DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125511

BLA APPROVAL

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 Natpara (parathyroid hormone).

We acknowledge receipt of your amendments dated November 11, 2013, and January 21, 24, 28, and 29, February 6 (2), 18 (2), and 20 , March 18 (2), April 2, 4, 15, 22, and 23, May 1, 5, 7, 15, 19(2), 27, and 30, June 10, 16(3), 17 (3), 19, 20(2), and 25, July 3, 15, 18, and 24, August 6 and 20 (2), September 4, 19, and 26, November 6, and December 17, 2014, and January 5 and 20, 2015. We also acknowledge receipt of your email dated January 23, 2015, that included the agreed-upon labeling and the agreed-upon risk evaluation and mitigation strategy (REMS) documents.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 1908 to NPS Pharmaceuticals, Inc., 550 Hills Dr., Bedminster, NJ 07921, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product Natpara (parathyroid hormone). Natpara is indicated as an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture parathyroid hormone drug substance at Boehringer Ingelheim RCV GmbH & Co. KG in Vienna, Austria. The final formulated product will be manufactured and filled at Vetter Pharma-Fertigung GmbH & Co. KG in Ravensburg,

Germany and labeled and packaged at [redacted] (b) (4) You may label your product with the proprietary name, Natpara, and market it in a multi-dose dual-chamber cartridge which contains lyophilized powder for injection (25 mcg, 50 mcg, 75 mcg, and 100 mcg per dose packaging configurations) and the preserved diluent

DATING PERIOD

The dating period for Natpara shall be 24 months from the date of manufacture when stored at 5±3°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4) °C.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Natpara to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Natpara, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling text for the package insert, Medication Guide, and Instructions for use. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)". Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved BLA 125511**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

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

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

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signals of serious risks of hypercalciuria and osteosarcoma in patients treated with Natpara (parathyroid hormone).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2856-1 A study in Fischer 344 rats to ascertain the effect of different Natpara (parathyroid hormone) dosing regimens on osteoblast proliferation, as an indicator of relative osteosarcoma risk.

The timetable you submitted on January 5, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	November 2015
Study Completion:	August 2016
Final Report Submission:	November 2016

2856-2 An enhanced pharmacovigilance study of osteosarcoma in patients with hypoparathyroidism treated with Natpara (parathyroid hormone). The study will include reports of osteosarcoma for a period of 15 years from the date of approval, and will include assessment and analysis of spontaneous reports of osteosarcoma in patients treated with Natpara (parathyroid hormone), with specialized follow-up to collect additional information on these cases.

The timetable you submitted on January 5, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	July 2015
Study Completion:	March 2030
Final Report Submission:	September 2030

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of hypercalciuria in patients treated with Natpara (parathyroid hormone).

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2856-3 A clinical pharmacology trial to assess the pharmacokinetics (PK) and pharmacodynamic effects (PD) of Natpara (parathyroid hormone) 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 trial.

The timetable you submitted on January 5, 2015, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	November 2015
Trial Completion:	September 2016
Final Report Submission:	March 2017

2856-4 A 26-week randomized, controlled clinical trial to evaluate the longer term safety and effect of an alternative dose(s) and/or dosing regimen(s) of Natpara (parathyroid hormone), including longer term safety with respect to hypercalciuria. This trial should not be initiated until the results from the clinical pharmacology trial (PMR 2856-3) and the nonclinical rat study (PMR 2856-1) have been submitted to and reviewed by the Agency.

The timetable you submitted on January 5, 2015, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	November 2017
Trial Completion:	November 2021
Final Report Submission:	May 2022

Submit the protocols to your IND 076514, with a cross-reference letter to this BLA. Submit all final reports to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: "**Required Postmarketing Protocol Under 505(o)**," "**Required Postmarketing Final Report Under 505(o)**," "**Required Postmarketing Correspondence Under 505(o)**."

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

2856-5 Provide bioburden method qualification data from two additional lots of the [redacted] and the drug substance. In addition, provide method qualification data from three lots of the [redacted]

The timetable you submitted on January 5, 2015, states that you will conduct this study according to the following schedule:

Study Completion:	November 2015
Final Report Submission:	December 2015

2856-6 Establish a bioburden limit for the [redacted] after the bioburden monitoring results for 10 more batches are available.

The timetable you submitted on January 5, 2015, states that you will conduct this study according to the following schedule:

Study Completion:	January 2020
Final Report Submission:	February 2020

2856-7 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 [redacted]

The timetable you submitted on January 5, 2015, states that you will conduct this study according to the following schedule:

Study Completion:	November 2015
Final Report Submission:	December 2015

Submit clinical protocols to your IND 076514 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Natpara to ensure the benefits of the drug outweigh the potential risk of osteosarcoma.

