

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125511Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

BLA # 125511
Product Name: Natpara (parathyroid Hormone (1-84) Human Recombinant injection)

PMR/PMC Description: 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.

PMR/PMC Schedule Milestones: Final Protocol Submission: November 2015
Study/Trial Completion: August 2016
Final Report Submission: November 2016
Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Natpara, PTH(1-84), is a nongenotoxic carcinogen, causing osteosarcomas in both sexes of rats exposed to the drug over a lifetime (2 years). A separate PMR has been established that requires the conduct of aPK/PD clinical trial to evaluate whether alternative dosing regimens (*e.g.*, BID dosing, sustained release) with Natpara are associated with better control of serum calcium and normalization of calcium excretion in urine, compared to that seen with QD dosing. This nonclinical PMR is intended to address whether there is a change in the risk of osteosarcoma development with alternative dosing regimens of PTH(1-84). Because osteosarcomas arise from cells within the osteoblast lineage, effects of PTH(1-84) on proliferation of osteoblasts/osteoblast precursors can be used as an indicator of relative osteosarcomagenic potential of the tested dose regimens.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

A carcinogenicity study in rats exposed to once daily PTH(1-84) for most of their lifetime resulted in the formation of osteosarcomas in both sexes at mean exposure levels that provide for only a 4-fold safety margin to the anticipated mean exposure levels in patients receiving a once daily dose of 100 µg of Natpara. A separate PMR has been established that requires the conduct of a PK/PD clinical trial to evaluate whether alternative dosing regimens (e.g., BID dosing, sustained release) with Natpara are associated with better control of serum calcium and normalization of calcium excretion in urine, compared to that seen with QD dosing. The extant carcinogenicity data, having been conducted only with QD dosing, cannot inform whether the risk of osteosarcoma is increased, decreased or unchanged by alternative dosing regimens. The proposed study will generate data regarding the effect of different dosing regimens on osteoblast/osteoblast precursor proliferation and survival, which is believed to be directly relatable to the osteosarcoma risk associated with PTH exposure.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

In this study, ~3 month old female Fischer 344 rats will be exposed to vehicle or PTH(1-84) using dosing regimens that differ in the timing of administration but result in the same overall dose of PTH(1-84), as follows: e.g., Group One, 50 µg/kg QD; Group Two, 25 µg/kg BID; etc. Dosing will be for ~18 days. Proliferation of osteoblasts/osteoblast precursors will be assessed by nuclear incorporation of 5-bromo-2'-deoxyuridine (BrdU). Osteoblast density (N.Ob/BS) and bone surface-referent bone formation rate (BFR/BS) will also be assessed. The basis for this study design is study PH04-025 submitted with the BLA.

Required

- Observational pharmacoepidemiologic study
 - Registry studies
 - Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
 - There is not enough existing information to assess these risks
 - Information cannot be gained through a different kind of investigation
 - The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
 - The trial will emphasize risk minimization for participants as the protocol is developed
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

BLA # 125511
Product Name: Natpara (parathyroid Hormone (1-84) Human Recombinant injection)

PMR/PMC Description: An enhanced pharmacovigilance study of osteosarcoma in patients with hypoparathyroidism treated with Natpara (parathyroid hormone). This 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.

PMR/PMC Schedule Milestones: Final Protocol Submission: July 2015
Study/Trial Completion: March 2030
Final Report Submission: September 2030
Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Natpara (rhPTH 1-84) is indicated for the replacement of endogenous parathyroid hormone (1-84) for the long-term treatment of hypoparathyroidism, a rare endocrine disorder. Natpara (rhPTH 1-84) was granted orphan drug designation and the clinical study program involved a small cohort with relatively short duration (6 months.) Thus, the lack of long-term safety data on Natpara remains a concern. Given the rarity of the indication and the availability of patients and person-years of exposure that contribute to our current understanding of the safety of Natpara (rhPTH 1-84), enhanced pharmacovigilance is required.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The basis of osteosarcoma as a potential safety concern for Natpara, (rhPTH 1-84) stems from preclinical findings. The incidence of osteosarcoma in rodent carcinogenicity studies increased in a dose-dependent manner. Osteosarcoma occurred at exposures that are clinically relevant in humans. Additionally, osteosarcoma was identified as a potential safety concern for Forteo, teriparatide, PTH(1-34), a closely-related product that is available in the US. FDA has received postmarketing reports of osteosarcoma associated with Forteo use. However, the quality of these spontaneous reports is limited and therefore limits a quality causality assessment. The non-clinical findings regarding osteosarcoma are comparable between the two products. Since osteosarcoma is a rare cancer, with an estimated incidence in humans of 1.7 to 4.4 per million, depending on age,¹ and its latency is unknown, FDA is left with few options to better study osteosarcoma as a potential drug related adverse event. Therefore, enhanced pharmacovigilance is reasonable alternative to improve the quality of spontaneous reports for Natpara postapproval. The goal of the enhanced pharmacovigilance is to gather consistent data to assess the signal of serious risk of osteosarcoma related to the long-term use of the drug. The study will continue for a period of 15 years from the date of approval.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

¹ Mirabello L, et al. Osteosarcoma incidence and survival rates from 1973 to 2004: Data from the Surveillance, Epidemiology, and End Results Program. Cancer. 2009; 115, 1531-1543.

Enhanced pharmacovigilance study of osteosarcoma in patients with hypoparathyroidism treated with Natpara (rhPTH, 1-84) for a period of 15 years from the date of approval.

The enhanced pharmacovigilance study will include the following:

a) Active query of reporters to obtain additional clinical information related to reports of osteosarcoma. The sponsor should actively query reporters for the following information:

(i) Patient demographics (age, sex, race, vital status), verbatim description from any pathology report (minimum data elements: histology, morphology, grade) describing primary and metastatic sites, diagnostic imaging findings, date of diagnosis, primary cancer site, presence and site of metastasis (if any), timing and duration of Natpara exposure, latency of disease, prior use of other drugs known to have osteoblastic activity, prior exposure to ionizing radiation, history of Paget's disease, history of any malignancy, prior injury or infection at tumor site, family history of osteosarcoma, and any other known or suspected risk factor for osteosarcoma.

(ii) Any other pertinent risk factors or clinical data that would aid the sponsor and FDA to conduct an effective causality assessment.

b) Expedited (15 day) reporting to FDA of all initial and follow-up reports of osteosarcoma, regardless of labeling status or expectedness of event. Interim analyses and summaries of new and cumulative safety information must be submitted annually, followed by the final report at the conclusion of the monitoring period.

Required

- Observational pharmacoepidemiologic study
 - Registry studies
 - Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
Enhanced pharmacovigilance
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

Other _____

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

BLA # 125511
Product Name: Natpara (parathyroid Hormone (1-84) Human Recombinant injection)

PMR/PMC Description: 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.

PMR/PMC Schedule Milestones: Final Protocol Submission: November 2015
Study/Trial Completion: September 2016
Final Report Submission: March 2017
Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

NATPARA is recommended for patients with hypoparathyroidism who cannot be well-controlled on current standard of care (i.e., patients with an unmet need). While the clinical development program supports the safety and efficacy of the current proposed dose (maximum of 100 mcg once-daily), further optimization of the dose and dosage regimen may decrease the risk of hypercalciuria.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Hypercalciuria is an important long-term safety concern, potentially leading to nephrolithiasis and nephrocalcinosis. The efficacy/safety results obtained in the registration trial and the PK/PD properties of Natpara indicate that control on hypercalciuria was not apparent with the once daily Natpara regimen. The system pharmacology model based simulations suggest that a more frequent dosing regimen or a dosing regimen with slow release profile will provide a better control on calcium excretion in urine and serum calcium. While the clinical development program supports the safety and efficacy of the current proposed dose (maximum of 100 mcg once-daily), further optimization of the dose and dosage regimen may decrease the risk of hypercalciuria.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A PK/PD trial in patients with hypoparathyroidism. This trial should evaluate and compare the PK and PD of the approved dosing regimen with alternate dosing regimens (e.g. twice-daily, TID). Modeling and simulations approach using mechanistic model based assessment of prior PK/PD data should be utilized to design the PK/PD trial.

Required

- Observational pharmacoepidemiologic study
 - Registry studies
 - Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

BLA # 125511
Product Name: Natpara (parathyroid Hormone (1-84) Human Recombinant injection)

PMR/PMC Description: 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 and the nonclinical rat study have been submitted to and reviewed by the Agency.

PMR/PMC Schedule Milestones: Final Protocol Submission: November 2017
Study/Trial Completion: November 2021
Final Report Submission: May 2022
Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

NATPARA is recommended for patients with hypoparathyroidism who cannot be well-controlled on current standard of care (i.e., patients with an unmet need). While the clinical development program supports the safety and efficacy of the current proposed dose (maximum of 100 mcg once-daily), further optimization of the dose and dosage regimen may decrease the risk of hypercalciuria.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Hypercalciuria is an important long-term safety concern, potentially leading to nephrolithiasis and nephrocalcinosis. The efficacy/safety results obtained in the registration trial and the PK/PD properties of Natpara indicate that control on hypercalciuria was not apparent with the once daily Natpara regimen. The system pharmacology model based simulations suggest that a more frequent dosing regimen or a dosing regimen with slow release profile will provide a better control on calcium excretion in urine and serum calcium. While the clinical development program supports the safety and efficacy of the current proposed dose (maximum of 100 mcg once-daily), further optimization of the dose and dosage regimen may decrease the risk of hypercalciuria.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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, including the longer term safety with respect to hypercalciuria. This trial should not be initiated until the results from the clinical pharmacology study and the nonclinical rat study have been submitted to and reviewed by the Agency, as the choice of dose(s)/dosing regimen(s) to be evaluated will depend on these data.

Required

- Observational pharmacoepidemiologic study
 - Registry studies
 - Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review microbiologist and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

BLA # 125511
Product Name: Natpara (parathyroid Hormone (1-84) Human Recombinant injection)

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

PMC Schedule Milestones: Study Completion: November 2015
Final Report Submission: December 2015

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDA 21 CFR 314.101 OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The sponsor provided method qualification data from one lot of material. The data showed that the (b) (4) and the drug substance did not inhibit or enhance detection of microorganisms.

2. Describe the particular review issue and the goal of the study.

Data from two additional lots of material was requested to confirm that product variability does not impact detection of microorganisms.

3. [OMIT – for PMRs only]
4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The sponsor will perform bioburden method qualification with two additional lots of the (b) (4) and the drug substance. The data will be submitted in a CBE-0 supplement.

5. To be completed by the Product Quality Microbiology Team Leader:
- Does the study meet criteria for PMCs?
 - Are the objectives clear from the description of the PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review microbiologist and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

BLA # 125511
Product Name: Natpara (parathyroid Hormone (1-84) Human Recombinant injection)
PMC Description: Establish a bioburden limit for the (b) (4) after the bioburden monitoring results for 10 more batches are available.
PMC Schedule Milestones: Study Completion: January 2020
Final Report Submission: February 2020

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The sponsor has (b) (4) bioburden monitoring data from the (b) (4) demonstrating adequate microbial control. The bioburden test results for the drug substance have met the specification.

2. Describe the particular review issue and the goal of the study.

The sponsor had not defined a bioburden limit for the (b) (4) which is the (b) (4). The sponsor has agreed to monitor (b) (4) for bioburden and to establish a bioburden limit after data has been collected from 10 batches.

3. [OMIT – for PMRs only]
4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The sponsor will collect bioburden data for the (b) (4) from 10 batches and set a bioburden limit for the (b) (4) based on process capability. The data will be submitted in a CBE-0 supplement.

5. To be completed by the Product Quality Microbiology Team Leader:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review microbiologist and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

BLA # 125511
Product Name: Natpara (parathyroid Hormone (1-84) Human Recombinant injection)

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

PMC Schedule Milestones: Study Completion: November 2015
Final Report Submission: December 2015

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The sponsor provided method qualification data from one lot of material. The data showed that the (b) (4) and the drug substance did not inhibit or enhance detection of bacterial endotoxin.

2. Describe the particular review issue and the goal of the study.

Data from two additional lots of material was requested to confirm that product variability does not impact detection of bacterial endotoxin.

3. [OMIT – for PMRs only]
4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The sponsor will perform endotoxin method qualification with two additional lots of the (b) (4), and the drug substance. The data will be submitted in a CBE-0 supplement.

5. To be completed by the Product Quality Microbiology Team Leader:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

JENNIFER R PIPPINS
01/23/2015

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)**

*****Pre-decisional Agency Information*****

Memorandum

Date: January 9, 2015

To: Elizabeth Chen, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Kendra Y. Jones, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: BLA 125511
OPDP labeling comments for NATPARA[®] (parathyroid hormone, human) for injection, for subcutaneous use

OPDP has reviewed the proposed draft prescribing information (PI) and carton container labels for NATPARA[®] (parathyroid hormone, human) for injection, for subcutaneous use (Natpara) submitted for consult on October 31, 2013.

