

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125511Orig1s000

CHEMISTRY REVIEW(S)

MEMO

From: Muthukumar Ramaswamy, Ph.D.
Office of New Drug Quality Assessment (ONDQA), CDER

To: File

Date: September 29, 2014

Subject: Final Quality Recommendation for BLA125511 - Natpara® (Parathyroid Hormone [rDNA]) for Injection

This memo documents the overall quality recommendation for BLA125511. Natpara® (Parathyroid Hormone [rDNA]) for Injection (BLA 125511), which is a drug device combination product. From quality perspective, BLA 125511 is recommended for approval.

This overall quality approval recommendation is based on approval recommendations from quality reviews performed by CMC (ONDQA), product quality microbiology (OPS and BMAB), CDRH (device quality), CDER Office compliance and CDRH Office compliance (review of manufacturing facilities associated with this application). Please refer to the following communications in DARRTS:

- Product Quality CMC review (Office of Quality Assurance, review dated 6/27/14)
- Product Quality Microbiology review (Biotech Manufacturing Branch, and Office of Pharmaceutical science, reviews dated 7/31/14 and 8/22/14)
- CDRH technical review for the pen delivery device and Natpara mixing device (Human Factors review dated 9/08/14) and device engineering review dated 9/08/14). CDRH's technical review of the pen injector and mixing device found no quality-specific deficiency.
- There are three post-marketing commitments for the drug substance portion of product quality review (BMAB). For additional information, please refer to the respective memos in DARRTS.
- CDER Office Compliance (OMPQ) and CDRH Office of Compliance (Division of Manufacturing Quality) have issued acceptable recommendation for facilities associated with the drug substance, drug product and device. Please refer to the following communications in DARRTS for additional details: E. Chen (For Vicky Verna) dated 9/08/14 and R. Prabhakara dated 9/26/14.

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Application: BLA125511/000
Stamp Date: 13-SEP-2013
Regulatory: 24-OCT-2014

Action Goal:
District Goal:

Applicant: (b) (4)

Brand Name:
Estab. Name:
Generic Name:

Priority: 1Y
Org. Code: 510

Product Number; Dosage Form; Ingredient; Strengths
 001; INJECTION, POWDER, LYOPHILIZED, FOR SOLUTION;
 PARATHYROID HORMONE; 25UG
 002; INJECTION, POWDER, LYOPHILIZED, FOR SOLUTION;
 PARATHYROID HORMONE; 50UG
 003; INJECTION, POWDER, LYOPHILIZED, FOR SOLUTION;
 PARATHYROID HORMONE; 75UG
 004; INJECTION, POWDER, LYOPHILIZED, FOR SOLUTION;
 PARATHYROID HORMONE; 100UG

Application Comment: THIS IS A BLA (on 03-DEC-2013 by P. KUMAR (HFD-800) 2404023722)

ON OCTOBER 24, 2013, NPS PHARMACEUTICALS SUBMITTED A BLA. THIS BLA IS FOR A RECOMBINANT HUMAN PARATHYROID HORMONE (RDNA). (on 18-APR-2014 by T. WILSON (J) 2404024226)

FDA Contacts:	M. RAMASWAMY	Prod Qual Reviewer		3017961676
	P. KUMAR	Product Quality PM	(HFD-800)	2404023722
	E. CHEN	Regulatory Project Mgr		2404023729

Overall Recommendation: ACCEPTABLE on 26-SEP-2014 by R. PRABHAKARA (J) 3017964668

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

/s/

MUTHUKUMAR RAMASWAMY
09/29/2014

DANAE D CHRISTODOULOU
09/29/2014

BLA 125511

**Natpara®
(Parathyroid Hormone [rDNA]) for Injection**

NPS Pharmaceuticals, Inc.

**Muthukumar Ramaswamy, PhD (Drug Substance Reviewer)
Joseph Leginus, PhD (Drug Product Reviewer)**

**Office of New Drug Quality Assessment
Division III, Branch VII**

**For the Division of
Metabolism and Endocrinology Products**

CHEMISTRY REVIEW #1

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Chemistry Review Data Sheet

1. BLA 125511
2. REVIEW #: 1
3. REVIEW DATE: June 27, 2014
4. REVIEWERS: Muthukumar Ramaswamy, PhD (Drug Substance)
Joseph Leginus, PhD (Drug Product and Sections S.4.2 and S.4.3 of Drug Substance)

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original BLA	23-Oct-2013
Amendment	20-Feb-2014
Amendment	24-Apr-2014
Amendment	09-May-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	NPS Pharmaceuticals, Inc.
Address:	550 Hills Dr., Bedminster, NJ 07921
Representative:	Jehan Rowlands, Director, Regulatory Affairs
Telephone:	908-450-5537

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Natpara®
- b) Non-Proprietary Name (INN): Parathyroid Hormone (1-84) Human Recombinant
- c) Code Name/# (ONDC only): NPSP558; rhPTH(1-84).
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: This BLA is submitted as a 351(a) application. In 2007, the FDA granted Orphan Drug Designation for rhPTH(1-84) for the treatment of hypoparathyroidism.

Chemistry Review Data Sheet

10. PHARMACOL. CATEGORY:

Parathyroid Hormone (1-84) human recombinant is indicated in the treatment of hypoparathyroidism.

11. DOSAGE FORM: Lyophilized Powder for Injection.

12. STRENGTH/POTENCY: 25, 50, 75 and 100 mcg per 71.4 µL.

13. ROUTE OF ADMINISTRATION: Subcutaneous Injection.

14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

Not a SPOTS product

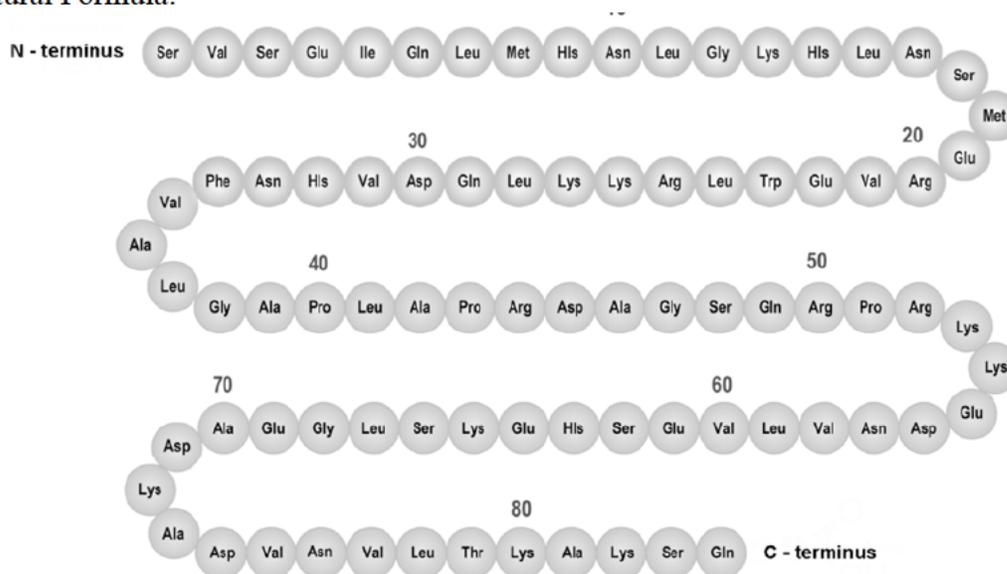
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name:

