

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125511Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Compliance
Office of Manufacturing and Product Quality
Biotech Manufacturing and Assessment Branch

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

REVIEWER: Colleen Thomas, Ph.D.
TEAM LEADER: Patricia Hughes, Ph.D.

BLA: 125511
Applicant: NPS Pharmaceuticals
US License Number: 1908
Product: Recombinant parathyroid hormone (1-84) - Natpara®
Indication: Treatment of hypoparathyroidism
Dosage Form: The drug product is supplied in a multi-dose dual-chamber cartridge containing sterile lyophilized powder for injection (25, 50, 75, or 100 mcg/dose) in one chamber and sterile diluent in the other chamber.
Manufacturing Site: The drug substance is manufactured at Boehringer Ingelheim, Vienna, Austria (FEI: 3003433722)
Action Date: 24 October 2014

Conclusion and Approvability Recommendation

The drug substance portion of the BLA was reviewed from a product quality microbiology perspective and is recommended for approval. There are three post-marketing commitments:

1. Establish a bioburden limit for the [REDACTED] (b) (4) after the bioburden monitoring results for 10 more batches are available.
2. Provide bioburden method qualification data from two additional lots of the [REDACTED] (b) (4) and the drug substance. In addition, provide method qualification data from three lots of the [REDACTED] (b) (4)

3. 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 [REDACTED] (b) (4)

Product Quality Microbiology Assessment: Drug Substance

Drug Substance Quality Microbiology Information Reviewed

Sequence number	Date	Description
0000	23 October 2013	Original BLA
0016	21 April 2014	Amendment
0020	9 May 2014	Amendment
0042	20 August 2014	Amendment

Module 3.2

S.1 General Information

The recombinant parathyroid hormone present in rhPTH drug substance (DS) is identical in structure to endogenous human parathyroid hormone. The DS is manufactured in a recombinant *E. coli* strain [REDACTED] (b) (4). The DS is a clear, colorless to light straw-colored aqueous solution containing up to [REDACTED] (b) (4).

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/s/

COLLEEN THOMAS
08/22/2014

PATRICIA F HUGHES TROOST
08/22/2014

Product Quality Microbiology Review

25 JUL 2014

BLA: 125511

Drug Product Name

Proprietary: Natpara

Non-proprietary: Recombinant human parathyroid hormone (rhPTH [1-84])

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
23 OCT 2013	23 OCT 2013	19 DEC 2013	19 DEC 2013
06 FEB 2014	06 FEB 2014	N/A	N/A
20 FEB 2014	20 FEB 2014	N/A	N/A
02 APR 2014	02 APR 2014	N/A	N/A
21 APR 2014	21 APR 2014	N/A	N/A
19 MAY 2014	19 MAY 2014	N/A	N/A
24 JUL 2014	24 JUL 2014	N/A	N/A

Applicant/Sponsor

Name: NPS Pharmaceuticals Inc.

Address: 550 Hills Drive
Bedminster, NJ 07921

Representative: Jehan Rowlands

Telephone: 908-450-5537

Name of Reviewer: Jessica G. Cole, PhD

Conclusion: Recommended for Approval

Product Quality Microbiology Data Sheet

- A. 1. **TYPE OF SUBMISSION:** New 351(a) BLA
2. **SUBMISSION PROVIDES FOR:** A new combination product composed of a new biologic drug product and associated devices
3. **MANUFACTURING SITE:**
Drug Product: Vetter Pharma-Fertigung GmbH& Co. KG
Schützenstrasse 87, 99-101
88212, Ravensburg,
Germany
4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
- Lyophilized powder for reconstitution in a dual chamber glass cartridge with a diluent, mixing device, and pen injector
 - Multi-dose, preserved presentation
 - 25, 50, 75, and 100 µg/dose
 - Subcutaneous injection
5. **METHOD(S) OF STERILIZATION:** [REDACTED] (b) (4)
6. **PHARMACOLOGICAL CATEGORY:** Treatment of hypoparathyroidism
- B. **SUPPORTING/RELATED DOCUMENTS:** The microbiology review for NDA 205-787 dated 07 March 2014. The BMAB microbiology review of the drug substance will be conducted by Colleen Thomas and was not in DARRTS when this review was completed.
- C. **REMARKS:** This BLA was in the eCTD format and is associated with IND 76,514. NPS previously submitted NDA [REDACTED] (b) (4) (withdrawn), [REDACTED] (b) (4) [REDACTED]. The microbiology filing review is dated 23 December 2013 and was a joint effort by Colleen Thomas from the CDER/Office of Compliance/Biotech Manufacturing Assessment Branch (BMAB) and this reviewer. The following comments were included in the 74-day letter sent on 06 January 2014 and a response was received on 06 February 2014 (Sequence 0006).

Microbiology Comments:

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 (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 (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 (b) (4) validation (media fill) data.
6. Insufficient information has been provided on the (b) (4) simulations. Provide a detailed description of the (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: (b) (4)
(b) (4)
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.

The following information request was sent to the applicant on 17 March 2014 and a response was received on 02 April 2014 and 21 April 2014.