Prescribing Information

OPDP's comments on the proposed draft PI are based on the version sent from Elizabeth Chen (RPM) on December 17, 2014, and are provided directly on the marked version below.

Carton/Container Labels

OPDP's comments on the proposed draft carton container labels are based on the version (provided directly below) sent from Elizabeth Chen on December 22, 2014. We have no further comments on the draft carton and container labeling at this time.

Medication Guide and Instructions for Use

OPDP's comments on the proposed draft medication guide and proposed draft instructions for use were previously provided under separate cover in conjunction with Division of Medical Policy Programs (DMPP) on January 2, 2015.

Thank you for the opportunity to comment on the proposed draft labeling.

If you have any questions, please contact Kendra Jones at 301.796.3917 or Kendra.jones@fda.hhs.gov.

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/s/

KENDRA Y JONES
01/09/2015

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: January 2, 2015

To: Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrine Products (DMEP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Robin Duer, MBA, BSN, RN
Acting Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Twanda Scales, RN, MSN/Ed.
Patient Labeling Reviewer, Patient Labeling Team
Division of Medical Policy Programs (DMPP)
Sharon W. Williams, MSN, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Kendra Y. Jones
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG) and
Instructions for Use (IFU)

Drug Name (established name): NATPARA (parathyroid hormone, human)

Dosage Form and Route: for injection

Application Type/Number: 125511

Applicant: NPS Pharmaceuticals, Inc. (NPS)

1 INTRODUCTION

On October 23, 2013, NPS submitted for the Agency's review a Biological License Application (BLA) 125511 for NATPARA (parathyroid hormone, human) for injection. NATPARA is a parathyroid hormone indicated as an adjunct or substitute for calcium and active forms of vitamin D to control hypocalcemia in patients with hypoparathyroidism with the following limitations of use:

- Because of the potential risk of osteosarcoma, NATPARA is recommended only for patients who cannot be well-controlled on calcium and active forms of vitamin D alone.
- NATPARA was not studied in patients with hypoparathyroidism caused by calcium-sensing receptor mutations.
- NATPARA was not studied in patients with acute post-surgical hypoparathyroidism

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Metabolism and Endocrine Products (DMEP) on November 4, 2014, and October 31, 2013, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for NATPARA (parathyroid hormone, human) for injection.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review was completed on October 3, 2014.

2 MATERIAL REVIEWED

- Draft NATPARA (parathyroid hormone, human) for injection, MG and IFU received on October 23, 2013 and received by DMPP on December 17, 2014.
- Draft NATPARA (parathyroid hormone, human) for injection, Prescribing Information (PI) received on October 23, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on December 17, 2014.
- Draft NATPARA (parathyroid hormone, human) for injection, MG and IFU received on October 23, 2013, and received by OPDP on December 17, 2014.
- Draft NATPARA (parathyroid hormone, human) for injection, Prescribing Information (PI) received on October 23, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on December 17, 2014.
- DMEPA review of the NATPARA (parathyroid hormone, human) for injection labeling dated October 3, 2014.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the MG and IFU document using the Verdana font, size 11.

In our collaborative review of the MG and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

TWANDA D SCALES
01/02/2015

KENDRA Y JONES
01/02/2015

ROBIN E DUER
01/02/2015

LASHAWN M GRIFFITHS
01/02/2015

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: October 3, 2014
Requesting Office or Division: Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number: BLA 125511
Product Name and Strength: Natpara (Recombinant Human Parathyroid Hormone) for Injection, 25 mcg, 50 mcg, 75 mcg, and 100 mcg
Submission Date: September 26, 2014
Applicant/Sponsor Name: NPS Pharmaceuticals
OSE RCM #: 2013-2499-1
DMEPA Primary Reviewer: Tingting Gao, PharmD
DMEPA Team Leader: Yelena Maslov, PharmD

1 PURPOSE OF MEMO

Division of Metabolism and Endocrinology Products (DMEP) requested that we review the revised container label, carton labeling, and Instructions for Use (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSIONS

The revised container label, carton labeling, and Instructions for Use are acceptable from a medication error perspective.

¹ Gao T. Label and Labeling Review for Natpara (BLA 125511). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 APR 18. 33 p. OSE RCM No.: 2013-2499

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/s/

TINGTING N GAO
10/03/2014

YELENA L MASLOV
10/07/2014



**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research**

Office of Biotechnology Products
Division of Therapeutic Proteins
Rockville, MD 20852

Memorandum

BLA #: 125511

Date Completed:

From: Montserrat Puig, Laboratory of Immunology
Through: Daniela Verthelyi, Laboratory of Immunology

Sponsor: NPS Pharmaceuticals

Product: Natpara® (rhPTH[1-84]) (recombinant human parathyroid hormone)

Subject: Immunogenicity BLA

Indication: replacement for endogenous parathyroid hormone for long term treatment of hypoparathyroidism

Dosage form and strength: Daily Injection (25, 50, 75 or 100 ug / dose)

Route of administration: Subcutaneous injection

Document date
CDER date

Meetings: Team meeting – February 19th, 2014
Mid cycle Internal– March 19th, 2014
Mid cycle with Sponsor – April 2nd, 2014

Related documents:

- IR letter 2/26/14
- IR letter 4/28/14

RECOMMENDATIONS

We recommend approval.

COMMENTS TO THE FILE:

The immunogenicity assessment is acceptable despite being based on a small number of samples tested using validated methods. Although no correlation was evident between product immunogenicity and safety or efficacy signals, this finding is tempered by the limited dataset available. Of note, the immunogenicity rate observed in these patients was higher than that reported in patients with osteoporosis receiving the same product; however it is not known at this time whether this is due to differences in the product (or container-closure system), differences in the assay used, or in the patient population.

SUMMARY-**BACKGROUND**

- Product
- PTH function
- Hypoparathyroidism
- Clinical trials
- BLA pre-submission regulatory activity
- Sponsor’s clinical conclusions on serum PD, efficacy and safety

RISK ASSESSMENT**REVIEW**

1. Introduction
2. Clinical trial studies
 - 2.1. C09-002
 - 2.2. CL1-11-040 (REPLACE)
 - 2.3. PAR-C10-007 (RELAY)
 - 2.4. PAR-C10-008 (RACE)
 - 2.5. PAR-C10-009 (REPEAT)
3. Possible adverse events (AE) related to PTH ADA
4. Immunogenicity effects on PK
5. Immunogenicity results
 - 5.1. In hypoparathyroidism studies
 - 5.2. In osteoporosis studies
6. Immunogenicity methods
 - 6.1. Hypoparathyroidism
 - Screening and confirmatory assay for ADA: RIA ((b) (4)) and MSD ECL assays ((b) (4))
 - NAb bioassay ((b) (4))
 - 6.2. Osteoporosis
 - Screening and confirmatory assay for ADA: ELISA ((b) (4)) and MSD-ECL assays ((b) (4))
 - NAb bioassay ((b) (4))
7. Sponsor’s answers to immunogenicity IR (SN023) from 4/28/14

BACKGROUND –

[Information in BLA module: 2.5. Clinical Overview]

Product -

Natpara's rhPTH is a recombinant protein made in *E. coli* and has an amino acid sequence identical to the natural full length parathyroid protein, consisting in 84 amino acids with a MW of 9.425 kDa. (b) (4)

Recombinant hPTH is intended for subcutaneous use. It is delivered using a glass dual chamber cartridge pen injector that allows multiple doses (up to 14). It is available in 4 nominal dosage strengths (25, 50, 75 or 100 µg / dose). The patient will self-administer a daily dose, alternating thighs, starting at 50 µg and adjusting it every 2-4 weeks up to 100 µg, with the possibility of decreasing the dose to 25 µg.

PTH half-life is approximately 4 min

PTH function –

PTH regulates bone metabolism, serum levels of calcium and phosphate in kidney, and bone turnover. It also has an indirect effect on calcium and phosphate absorption in the gastrointestinal tract, through vitamin D. Calcium sensing receptor is widely distributed in various tissues, but is highly present on the plasma membrane of parathyroid cells, and it is the sensor for PTH release. A rise in serum calcium levels will inhibit PTH secretion and increase in vitamin D. PTH also affects magnesium levels.

Hypoparathyroidism –

- This condition is **defined** as the inappropriately low circulating PTH levels, in association with hypocalcemia and hypophosphatemia. It is considered a rare disease, affecting between 65 and 100,000 patients in the US.
- The disease is characterized by low or absent PTH, decreased serum calcium with high calcium excretion, and increased serum phosphate because the phosphate excretion is low in urine. In addition they have a disrupted vitamin D metabolism. Despite PTH affects magnesium levels, hypoparathyroid patients do not have abnormal serum magnesium. The condition can be inherited, but it is also encountered after thyroid or parathyroid gland surgery, and it can be autoimmune. The clinical signs of acute disease due to depleted serum calcium are reversible. Patients suffer neuromuscular disorders, seizures, arrhythmias, cardiomyopathy, laryngeal spasms, and they have difficulty to concentrate. Patients present accrual of bone instead of turnover and remodeling, and they show increased mineral density. The endogenous levels of 1.25(OH)₂ vitamin D in those patients are low since the activity of the 1-α hydroxylase enzyme is PTH dependent, leading to an abnormal absorption of dietary calcium and phosphate.
- **Disease etiology:** commonly, hypoparathyroidism is induced by the permanent damage to or removal of parathyroid glands or their blood supply during neck surgery, with an incidence of 70-80% of the patients. A total of 0.9-6.6% of the patients that have total thyroidectomy due to cancer, will also suffer post-surgery hypoparathyroidism. Finally,

other causes of the condition are autoimmune disease, congenital absence of glands, radiation damage.

● **Current treatment:** Since there is not yet any replacement therapy approved for PTH, hypoparathyroidism patients are currently managed by oral treatment with high doses of calcium (calcium bicarbonate or calcium citrate) and vitamin D. The therapeutic doses exceed the usual oral daily intake levels, and have adverse events associated such as hypercalciuria (which can lead to long term renal damage) or calcium-phosphate deposition in the brain, major arteries and joints.

The rhPTH replacement therapy would allow reduction in the amount of calcium and vitamin D intake, ameliorating the adverse events.

Clinical trials –

The sponsor provides data on 12 pharmacology studies, 5 efficacy and safety studies and 7 supporting studies in osteoporosis.

Table 5-1 Enumeration of Subjects in the Primary Data Source by Study Group – Safety Population

Study Group	Comparator		rhPTH(1-84)		Total n (m)
	Placebo n	Active Control n	Alone n (m)	In combi- nation n (m)	
Clinical Pharmacology Studies (12 Studies)					
Subtotal Unique Subjects	49	0	361	0	361
Efficacy and Safety Studies in Hypoparathyroidism					
NPS Sponsored Studies (4 Studies)					
Placebo-controlled					
CL1-11-040 - REPLACE	44	0	90	0	90
Dose Comparison Concurrent Controlled PAR-C10-007 - RELAY	0	0	47 (19)	0	47 (19)
Uncontrolled					
PAR-C10-008 - RACE*	0	0	53 (50)	0	53 (50)
PAR-C10-009 - REPEAT	0	0	24 (16)	0	24 (16)
Subtotal Unique Subjects (NPS Sponsored Studies)	44	0	132 (3)	0	132 (3)
Bilezikian IIT*	0	0	79 (9)	0	79 (9)
Subtotal Unique Subjects (Efficacy and Safety Studies in Hypoparathyroidism)	44	0	202 (3)	0	202 (3)
Efficacy and Safety Studies in Osteoporosis (3 Placebo-controlled, 2 Active Controlled, 2 Long-term Extensions)					
Subtotal Unique Subjects	1425	150	2715	149	2864
Grand Total Unique Subjects - Primary Data Source	1518	150	3275	149	3424

IIT = Investigator Initiated Trial; m = number of subjects who have already been counted in the previous study among the primary data source in the treatment group; n = number of subjects in the treatment group; PK = pharmacokinetics

Note: In Clinical Pharmacology Study CL1-11-012, subjects were only exposed to (b) (4) formulation.

Note: Subjects who received both rhPTH(1-84) and placebo across successive studies are counted once in the Placebo column, once in the rhPTH(1-84) column, and once in the Total column.

*PAR-C10-008 and Dr. Bilezikian's IIT are currently ongoing with data cutoff date of 3/25/13 and 5/7/2012, respectively.