L-seryl- L-valyl- L-seryl- L-glutamyl- L-isoleucyl- L-glutamyl- L-leucyl- L-methionyl- L-histidyl- L-asparaginy- L-leucyl- glycy- L-lysyl- L-histidyl- L-leucyl- L-asparaginy- L-seryl- L-methionyl- L-glutamyl- L-arginyl- L-valyl- L-glutamyl- L-tryptophyl- L-leucyl- L-arginyl- L-lysyl- L-lysyl- L-leucyl- L-glutamyl- L-aspartyl- L-valyl- L-histidyl- L-asparaginy- L-phenylalanyl- L-valyl- L-alanyl- L-leucyl-glycy- L-alanyl- L-prolyl- L-leucyl- L-alanyl- L-prolyl- L-arginyl- L-aspartyl- L-alanyl- glycy- L-seryl- L-glutamyl- L-arginyl- L-prolyl- L-arginyl- L-lysyl- L-lysyl- L-glutamyl- L-aspartyl- L-asparaginy- L-valyl- L-leucyl- L-valyl- L-glutamyl- L-seryl- L-histidyl- L-glutamyl- L-lysyl- L-seryl- L-leucyl- glycy- L-glutamyl- L-alanyl- L-aspartyl- L-lysyl- L-alanyl- L-aspartyl- L-valyl- L-asparaginy- L-valyl- L-leucyl- L-threonyl- L-lysyl- L-alanyl- L-lysyl- L-seryl- L-glutamine

Chemistry Review Data Sheet

Structural Formula:



Molecular Formula: $C_{408}H_{674}N_{126}O_{126}S_2$

Molecular Weight: 9424.77 Da

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code ¹	Status ²	Date Review Completed
(b) (4)	III	(b) (4)	(b) (4)	1	Adequate	14-Nov-2013 by C. Evans
(b) (4)	III	(b) (4)	(b) (4)	1	Adequate	28-Jan-2011 by Y. Lu

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	76514	rhPTH(1-84) injection; recombinant parathyroid hormone.

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending.		N/A
Pharm/Tox	Not required for protein product. Limits on impurities will be based on batch release data of clinical and toxicology batches.		
Biopharm	Not applicable. This is an injectable product, and the commercial formulation was used in Phase 3 studies.		
Methods Validation	Not required. No novel methods.		
EA	Conducted by CMC reviewers.	06/27/2014	M. Ramaswamy, J. Leginus
Microbiology	Drug Substance: Preservative effectiveness, sterility, endotoxins, and container closure integrity will be reviewed by the Biotech Manufacturing Assessment Branch (BMAB) in Compliance.	Pending	C. Thomas
	Drug Product	Pending	J. Cole

19. ORDER OF REVIEW: N/A

The Chemistry Review for BLA 125511

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The recommendation from a CMC perspective is Approval, pending:

A recommendation from the Office of Compliance, Biotech Manufacturing Branch currently pending.

Assessments of the acceptability of microbiology information regarding sterility assurance of the drug substance and drug product currently pending.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not applicable.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

DRUG SUBSTANCE

The drug substance, recombinant human parathyroid hormone 1-84 (rhPTH (1-84)) is a single-chain protein with 84 amino acids [REDACTED] (b) (4). The molecular formula for this protein is C₄₀₈H₆₇₄N₁₂₆O₁₂₆S₂ and the molecular weight is 9424.8 Da. The amino acid sequence of the rhPTH (1-84) is identical to endogenous human parathyroid hormone. The primary sequence of the rhPTH is shown below.

[REDACTED] (b) (4)

The rhPTH (1-84) is overexpressed in a modified strain of *E. coli* [REDACTED] (b) (4)

[REDACTED]

Executive Summary Section

A two-tiered cell banking system (MCB and WCB) is proposed to support the PTH manufacturing process. Master and working cells from cell banks were characterized using appropriate test methods including culture purity, viability, phenotypic characteristics, bacteriophage test, plasmid DNA sequence, plasmid stability, plasmid identity, plasmid copy number. End of the production cells from representative production scale batches were tested by the same test methods.

The drug substance is a clear, colorless to light straw colored liquid and contains (b) (4) rhPTH(1-84) in (b) (4) citrate buffer and (b) (4) sodium chloride, pH (b) (4). The size, charge, primary, secondary, and tertiary structure, aggregation properties and biological activity of recombinant PTH were elucidated by a variety of analytical techniques. Such studies include amino acid analysis, N-terminal amino acid sequencing, peptide mapping, mass spectrometry (MALDI-TOF MS), circular dichroism (CD), ultraviolet (UV), dynamic light scattering, analytical ultracentrifugation, reverse phase (RP HPLC) and cation exchange (CEX) chromatography and high performance size exclusion chromatography (HPSEC).

Product related substances and product related impurities that arise by chemical or physical degradation of rhPTH(1-84), (b) (4) were characterized (b) (4). Specific product-related impurities (b) (4) are routinely measured in PTH drug substance as part of release testing. (b) (4). Process related impurities (endotoxin, bioburden, (b) (4)) are measured using appropriate analytical methods.

(b) (4)

The proposed reference standard for releasing the commercial and stability batches was produced from a commercial scale batch. The current rhPTH(1-84) Reference Standard (Batch No. 11PSA01) was qualified against current release specifications.

The proposed release specifications include appearance, identification (peptide mapping and HPLC), assay/peptide content (HPLC), bioactivity (cell-based assay), individual peptide related impurities (RP HPLC, cation exchange (CEX) and size exclusion chromatography (SEC), (b) (4) bioburden, and bacterial endotoxin. The proposed drug substance specifications are based on significant manufacturing experience with the process that includes manufacturing of 18 commercial scale batches at the proposed commercial site (BI RCV, Vienna). The proposed regulatory methods have been validated. Reference standards for the API have been developed and characterized. The biological activity of rhPTH is based on the principle that binding of PTH to its receptor stimulates adenylate cyclase activity in UMR-106 rat osteosarcoma cells. (b) (4)

A shelf life of (b) (4) months will be granted for the drug substance when stored at (b) (4) °C or lower temperatures. This is based on acceptable long-term stability results from real-time stability studies from Primary Stability batches at production scale and consistent with principles outlined under ICH Q5C ("Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products").

DRUG PRODUCT

Natpara for injection is a lyophilized formulation of recombinant human parathyroid hormone rhPTH(1-84) for subcutaneous administration supplied in a disposable multiple-dose dual-

Executive Summary Section

chamber glass cartridge where one chamber contains a sterile lyophilized powder consisting of recombinant human parathyroid hormone and compendial excipients. The other chamber, separated by a rubber septum, contains the sterile diluent for reconstitution (aqueous metacresol). There are four dosage strengths: 25, 50, 75, and 100 µg/dose, each differing only by the amount of drug substance in their formulations.

The Natpara drug product is designed specifically to be used with the Natpara® Mixing Device for reconstitution and the Natpara® Reusable Pen for subcutaneous injection. The glass cartridge is packaged within a disposable plastic cartridge holder, which is designed for attachment to the Natpara Mixing Device. The Mixing Device is used to reconstitute the drug product by mixing the diluent in one chamber with the lyophilized drug product in the other. After reconstitution, the cartridge holder is unscrewed from the Mixing Device and screwed onto the reusable pen injector base where it is readied for use. All three items (cartridge/holder, mixing device, pen injector) are packaged separately.

Cartridges are designed to deliver 14 doses of 74.1 µL per dose at four rhPTH(1-84) strengths. Cartridge holders for each of the four strengths are distinguished from each other by colors and labeled dosage strength (25 mcg/dose – purple; 50 mcg/dose – red; 75 mcg/dose – gray; 100 mcg/dose – dark blue).