Microbiology Comment:

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

1. We refer to the (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.

The following information request was sent to the applicant on 22 April 2014 and a response was received on 19 May 2014 and 24 July 2014.

Microbiology Comment:

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 of (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) used for (b) (4) validation (media fill) studies.

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Executive Summary

I. Recommendations

- A. Recommendation on Approvability** - Recommended for Approval
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – Not applicable.

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – This is an (b) (4) drug product. One compartment of the cartridge is filled, lyophilized, and stoppered before the preserved diluent is filled into the second chamber. The drug cartridge is later loaded into a cartridge holder that interfaces with the pen injector and packaged with the mixing device.
- B. Brief Description of Microbiology Deficiencies** – Not applicable.
- C. Assessment of Risk Due to Microbiology Deficiencies** – Not applicable.
- D. Contains Potential Precedent Decision(s)**- Yes No

III. Administrative

- A. Reviewer's Signature** _____
Jessica G. Cole, PhD
- B. Endorsement Block** _____
Bryan Riley, PhD
Microbiology Team Leader
- C. CC Block**
In DARRTS

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/s/

JESSICA COLE
07/25/2014

BRYAN S RILEY
07/25/2014
I concur.

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

BLA/NDA Number: **Applicant:** **Stamp Date:**
BLA 125511 **NPS Pharmaceuticals, Inc.** **23 October 2013**

Established/Proper Name: **BLA/NDA Type:**
Parathyroid hormone (1-84) **Standard**
human recombinant

On **initial** overview of the BLA/NDA application for filing:

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	Y	
Form 356h completed	Y	
<input type="checkbox"/> including list of all establishment sites and their registration numbers	Y	
Comprehensive Table of Contents	Y N	NA (electronic application)
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y	
Labeling:	Y N	Defer to OND
<input type="checkbox"/> PI –non-annotated	Y N	
<input type="checkbox"/> PI –annotated	Y N	
<input type="checkbox"/> PI (electronic)	Y N	
<input type="checkbox"/> Medication Guide	Y N	
<input type="checkbox"/> Patient Insert	Y N	
<input type="checkbox"/> package and container	Y N	
<input type="checkbox"/> diluent	Y N	
<input type="checkbox"/> other components	Y N	
<input type="checkbox"/> established name (e.g. USAN)	Y N	
<input type="checkbox"/> proprietary name (for review)	Y N	

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include: <input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> compatible file formats <input type="checkbox"/> navigable hyper-links <input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays <input type="checkbox"/> summary reports reference the location of individual data and records <input type="checkbox"/> all electronic submission components usable (e.g. conforms to published	Y	

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

Examples of Filing Issues	Yes?	If not, justification, action & status
guidance)		
Companion application received if a shared or divided manufacturing arrangement	Y N	NA

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y N	
Introduction to the summary documents (1 page) [2.2]	Y N	
Quality overall summary [2.3]	Y	
<input type="checkbox"/> Drug Substance	Y	
<input type="checkbox"/> Drug Product	Y	
<input type="checkbox"/> Facilities and Equipment	Y	
<input type="checkbox"/> Adventitious Agents Safety Evaluation	Y	
<input type="checkbox"/> Novel Excipients	Y N	Defer to ONDQA
<input type="checkbox"/> Executed Batch Records	Y	
<input type="checkbox"/> Method Validation Package	Y	
<input type="checkbox"/> Comparability Protocols	N	Provided in section 3.2.S.2.2

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	Y N	NA (electronic application)
Drug Substance [3.2.S]		
<input type="checkbox"/> general info	Y	
<input type="checkbox"/> nomenclature		
<input type="checkbox"/> structure (e.g. sequence, glycosylation sites)		
<input type="checkbox"/> properties		
<input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)	Y	
<input type="checkbox"/> description of manufacturing process and process control	Y	
<input type="checkbox"/> batch numbering and pooling scheme		
<input type="checkbox"/> cell culture and harvest		
<input type="checkbox"/> purification		
<input type="checkbox"/> filling, storage and shipping		
<input type="checkbox"/> control of materials	Y N	Defer to ONDQA
<input type="checkbox"/> raw materials and reagents		
<input type="checkbox"/> biological source and starting materials		
<input type="checkbox"/> cell substrate: source, history, and generation		
<input type="checkbox"/> cell banking system, characterization, and testing		