Pursuant to 505-1(f)(1), we have also determined that Natpara can be approved only if elements necessary to assure safe use (ETASU) are required as part of a REMS to mitigate the potential risk of osteosarcoma that is listed in the labeling. The ETASU include prescriber and pharmacy certification and documentation of safe use conditions (i.e. documentation that patients are counseled about the potential risk of osteosarcoma). The ETASU will ensure that prescribers are educated about the potential risk of osteosarcoma associated with the use of Natpara, appropriate patient selection and safe use conditions required for prescribing Natpara. In addition, the ETASU will ensure that Natpara is dispensed only to patients informed about the potential risk of osteosarcoma associated with the use of Natpara.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Your proposed REMS, submitted via email on January 23, 2014, and appended to this letter, is approved. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Natpara into interstate commerce.

The REMS assessment plan must include, but is not limited to, the following:

1. REMS implementation and operation metrics
    a. Product launch date.
    b. Number of prescribers targeted by the REMS by specialty.
    c. REMS Website
        i. Date when the REMS website went live.
        ii. Number of unique site visits during the assessment period and cumulatively.
    d. An assessment of compliance with prescriber certification requirements, including the following:

i. Number of prescribers certified during the reporting period and cumulatively. Prescriber information, including degree, specialty, and practice setting (i.e., type of practice, geographic location).

ii. Number of prescriptions for each prescriber.

iii. Number of prescriptions by specialty.

iv. Total number and percentage of prescriptions for Natpara that were written by a certified prescriber versus those prescribed by non-certified prescribers.

v. Number of prescribers who were noncompliant with Natpara REMS Program requirements, detailed description of root cause of noncompliance, and a report of corrective actions taken to address noncompliance including number of prescribers whose certification in the Natpara REMS Program was revoked during the reporting period and cumulatively and the reason for the revocation.

e. An assessment of compliance with pharmacy certification requirements, including the following:

i. Number of pharmacies certified during the reporting period and cumulatively.

ii. Total number of orders shipped to pharmacies during the reporting period and cumulatively. Stratify results by pharmacy certification status.

iii. Total number of prescriptions dispensed during the reporting period and cumulatively. Stratify results by pharmacy certification status.

iv. Number of pharmacies that were noncompliant with Natpara REMS Program requirements, detailed description of root cause of noncompliance, and a report of corrective and/or preventive actions taken to address noncompliance, including number of pharmacies whose certification in the Natpara REMS Program was revoked during the reporting period and cumulatively and the reason for the revocation.

v. Report findings of pharmacy audits occurring during the reporting period and cumulatively.

f. An assessment of compliance with the documentation of safe use condition (i.e., *Natpara REMS Patient-Prescriber Acknowledgment Form*)

i. The number, age, and gender of patients treated with Natpara during the reporting period and cumulatively (by year).

ii. Duration of therapy for patients (mean, median, range).

iii. Total number and percentage of new patients treated with Natpara who had a complete, signed *Natpara REMS Patient-Prescriber Acknowledgment Form* on record (at the Natpara REMS Program Coordinating Center) versus those who did not.

g. Report findings of distributor audits occurring during the reporting period and cumulatively.

h. Report of number, length, and reasons for shipment delays to patients.

i. Summary of issues and complaints received by the Natpara REMS Program coordinating center; summary of resolution of the issues and complaints.

2. Knowledge, Attitudes, and Behavior (KAB) Survey Metrics: Prescribers

   a. Evaluation of prescribers'

      i. knowledge of indication for Natpara and limitations of use (appropriate patient selection)

      ii. knowledge of the potential risk for osteosarcoma associated to Natpara

      iii. knowledge of Natpara REMS Program requirements

      iv. awareness of Natpara REMS materials

      v. sources of knowledge about appropriate patient selection, the risks associated with Natpara, and REMS program requirements.

   Results will be stratified by type of prescriber (e.g., endocrinologists, internists, pediatricians, physician assistants, nurse practitioners, surgeons).

3. Knowledge, Attitudes, and Behavior (KAB) Survey Metrics: Patients

   a. Evaluation of patients' knowledge of

      i. knowledge of indication for Natpara and limitations of use (appropriate patient selection)

      ii. knowledge of the potential risk for osteosarcoma associated to Natpara

      iii. knowledge of Natpara REMS Program requirements

      iv. awareness of relevant Natpara REMS Program materials (i.e., *Natpara Patient Brochure* and *Natpara REMS Patient-Prescriber Acknowledgment Form*).

4. Evaluation of the extent to which the elements of the Natpara REMS Program are meeting the goal and objectives of the REMS and whether modifications to the elements or goals and objectives are needed.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a

new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

BLA 125511 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

BLA 125511 REMS ASSESSMENT

NEW SUPPLEMENT FOR BLA 125511
PROPOSED REMS MODIFICATION

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 125511
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

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

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For

more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20903

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

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

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H
Director
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling
REMS

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

/s/

CURTIS J ROSEBRAUGH
01/23/2015