The manufacturing process of the drug product is the standard common process for this type of dosage form: (b) (4) and lyophilization. During development, the primary change in the formulation involved moving (b) (4) to the multiple dose dual-chamber cartridge that includes both the lyophilized powder and the diluent required for reconstitution.

The drug product specifications includes standard tests for biological products, such as appearance, identity, PTH(1-84) assay/peptide content, uniformity of dosage forms (content uniformity), PTH biological activity, (b) (4), impurities, sterility, m-cresol content, container closure integrity, endotoxins, pH, particulate matter, reconstitution time, extractable volume, opalescence, and osmolality. Testing also includes an assessment of appearance, opalescence, and particulate matter for each lot of reconstituted solution after a 14 day use period. The analytical procedures have been properly described and the proposed regulatory methods have been validated.

Batch release data for 65 commercial drug product batches produced at commercial scale at the commercial site using the commercial process show that the drug product meets the specifications proposed.

The primary container closure system for the drug product consists of a clear, colorless 1 mL Type 1 glass dual-chamber cartridge, 2 rubber stoppers and an aluminum crimp cap containing a rubber septum. The same glass cartridge is used for all four strengths. The secondary packaging is a disposable plastic cartridge holder that the dual-chamber glass cartridge is inserted. The holder has threaded fittings at each end that allows it to be interfaced with the Natpara® Mixing Device (for reconstitution) and the Natpara® Reusable Pen injector (for drug delivery).

Results from stability studies show that prior to reconstitution, the drug product for each of the four dosage strength remains stable through a) a minimum of 24 months at the long-term storage condition of 5°C ± 3°C, and b) 6 months at the accelerated condition of 25°C ± 2°C. Based on

Executive Summary Section

these data, and following the recommendations outlined in ICH Q5C (“Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products”), a shelf-life of 24 months is granted for Natpara drug product 25, 50, 75, and 100 mcg/dose when stored at 5°C ± 3°C.

The reconstituted Natpara Drug Product solution has been demonstrated to be stable for up to 27 days when stored at 2°C to 8°C, with daily exposure to room temperature (up to 25°C) for 40 to 60 minutes, which supports its in-use period of 14 days. (b) (4)

Due to findings in the photostability study, labeling will include a statement that the product should be kept in its secondary package during storage and when not in use in order to minimize its exposure to light.

B. Description of How the Drug Product is Intended to be Used

Natpara® (rhPTH[1-84]) for injection is a replacement for endogenous parathyroid hormone (1-84) indicated for the long-term treatment of hypoparathyroidism. Hypoparathyroidism is a rare condition where the body secretes abnormally low levels of parathyroid hormone. This hormone is involved in regulating and maintaining a balance of calcium and phosphorus. The low production of parathyroid hormone in leads to abnormally low ionized calcium and increased phosphorus levels in blood and bones.

Natpara is self-administered once daily by subcutaneous injection into alternating thighs. The recommended starting dose is 50 µg. Natpara can be titrated at approximately 2 to 4 week intervals upward to doses of 75 µg and then 100 µg.

C. Basis for Approvability or Not-Approval Recommendation

From CMC perspective, BLA is recommended for approval. All chemistry related issues are satisfactorily resolved at this stage.

At this time, the following items are pending:

- Office of Compliance has not issued an acceptable cGMP recommendation for the manufacturing facilities.
- Assessments of the acceptability of microbiological control information (bioburden, endotoxin control, sterility assurance) for the drug substance manufacturing process from Biotech Manufacturing and Assessment Branch, (BMAB) is not complete at this time.

Assessments of the acceptability of microbiological control information (bioburden, endotoxin control, sterility assurance) for the drug product manufacturing process and controls from the OPS microbiology reviewer is not complete at this time.

An Inspection Waiver Memo (5/15/2014) for the drug substance manufacturing facility located at Boehringer Ingelheim RCV GmbH & Co KG, Dr. Boehringer-Gasse 5 – 11, A-1121 Vienna, Austria (FDA Establishment ID: 3003433722) was approved in DARRTS on 6/11/14. The waiver was based on the premise that the manufacturing site was inspected by CDER from (b) (4) and classified NAI. This was a PLI and GMP inspection for (b) (4)

Executive Summary Section

(b) (4) covering biotech drug substance manufacturing operations. The CBI and TRP profiles were updated and are acceptable.

The Inspection Waiver Memo (5/15/2014) for the drug product recommended that the pre-approval inspection of the Vetter Pharma-Fertigung GmbH & Co. KG, Schützenstrasse, Ravensburg, Germany (FEI 3002270322) which manufactures the Natpara multi-dose dual-chamber syringe be waived. The Vetter Pharma-Fertigung GmbH & Co. KG, Schützenstrasse site was inspected by IOG (International Operations Group) from 10/29/2012 to 11/9/2012 and classified VAI (Voluntary Action Indicated). This was a routine GMP surveillance inspection covering sterile drug product manufacturing operations. The BTP (Biologic Therapeutic Product), SVS (Sterile-filled Small Volume Parenteral), and SVL (Small Volume Parenteral - Lyophilized) profiles were updated and are acceptable.

This BLA is submitted as a 351(a) application. In 2007, the FDA granted Orphan Drug Designation for rhPTH(1-84) for the treatment of hypoparathyroidism. IND 76514 for rhPTH (1-84) injection was received on 9/19/2008. A pre-BLA meeting was held on 5/15/2012. The original BLA was submitted on 10/23/2013.

The drug substance (rhPTH(1-84)) will be manufactured at (b) (4) scale by Boehringer Ingelheim RCV GmbH & Co KG located in Vienna, Austria. Commercial scale batches manufactured at BI RCV were used for phase 3 clinical studies and primary stability studies. The applicant has also provided data to support the comparability of clinical batches manufactured (b) (4) scale (SynCo, Netherlands) and the current commercial process (BIRCV, Austria). The process at the commercial manufacturing site has been validated originally in 2004 and recently in 2012.

The drug product, Natpara for injection will be manufactured by Vetter Pharma-Fertigung GmbH & Co. KG located in Ravensburg Germany. The drug product will be available in a multi-use, disposable pen injector for delivery of 25, 50, 75, and 100 µg per injection.

The commercial process was used to produce all drug product batches reported in the BLA (used for phase 3 clinical studies and primary stability studies). The commercial process validation was completed for the 100 µg dosage strength. The same process is used for the other three strengths and per agreement by FDA at the Pre-BLA meeting. The revalidation will be ongoing during the BLA review.

All methods for release testing of the drug product have been adequately described and are validated. The selected parameters tested on drug product have been adequately justified and are considered acceptable. Sufficient batch analysis results confirm the consistency of the drug product. No new impurities are formed during the manufacture of the drug product and the purity profile of the drug product is comparable to that of the drug substance. The proposed limits are considered acceptable.

Stability of the drug product has been adequately established in the primary container closure system (disposable multiple-dose dual-chamber glass cartridges) to grant a shelf-life (prior to reconstitution) of 24 months when stored at refrigerated conditions, and 14 days (post-reconstitution) when used according to the labeled in-use instructions.

Executive Summary Section

The risk associated with Natpara® appears to be low with respect to the drug. With the exception of the pen-injector, Natpara® is the same drug-device combination product as Preos® (NDA (b) (4)) intended for the treatment of postmenopausal women with osteoporosis. (b) (4)

however, on 3/24/2011, the Applicant withdrew this NDA and re-focused their developmental efforts for the use of rhPTH (1-84) as a hormone replacement therapy in subjects with hypoparathyroidism as described in the current BLA 125511. In addition, Preos® (labeled as Preotact) has been commercially available in Europe following its approval by the EMEA in April 2006.