Source: Adapted from ISS Table 6-4

The primary registration efficacy and safety study is CL1-11-040, a randomized, double blind, placebo controlled study with 90 patients treated with PTH and 44 treated with placebo (3 doses for 24 weeks).

BLA pre-submission regulatory activity

rhPTH(1-84) is approved for osteoporosis and commercialized in Europe (Preotact). In the US, the NDA for rhPTH(1-84) (Preos) was approved for the treatment of postmenopausal women with osteoporosis in 2006. However, the NDA was withdrawn without prejudice in 2011 due to the lack of sponsorship for an additional Phase 3 clinical trial to address post-approval key issues (hypercalcemia safety concern and reliability of delivery with the device used). Upon a change in the company's focus towards developing products with orphan drug designation in 2007, Natpara proposed the same drug formulation for hypoparathyroidism and started clinical trial for the new indication in 2008. In a type C meeting (2011), FDA agreed to NPS proposal of using investigator-initiated trials in hypoparathyroidism as well as safety clinical data from osteoporosis trials to support the BLA application. The BLA submission was filed in May 2012.

Sponsor's clinical conclusions

- **Serum PD:** the sponsor found similar increases in serum calcium in patients and healthy volunteers. The mean serum calcium peaked 6-8 h after s.c. dose in abdomen or 10-12h in s.c. thigh. These values were sustained for more than 24h. The changes in serum phosphate were inversely correlated with PTH levels over 4 h after dosing. The decrease was more sustained for a longer period in patients than healthy volunteers (4-6 h). The vitamin D maximum levels were recorded at 12, returning to baseline at 24h in both cohorts.

- **Efficacy:** Primary registration study is CL1-11-040, which was designed according to 21 CFR 314.126

The primary end points of the study (by week 24) included $\geq 50\%$ reduction from baseline in oral calcium, $\geq 50\%$ reduction from baseline in active vitamin D intake, albumin-corrected total serum calcium maintained above baseline and below upper limit of normal.

A total of 134 eligible subjects (90 rhPTH treated and 44 placebo) participated in the study, from which, 13 (9.7%) discontinued the study for different reasons (6 treated vs 7 placebo).

- **Safety:** A total of 22 studies were completed and 2 are still ongoing (see table 5.1. above). The sponsor reports that no serious AE were related to the drug intake. Nine subjects had severe AE leading to discontinuation in different studies (3 in pivotal). No subjects discontinued due to an on-treatment event of hypercalcemia, hypocalcemia or hypercalcinuria.

The Ab to PTH were assessed in PK/PD study C09-002, NPS-sponsored efficacy and safety studies and in Efficacy and safety studies in osteoporosis. Twelve out of 132 in the 4 NPS studies developed positive specific ADA (measured by MSD-ECL method). Two more patients were included in this list at the 4 month update, while participating in the PAR-C10-008 ongoing study. The summary of the immunogenicity positive patients is included in table 2.9 of the 5.3.5.3. ISI (pp35-36). Of note, the number of evaluable patients was reduced to 87 during the review resulting in an ADA incidence of 16.1%.

Table 2-9 Subjects in Studies CL1-11-040, PAR-C10-007, PAR-C10-008, and PAR-C10-009 with Specific Antibodies to PTH Based on the MSD Method

Subject Number	Study CL1-11-040 (N = 134)		Study PAR-C10-007 (N = 47)		Study PAR-C10-008 (N = 53)			Study PAR-C10-009 (N = 24)		
	Week 24	Week 28	Baseline	Week 8	Baseline	Week 24	Week 40	Week 52	Baseline	Week 24
rhPTH(1-84) Treatment in Study CL1-11-040										
1001-0004	Positive Non-spec.	Positive Specific	NA	NA	Negative	Negative	Negative	Positive Specific	NA	NA
1004-0003	ND ^a	ND	Positive Specific	Positive Specific ^a	ND	Positive Specific ^a	Positive Non-spec. ^a	Positive Specific	NA	NA
1010-0010	ND ^a	Positive Non-spec.	NA	NA	Positive Non-spec.	Positive Non-spec.	Positive Non-spec.	Not deter. Specific	NA	NA
1015-0001	ND	ND	Positive Specific	Positive Specific ^a	ND	Negative	Negative	Negative	NA	NA
1018-0005	ND ^a	ND	Positive Specific	ND ^a	Negative	Negative ^a	Negative	Negative	NA	NA
8001-0005 ^b	Positive Non-spec. ^a	Positive Non-spec.	NA	NA	NA	NA	NA	NA	Negative	Positive Specific
8001-0007 ^b	Positive Non-spec. ^a	Negative	NA	NA	NA	NA	NA	NA	Negative	Not deter. Specific
8001-0010 ^d	Positive Specific ^a	Positive Non-spec.	NA	NA	NA	NA	NA	NA	Positive Specific	Positive Specific
8002-0001 ^d	Positive Specific	Positive Non-spec.	NA	NA	NA	NA	NA	NA	Positive Specific	Positive Specific ^b
Placebo Treatment in Study CL1-11-040 or Discontinued Study CL1-11-040 prior to treatment with study drug										
1018-0003	ND ^a	ND	Positive Specific	ND	ND	Negative	Negative	Not deter. Non-spec.	NA	NA
3001-0011	Positive Specific ^a	Positive Non-spec.	NA	NA	NA	NA	NA	NA	NA	NA
8003-0003 ^b	ND ^a	Negative	NA	NA	NA	NA	NA	NA	Not deter. Non-spec.	Positive Specific
1011-0004 ^e	NA	NA	Positive Specific	Positive Specific ^c	Positive Non-spec. ^c	Positive Non-spec.	Not deter. Non-spec.	Negative	NA	NA

Table 2-9 Subjects in Studies CL1-11-040, PAR-C10-007, PAR-C10-008, and PAR-C10-009 with Specific Antibodies to PTH Based on the MSD Method

Subject Number	Study CL1-11-040 (N = 134)		Study PAR-C10-007 (N = 47)		Study PAR-C10-008 (N = 53)			Study PAR-C10-009 (N = 24)		
	Week 24	Week 28	Baseline	Week 8	Baseline	Week 24	Week 40	Week 52	Baseline	Week 24
Total Specific Antibodies Reported	3	1	5	3	0	1	0	2	2	5

MSD = Meso-Scale Discovery; n = number of samples drawn for MSD testing; N = total number of subjects in a study; NA = not applicable; ND = not done; Not spec. = not specific; Not deter. = not determined

Note: Week 28 of Study CL1-11-040 was a poststudy follow-up week; no response data was collected at this time point.

^a Non-responder based on Investigator-prescribed data.

^b Neutralizing antibodies were detected for Subject 8002-0001

^c Subject 1011-0004 also had positive non-specific results at an unscheduled assay at baseline of this study, PAR-C10-008.

^d Follow-up labs for antibodies to PTH in Study PAR-C10-009 were drawn for Subjects 8001-0005, 8001-0007, 8001-0010, and 8003-0003 at 3- and 6-month after study completion. Subject 8001-0010 had positive, non-specific results at the 3 month follow-up and negative results at the 6 month follow-up; results for the other 3 subjects were all negative at each poststudy time point. The follow-up testing for Subject 8002-0001 was not done.

^e Discontinued Study CL1-11-040 prior to treatment with study drug

Source: Appendix 1.2, Study CL1-11-040 CSR, Listings 16.2.6.1 and 16.2.9.6; Study PAR-C10-007 CSR, Listings 16.2.6.1 and 16.2.8.9; Study PAR-C10-008 CSR, Listings 16.2.6.1 and 16.2.8.9.1; Study PAR-C10-009 CSR, Listings 16.2.6.1 and 16.2.8.9

Note that confirmed positive ADA results are highlighted. Two additional patients (ID #1004-0003 and 10006-0003) were positive in study PAR-C10-008 at 4 month follow-up. Only 1 patient (8002-0001) had NAb, in study PAE-C10-009.

The sponsor reported the following AE for those patients that were ADA positive: 1 subject in CL1-11-040 had an injection site reaction at wk28, 4 weeks after finalizing the study. Another subject that had ADA positive results in PAR-C10-008 reported mild hives while in the pivotal study but not during the extended study PAR-C10-008. This same patient had SAR to magnetic resonance dye which was not PTH related.

RISK ASSESSMENT -

As with all therapeutic proteins, there is potential for immunogenicity with rhPTH treatment. Development of anti-rhPTH antibodies (ADA) could lead to changes in PK/PD

and in neutralization of existing native PTH or other homologous proteins placing the patients at risk of more severe hypoparathyroidism. In addition, neutralizing Ab against the product has a potential to decrease the efficacy of the replacement therapy.

The presence of Ab could also impact on PK/PD parameters. Binding antibodies that alter PK/PD could increase in the C_{max} of rhPTH to pose a risk for hypercalcemia and/or hypercalcinuria, a condition that has been observed in patients participating in clinical studies. Also, the discontinuation of the rhPTH treatment can lead to hypocalcemia. The evaluation of the benefits vs the risks of the replacement therapy compared to the current recommended intake of calcium and active vitamin D is critical to support the sponsor's proposal.

REVIEW –

1. Introduction

This report focuses on the immunogenicity data provided by the sponsor to support the BLA application for rhPTH, including sections:

- 5.3.5.3. Integrated summary Immunogenicity (ISI)
- Immunogenicity data from the clinical studies
- Assay development and validation reports
- 4-month safety update Addendum
- Several IR letters

2. Clinical trial studies

The following tables (5.3.5.3.ISI pp13-14) summarize the clinical studies from which NPS immunogenicity data was extracted, and the methods used for the ADA determination. ADA screening/confirmatory/titer assay was changed from RIA ((b) (4)) to MSD-ECL ((b) (4)). The sponsor developed an assay to measure anti-ECP (*E.coli* host cell protein) antibodies.

Table 1-1 Overview of Studies with Antibody Analysis

Study Number	Product(s), Number of Subjects	Duration of Treatment	Anti-PTH Assays (Neutralizing Antibodies)	Anti-ECP Coli Protein Assay	Method (Laboratory)	Sample Times
Studies in Subjects with Hypoparathyroidism^a						
C09-002	rhPTH(1-84) 50 and 100 µg SC in the thigh, 7	1 day for each dose level	Yes (no)	No	RB (b) (4)	BL, Day 1
CL1-11-040 (REPLACE)	Varying doses of rhPTH(1-84) 50, 75, and 100 µg SC in the thigh daily, 90 or Placebo, 44	6 months	Yes (no)	No	RB (b) (4) MSD ^b (b) (4)	BL, Weeks 24 and 28
PAR-C10-007 (RELAY)	Fixed doses of rhPTH(1-84) 25 or 50 µg SC in the thigh daily, 23 in the 25 µg group, 24 in the 50 µg group, 47 total	8 weeks	Yes (yes)	Yes	RB (b) (4) MSD, NAB (b) (4)	BL, Week 8
PAR-C10-008 (RACE)	Varying doses of rhPTH(1-84) 25, 50, 75, and 100 µg SC in the thigh daily, 53	12 months + extension ONGOING	Yes (yes)	Yes	MSD, NAB (b) (4)	BL, Weeks 24, 40, 52, and Follow-up at 2, 3, 6, 18 and 24 months
PAR-C10-009 (REPEAT)	Varying doses of rhPTH(1-84) 50, 75, and 100 µg SC daily, 24	6 months	Yes (yes)	Yes	RB (b) (4) MSD, NAB (b) (4)	BL, Week 24, Follow-up at 2, 3, and 6 months
Studies in non-Hypoparathyroidism Subjects^a						
ALX1-11-821	PlaceboPTH, 55 50 µg PTH, 52 75 µg PTH, 55 100 µg PTH, 55 in the abdomen or thigh	12 months	Yes (no)	Yes	ELISA (b) (4)	BL, 1 and 2 months

Table 1-1 Overview of Studies with Antibody Analysis

Study Number	Product(s), Number of Subjects	Duration of Treatment	Anti-PTH Assays (Neutralizing Antibodies)	Anti-ECP Coli Protein Assay	Method (Laboratory)	Sample Times
Studies in non-Hypoparathyroidism Subjects^a (continued)						
ALX1 11 93001 (TOP)	PlaceboPTH, 1246 100 µg PTH, 1286 in the abdomen or thigh	18 months	Yes [yes]	Yes	ECL (b) (4) NAB (b) (4)	BL, 12, 18 months
CL1-11-002 (OLES)	PlaceboPTH /100 µg PTH, 900 100 µg PTH/100 µg PTH, 781 in the abdomen or thigh	6 months (24 months 18 TOP + 6 OLES)	Yes [yes]	No	ECL (b) (4) NAB (b) (4)	BL, 3, 6, and 18 months
CL1-11-016 (TRES)	PlaceboPTH/100 µg PTH/ 100 µg PTH in the abdomen, 98	36 months (TOP placebo +OLES +TRES)	Yes [no]	No	ECL (b) (4)	BL, 18 months
CL1-11-003 (POWER)	HRT + placeboPTH, 90 HRT + 100 µg PTH, 90 in the abdomen or thigh	18 months (variable)	Yes [no]	Yes	ECL (b) (4)	BL, 12 (24, 36; stop at 18 months)

BL = baseline; ECL = electrochemiluminescence; ECP = E. coli protein; ELISA = enzyme linked immunosorbent assay; MSD = Meso-Scale Discovery; NAB = neutralizing antibody; PTH = parathyroid hormone; RB = radiobinding

^aSubjects in both the hypoparathyroid and osteoporosis studies may have enrolled and been treated in more than one study. There were 132 unique subjects in the hypoparathyroid studies with testing for antibodies.

