Product Name:** Natpara (parathyroid Hormone (1-84) Human Recombinant injection)  
**Indication:** Replacement for endogenous parathyroid hormone (1-84) for the long-term treatment of hypoparathyroidism  
**Applicant Name:** NPS Pharmaceuticals Inc.

### INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, Division Director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

### BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

#### 1. Discipline Review Letters

No Discipline Review letters have been issued to date.

#### 2. Substantive Review Issues

The following substantive review issues have been identified to date:

- **Data Integrity Issues:** The impact that exclusion of data from site 1002 will have on the overall application.
- **Clinical Pharmacology:** The Agency has concerns that the once daily dosing regimen proposed for Natpara may not be optimal for controlling hypercalciuria. We believe that no adequate dose ranging studies were conducted for dose selection of Natpara before proceeding to the registration trial.

We have reviewed the PK/PD data of Natpara (C09-002 and Mosekilde-IIT) along with the efficacy/safety results from the registration trial, and have reached the opinion that Natpara doses up to 100 µg once daily do not provide optimal systemic exposures to control the excretion of calcium in urine. This is primarily due to short half-life (~ 3 hours) of Natpara which results in PTH concentrations returning to baseline by 10-12 hours, similar to what you have acknowledged in the clinical pharmacology summary document (Section 2.7.2 Summary of clinical pharmacology studies, page 41 and 124). We believe that duration of stimulatory action of Natpara on calcium re-absorption is not long enough to control the excretion of calcium regardless of whether patients achieve normocalcemia.

Our preliminary simulations, utilizing one of the several systems pharmacology models of calcium homeostasis available in public domain, demonstrate that a regimen more frequent than once a daily dosing regimen is desirable to facilitate adequate control on hypercalciuria. Therefore, we think that there is an opportunity to optimize the dosing regimen of Natpara to improve the benefit-risk profile of PTH therapy. We believe that adequate understanding of the reasons behind hypercalciuria and possible mitigation of this safety concern is essential for Natpara since hypercalciuria is one of the primary safety concerns for the conventional therapy.

## **ADVISORY COMMITTEE MEETING**

**Date of AC meeting:** September 12, 2014

**Date AC briefing package will be sent under separate cover by the Division of Advisory Committee and Consultant Management:** August 22, 2014

**Potential questions and discussion topics for AC Meeting are as follows:**

- Efficacy
- Safety
- Risk-benefit

We look forward to discussing our plans for the presentations of the data and issues for the upcoming AC meeting. Final questions for the Advisory Committee are expected to be posted

two days prior to the meeting at this location:

<http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm>

## **REMS OR OTHER RISK MANAGEMENT ACTIONS**

No issues related to risk management have been identified to date.

## **LCM AGENDA**

### 1. Introductory Comments – 5 minutes (RPM/CDTL)

Welcome, Introductions, Ground rules, Objectives of the meeting

### 2. Discussion of Substantive Review Issues – 10 minutes

- Data Reliability/Integrity
- Clinical Pharmacology

### 3. Discussion of Minor Clinical Review Issues – 20 minutes

- **Clinical Benefit:** The efficacy of the drug appears to be limited to a reduction in vitamin D and calcium supplements. Other clinically meaningful benefits, including an important reduction/normalization of 24 hour urinary calcium, have not been demonstrated. While an increase in bone markers is observed, the clinical significance of this is unclear, especially since you have stated that the reference ranges for bone markers were established for the osteoporosis population.
- **Protocol Amendment:** Amendment 7 changed the third component of the primary endpoint so that calcium levels reaching the upper limit of normal were acceptable. Results using the definition in the original protocol compared to the results using the definition from Amendment 7 are markedly different. Clinical guidelines recommend that serum calcium of patients with hypoparathyroidism be maintained at the lower end of the normal range. Therefore, the clinical relevance of the definition of responder according to Amendment 7 is unclear.
- **Safety:** Overall, hypocalcemia and hypercalcemia were problematic in both Natpara and placebo groups. Natpara does not appear to be advantageous from a safety perspective.
- **Titration regimen:** The titration instructions incorporated in the study protocol were extensive and used a complex algorithm. Converting these detailed instructions into practical labeling advice while remaining true to tested algorithm from the REPLACE trial will pose a definite challenge.

4. Information Requests from Product Quality Microbiology (Drug Substance) – 5 minutes

An information request will be sent by the beginning of August 2014.

5. Discussion of Upcoming Advisory Committee Meeting – 10 minutes

6. Postmarketing Requirements/Postmarketing Commitments from Product Quality Microbiology (Drug Substance) – 5 minutes

- Establish a bioburden limit for the (b) (4) after data from 10 lots is available. In addition, qualify the bioburden method for the (b) (4) with three different lots of material.
- Bioburden and endotoxin method qualification studies for the drug substance and in-process intermediates were performed with only one lot of material. Provide method qualification data from two additional lots of material.

7. Major labeling issues – None at this time.

8. Review Plans – None at this time.

9. Wrap-up and Action Items – 5 minutes

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/s/  
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JEAN-MARC P GUETTIER  
07/24/2014