III. Administrative

- A. Reviewer's Signature:** in DARRTS
- B. Endorsement Block:** in DARRTS
- C. CC Block:** in DARRTS

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

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

/s/

JOSEPH LEGINUS

06/27/2014

MUTHUKUMAR RAMASWAMY

06/27/2014

DANAE D CHRISTODOULOU

06/27/2014

I concur with the reviewers' conclusion and recommendation

**Determining When Pre-License / Pre-Approval Inspections are Necessary
Inspection Waiver Memorandum**

Date: 15 April 2014

From: Colleen Thomas, Ph.D., OC/OMPQ/DGMPA/BMAB
Muthukumar Ramaswamy, Ph.D., OPS/ONDQA/DNDQAIII/BRVII

To: BLA File, STN 125511/0

Endorsed: Patricia F. Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMPA/BMAB

Subject: Recommendation to waive a drug substance pre-license inspection.

Applicant: NPS Pharmaceuticals

Facility: Boehringer Ingelheim RCV GmbH & Co KG
Dr. Boehringer Gasse 5-11
A-1121 Vienna, Austria
FEI: 3003433722

Product: Natpara® (recombinant parathyroid hormone)

Dosage: 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.

Indication: Treatment of hypoparathyroidism

Waiver Recommendation

We recommend that the pre-approval inspection of Boehringer Ingelheim in Vienna, Austria (FEI: 3003433722) which manufactures Natpara drug substance be waived. The site was inspected by CDER from [REDACTED] (b) (4) and classified NAI. This was a PLI and GMP inspection for [REDACTED] (b) (4) covering biotech drug substance manufacturing operations. The CBI and TRP profiles were updated and are acceptable.

Summary

BLA 125511 was submitted on 22 April 2013 to license Natpara for treatment of patients with hypoparathyroidism. The recombinant parathyroid hormone present in Natpara is identical in structure to endogenous human parathyroid hormone. The drug substance is produced in a recombinant *E. coli* strain [REDACTED] (b) (4). The drug substance is manufactured at the Boehringer Ingelheim site located in Vienna, Austria (BI Pharma). 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. The drug product is manufactured by [REDACTED] (b) (4) at the Vetter Pharma site located in Ravensburg, Germany.

Facility Information

Natpara drug substance is manufactured by BI Pharma (FEI: 3003433722). The BI Pharma site manufactures products for Boehringer Ingelheim International GmbH and also provides GMP contract manufacturing services. The site is designed and licensed for multi-product cGMP manufacturing. BI Pharma uses facility and equipment design features, operating procedures, in process controls, training, and changeover to prevent contamination and cross-contamination. Products manufactured at the site include (b) (4)

The following information is provided in support of waiving the pre-approval inspection:

1. *The manufacturer does not hold an active U.S. license, or in the case of a contract manufacturer, is not approved for use in manufacturing a licensed product.*
 - a. The BI Pharma site (FEI: 3003433722) will manufacture Natpara drug substance which is the subject of BLA 125511 that is currently under review at the Agency.
 - b. The facility is licensed for manufacturing licensed products such as (b) (4) and Kineret.
2. *FDA has not inspected the establishment in the last 2 years.*

The BI Pharma site was inspected by CDER from (b) (4) and classified NAI. This was a PLI and GMP inspection for (b) (4) covering biotech drug substance manufacturing operations. The CBI and TRP profiles were updated and are acceptable.
3. *The previous inspection revealed significant GMP deficiencies in areas related to the processes in the submission (similar processes) or systematic problems, such as QC/QA oversight.*

The previous inspection was conducted by CDER from 22-26 April 2013. The inspection was a PLI for transfer of Kineret drug substance manufacturing to BI Pharma (PAS 103950/5148) and a GMP surveillance inspection. The inspection was classified VAI and acceptable for the TRP and CBI profiles.
4. *The establishment is performing significant manufacturing step(s) in new (unlicensed) areas using different equipment (representing a process change). This would include areas that are currently dedicated areas that have not been approved as multi-product facilities/buildings/areas.*

The BI Pharma site is approved to manufacture multiple products. The most recent inspection covered the TRP and CBI profiles.
5. *The manufacturing process is sufficiently different (new production methods, specialized equipment or facilities) from that of other approved products produced by the establishment. Point to consider:*

The Natpara drug substance manufacturing process is similar to that for other drug substances manufactured in the same facility.

Signatures:

Colleen Thomas, Ph.D., OC/OMPQ/DGMPA/BMAB

Muthukumar Ramaswamy, Ph.D., OPS/ONDQA/DNDQAI/BRVII

Clearance Routing

Danae Christodoulou, Ph.D., Branch Chief, Division of New Drug Quality Assessment III, Office of New Drug Quality Assessment, Office of Pharmaceutical Science, CDER

David Doleski,
Director, Division of Good Manufacturing Practice Assessment,
Office of Manufacturing and Product Quality, Office of Compliance, CDER

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/s/

COLLEEN THOMAS
04/15/2014

PATRICIA F HUGHES TROOST
04/15/2014

MUTHUKUMAR RAMASWAMY
04/15/2014

DANAE D CHRISTODOULOU
04/24/2014

JOSEPH D DOLESKI
06/11/2014

**Determining When Pre-License / Pre-Approval Inspections are Necessary
Inspection Waiver Memorandum**

Date: 15 April 2014

From: Colleen Thomas, Ph.D., OC/OMPQ/DGMPA/BMAB
Jessica Cole, Ph.D., OPS/NDMS
Joseph Leginus, Ph.D., OPS/ONDQA/DNDQAI/BrVII

To: BLA File, STN 125511/0

Endorsed: Patricia F. Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMPA/BMAB

Subject: Recommendation to waive a drug product pre-license inspection.

Applicant: NPS Pharmaceuticals

Facility: Vetter Pharma-Fertigung GmbH & Co. KG
Schützenstrasse 87, 99-101
88212 Ravensburg, Germany
FEI: 3002270322

Product: Natpara® (recombinant parathyroid hormone)

Dosage: 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.

Indication: Treatment of hypoparathyroidism

Waiver Recommendation

We recommend that the pre-approval inspection of the Vetter Pharma-Fertigung GmbH & Co. KG, Schützenstrasse, Ravensburg, Germany (FEI 3002270322) which manufactures the Natpara multi-dose dual-chamber syringe be waived. The Vetter Pharma-Fertigung GmbH & Co. KG, Schützenstrasse site was inspected by IOG from [REDACTED] (b) (4) and classified VAI. This was a routine GMP surveillance inspection covering sterile drug product manufacturing operations. The BTP, SVS, and SVL profiles were updated and are acceptable.

Summary

BLA 125511 was submitted on 22 April 2013 to license Natpara for treatment of patients with hypoparathyroidism. The recombinant parathyroid hormone present in Natpara is identical in structure to endogenous human parathyroid hormone. The drug substance is produced in a recombinant *E. coli* strain [REDACTED] (b) (4). The drug substance is manufactured at the Boehringer Ingelheim site located in Vienna, Austria. 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. The drug product is manufactured by [REDACTED] (b) (4) at the Vetter Pharma site located in Ravensburg, Germany.