^bThe (b) (4) MSD assays were developed during the hypoparathyroid program. Samples from about one-third of the subjects in this study were available to test using the (b) (4) MSD assay.

Reviewer's comments:

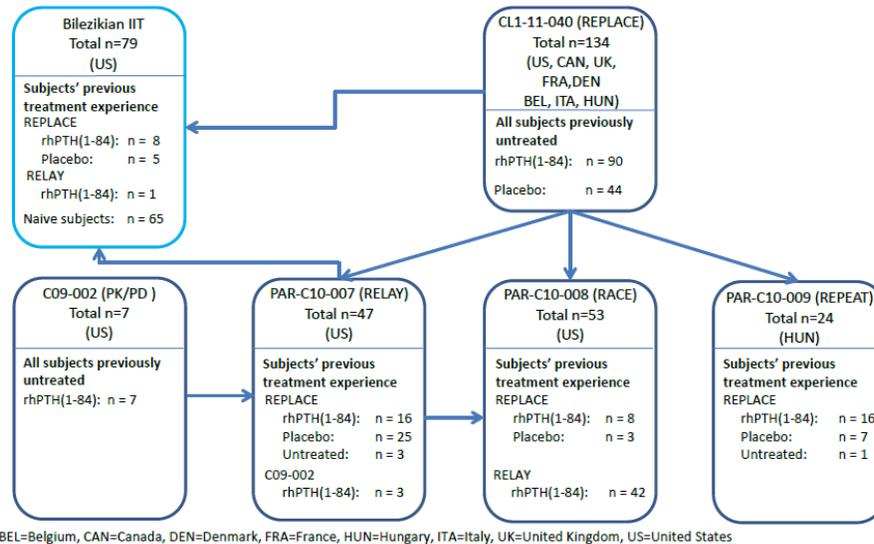
Based on the NPS proposal and FDA agreement from a Type C meeting held in 2011, the immunogenicity data from the osteoporosis studies used to support safety and efficacy will be accepted to support the hypoPT studies results.

The sponsor developed assays to monitor the levels of anti-E.coli protein (ECP) antibodies in the serum of treated subjects. However, the incidence of anti-ECP Ab is high in the general population as well as pre-treatment samples of patients. Therefore, the increase in the levels of anti-ECP due to rhPTH manufacturing process might not have a clinical impact. In addition, this has been supported by immunogenicity results in osteoporosis studies, in which, no association was found between anti-ECP Ab level increases and adverse events or treatment efficacy. Therefore, data regarding anti-ECP Ab detection or assays will not be considered in this review.

Some of the subjects participated in more than one study, as indicated in the following diagram (Fig.2-1). The sponsor reports that a total of 132 subjects were naively treated with rhPTH, including (1) 90 participants from CL1-11-040, (2) 25+3+7 placebo-treated

patients or 3+1 untreated patients from CL1-11-040 that received the hormone in one of the PAR studies, and (3) 3 patients from the C09-002 (PKPD) study that only received rhPTH twice (50 µg/dose) and the sponsor considered them “naïve” to treatment in study PAR-C10-007.

Figure 2-1 Flow of Subjects Across NPS Sponsored Efficacy and Safety Studies in Hypoparathyroidism and the Bilezikian Investigator Initiated Trial



- 2.1. Study C09-002: Open-label, escalating, single-dose study for PK/PD evaluation. Single dose was administered in treatment periods 1 (50 ug) and 2 (100 ug) with a 7-day washout period between treatments. ADA were tested prior to treatment 1 (pre-dose). One of 7 patients had pre-existing anti-rhFSH Ab, who had a thyroidectomy and allergies to food and drugs. No AE were observed.
- 2.2. Study CL1-11-040 (REPLACE): Randomized, double-blind, placebo-controlled phase 3 study, for a treatment period of 24 weeks. The treated patients received 50 µg dose rhPTH and could be further increased to 75 µg and then 100 µg. ADA were measured at 24 and 28 weeks (follow-up), first with a RIA assay (b) (4). About one-third of the samples were retested with a new assay, MSD-ECL, developed and validated by (b) (4) which did not include any of the baseline samples due to unavailability. See result provided from both assays on the tables below.

Table 2-1 Number (%) of Subjects in Study CL1-11-040 with PTH Antibodies Based on the (b) (4) Radiobinding Assay – Safety Population

Antibodies	Visit	Placebo (N=44) n (%) ^a	rhPTH(1-84) (N=90) n (%) ^a
PTH	Baseline	42	90
	Positive	0	0
	Negative	42 (100.0)	90 (100.0)
	Week 24 (Visit 16)	36	83
	Positive	0	0
	Negative	36 (100.0)	83 (100.0)
	Week 28 (Visit 18)	33	77
	Positive	1 (3.0)	1 (1.3)
	Negative	32 (97.0)	76 (98.7)

PTH = parathyroid hormone; N = number of subjects

Note: n is the number of subjects having antibodies to PTH at the analysis visit for those subjects who have a valid measurement at the visit.

^aThe percentage is calculated based on the number of subjects having PTH antibody tests at the visit. Samples drawn outside analysis visit windows are not included in this number.

Source: Study CL1-11-040 CSR Table 14.3.7.1 and Listing 16.2.9.6

Table 2-2 Number (%) of Subjects in Study CL1-11-040 with PTH Antibodies Based on the (b) (4) MSD Assay – Safety Population

Antibodies	Visit	Placebo (N=44) n (%) ^a	rhPTH(1-84) (N=90) n (%) ^a
PTH	Week 24 (Visit 16)	15	31
	Positive	2 (13.3)	8 (25.8)
	Specific	1 (6.7)	2 (6.5)
	Non-Specific	1 (6.7)	6 (19.4)
	Negative	13 (86.7)	23 (74.2)
	Week 28 (Visit 18)	17	34
	Positive	2 (11.8)	8 (23.5)
	Specific	0	1 (2.9)
	Non-Specific	2 (11.8)	7 (20.6)
	Negative	15 (88.2)	26 (76.5)

MSD = Meso-Scale Discovery; N = number of subjects; PTH = parathyroid hormone

Note: n is the number of subjects having antibodies to PTH at the analysis visit for those subjects who have a valid measurement at the visit

^aThe percentage is calculated based on the number of subjects having PTH antibody tests at the visit. Samples drawn outside analysis visit windows are not included in this number.

Source: Study CL1-11-040 CSR Table 14.3.7.2, Listing 16.2.9.6 and TN11-193

Reviewer's comments:

The sponsor reports the immunogenicity results for study REPLACE obtained with the MSD-ECL method, from which only 1/3 of the samples were available for re-testing using the validated assay. Importantly, none of the baseline samples from any of the subjects were available for re-testing. In addition, none of the positive results obtained by the originally used method (RIA, (b) (4)) were confirmed by the more recently adopted MSD-ECL method, since they were not re-tested. This situation makes the interpretation of the results very difficult, due to the low number of subjects tested (n=31-34) by MSD-ECL, and due to the impossibility to assess the ADA levels prior to rPTH treatment.

- 2.3. Study PAR-C10-007 (RELAY): Randomized, double-blind, safety/efficacy study. The treated patients received a daily s.c. fixed dose of 25 or 50 µg of rhPTH. ADA were measured at baseline and 8 weeks (follow-up). The majority of the samples were tested with RIA assay ((b) (4)) and the MSD-ECL assay ((b) (4)) approx. 30 samples / timepoint; however, ADA+ by RIA was not confirmed by MSD method. The results considered were those from the MSD

assay. The Ab titers (referred to the 1:10 MRD of the raw serum) were low and no NAb were detected.

Table 2-4 Subjects in Study PAR-C10-007 with Specific Antibodies to PTH in MSD Assay

Dose Group	Subject Number	Study Week	Titer	NAB	Investigator Efficacy Data Responder
rhPTH(1-84) 25 µg	1015-0001	BL	< 0.00	NA	NA
		8	< 0.00	No	No
	1018-0003	BL	0.198	NA	(Responder at Week 8)
	1018-0005	BL	< 0.00	NA	(Not a responder at Week 8)
rhPTH(1-84) 50 µg	1004-0003	BL	0.523	NA	NA
		8	0.588	No	No
	1011-0004	BL	0.581	NA	NA
		8	0.528	No	No

BL = baseline; MSD = Meso-Scale Discovery; NA = not applicable; NAB = neutralizing antibody assay
Source: Study PAR-C10-007 CSR 2, Listing 16.2.6.1, Listing 16.2.8.9 and TNJR11-194

2.4. Study PAR-C10-008 (RACE): ongoing long-term, open-label clinical extension study, for safety/tolerability, for subjects that have completed the REPLACE or RELAY studies. Treatment started with a 25 or 50 µg dose that could be adjusted up to a maximum of 100 µg, in order to achieve serum calcium levels of 8-9 mg/dL, with minimum doses of supplements possible. ADA assessment was done at baseline (final results of RELAY), wk 24, 40 and 52 and every 6 months during the extension period. Subjects that are ADA positive at final visit, there will be followup visits at month 2, 3 and 6 post-study until 2 successive samples are negative for ADA.

Table 2-6 Subjects in Study PAR-C10-008 with Specific Antibodies to PTH by the MSD Assay

Subject Number	Study Week	Titer	NAB	Investigator Efficacy Data Responder
1001-0004	52	< 0.00	No	Yes
1004-0003	BL ^a	0.588	No	NA
	24	< 0.00	No	No
	40	Not specific	NA	No
	52	< 0.00	No	Yes
1010-0010	Month 18	Negative	NA	NA
	52	0.616	No	Yes
1010-0010	Month 18	Negative	NA	NA
	52	0.616	No	Yes
1011-0004 ^b	BL ^a	0.528	No	NA
1015-0001	BL ^a	<0.00	No	NA

BL = Baseline; MSD = Meso-Scale Discovery; NA = not applicable; NAB= neutralizing antibody assay; PTH = parathyroid hormone

^a Baseline of this study are the results from Week 8 of Study PAR-C10-007.

^b Subject 1011-0004 also had positive non-specific results at an unscheduled assay at baseline of this study.

Source: Study PAR-C10-007 CSR, Listing 16.2.6.1, Listing 16.2.8.9 and TNJR11-194; Study PAR-C10-008 CSR, Listing 16.2.6.1, Listing 16.2.8.9.1

Follow-up data from this study was provided in a 4-month safety update addendum. Two more patients, 1006-0003 and 1010-0004 were ADA+ at month 24. Two subjects (1004-0003 and 1006-0004) were initially reported positive for

NAb, but later confirmed negative. An errata was submitted justifying the invalidation of the initial assay due to the PC performance.

Reviewer’s comments – The sponsor provided the NAb raw data from these two patients supporting the correction of the results. No further action needs to be taken.

2.5. Study PAR-C10-009 (REPEAT): 6-month open-label clinical extension study for safety and tolerability. Subjects were initially treated with a dose of 50 µg s.c. daily, with possibility of adjustment, for 24 weeks, to maintain serum calcium levels of 2-2.5 nmol/L. All subjects had previously been enrolled in CL1-11-040 study. Subjects that were ADA+ at end of the study were followed up at month 2, 3 and 6 post-study, until results of two successive visits were negative. All 24 subjects enrolled in the study were tested for ADA with RIA and MSD-ECL assays. Three of the 4 subjects that were confirmed positive for ADA, had negative samples at 3 and 6 month follow-up. The fourth subject tested positive for NAb.