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

CTD Module 3 Contents	Present?	If not, justification, action & status
<input type="checkbox"/> control of critical steps and intermediates <ul style="list-style-type: none"> <input type="checkbox"/> justification of specifications <input type="checkbox"/> stability <input type="checkbox"/> process validation (prospective plan, results, analysis, and conclusions) <input type="checkbox"/> manufacturing process development (describe changes during non-clinical and clinical development; justification for changes) <input type="checkbox"/> characterization of drug substance <input type="checkbox"/> control of drug substance <ul style="list-style-type: none"> <input type="checkbox"/> specifications <ul style="list-style-type: none"> <input type="checkbox"/> justification of specs. <input type="checkbox"/> analytical procedures <input type="checkbox"/> analytical method validation <input type="checkbox"/> batch analyses <input type="checkbox"/> reference standards <input type="checkbox"/> container closure system <input type="checkbox"/> stability <ul style="list-style-type: none"> <input type="checkbox"/> summary <input type="checkbox"/> post-approval protocol and commitment <input type="checkbox"/> pre-approval <ul style="list-style-type: none"> <input type="checkbox"/> protocol <input type="checkbox"/> results <input type="checkbox"/> method validation 	<p>Y</p> <p>Y</p> <p>Y N</p> <p>Y N</p> <p>Y</p> <p>Y N</p> <p>Y</p> <p>Y N</p> <p>Y N</p> <p>Y N</p> <p>Y N</p> <p>Y N</p>	<p>Defer to ONDQA</p> <p>Defer to ONDQA</p> <p>Defer to ONDQA</p> <p>Defer to ONDQA. (b) (4)</p>
<p>Drug Product [3.2.P] [Dosage Form]</p> <input type="checkbox"/> description and composition <input type="checkbox"/> pharmaceutical development <ul style="list-style-type: none"> <input type="checkbox"/> preservative effectiveness <input type="checkbox"/> container-closure integrity <input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved) <input type="checkbox"/> batch formula <input type="checkbox"/> description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities) <input type="checkbox"/> controls of critical steps and intermediates <input type="checkbox"/> process validation including aseptic processing & sterility assurance: <ul style="list-style-type: none"> <input type="checkbox"/> Filter validation <input type="checkbox"/> Component, container, closure depyrogenation 	<p>Y</p>	<p>Applicant should include a (b) (4) bioburden sample for the drug product chamber</p> <p>(b) (4) were validated in 2005 Only a single revalidation cycle was provided for review</p>

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present?	If not, justification, action & status
<ul style="list-style-type: none"> ○ manufacturing flow; adjacent areas ○ other products in facility ○ equipment dedication, preparation, sterilization and storage ○ procedures and design features to prevent contamination and cross-contamination □ adventitious agents safety evaluation (viral and non-viral) e.g.: <ul style="list-style-type: none"> ○ avoidance and control procedures ○ cell line qualification ○ other materials of biological origin ○ viral testing of unprocessed bulk ○ viral clearance studies ○ testing at appropriate stages of production □ novel excipients 	Y	referenced for some of the DS manufacturing site information. Viral testing and viral clearance are not applicable.
	Y N	Defer to ONDQA
USA Regional Information [3.2.R]		
<ul style="list-style-type: none"> □ executed batch records □ method validation package □ comparability protocols 	Y Y N	Provided in section 3.2.S.2.2
Literature references and copies [3.3]	Y	

Examples of Filing Issues	Yes?	If not, justification, action & status
Includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)	Y	
Includes data demonstrating consistency of manufacture	Y	
Includes complete description of product lots and manufacturing process utilized for clinical studies	Y N	Defer to ONDQA
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y N	Defer to ONDQA
Data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y N	Defer to ONDQA
Certification that all facilities are ready for inspection	Y	

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

Examples of Filing Issues	Yes?	If not, justification, action & status
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y	
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: <input type="checkbox"/> LAL instead of rabbit pyrogen <input type="checkbox"/> mycoplasma <input type="checkbox"/> sterility	Y N Y N Y N	Not applicable NA (b) (4)
Identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y N	NA
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y	DMF (b) (4) (LOA provided) is referenced for some of the DS manufacturing site information.
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y	DMF (b) (4) (LOA provided) is referenced for some of the DS manufacturing site information.

Additional Comments:

The drug product configuration is a dual chamber cartridge with the lyophilized active ingredient and excipients in chamber 1 and the m-cresol diluent in chamber 2. The applicant proposes 4 strengths (100, 75, 50, and 25 µg/dose rhPTH (1-84)). The cartridge is loaded into a pen injector and is supplied with a mixing device. Patients will reconstitute the active ingredient using the mixing device and pen injector and then administer one subcutaneous injection daily for 14 days.

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? Yes

Review issues to be forwarded to the Applicant in the 74-day letter

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

- The proposed manufacturing process (b) (4)
- Provide the results from three recent sterilization validation studies for the (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>

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

3. Provide the results from three recent validation studies for the (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. (b) (4)
6. Insufficient information has been provided on the (b) (4) simulations. Provide a detailed description of the (b) (4) simulations to include a description of the process and the routine and non-routine interventions. Include information on the process for (b) (4). For more information please refer to the following Guidance: Sterile Drug Products Produced by Aseptic Processing- Current Good Manufacturing Practice (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070342.pdf>)
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 (b) (4) 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.

Colleen Thomas, PhD (Module 3 Drug Substance section)

Jessica Cole, PhD (Module 3 Drug Product and Information request)

23 December 2013

Reviewing Microbiologist

Date

Kalavati Suvarna, PhD

Bryan Riley, PhD

23 December 2013

Microbiology Secondary Reviewer/Team Leader

Date

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/s/

KALAVATI C SUVARNA on behalf of COLLEEN THOMAS
12/23/2013

BRYAN S RILEY
12/23/2013
I concur.

KALAVATI C SUVARNA
12/23/2013

JESSICA COLE
12/23/2013