Facility Information

Natpara drug product is manufactured under contract by Vetter Pharma. The Vetter manufacturing facilities are designed and licensed for multi-product cGMP manufacturing. Vetter uses facility and equipment design features, operating procedures, in process controls, training, and changeover to prevent contamination and cross-contamination. (b) (4)

The following information is provided in support of waiving the pre-approval inspection:

1. *The manufacturer does not hold an active U.S. license, or in the case of a contract manufacturer, is not approved for use in manufacturing a licensed product.*
 - a. The Vetter Pharma site (FEI 3002270322) will manufacture Natpara drug product which is the subject of BLA 125511 that is currently under review at the Agency.
 - b. The facility is licensed for manufacturing licensed products such as (b) (4)
2. *FDA has not inspected the establishment in the last 2 years.*

The Vetter Pharma site was inspected by IOG from (b) (4) and classified VAI. This was a GMP surveillance inspection covering sterile drug product manufacturing operations. The BTP, SVS, and SVL profiles were updated and are acceptable.
3. *The previous inspection revealed significant GMP deficiencies in areas related to the processes in the submission (similar processes) or systematic problems, such as QC/QA oversight.*

A pre-approval inspection of Vetter Pharma was conducted by IOG from 10-17 April 2012 for NDA 203684. The inspection was classified VAI and acceptable for profiles BTP, SVS, and SVL.
4. *The establishment is performing significant manufacturing step(s) in new (unlicensed) areas using different equipment (representing a process change). This would include areas that are currently dedicated areas that have not been approved as multi-product facilities/buildings/areas.*

The Vetter Pharma site is approved to manufacture multiple products. The most recent inspection covered the BTP, SVS, and SVL profiles.
5. *The manufacturing process is sufficiently different (new production methods, specialized equipment or facilities) from that of other approved products produced by the establishment. Point to consider:*

The Natpara drug product manufacturing process is similar to that for other products manufactured in the same facility.

Signatures:

Colleen Thomas, Ph.D., OC/OMPQ/DGMPA/BMAB

Jessica Cole, Ph.D., OPS/NDMS

Joseph Leginus, Ph.D., OPS/ONDQA/DNDQA III/Branch VII

Clearance Routing

Bryan Riley, Ph.D., Team Leader (Acting), New Drug Microbiology Staff, Office of Pharmaceutical Science, CDER

Danae Christodoulou, Ph.D., Branch Chief, Division of New Drug Quality Assessment III, Office of New Drug Quality Assessment, Office of Pharmaceutical Science, CDER

David Doleski,
Director, Division of Good Manufacturing Practice Assessment,
Office of Manufacturing and Product Quality, Office of Compliance, CDER

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/s/

COLLEEN THOMAS
04/15/2014

PATRICIA F HUGHES TROOST
04/15/2014

JESSICA COLE
04/15/2014

JOSEPH LEGINUS
04/15/2014

BRYAN S RILEY
04/21/2014
I concur.

DANAE D CHRISTODOULOU
04/24/2014

JOSEPH D DOLESKI
06/11/2014

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.0

Instructions:

The review team should email this form to the email account “CDER-TB-EER” to submit:

- 1) an initial TB-EER within 10 business days of the application filing date
- 2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing¹ locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA/BsUFA Action Date: October 24, 2014

Applicant Name: NPS Pharmaceuticals Inc.

U.S. License #:

STN(s): 125511-original

Product(s): Natpara® (recombinant human parathyroid hormone [rDNA]) Injection

Short summary of application: On October 24, 2013, NPS Pharmaceuticals submitted a BLA. This BLA is for a Recombinant Human Parathyroid Hormone (rDNA).

FACILITY INFORMATION

Manufacturing Location:

Firm Name:

Address:

FEI:

Short summary of manufacturing activities performed: Manufacturing and Release of Natpara Mixing Device.

There is no FDA inspectional history for this site. BMAB (with the input of OBP) will determine whether this site requires a PLI for this BLA. Please resubmit this TB-

¹The regulations at 21 C.F.R. § 207.3(a)(8) defines “manufacturing or processing” as “the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer.”

EER 15-30 days prior to the planned action date for an updated compliance evaluation of this site.

Manufacturing Location: Austria
 Firm Name: Boehringer Ingelheim RCV GmbH & Co KG
 Address: Dr. Boehringer-Gasse 5-11
 Vienna, Austria
 FEI: 3003433722

Short summary of manufacturing activities performed: (b) (4)

This site was inspected by CDER from (b) (4) and is not yet classified. This was a PLI and a routine CGMP surveillance inspection covering biotech drug substance manufacturing operations. **BMAB (with the input of OBP) will determine whether this site requires a PLI for this BLA.** Please resubmit this TB-EER 15-30 days prior to the planned action date for an updated compliance evaluation of this site.

Manufacturing Location: (b) (4)
 Firm Name: (b) (4)
 Address: (b) (4)

FEI: (b) (4)
 Short summary of manufacturing activities performed: (b) (4)

This site was inspected by (b) (4)-DO from (b) (4) and classified NAI. This was a routine CGMP surveillance inspection covering biotech drug testing operations. The CTL profile was updated and is acceptable.

Manufacturing Location: (b) (4)
 Firm Name: (b) (4)
 Address: (b) (4)

FEI: (b) (4)
 Short summary of manufacturing activities performed: (b) (4)

This site was inspected by IOG from (b) (4) and classified VAI. This was a routine CGMP surveillance inspection covering biotech drug testing operations. The CTL profile was updated and is acceptable.

Manufacturing Location:
Firm Name:
Address:

(b) (4)

FEI:

Short summary of manufacturing activities performed:

(b) (4)

This site was inspected by (b) (4) -DO from (b) (4) and classified NAI. This was a routine CGMP surveillance inspection covering drug substance testing operations. The CTL profile was updated and is acceptable.

Manufacturing Location:
Firm Name:
Address:

(b) (4)

FEI:

Short summary of manufacturing activities performed:

(b) (4)

This site was inspected by IOG from (b) (4) and classified VAI. This was a routine CGMP surveillance inspection covering drug testing operations. The CTL profile was updated and is acceptable.

Manufacturing Location:
Firm Name:
Address:

(b) (4)

FEI:

Short summary of manufacturing activities performed:

(b) (4)

There is no FDA inspectional history for this site. **BMAB (with the input of OBP) will determine whether this site requires a PLI for this BLA.** Please resubmit this TB-EER 15-30 days prior to the planned action date for an updated compliance evaluation of this site.

Manufacturing Location: Bedminster, NJ
Firm Name: NPS Pharmaceuticals, Inc.

Address: 550 Hills Drive, 3rd Floor
Bedminster, NJ 07921

FEI: 3009694025

Short summary of manufacturing activities performed: Quality Assurance (QA) and final release of WCB and MCB; QA and final release of rhPTH (1-84) Drug substance for use in manufacture of Natpara Drug Product; QA and final release of drug product.

This site was inspected by NWJ-DO from November 15 – December 4, 2012 and classified VAI. This was the first FDA inspection of this facility, and did not offer CGMP coverage. **BMAB (with the input of OBP) will determine whether this site requires a PLI for this BLA.** Please resubmit this TB-EER 15-30 days prior to the planned action date for an updated compliance evaluation of this site.

In addition, CDRH has indicated that this site should be subjected to a device inspection due to lack of device inspectional history. A FACTS assignment request has been created (FACTS assignment number 8743373). Please resubmit this TB-EER 15-30 days prior to the planned action date for an updated compliance evaluation of this site.

Manufacturing Location: Ravensburg, Germany
Firm Name: Vetter Pharma-Fertigung GmbH & Co. KG
Address: Schutzenstrasse 87, 99-101, 88212
Ravensburg, Germany
FEI: 3002270322

Short summary of manufacturing activities performed: Manufacture and primary packaging of drug product; Quality control testing during production of drug product; Visual inspection of drug product; Release testing of drug product.