Table 2-8 Subjects in Study PAR-C10-009 with Specific Antibodies to PTH by the MSD Assay

Dose Group	Subject Number	Study Week	Titer	NAB	Investigator Efficacy Data Responder
rhPTH(1-84)	8001-0005	24	1.08	No	Yes
	8001-0007	24	Negative (< 0.00)	No	Yes
	8001-0010 ^a	BL	0.552	No	
		24	0.608	No	Yes
	8002-0001 ^a	BL	1.36	No	
		24	Negative (< 0.00)	Yes	Yes
	8003-0003 ^b	24	1.82	No	No

BL = baseline; MSD = Meso-Scale Discovery; NAB = Neutralizing antibody assay

^aSubjects had specific antibodies to PTH (MSD method) in Study CL1-11-040. Testing for neutralizing antibodies was not done in Study CL1-11-040.

^bSubject received placebo in Study CL1-11-040

Source: Study PAR-C10-009 CSR Listings 16.2.6.1, 16.2.8.9 and TNJR11-196

3. Possible adverse events (AE) related to PTH ADA

Some of the study participants reported injection site AE, which were associated with injection trauma. One of the 12 patients that had ADA+, had a recurrent hematoma at the injection site, recurrent with dose increase but it resolved after termination of treatment. Other patients reported hives, although it was independent of having ADA+ or not (see Table 1 in section 5 of this review report “summary of immunogenicity results”).

Reviewer’s comments – The clinical team agreed on that the AE reported by the sponsor were correctly assessed for the patients that had confirmed ADA, and were not a consequence of the ADA levels.

4. Immunogenicity effects on PK

This assessment was done from data from visits 14 and 16 of hypoPT studies CL1-11-040, PAR-C10-007 and PAR-C10-008 (MSD assay), and visits at month 12 and 18 on

osteoporosis studies ALX1-11-93001 and CL1-11-016. There were a total of 13,383 and 790 patients evaluated for each indication, respectively. The sponsor identified 4 subjects with hypoPT and 9 with osteoporosis with an association between ADA and a PK blood sample. They also observed that typically the CL/F V/F of PTH was 47% higher in subjects with ADA than those that did not have. No conclusions could be drawn though due to few subjects. The half-life of rhPTH in ADA positive individuals was determined to be 1.6 times longer than without, although the difference was not statistically significant. The example of subject 002-001 in study C09-002 is discussed in this section to show that even with the presence of Ab and an elongated PTH circulation time, the levels and kinetics of the hormone were similar to the patients without ADA in the same study.

Assessment of drug tolerance was studied by determining whether residual rhPTH in serum could interfere in the NAb assay. For that, neat pooled normal human serum containing 5-2 µg/ml rabbit anti-PTH IgG was spiked in serum containing rhPTH dilutions from 500 to 0 pg/ml. The assay sensitivity of 3.332 µg/ml was not affected in any of the dilutions tested. These results were confirmed with the updated assay, with a sensitivity of 0.600 µg/ml.

After a dose of 100 µg, the C_{max} of PTH was calculated to be 275 (120SD) pg/ml, which was below the maximum concentration tested in the drug interference test.

Reviewer's comments – It appears from the data presented in this section, that despite finding an association between ADA and PK parameters, the subject sample size is too small to draw conclusions. The more detailed follow up of drug kinetics and C_{max} in the serum of one patient with ADA seemed to indicate that it was no different from ADA negative subjects. Up to date, the pharmacology team has not expressed any concerns in this regard in internal meetings. The sponsor correctly showed that the concentration of circulating PTH after the maximum rhPTH dose will not affect the evaluation of Ab, within the limit of assay sensitivity.

5. Immunogenicity results

A total of 2864 individuals were treated in hypoPT and osteoporosis studies with rhPTH. These subjects could enroll in more than 1 study; in the NPS sponsored studies, the exposure to drug was up to 2.6 years.

5.1. IMMUNOGENICITY RESULTS HYPOPARATHYROIDISM STUDIES:

The sponsor initially reported that a total of 140 subjects were tested for ADA: 132 subjects from the NPS-sponsored studies, and eight subjects from the Bilezikian trial (investigator initiated). However and importantly, only 1/3 of the 132 patients treated and enrolled in the pivotal study CL1-11-040 were tested with a MSD-ECL assay developed and validated by (b) (4). Table 1 was prepared by the reviewer to summarize the results of all the NPS-sponsored studies. All 8 subjects from the Bilezikian trial screened negative (taking in consideration that the ADA read outs were done at 1, 2, 3 years after treatment completion).

Table 1 - Subjects who developed Anti-rhPTH antibodies							
ISI Addendum (4-month safety update)							
subject	Timepoint for antibody positivity	Neutralizing Ab	Adverse events?	Supplements	TEAE	medical history	Responder/non-responder in pivotal (and overall)
1001-0004	Wk 28 (REPLACE) Wk 52 (008)	NAb assay not performed (REPLACE) NAb negative (008)	Moderate injection site hematoma 2 weeks after study drug initiated; persisted until the end of treatment (pp22 ISI; pp116 AE); no injection site or hypersensitivity reactions in 008	no changes in supplements	No TEAE	thyroidectomy, drug hypersensitivity	R (R.)
1004-0003	Baseline, Wk 8 (RELAY) Wk 24, Wk 52, Month24 (008)	NAb negative (RELAY) NAb negative (008) (see note1)	No systemic hypersensitivity reaction (relay); no injection site or hypersensitivity reactions in 008	no changes in supplements	No TEAE	thyroidectomy, season allergy	NR (R.)
1010-0010	Wk 52, Month24 (008)	NAb negative	Had mild hives only in (REPLACE) but resolved with diphenhydramine (pp23 ISI) and not in 008; developed a severe anaphylactic reaction to MRI dye that resolved (in 008) (pp27 ISI)	No changes in supplements	moderate and mild hypocalcemia , prior to month 24	thyroidectomy, hypersensitivity, environmental allergies	NR (R.)
1015-0001	Baseline, Wk 8 (007)	NAb negative	No injection site or systemic hypersensitivity reactions in 007	No changes in supplements	No TEAE of hypo or hypercalcemia	parathyroidectomy, chronic sinusitis	R (R.)
1018-0005	Baseline (007)	NAb not determined	No injection site or systemic hypersensitivity reactions in 007			thyroidectomy, season allergy, chronic sinusitis, asthma	NR (R.)
8001-0005	Wk24 (009)	NAb negative	no injection site or hypersensitivity reactions in 009			osteomyelitis	NR (R.)
8001-0007	Wk24 (009)	NAb negative	no injection site or hypersensitivity reactions in 008			congenital anomalies	NR (R.)
8001-0010	Wk 24 (REPLACE) Baseline, Wk 24 (009)	NAb assay not performed (REPLACE) NAb negative (009)	No systemic hypersensitivity reaction; no injection site or hypersensitivity reactions in 009			thyroidectomy	NR (R.)
8002-0001	Wk 24 (REPLACE) Baseline, Wk 24 (009)	NAb assay not performed (REPLACE) NAb POSITIVE (009)	No systemic hypersensitivity reaction; no injection site or hypersensitivity reactions in 009. Had AE that were not allergic, mild intermittent headache, flu symptoms and hypocalcemia; all resolved			thyroidectomy and other health history, taking concomitant medications (pp32 ISI)	R (R.)
1018-0003	Wk28 (REPLACE) by RIA, not determined by ECL Baseline (007)	NAb assay not performed (REPLACE) NAb not determined (007)	No systemic hypersensitivity reaction; no injection site reaction in 007			thyroidectomy, autoimmune thyroiditis, Grave's disease	PBO
8003-0003	Wk24 (009)	NAb negative	no injection site or hypersensitivity reactions in 009			thyroidectomy	PBO - NR
1011-0004	Baseline, Wk 8 (007)	NAb negative	No injection site or systemic hypersensitivity reactions in 007			thyroidectomy, drug allergies, Celiac disease	Discontinued before dose
1006-0003	Month 24 (008)	NAb negative (see note 1)		No changes in supplements	moderate and mild hypocalcemia , prior to month 24	thyroidectomy	Maintained response (R.)
1010-0004	Month 24 (008)	NAb negative		No changes in supplements	No TEAE of hypo or hypercalcemia	thyroidectomy	Maintained response (R.)
3001-0011	wk24 (REPLACE) . Placebo treated	NAb negative				thyroidectomy	
REPLACE	trial C1-11-040		(AE - Study CL1-11-040 CSR, Listing 16.2.7.1)				
RELAY	trial PAR-C10-007		(AE-Study PAR-C10-007 CSR, Listing 16.2.7.2)				
RACE	trial PAR-C10-008		(AE - Study PAR-C10-008 CSR, Listing 16.2.7.2)				
REPEAT	trial PAR-C10-009		(AE - Study PAR-C10-009 CSR, Listing 16.2.7.2).				
NOTE(1) Initially identified to have NAb+ at month 24 but were retested and concluded to be negative for NAb							
Subjects with pre-existing Ab were 3001-0011, 1018-0003, 1011-0004 and an additional subject from PK/PD study: 002-001							

The sponsor calculated and reported the following Ab incidence:

- Pre-treatment: 4/132 (3%) ADA positive subjects were reported in CL1-011-040 study before the initiation of the treatment or when treated with placebo. These patients had developed hypoPT after thyroidectomy. From the osteoporosis program, one patient that received placebo had also pre-existing Ab but had no thyroidectomy history (further details in response to IR 2/26/14).

- Post-treatment: According to the sponsor, 12/132 (9%) subjects had confirmed ADA in post-treatment samples, from which 7/12 were positive after first treatment study, and 5/12 became positive at a second study. The sponsor stated that there was no increase in the Ab titers over time in these patients.

In the 4-month safety update addendum, the sponsor reported two more ADA-positive subjects in study PAR-C10-008 (month 24 sample). In addition, none of the 8 ADA tested patients of study Bilezikian (investigator sponsored study) were positive. Thus, the more updated incidence of ADA is 14/140 (10%), according to the sponsor.

The sponsor indicated that about 1% rate of presence of ADA was also similarly reported by other methods (RIA) and in the osteoporosis study.

- NAb: Subject 8002-001 (CL1-11-040 and PAR-C10-009) had confirmed NAb at week 24 of the second study (end of study sample) although the ADA titers were negative. This same patient had a low ADA titer in sample week 24 of the first study. No NAb positives were reported in the osteoporosis program.

In the 4-month safety update addendum, the sponsor initially reported two more patients as NAb positive, 1004-0003 and 1006-0003. These two patients' samples were re-tested since a technical error was identified in the test plates. The sponsor provides the justification for retesting as an *errata* to the addendum, and the final NAb result being negative.

The sponsor was asked on an IR letter (4/28/14) to recalculate the incidence of ADA based on the actual number of samples tested for immunogenicity instead of the number of drug-naïve subjects enrolled in the studies. The final evaluation of the overall post-treatment ADA incidence in the NPS sponsored studies shows that 14 out of 87 (16.1%) tested subjects had confirmed ADA, from which 8/14 were positive at the first trial in which they received treatment and 6/14 became positive at a second trial in which they were treated with rPTH again (all 14 were enrolled in the pivotal trial). NAb were not measured in the pivotal trial. One subject (8002-001) had confirmed Nab at Week 24 of the second study (Trial 009) although the ADA titers were negative

Reviewer's comment: The sponsor correctly recalculated the ADA incidence based on the number of subjects evaluated for immunogenicity (excluding the results from the Bilezikian trial). This value should be reflected in the label of the product, for the hypoparathyroidism indication.

5.2. IMMUNOGENICITY RESULTS OSTEOPOROSIS STUDIES:

Study Name	subjects	Screening method	ADA pos	ADA neg	n/a	NAb method	NAb pos	Titer
ALX1-11-821	186	ELISA	185	1	2	n/a		Lower than detection range
ALX1-11-93001 (TOP)	1246 placebo 1286 rhPTH	ECL	1(0.1%) 36 screening 35 (2.7%) confirmed	1245 1250 1251		bioassay	0 0	11/28 (39.3%) positive titers at m12 but not m18
CL1-11-002 (OLES)	900 placebo 781 treated	ECL	3m – 0 6m – 1 18m – 2 All visits – 3 (1%) 3m – 2 6m – 3 18m – 2 All visits –12 (4.8%)	46 131 243 36 193 219 240		bioassay	0 0	
CL1-11-016 (TRES)	98	ECL	0	92		n/a		
CL1-11-003 (POWER)		ECL	1 (not specific) at 12m			bioassay	0	

- ALX1-11-93001 (TOP): 18 month double blind, placebo controlled, phase3 trial. Placebo or 100 µg/day. Samples for ADA evaluation: month12 and month18
- CL1-11-002 (OLES): 18 months, open label, extension study. Safety and efficacy from ALX1-11-93001. Maximum 24 months exposure with the 2 trials combined. Dose was 100 µg/day.
- CL1-11-016 (TRES): 18 months, open label, extension study. Dose was 100 µg/day. Safety trial, up to 36 months
- CL1-11-003 (POWER): Phase 3 trial. Women with low bone mass who were or are in stable estrogen replacement therapy. Dose was 100 µg/day, up to 24 months.