This site was inspected by IOG from [REDACTED] ^{(b) (4)} and classified VAI. This was a routine CGMP surveillance inspection covering sterile drug product manufacturing and testing operations. The BTP and SVL profiles were updated and are acceptable. **BMAB (with the input of OBP) will determine whether this site requires a PLI for this BLA.** Please resubmit this TB-EER 15-30 days prior to the planned action date for an updated compliance evaluation of this site.

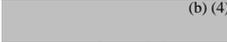
Manufacturing Location: Ravensburg, Germany
Firm Name: Vetter Pharma-Fertigung GmbH & Co. KG
Address: Holbeinstrasse 40, 88212
Ravensburg, Germany
FEI: 3002270322

Short summary of manufacturing activities performed: Visual inspection of drug product; Storage of drug product.

This site was inspected by IOG from [REDACTED] ^{(b) (4)} and classified VAI. This was a routine CGMP surveillance inspection covering sterile drug product manufacturing and testing operations. The BTP and SVL profiles were updated and are acceptable.

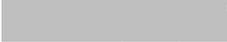
Manufacturing Location: Langenargen, Germany
 Firm Name: Vetter Pharma-Fertigung GmbH & Co. KG
 Address: Eisenbahnstrasse 2-4, 88085
 Langenargen, Germany
 FEI: 3002808846

Short summary of manufacturing activities performed: Quality control testing during production of drug product; Visual inspection of drug product; Release testing of drug product.

This site was inspected by IOG from ^{(b) (4)} and classified NAI. This was a routine CGMP surveillance inspection covering biotech drug product manufacturing and testing operations. The SVL profile was updated and is acceptable.

Manufacturing Location: Ravensburg, Germany
 Firm Name: Vetter Pharma-Fertigung GmbH & Co. KG
 Address: Helmut-Vetter-Str. 10, 88213
 Ravensburg, Germany
 FEI: 3009560142

Short summary of manufacturing activities performed: Visual inspection of drug product; Storage of drug product.

This site was inspected by IOG from ^{(b) (4)} and classified NAI. This was a routine CGMP surveillance inspection covering drug product testing and storage operations. The CTL profile was updated and is acceptable.

Manufacturing Location: Ravensburg, Germany
 Firm Name: Vetter Pharma-Fertigung GmbH & Co. KG
 Address: Mooswiesen 2, 88214
 Ravensburg, Germany
 FEI: 3005987757

Short summary of manufacturing activities performed: Quality control testing during production of drug product; Visual inspection of drug product; Release testing.

This site was inspected by IOG from ^{(b) (4)} and classified NAI. This was a routine CGMP surveillance inspection covering biotech drug product testing operations. The SVL profile was updated and is acceptable.

Manufacturing Location: ^{(b) (4)}
 Firm Name: 
 Address: 
 FEI: 

Short summary of manufacturing activities performed: Secondary Packaging, labeling, storage and shipping of drug product

This site was inspected by (b) (4) -DO from (b) (4) and classified NAI. This was a routine CGMP surveillance inspection covering drug packaging operations. The SVL profile (repacks only) was updated and is acceptable.

Manufacturing Location: (b) (4)
 Firm Name:
 Address:

FEI:

Short summary of manufacturing activities performed: Release testing of drug product; Stability testing of drug product (only container closure integrity test).

This site was inspected by (b) (4) -DO from (b) (4) and classified NAI. This was a routine CGMP surveillance inspection covering drug testing operations. The CTL profile was updated and is acceptable.

Manufacturing Location: (b) (4)
 Firm Name:
 Address:

FEI:

Short summary of manufacturing activities performed: Manufacturing and release of Cartridge holder and Natpara Reusable pen.

There is no FDA inspectional history for this site. **BMAB (with the input of OBP) will determine whether this site requires a PLI for this BLA.** Please resubmit this TB-EER 15-30 days prior to the planned action date for an updated compliance evaluation of this site.

OVERALL RECOMMENDATIONS:

Please resubmit this TB-EER 15-30 days prior to the planned action date for an updated compliance evaluation.

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/s/

RANJANI PRABHAKARA
01/16/2014

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA**

BLA Number: 125511

**Applicant:
NPS Pharmaceuticals Inc.**

Stamp Date: 24-OCT-2013

Established/Proper Name: Parathyroid hormone
BLA Type: 1

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 <input type="checkbox"/> including list of all establishment sites and their registration numbers	Y Y	
Comprehensive Table of Contents	Y N	n/a This is an electronic application
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y	
Labeling: <input type="checkbox"/> PI –non-annotated <input type="checkbox"/> PI –annotated <input type="checkbox"/> PI (electronic) <input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Insert <input type="checkbox"/> package and container <input type="checkbox"/> diluent <input type="checkbox"/> other components <input type="checkbox"/> established name (e.g. USAN) <input type="checkbox"/> proprietary name (for review)	Y Y Y Y Y Y Y N Y N Y Y	 n/a Co-packaged diluent in same cartridge n/a

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 guidance)	Y Y Y Y Y Y	
Companion application received if a shared or divided manufacturing	Y N	n/a

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA**

Examples of Filing Issues	Yes?	If not, justification, action & status
arrangement		

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y N	n/a This is an electronic application
Introduction to the summary documents (1 page) [2.2]	Y	
Quality overall summary [2.3]	Y	n/a
<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	
<input type="checkbox"/> Executed Batch Records	Y	
<input type="checkbox"/> Method Validation Package	Y	
<input type="checkbox"/> Comparability Protocols	Y	

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	Y	
Drug Substance [3.2.S]	Y	
<input type="checkbox"/> general info	Y	
<input type="checkbox"/> nomenclature	Y	
<input type="checkbox"/> structure (e.g. sequence, glycosylation sites)	Y	
<input type="checkbox"/> properties	Y	
<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	Y	
<input type="checkbox"/> cell culture and harvest	Y	
<input type="checkbox"/> purification	Y	
<input type="checkbox"/> filling, storage and shipping	Y	
<input type="checkbox"/> control of materials	Y	
<input type="checkbox"/> raw materials and reagents	Y	
<input type="checkbox"/> biological source and starting materials	Y	
<input type="checkbox"/> cell substrate: source, history, and generation	Y	
<input type="checkbox"/> cell banking system, characterization, and testing	Y	
<input type="checkbox"/> control of critical steps and intermediates	Y	

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA**

CTD Module 3 Contents	Present?	If not, justification, action & status
<p>contract] facilities)</p> <ul style="list-style-type: none"> <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 and sterilization validation <input type="checkbox"/> Validation of aseptic processing (media simulations) <input type="checkbox"/> Environmental Monitoring Program <input type="checkbox"/> Lyophilizer sterilization validation <input type="checkbox"/> Other needed validation data (hold times) <input type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients) <input type="checkbox"/> control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities) <input type="checkbox"/> reference standards <input type="checkbox"/> container closure system <ul style="list-style-type: none"> <input type="checkbox"/> specifications (vial, elastomer, drawings) <input type="checkbox"/> availability of DMF & LOAs <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 		
<p>Other components to be marketed (full description and supporting data, as listed above):</p> <ul style="list-style-type: none"> <input type="checkbox"/> other devices <input type="checkbox"/> other marketed chemicals (e.g. part of kit) 	<p>Y</p> <p>Y</p>	<p>Pen injector</p>

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA**

Examples of Filing Issues	Yes?	If not, justification, action & status
trial to commercial production lots		
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	
Certification that all facilities are ready for inspection	Y	
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 Y Y	n/a No viral component used
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	
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y	
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y	

Additional information:

Trade or Proprietary Name:	Natpara (proposed)
Established or Non-Proprietary Name (USAN):	Parathyroid hormone
Dosage Form:	Powder for reconstitution as injectable solution
Route of Administration	Subcutaneous injection
Strength/Potency	25, 50, 75, and 100 mcg/dose
Rx/OTC Dispensed:	Rx

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA**

Natpara Drug Product is a combination product designed specifically to be used with the Natpara[®] Mixing Device for reconstitution, and the Natpara[®] Reusable Pen for subcutaneous injection.

The Natpara Drug Product is a lyophilized formulation consisting of recombinant human parathyroid hormone, rhPTH(1-84), formulated with various excipients. The drug product is manufactured into a disposable multiple dose glass dual-chamber cartridge (see [Figure 3.2.P.7-1](#)), provided in 4 dosage strengths 25, 50, 75, and 100 mcg/dose.

The cartridge is designed for use with a reusable mixing device for product reconstitution and a reusable pen for drug delivery. The Natpara[®] Reusable Pen is designed to deliver 14 doses of a fixed volumetric dose targeted at 71.4 µL.

Table 2.3.S.1-1 Nomenclature

Product Name	Parathyroid Hormone (1-84) Human Recombinant
INN/USAN/BAN/JAN	Parathyroid Hormone (1-84) human
Compendial Name	Not applicable
Chemical Name	Parathormone (human recombinant), parathyrin
Amino Acid Sequence	L-seryl- L-valyl- L-seryl- L-glutamyl- L-isoleucyl- L-glutaminy- L-leucyl- L-methionyl- L-histidyl- L-asparaginy- L-leucyl- glycy- L-lysyl- L-histidyl- L-leucyl- L-asparaginy- L-seryl- L-methionyl- L-glutamyl- L-arginyl- L-valyl- L-glutamyl- L-tryptophyl- L-leucyl- L-arginyl- L-lysyl- L-lysyl- L-leucyl- L-glutaminy- L-aspartyl- L-valyl- L-histidyl- L-asparaginy- L-phenylalanyl- L-valyl- L-alanyl- L-leucyl-glycy- L-alanyl- L-prolyl- L-leucyl- L-alanyl- L-prolyl- L-arginyl- L-aspartyl- L-alanyl- glycy- L-seryl- L-glutaminy- L-arginyl- L-prolyl- L-arginyl- L-lysyl- L-lysyl- L-glutamyl- L-aspartyl- L-asparaginy- L-valyl- L-leucyl- L-valyl- L-glutamyl- L-seryl- L-histidyl- L-glutamyl- L-lysyl- L-seryl- L-leucyl- glycy- L-glutamyl- L-alanyl- L-aspartyl- L-lysyl- L-alanyl- L-aspartyl- L-valyl- L-asparaginy- L-valyl- L-leucyl- L-threonyl- L-lysyl- L-alanyl- L-lysyl- L-seryl- L-glutamine
Structural Formula:	rhPTH(1-84) is a single-chain protein containing 84 amino acid residues shown in Figure 2.3.S.1-1 . (b) (4) . The sequence of rhPTH(1-84) is identical to that of native human parathyroid hormone (hPTH). Further characterization information can be found in Section 3.2.S.3.1 [BI RCV] .
Molecular Formula:	C ₄₀₈ H ₆₇₄ N ₁₂₆ O ₁₂₆ S ₂
Molecular Weight:	9424.77 Da

See the attachments at the end of this review: drug product composition, drug product specification, and drug substance specification.

PRODUCT QUALITY (Biotechnology) FILING REVIEW FOR ORIGINAL BLA

The drug substance is parathyroid hormone, produced from the (b) (4) E. coli strain (b) (4). The commercial manufacturing process was used to produce all drug substance batches reported in the BLA (used for clinical, toxicology, and stability studies). The commercial process validation was completed in 2010. The drug substance specification (copied at the end of this review) has standard attributes for this type of drug substance, including peptide mapping, bioassay, aggregates, residual host cell proteins, and residual antibiotic. The bioassay (b) (4) will be evaluated by the reviewer. Batch release data are provided for 18 commercial drug substance batches produced full-scale at the commercial site using the commercial process. The reviewer will finalize the specification, especially limits on impurities (process and product) and product-related substances, based on the batch release data of clinical and toxicology batches. Stability data are submitted for seven full-scale drug substance batches produced at the commercial site by the commercial process, and the data cover 18-110 months at the long term storage condition of (b) (4) °C as well as up to 6 months at (b) (4) °C. The applicant proposes a retest period of (b) (4) months, which will be evaluated by the reviewer (note: the reviewer will grant an expiration dating period for the drug substance, not a retest period). The expiry will be based on available long-term data with no extrapolation.

The drug product is a sterile lyophilized powder co-packaged with the diluent, aqueous m-cresol. Both are packaged in a dual-chamber cartridge (one chamber for the lyophilized drug and one chamber for the diluent). There are four dosage strength, 25, 50, 75, and 100 mcg, all differing only by the amount of drug substance in the formulation (copied at the end of this review). There is no novel excipient. The same cartridge and volume are used for all four strengths. Each cartridge contains 14 doses. The drug cartridge is for specific use with a mixing device and a pen injector, all three are separately packaged. The mixing device and pen injector will be reviewed by OSE and CDRH. How the delivery system works: Prior to use, the patient attaches the drug cartridge to the mixing device, which pushes the diluent from its chamber into the drug chamber to reconstitute the drug, and then the patient attaches the pen injector to this assembly. The assembled multidose delivery system is stored under refrigeration for up to 14 days during use. Stability data are included in the BLA in support of this in-use period, with additional data to cover excursions such as an in-use period beyond 14 days and inadvertent storage at room temperature.

The manufacturing process is standard for this type of drug substance and dosage form. It consists of (b) (4). The commercial process was used to produce all drug product batches reported in the BLA (used for phase 3 clinical studies and primary stability studies). The commercial process validation was completed for the 100 mcg dosage strength. The same process is used for the other three strengths and per agreement by FDA at the Pre-BLA meeting on 15-MAY-2012, the revalidation will be ongoing during the BLA review.

The drug product specifications (copied at the end of this review) have standard attributes for the lyophilized drug (e.g., (b) (4)), reconstituted drug (e.g., drug content, pH, opalescence, bioassay, reconstitution time, aggregates), and diluent. It is noted that the drug is (b) (4) and the drug product specification includes acceptance criteria for the biological activity. Batch release data are provided for 65 commercial drug product batches produced full-scale at the commercial site using the commercial process. The reviewer will finalize the drug product specification based on the batch release data of clinical and toxicology batches. Preservative effectiveness, sterility, endotoxins, and container closure integrity will be reviewed by part of the assessment by Compliance/BMAB.

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A sufficient amount of stability data are submitted for the BLA filing: all primary stability batches are full-scaled, produced at the commercial site by the commercial process, and packaged in the commercial cartridge [REDACTED] ^{(b) (4)} The 100 mcg strength has four batches with up to 36-month at the long-term 5 °C and 6-month at 25 °C/60% RH, the 75 mc strength has three batches with up to 42-month at the long-term 5 °C and 6-month at 25 °C/60% RH, the 50 mcg strength has four batches with up to 42-month at the long-term 5 °C and 6-month at 25 °C/60% RH, and the 25 mcg strength has four batches with up to 24-month at the long-term 5 °C and 6-month at 25 °C/60% RH. The expiry will be determined by the reviewer and be based on available long-term data with no extrapolation. Additional stability reports include photostability and in-use (in the assembled delivery system with the mixing device and pen injector).