Reviewer's comments: The anti-rhPTH Ab incidence in osteoporosis subjects of ~3-5% is lower than in hypoparathyroidism subjects, considering that % of ADA+ subjects within those tested in the NPS-sponsored studies ~14/87 (16.1%). For some hypoparathyroid patients, who had very low levels or no expression of PTH for life, it is not unexpected that they might have a higher risk of anti-PTH Ab upon treatment with the recombinant protein. However, for those who acquired hypoparathyroidism upon thyroidectomy, for example, we don't fully understand the mechanism by which they break tolerance. There are several mechanisms involved in maintenance of immunological tolerance, including the requirement of having a certain level of protein in circulation, which could be important in this case. It is important to note that there are some differences in the product presentation such as the use of an autoinjector which could have an impact on immunogenicity. Since at the moment we don't know what mechanisms are involved in the different rate of developing ADA in both subject populations, we asked the sponsor to not combine the numbers and instead report them separately for both indications in the

label of the product. The sponsor has agreed to FDA recommendations (see IR response at the end of this report).

6. Immunogenicity methods (reviewed information from section 6 of ISI and individual assay validation reports and SOPs)

6.1. FOR HYPOPARATHYROIDISM STUDIES

The screening assay was initially developed and validated by (b) (4) based on a radioimmunoassay (RIA) with ¹²⁵I-PTH. It was used to test samples from the PK/PD and 3 of the NSP efficacy-safety studies. The sponsor reported that (b) (4) did not want to transfer validation data reports to NSP, and therefore they contracted (b) (4) to develop and validate a MSD-ECL based assay for screening/confirmatory/titer anti-rhPTH Ab, and a NAb bioassay. A fraction of the samples from the pivotal and PAR studies were retested with the MSD-ECL method, which continues being used in the ongoing studies. NAb were not evaluated in samples of the pivotal study.

ADA (rhPTH) MSD-ECL assay: (b) (4) (validation report TNJS11-172; TLIAM-207 SOP (appA), validation plan (appB)).

- The ADA are complexed between biotinylated drug and ruthenylated drug.
- SERUM SAMPLES are tested (b) (4)
- POSITIVE CONTROLS: screening PC: LPC=10 ng/ml; MPC=100 ng/ml; HPC=1000 ng/ml spiked in normal human serum; NC= normal human serum pool (new pools are compared to old pools for validation prior to use). Titer PC=HPC serially diluted 1:5.

TITER calculation: the end point of the test is the log₁₀ of the reciprocal dilution, obtained by interpolating the dilution at the cut point except where results from both duplicate wells are lower than the cut point. The titer PC must fall between log₁₀ values of 2.61 and 2.98 (mean 2.73) (See below Table11 -sensitivity, pp20). To accept the confirmatory controls, the % interference of MPC with and without drug, must be ≥86%.

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UPDATED METHOD REVALIDATION:

- The ratio cut point was established at 1.34 (99th percentile), based on the analysis of 32 individual normal human serum samples tested in 6 runs, with and without spiked 2.5 µg/ml of anti-rhPTH, in the presence of 6 nM rhPTH. The LPC and HPC were set at 2.5 and 10 µg/ml, respectively.

- Precision evaluation showed interassay precision for the HPC and NC to be higher than 30%CV. The sponsor is planning to test both pre and post-dose samples of the same subject in the same plate to ensure meeting acceptance criteria of the assay.
- PC Stability: LPC and HPC stability was tested by incubating the antibodies in matrix at different temperatures. Stability at -70°C was tested up to 12 days; the sponsor indicated that results from a 3 month period will be also provided in an addendum.
- Sensitivity and drug tolerance: despite it was tested for the original method, these parameters have not been revalidated for the updated method. The sponsor indicated in the BLA submission that was planning to report the data in an addendum, upon completion.

Reviewer's comments:

- (1) *A request for a complete validation report for the updated method was sent out in the IR letter from February 2014. The sponsor's response included a table with validation parameters still corresponding to the original method validation. This issue will be brought for discussion at the mid-cycle meeting with the sponsor in April 2nd. A new IR was sent to the sponsor in April 28th seeking clarification.*
- (2) *The sponsor provided the additional validation parameters in the response to April 28th IR (the end of this report). The neutralization assay is adequately validated.*

1.2. FOR OSTEOPOROSIS STUDIES

In these studies, postmenopausal women received up to 100 µg/ day for up to 36 months, different assays were used to evaluate the presence of ADA throughout studies conducted from 1997-2005).

ELISA (validated by (b) (4)) was used in study ALX1-11-821. The method protocol included a serial dilution of the samples and PC for titration.

MSD-ECL detection in M-series analyzer (validated by (b) (4)) was used in ALX1-11-93001, CL1-11-002, CL1-11-16, CL1-11-003.

- The method to detect PTH Ab is IGEN 440-0101
- The standards, quality controls and samples are diluted (b) (4)
- Data analysis is based in 4-parameter logistic algorithm.

- (b) (4)
- Cut point determination (based on 1997-2003 standards) – CP was initially set to be equal to 2 items the lower limit of quantitation of the assay, or 700 ng PTH/ml. Upon evaluating the results of baseline samples (505-11685 (median=1385) counts) and negative control (1170 counts), the cut point was recalculated with

the results of 18 assays (statistical CP) as mean+3SD and found to be 781 ng PTH/ml. Since this value was higher than the initial CP (700 ng/ml), the sponsor decided to use the original value.

- **Specificity:** The cut point of the confirmatory assay was established by analyzing the samples with and without labeled analyte. At this point, a MPC and HPC were added, which had to demonstrate $\geq 50\%$ inhibition in the presence of excess of PTH for the assay to be accepted.

NAb bioassay (validated by (b) (4)) was used in ALX1-11-93001 and CL1-11-002. None of the samples tested positives for NAb (based on 2005 regulatory standards).

- The bioassay uses (b) (4)
- Cut point was 170.745 pmol cAMP/ml, calculated with 25 lots of serum from elderly women (≥ 55 years of age) and 25 lots of serum from postmenopausal women of the target population, analyzed in three independent experiments. The cut point was reevaluated with pretreatment samples from study ALX1-11-93001 and established at 258.151 pmol cAMP/ml

7. Sponsor's answers to Immunogenicity IR (SN023) from 4/28/14

1. Regarding the ADA incidence on subjects with hypoparathyroidism:

FDA Request:

a. You calculated the % of ADA+ subjects based on 132 drug-naïve treated patients that received rhPTH therapy in the NSP-sponsored studies, including 90 subjects from study CL1-11-040. However, only approximately 1/3 of these 90 subjects' samples were tested using the validated MSD-ECL assay. Since the anti-rhPTH antibody incidence reported is based on the MSD-ECL results, please recalculate the percent of ADA+ samples considering the total number of subjects tested instead of the number of subjects treated with rhPTH.

NPS Response:

NPS has recalculated the % of ADA+ subjects based on MSD-ECL results and will update the label during labeling negotiations with the Agency using the recalculated number of subjects. The recalculated number of subjects tested with the validated MSD-ECL assay is (b) (4). Therefore, the label will be updated to reflect this change.

FDA Request

b. The results from the Bilizekian study samples (n=8) should not be combined with those from the NSP-sponsored studies, since the tested samples were collected 1-3 years after the end of treatment, and the short term assessment for the development of ADA is lacking.

NPS Response:

NPS agrees and will not combine our antibody results with the Bilizekian study.

FDA Request:

c. The incidence of ADA in the hypoparathyroidism study appears to be higher than that reported for the osteoporosis patients. Differences in the sensitivity of the assay as well as differences in the patient populations may have contributed to the distinct rates of ADA.

Therefore immunogenicity data obtained from hypoparathyroidism and osteoporosis studies should not be pooled together but could be reported separately, indicating that the serum ADA levels were evaluated with different methods and acknowledging potential differences in the susceptibility of the two populations to develop Ab against rhPTH.

NPS Response:

NPS agrees and will not pool hypoparathyroidism and osteoporosis studies when providing updates on immunogenicity. In the integrated summary of immunogenicity we reported the results for hypoparathyroidism and osteoporosis studies separately (ISI section 2.1 and 2.2), however, in the conclusion we did pool the data.

Reviewer's comments:

The answers to question 1b and 1c are acceptable. In response to question 1a, the sponsor claims to have a new value for the incidence of ADA based on (b) (4) subjects screened for the presence of ADA by MSD-ECL (instead of the original referred 132 subjects that were enrolled). These data has not been included in this submission, nor the details of the (b) (4) subjects considered in the calculations. According to our assessment, only 87 subjects were evaluated by the MSD-ECL assay. These discrepancies will be further discussed on the labelling section.

2. Regarding the immunogenicity assays and their validation:

FDA Request:

a. You report the Ab titer from ADA+ confirmed samples as the log10 of the reciprocal dilution in which the result is above the CP of the assay. Confirm that the initial dilution of the serum (b) (4) is considered in the titer determination or recalculate and resubmit the data as needed.

NPS Response:

There are two dilutions that we need to define. The first dilution is the minimum required dilution (MRD) and it is part of the assay procedure like incubations and plate washing. It is a constant item that cannot be taken into account when we calculate concentrations or titers. The second dilution is defined as the titration dilution which is the dilution of the samples that will result in at least one result below the cut point of the plate (negative result).

This titer dilution is applied only to certain samples and it is not a constant factor that will impact the whole plate.

The (b) (4) MRD is not included in the titer calculations. The MRD is part of the assay procedure. The negative controls undergo the MRD procedure and therefore the cut point response is related and dependent on the MRD performed. The dilution of the samples until a value is obtained below the cut point of the assay is therefore dependent on the MRD. Therefore the dilution cannot be multiplied by the MRD. We list the titer series as 1, 5, 25, etc. with the 1 being the initial dilution of the MRD.

Reviewer's comments:

The sponsor reports the Ab titer as the log10 of the reciprocal dilution obtained by interpolating the dilution at the cut point except where results from both duplicate wells are lower than the cut point. Titer values are referred to the MRD of the sample ((b) (4) dilution from the raw serum sample). The sponsor should clearly state in the application that the titers are not for the raw serum samples, or adjust the titer value accordingly.

FDA Request:

(b) (4)

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Reviewer's comments:

The sponsor reiterates the explanations given in the BLA application regarding the evolution and current status of the neutralization assay validation. This narrative of the events was and is perfectly understood.

However, the issues from question 2b were not addressed in this response.

(b) (4)



(b) (4)

Given the fact that the NAb method has been changed and adequately revalidated, no further action is needed regarding the validation parameters of the original method.

FDA Request:

c. The information regarding full validation for the updated (modified) NAb assay requested in an IR letter from February 26th, 2014 is still pending, since the table referenced in your response includes validation parameters from the original assay validation report (drug tolerance and sensitivity) that were not confirmed using the method used to test the clinical samples. As per your statement in the TNJR11-174 report saying “Drug tolerance and sensitivity will be conducted with the revised method and reported as an addendum (with additional long term stability [at -70°C]) to the validation report”, please provide these updates or clarify your response to our IR letter.

NPS Response:

The [addendum to the validation report TNJR11-174](#) that identifies additional sensitivity, drug tolerance and long term stability, is attached.

The requested parameter results have been provided in the above mentioned addendum. The sensitivity of the revised method was established to be (b) (4) and the drug tolerance was determined to be (b) (4) in pNHS spiked with the HPC and LPC Ab concentrations. Long-term stability was tested up to 285 days at the nominal temperature of storage (-70°C), showing stability of the PC throughout this period of time.

Reviewer’s comments

The method is considered completely validated. The sponsor should update the summary table with the validated parameter values determined for this assay.

FDA Request 3:

We are concerned that proposed the endotoxin specifications allow for up to (b) (4). Low levels of endotoxin can contribute to product immunogenicity. Revise your product release specifications to reflect your manufacturing experience and reduce the immunogenicity risk.

NPS Response 3:

The proposed endotoxin limit of NMT (b) (4) was established using the calculation method as defined in the USP/NF<85> monograph. Using the compendium calculation with a “K” value of (b) (4) and body weight of (b) (4), an endotoxin exposure of (b) (4) is considered acceptable. The Sponsor has established the acceptance criterion for the limit specification at (b) (4). The endotoxin exposure from Natpara for Injection, having a daily injection volume of only 71.4 µL (0.0714 mL) at the maximum proposed endotoxin limit of (b) (4) results in a worse-case patient exposure of (b) (4) per day, or less than (b) (4) of endotoxin level considered safe by the USP/NF.