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? Yes

The BLA is recommended for team review with expertise in recombinant synthesis.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
None.

This document will be electronically signed in DARRTS

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Table 2.3.P.1-1 Composition of Natpara Drug Product (prior to reconstitution)

Ingredient	Amount per Cartridge				Function	Quality Standard
	25 mcg/dose strength	50 mcg/dose strength	75 mcg/dose strength	100 mcg/dose strength		
Chamber 1						
rhPTH(1-84)	0.40 mg ^a	0.80 mg ^a	1.21 mg ^a	1.61 mg ^a	Active Ingredient	NPS In-house Standard
Sodium Chloride	4.5 mg				(b) (4)	USP-NF
Mannitol	30 mg					USP-NF
Citric Acid Monohydrate	1.26 mg					USP-NF
(b) (4)						USP-NF
						USP-NF
						USP-NF
Chamber 2						
m-Cresol	(b) (4)				(b) (4)	USP-NF
(b) (4)						USP-NF
						USP-NF

NPS = NPS Pharmaceuticals, Inc.; rhPTH(1-84) = recombinant human parathyroid hormone; q.s. = quantity sufficient; USP-NF= United States Pharmacopeia–National Formulary

(b) (4)

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Table 2.3.P.1-2 Composition of Natpara Drug Product (after reconstitution)

Ingredient	Concentration				Function	Quality Standard
	25 mcg/dose strength	50 mcg/dose strength	75 mcg/dose strength	100 mcg/dose strength		
rhPTH(1-84)	(b) (4)				Active Ingredient	NPS In-house Standard
Sodium Chloride					(b) (4)	USP-NF
Mannitol					USP-NF	
Citric Acid Monohydrate					USP-NF	
(b) (4)					USP-NF	
m-Cresol					USP-NF	
(b) (4)					USP-NF	

NPS = NPS Pharmaceuticals, Inc.; rhPTH(1-84) = recombinant human parathyroid hormone; q.s. = quantity sufficient; USP-NF = United States Pharmacopoeia-National Formulary

(b) (4)

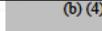
Table 2.3.P.1-3 Container Closure System Overview for Natpara Drug Product

Component	Description
Cartridge	(b) (4)
Middle and End Stoppers	
Crimp Cap	

USP = United States Pharmacopoeia

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Table 2.3.P.5-1 Natpara Drug Product Specifications

Test	Method No. ^a	Acceptance Criteria
Tests Performed on Chamber 1 (Lyophilized Powder)		
Appearance (Visual)	QC-ANP-PTH-5015	White to off-white powder
RP-HPLC Impurities (b) (4)  Other individual impurities Total impurities	QC-ANP-PTH-5006	(b) (4) 
CEX-HPLC Impurities (b) (4)  Other individual impurities Total impurities	QC-ANP-PTH-2110	
HPSEC Impurities Aggregates Low molecular weight impurities	QC-ANP-PTH-5018	
(b) (4)		
Tests Performed on Chamber 2 (Diluent for Reconstitution)		
Appearance (Visual)	QC-ANP-PTH-5015	(b) (4) 
Identity- m-Cresol ^b (RP-HPLC)	QC-ANP-PTH-2106	Comparable to m-Cresol Reference Standard
m-Cresol Content (RP-HPLC)		(b) (4) 
Tests Performed on Reconstituted Drug Product		
Appearance (Visual)	QC-ANP-PTH-5015	(b) (4) 
pH (Potentiometric)	USP <791>	(b) (4) 
Opalescence (Visual)	Ph. Eur. 2.2.1	≤ Reference Suspension III

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Test	Method No. ^a	Acceptance Criteria			
Identity-PTH ^b (RP-HPLC)	QC-ANP-PTH-5008	Comparable to PTH(1-84) Reference Standard			
PTH(1-84) Assay/Peptide Content (RP-HPLC)		100 mcg/dose strength	75 mcg/dose strength	50 mcg/dose strength	25 mcg/dose strength
		(b) (4)			
Uniformity of Dosage Units by Content Uniformity ^b		Meets USP <905> Requirements for Content Uniformity Where L1 = 15.0 and, L2 = 25.0			
PTH Biological Activity (b) (4)	QC-ANP-PTH-0400 QC-ANP-PTH-5043 (alternate method)	(b) (4)			
Reconstitution Time (Visual)	QC-ANP-PTH-5021	(b) (4)			
Osmolality ^b (Osmometer)	QC-ANP-PTH-5023	(b) (4)			
Endotoxins ^b (b) (4)	USP <85>	(b) (4)			
(b) (4)					
Sterility ^b (b) (4)	USP <71>				
Container Closure Integrity (Spectrophotometric)	QC-ANP-PTH-5024				
Particulate Matter (Light obscuration)	USP <788>				
Extractable volume	QC-ANP-PTH-5027				
14-Day Reconstitution Assessment QC-ANP-PTH-5007					
Appearance (Visual)	QC-ANP-PTH-5015	(b) (4)			
Opalescence (Visual)	Ph. Eur. 2.2.1	≤ Reference Suspension III			
Particulate Matter (Light obscuration)	USP <788>	≥ 10 μm ≤ 6000 particles per cartridge ≥ 25 μm ≤ 600 particles per cartridge			

CEX-HPLC = cation exchange-high performance liquid chromatography; EU = endotoxin units; HPSEC= high performance size exclusion chromatography; Ph. Eur. = European Pharmacopoeia; PTH = parathyroid hormone; RP-HPLC = reverse phase-high performance liquid chromatography; USP = United States Pharmacopoeia

^aRegulatory test methods provided.

^bTested only at release.

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Table 2.3.S.4-1 rhPTH(1-84) Drug Substance Specifications

Test	Method No. ^a	Acceptance Criteria
Appearance (Visual)	QC-ANP-PTH-5015	Clear, colorless to light straw-colored liquid
pH		(b) (4)
Identity ^b (RP-HPLC)	QC-ANP-PTH-5008	The retention time of the PTH peak corresponds to that of the standard preparation as obtained in the Assay
Identity by Peptide Map ^b (Enzymatic and RP-HPLC peptide map)	QC-ANP-PTH-5016	Comparable to PTH(1-84) Reference Standard
PTH(1-84) Assay/Peptide Content (RP-HPLC)	QC-ANP-PTH-5008	(b) (4)
RP-HPLC Impurities (b) (4) Other individual impurities Total impurities	QC-ANP-PTH-5006	(b) (4)
CEX-HPLC Impurities (b) (4) Other individual impurities Total impurities	QC-ANP-PTH-2110	(b) (4)
HPSEC Impurities Aggregates Low molecular weight impurities	QC-ANP-PTH-5018	(b) (4)
PTH Biological Activity (b) (4)	QC-ANP-PTH-0400 QC-ANP-PTH-5043 (alternate method)	(b) (4)
(b) (4)	QC-ANP-PTH-5026	(b) (4)

Test	Method No. ^a	Acceptance Criteria
Endotoxin ^b	USP <85>	(b) (4)
(b) (4)	QC-ANP-PTH-0501	(b) (4)

CEX-HPLC = cation exchange-high performance liquid chromatography; (b) (4) EU = Endotoxin unit; HPSEC = high performance size exclusion chromatography; PTH = parathyroid hormone; RP-HPLC = reverse phase-high performance liquid chromatography; USP = United States Pharmacopeia

^aRegulatory test methods provided.

^bTested only at release.

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/s/

SUONG T TRAN
11/20/2013

DANAE D CHRISTODOULOU
11/20/2013