The proposed endotoxin limit of NMT (b) (4) is supported with data obtained from 69 commercial scale batches. Table 3.2.P.5.4-6 in the BLA, lists the endotoxin limit values obtained demonstrating they range from (b) (4). The results are reported as a function of the lowest endotoxin standard dilution concentration used in the assay method.

The overall sensitivity of the method is dependent on the sensitivity of the LAL reagents and the sample dilution required to obtain acceptable recovery. Based on these data, the Sponsor has proposed a commercial specification limit for endotoxin (NMT (b) (4)) as appropriate for Natpara for Injection. This limit is consistent with the historical manufacturing experience for the product.

In response to Information Request 13, Question 5, the Sponsor summarized the clinical experience wherein there was no evidence of immune-mediated pathologies or hypersensitivity events specific to rhPTH(1-84) or the development of non-neutralizing anti-PTH antibodies in the subjects treated with rhPTH(1-84) in the hypoparathyroidism and osteoporosis studies. The presence of non-neutralizing anti-PTH antibodies, while observed, was determined to be within a range typical of protein therapeutics. There have been no recommended changes to treatment based on the presence of these antibodies.

Reviewer’s comments

The sponsor currently bases the specs for endotoxin on the maximal allowable dose of endotoxin per day per (b) (4) patients. Since endotoxin not only is important due to the pyrogenicity issues associated with it but also as a measurement of manufacturing control, will ask the Sponsor to change the spec and to base it on the manufacturing history need to change the lot specifications. Endotoxin levels on drug product clinical lots should be reported as the actual value obtained through manufacturing experience rather than the maximum level recommended by USP/NF monograph.

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

/s/

MONTSERRAT PUIG
09/12/2014

DANIELA I VERTHELYI
09/12/2014



Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

CDRH Human Factors Review

*** This document contains proprietary information that cannot be released to the public***

DATE: September 5, 2014

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID
TO: Elizabeth Chen, Regulatory Project Manager, CDER/OND/ODEII/DMEP

SUBJECT: **BLA 125511**
Applicant: NPS Pharmaceuticals
Device Constituent: Natpara Pen and Mixing Device
Drug Constituent: parathyroid hormones (ALXI-11)
Intended Treatment: replacement of endogenous parathyroid hormone
CDRH CTS Tracking No. 1400236

Digitally signed by Quynhnhu T. Nguyen -S
Date: 2014.09.08 15:59:42 -04'00'

QuynhNhu Nguyen, Combination Products Human Factors Specialist
(Human Factors Premarket Evaluation Team - HFPMET)

Ronald D. Kaye -S

Digitally signed by Ronald D. Kaye -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, cn=Ronald D. Kaye -S,
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Date: 2014.09.08 16:14:42 -04'00'

Ron Kaye, Human Factors and Device Use-Safety Team Leader (HFPMET)

CDRH Human Factors Review

Overview and Recommendation

The , Center for Drug Evaluation and Research, requested CRH Human Factors Premarket Evaluation Team (HFPMET) consultative review of the human factors validation study report included in the BLA 125511 (available at: <http://cberedrweb.fda.gov:8080/esp/cberedr.jsp?folderObjId=0bbcaea681333995>).

This human factors validation study consisted of training and testing sessions for 3 user groups: experienced lay people (ELP), inexperienced lay people (ILP), and health care providers (HCP). The lay people (LP) participated in 3 testing sessions (day 2, day 15, and day 29, and day 1 being the training day) and the HCPs participated in 1 testing session. In the testing sessions, participants were asked to perform a series of tasks and answer open-ended questions. Both observational data and subjective evaluations from the participants were collected. There were 15 healthcare providers and 39 lay people participated in the study.

This human factors reviewer discussed the results associated with multiple and single missed dose and underdosing via email. This human factors consultant stated that there were multiple use errors that would result in single underdose/missed dose and of multiple underdoses/missed doses. And the Sponsor is stating that the clinical significance associated with these errors are “slight,” which means that hazard may cause temporary impairment of a body function or temporary damage to a body structure and does not require medical/surgical intervention to prevent permanent damage. The Sponsor did not implement additional mitigations to effectively reduce these use errors. Therefore, this reviewer would like to defer to CDER’s clinical expertise. If CDER believes that instances of single underdose/missed dose and of multiple underdoses/missed doses can cause serious harm, then this consultant will develop deficiencies to have the Sponsor address our concerns. If CDER believes that the Sponsor’s approach is acceptable, then I do not have any deficiencies. CDER medical officer indicated that missing a single dose can result in clinically important hypocalcemia, esp. if a patient was on an otherwise stable dose of drug and calcium/vitamin D supplements. Theoretically, the patient would have symptoms reflective of hypocalcemia and would take extra supplements (this population is used to this issue). But, this can cause serious harm, and would be worsened by multiple missed doses. Based on this feedback, this human factors reviewer formulated several information requests that were issued to the Sponsor. Please see appendix 1 for more details.

The Sponsor stated in their response to the information requests that they agree that any missed dose or underdose is not desirable, however, the FDA’s primary assertion that single missed doses or underdoses could lead to clinically important hypocalcemia is inconsistent with the clinical data available on the drug. The human factors reviewer emailed the medical officer to clarify that the Sponsor continues to believe that a single underdose is not clinically significant (based on the study referenced in my previous email) and no further changes necessary to the product is necessary. The human factors reviewer requested for clinical’s input regarding this assessment. The medical officer indicated that in regards to the hypocalcemia issue, these patients know what happens when they do not take their medicine (currently calcium and vitamin D), and in this regard their awareness will not change. From a missed dose perspective, there is little the Applicant can do. As far as underdosing, clearly repeated underdosing (from a device

failure) is not acceptable. However, these patients are familiar with the signs and symptoms of hypocalcemia. There may be instances of hypocalcemia even with proper dosing (for unclear reasons, as we occasionally saw in the clinical trial), and therefore the medical officer suggested that there should be an emphasis on the IFU and training. To this point, the Sponsor has provided a Proposed Commercial Support and Risk Mitigation Strategy to further address these concerns. Please see Appendix 2 for more details on this strategy. In addition, the Sponsor reported that changes were made to the IFU after the validation study was completed. (b) (4)

After re-analysis of validation test findings and evaluation of Sponsor's response, this human factors reviewer believes that the Sponsor has adequately responded to the concerns associated with the use errors associated with risks of underdosing and overdosing by indicating that further modification to the device is impractical, however, the Sponsor will specify that training will be a requirement prior to use. The Sponsor's Proposed Commercial Support and Risk Mitigation Strategy will ensure that every patient is to be properly trained at the initiation of their Natpara therapy and then again at Day 15 for a refresher training session; at Day 15 the patient will have an option to have the refresher training over the but the face to face training will be encouraged (continued 24/7 telephone support will remain available at any time). In addition, The pen, which is included in the starter-kit, will be delivered to the patient by the trainer during the first training visit, making it impossible for the patient to self-inject Natpara medication before being trained to proficiency on correct use of the Q-Cliq pen. In addition, the Sponsor has revised the training manual to address each comment made by this reviewer. The changes that have been made to (1) provide clear instructions and reinforce to patients that they need to verify that the device components have been properly assembled prior to performing the priming and administration step, (2) clearly communicate the specific device (tactile/auditory/visual) feedback in each of the preparatory steps, (3) reinforce the availability of the 1-855-NATPARA number in case patients have any questions or need further assistance, (4) emphasize the need to hold for 10 seconds after injection, and how important it is, and (5) reinforce the importance of keeping the large needle cap for further recapping of the pen and demonstrate proper technique

This human factor reviewer agrees that the use events that may lead to multiple missed doses or underdoses without user awareness that were observed in the current study are limited to short periods of time (one cartridge or less than 2 weeks) and are unlikely to recur over the life of therapy. The product design includes a dose indicator scale displays to users that doses are not being delivered, thereby providing feedback that patients can use to self-correct. In addition, users in have access to the 1-800 phone number for assistance.

As a result, this reviewer accepts the human factors study results and the Sponsor's proposed Commercial Support and Risk Mitigation Strategy with one recommendation that the Sponsor emphasize the requirement on training in the product IFU and communication to prescribing physicians.

CDRH Human Factors Review

Combination Product Device Information

Submission No.: [BLA 125511](#)

Applicant: NPS Pharmaceuticals

Device Constituent: Natpara Pen and Mixing Device

Drug Constituent: parathyroid hormones (ALXI-11)

Intended Treatment: replacement of endogenous parathyroid hormone

CDRH Human Factors Involvement History

- 10/31/2014: CDRH HFPMET received a request to review human factors validation study report
- 4/1/2014: CDRH HFPMET reported for the mid-cycle meeting that the review is on-going but the report identified critical task failures and the Sponsor asserted that the residual risks are acceptable.
- 4/23/2014: CDRH HFPMET contacted the medical officer and requested for clinical input regarding the assessment of clinical significance associated with instances of single and multiple underdose/missed doses.
- 5/2/2014: CDRH HFPMET emailed project manager a list of information responses regarding concerns associated with use errors that could result in single and multiple underdose/missed doses. These IRs incorporated input from medical officer.
- 5/22/2014: CDRH HFPMET received the Sponsor's response to the IRs.
- 6/5/2014: CDRH HFPMET emailed the medical officer indicating that the Sponsor appears to have a different assessment of risk associated with single and multiple underdose/missed doses. Response from medical officer was received on the same day.
- 9/8/2014: CDRH HFPMET provided review recommendation to CDER.

Summary of Human Factors Related Information

This human factors validation study consisted of training and testing sessions for 3 user groups: experienced lay people (ELP), inexperienced lay people (ILP), and health care providers (HCP). The lay people (LP) participated in 3 testing sessions (day 2, day 15, and day 29, and day 1 being the training day) and the HCPs participated in 1 testing session. In the testing sessions, participants were asked to perform a series of tasks and answer open-ended questions. Both observational data and subjective evaluations from the participants were collected. There were 15 healthcare providers and 39 lay people participated in the study.

15 HCPs were tested the day after they were trained. During the HCPs' testing sessions they were asked to demonstrate how to use the device as if they were instructing a new patient. Their demonstration included mixing a new cartridge, attaching the new cartridge onto the pen, priming the pen, and performing an injection. Eight HCPs successfully completed the testing scenario with no use events. Two HCPs had some difficulty, but successfully used the product, and 5 HCPs failed to correctly complete the testing scenario due to difficulty on 1 of the 3 different tasks.

For LPs, the first testing session, "Day 2", was the day after training in order to simulate real life initial use of the device at home. During the LPs' "Day 2" testing sessions they were provided with the product that had previously been assigned to them during training. At the end of

training, they had used their own assigned device to inject their first dose into a thigh pad (which simulated “Day 1” dosing). On “Day 2” LPs were asked to pretend they were at home and to deliver their second dose/injection. All 39 LPs participated in “Day 2” testing. Of those, 29 completed the testing scenario with no use events. Five LPs (4 ILPs and 1 ELP) had some difficulty, but successfully used the product, and 5 LPs (2 ILPs and 3 ELPs) failed to correctly complete the “Day 2” testing scenario due to difficulty on at least 1 of 4 different tasks. The second testing session, “Day 15”, was scheduled at least a week after “Day 2” testing for each participant and simulated the transition from the first 14-day cartridge to the second 14-day cartridge. A 1-week delay approximates the memory decay that occurs in real life over 2 weeks. Thirty-eight LPs participated in “Day 15” testing. Thirty-two LPs completed the testing scenario with no use events. Four LPs (2 ILPs and 2 ELPs) had some difficulty, but successfully used the product, and 2 ILPs failed to correctly complete the “Day 15” testing scenario due to difficulty on the same task. The final testing session, “Day 29”, was scheduled exactly 2 weeks after the “Day 15” testing sessions so that the Medication Cartridge Trackers filled out during their “Day 15” scenarios correctly matched the date of their “Day 29” testing scenarios. The participant needed to recognize that the cartridge was empty and replace it by mixing a new cartridge and preparing the pen. Thirty-eight LPs participated in “Day 29” testing. Sixteen completed the testing scenario with no use events. Eleven LPs (5 ILPs and 6 ELPs) had some difficulty, but successfully used the product, and 11 LPs (7 ILPs and 4 ELPs) failed to correctly complete the scenario due to difficulty on at least one of 6 tasks.

The use events observed or reported that are associated with slight harm follow and are organized by hazard, which in all cases were dosing error or needlestick.

- a Multiple missed doses/underdoses per cartridge
- b Single missed dose/underdose per cartridge
- c Missed doses/underdoses during initial use of the 1st cartridge or only affecting one cartridge
- d Needlestick

The following section provides a summary of the use errors observed in the study.

Multiple missed doses/underdoses per cartridge

- Task 4. Screws the pen needle tightly onto the medication cartridge
Two participants (2 HCPs) did not attach needles before attempting to mix. The Sponsor clarified that the residual risk of not attaching a needle before mixing leading to stoppers in the incorrect position. In addition, the study has demonstrated that trained users are likely to recognize if the stoppers are not together and subsequently self-correct and/or call for support.
- Task 8. Turns the wheel until the 2 stoppers no longer move and the wheel turns freely
Three participants (2 ILPs and 1 ELP) turned the wheel until the stoppers came together but not until the wheel turned freely. The Sponsor clarified that if the user orients the pen base in an upward direction while attaching the cartridge, no medication will leak out, and the rod on the pen base will move the stoppers into the correct position. The Sponsor confirmed that all three participants in the study oriented the pen in the correct direction.
- Task 23. Inverts pen with needle pointing down and taps air bubbles that may be present away from the needle end of the medication cartridge

The Sponsor reported that two participants (1 ILP and 1 HCP) tapped the cartridge with the needle pointing up. This human factors consultant believes that these should not have been reported as errors since the participants pointed the needle up which did not cause any drug loss.

- Task 31. Counts to at least 10 after pressing the injection button before removing the pen from the foam injection pad (i.e., simulated skin)
Two participants (1 ILP and 1 HCP) did not count to 10 before removing the pen. Both of the participants who failed to count to 10 held the button long enough to deliver a full dose and because neither of these participants attempted to inject a second time.

Single missed dose/underdose per cartridge

- Task 2. Fills in Medication Cartridge Tracker
Two participants (2 ILPs) said they could still use the medication on the “Discard on” date. The Sponsor clarified that this use event would only result in a single missed dose per cartridge.
- Task 15. Ensures that the dose window on the pen is set to the zero position (0 mark) [before attaching cartridge]
One participant (1 HCP) checked to ensure the pen was set in the 0 position after attaching the cartridge (it was) to the pen base, instead of before. Six participants (3 ILP, 2 ELP, 1 HCP) did not check to see if their pens were set to 0 before attaching the cartridges (they were all already set to 0) to the pen base, which may lead to a single underdose per cartridge.
- Task 20. While holding the pen with the needle pointing up, presses the injection button on a flat surface, such as a table top, all the way until it stops and the 0 mark becomes visible in the dose window. Four participants (2 ILPs and 2 ELPs) did not prime and 1 participant (1 HCP) indicated confusion about how to complete the priming step. These results would lead to a single underdose per cartridge.
- Task 37. Recognizes on the empty medication cartridge
Four participants (3 ILPs and 1 ELP) attached needles to empty cartridges and tried to turn the dosage knob to "GO." They felt resistance, stopped, and then mixed new cartridges. One participant (1 ELP) was not sure if the medication cartridge was empty on “Day 29” and called 1-800 phone support. One participant (1 ILP) turned the dosage knob most of the way to "GO" and then attempted dose delivery with an empty cartridge.

Missed doses/underdoses during initial use of the 1st cartridge or only affecting one cartridge

- Task 18. Screws the medication cartridge onto the pen
Three participants (3 ILPs) failed to fully attach the cartridge to the pen base. Two additional participants (1 ILP and 1 ELP) resolved an initial difficulty of attaching the cartridge onto the pen base by pushing hard and repeatedly screwing and unscrewing the cartridge until it was fully attached. The Sponsor clarified that the system is designed to provide feedback via the stoppers progressing along the dose indicator scale.
- Task 24. Turns the blue dosage knob so that "GO" is visible in the dose window (instead of 0)
Two participants (2 HCPs) did not turn the knob to "GO," but self-corrected the mistake before delivering a dose. The Sponsor clarified that the system is designed to provide feedback via the stoppers progressing along the dose indicator scale. The results of the

study indicate that this feedback will prompt some users to subsequently preempt this use event thereby limiting the use event to the initial cartridge. Users who begin using the device correctly will likely not develop this problem with later cartridges because they will learn the feel of pressing the cocked injection button.

Needlestick

- Task 34. Places needle cap on the pen needle and discards both in a puncture resistant container

Two participants (2 ILPs) discarded the large needle cap before recapping their needle. The residual risk of a needlestick is acceptable because no participants had an accidental needlestick. All participants properly disposed of their needles and all participants evaluated understood the labeling regarding proper disposal of needles.

Appendix 1: Information Requests and Evaluation of Sponsor's Responses

FDA Information Response # 1:

We are unable to conclude that the Human Factors (HF) validation study demonstrates that the device can be used safely and effectively by intended users. There were multiple reports of critical use errors which may lead to single and multiple missed-doses, and underdose and needle stick injuries that could lead to patient harm. You stated that the severity of harm associated with the instances are "slight" meaning that the hazard may cause temporary impairment of a body function or temporary damage to a body structure and does not require medical/surgical intervention to prevent permanent damage. However, we believe that the clinical harm associated with a single missed-dose or underdose could lead to clinically important hypocalcemia, and consequently, multiple missed-dose (s) and underdose(s) can exacerbate the patient conditions. In addition, needle stick injuries represent a known risk with needle-based devices that should be adequately mitigated.

Summary and Evaluation of Response: The Sponsor stated that they agree that any missed dose or underdose is not desirable, however, the FDA's primary assertion that single missed doses or underdoses could lead to clinically important hypocalcemia is inconsistent with the clinical data available on the drug [see Attachment 1 for the Summary of Hypocalcemia Events in REPLACE (Study CL-11-040)]. The human factors reviewer emailed the medical officer to clarify that the Sponsor continues to believe that a single underdose is not clinically significant (based on the study referenced in my previous email) and no further changes necessary to the product is necessary. The human factors reviewer requested for clinical's input regarding this assessment. The medical officer indicated that in regards to the hypocalcemia issue, these patients know what happens when they do not take their medicine (currently calcium and vitamin D), and in this regard their awareness won't change. From a missed dose perspective, there is little the Applicant can do. As far as underdosing, clearly repeated underdosing (from a device failure) is not acceptable. However, these patients are familiar with the signs and symptoms of hypocalcemia. There may be instances of hypocalcemia even with proper dosing (for unclear reasons, as we occasionally saw in the clinical trial), and therefore the medical officer suggested that there should be an emphasis on the IFU and training.

FDA Information Response part 1a:

There are three specific areas of concern:

- a. We note that the use of the device requires manual assembly of different components prior to priming and administration of the drug i.e. attaching the needle, attaching the medication cartridge onto the pen, turning the wheel on the mixing device, turning the blue dosage knob so that the dose window shows the word "GO", etc. Consequently, the HF study showed that use errors largely occurred while users performed these preparatory steps. And comments from study participants indicated some notable concerns regarding the tactile/auditory feedback when attaching the needle, confusion regarding the stoppers stop moving versus the wheel stop moving, visual feedback from the stoppers, the needle to keep the needle in place while priming, holding the device in the up-right orientation when tapping when some users may be accustomed to holding it downwards, etc.

Summary and Evaluation of Response: User comments on preparation and Errors during Preparatory Steps

- Tactile/Auditory feedback when attaching the needle: It should be noted, these were comments and preferences. There were no use errors in the summative study where the user could not successfully attach the needle.
- Confusion regarding the stoppers stop moving vs. the wheel stop moving, visual feedback from the stoppers. The Sponsor clarified that they recognize that patients might have difficulty in regards to the stoppers position and while there is a visual feedback during mixing in place, and they have reinforced the descriptions in the Training Manual and NPS believes the extensive and personalized training provided for all patients is the optimal mitigation for this concern.
- Keep Needle in place while priming: Only one user removed the needle during priming. The potential consequence of removing the needle during priming is a potential underdose only if the user reattaches the needle without the pen in an up-right position – otherwise there are no consequences. A single underdose is not clinically relevant, as it will not impact the patient’s treatment. Finally, changing the IFU is unlikely to address the user’s misconceptions which can only be changed through training. The Sponsor has provided a Proposed Commercial Support and Risk Mitigation Strategy as part of this response.
- Holding (the pen) in an upright position when users may be accustomed to holding it down: The users are instructed to hold the pen in an upright position when priming and tapping. All users successfully followed the instructions while priming. While some users inverted the pen after tapping, the Sponsor does not believe this would lead to significant consequences and considering the personalized training.

FDA Information Response part 1b:

- b. We recommend that you further optimize your Instructions for Use (IFU) and training to successfully communicate to users the critical information, and to clearly communicate the specific device (tactile/auditory/visual) feedback in each of the preparatory steps. There is also a need to provide clear instructions to users that they need to verify that the device components have been properly assembled prior to performing the priming and administration steps, and if they need additional assistance, then they should be directed to call the 1-800-number.

Summary and Evaluation of Response: Although the users expressed these comments and preferences, these instructions and training have been developed, refined and fully optimized over several studies and the actual use experience from this summative study demonstrated that the critical information, including specific device (tactile/auditory/visual) feedback in each of the preparatory steps was understandable, and that the users were able to follow them without a pattern of use errors that could cause harm. In addition the IFU calls out the 800 number in eleven (11) different locations.

FDA Information Response part 1c:

- c. There were two use errors observed with the step of holding the device at the injection site for 10 seconds. The 10 seconds duration and the clinical consequence of underdose should be further emphasized in your IFU.

Summary and Evaluation of Response: The Sponsor continues to believe that a single underdose is not a clinically significant error. This is a manual injection, not an Autoinjector, thus removing the needle prematurely after a manual injection may result in a very slight underdose, unlike Autoinjectors where the injection may still be in progress. Clear instructions have been updated and improved based on formative studies, which resulted in reduced frequency. The Sponsor has provided a Proposed Commercial Support and Risk Mitigation Strategy as part of this response.

FDA Information Response part 1d:

- d. There were two use errors observed when two participants discarded the large needle cap prior to recapping. The importance of placing the cap onto the needle prior to discarding should be emphasized in your IFU.

Summary and Evaluation of Response: The Sponsor confirmed that in both cases, needle sticks did not occur and the users safely removed the needles. The Sponsor believes that the instructions are consistent with general use of Pen Needles. The Sponsor has provided a Proposed Commercial Support and Risk Mitigation Strategy as part of this response to further address this issue.

FDA Information Response part 1e:

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

Summary and Evaluation of Response: The Sponsor believes that although there were use errors identified in this summative study, we do not think that they would have caused patient harm. The Sponsor has provided a Proposed Commercial Support and Risk Mitigation Strategy as part of this response to further address this issue.

Appendix 2: Proposed Commercial Support and Risk Mitigation Strategy

(reference: sequence 0024,

<http://cberedrweb.fda.gov:8080/esp/cberedr.jsp?folderObjId=0bbcaea681333995>)

The risk of hypocalcemia following interruption or discontinuation of Natpara treatment has been identified in our Risk Management Plan for this orphan population. The key premise of our risk mitigation strategy for the use of Natpara/Natpara Q-Cliq is based on our ability to train each individual patient to proficiency by a national HCP network (mostly nurses/healthcare providers) before first use and at second use of the Natpara Q-Cliq. We submitted a refinement of our commercial support plan and details of this risk mitigation strategy in NPS Response to FDA Request #14 in the Filing Communication (74-Day) Letter. Key features of this risk mitigation strategy are highlighted below:

- Every patient is to be properly trained to proficiency individually (by a team of NPS representatives, mostly nurses/healthcare providers) on the use of the pen before the first injection (Day 1) and before the first change in cartridge/next reconstitution (Day 15). This plan removes from the process variations such as availability or ability of a HCP to train the patients.
- These nurses/healthcare providers will be scheduled and sent to a Natpara patient's home at Day 1 of initiation of their Natpara therapy and then again at Day 15 for a refresher training session; at Day 15 the patient will have an option to have the refresher training over the phone – as per Simulated Use Validation (Summative) Testing - but the face to face training will be encouraged (continued 24/7 telephone support will remain available at any time). NPS will utilize the training for proficiency assessment used in the Simulated Use Validation Testing of Natpara, with reporting and feedback mechanism to ensure these training sessions are completed and the patient is considered proficient in the mixing and administration of Natpara with the Q-Cliq.
- Additionally, if after the first training session the nurse (healthcare provider) does not feel that the patient is sufficiently trained, they can schedule additional daily home visits, as needed. A training kit that includes the actual device will be available for use by patients during the training sessions by the nurse.
- Each NPS representative (nurses/healthcare providers) who will conduct patients' training will each first be trained to ensure consistency. They will be tested and certified prior to them visiting and training a Natpara patient using the Training Manual (now revised to address FDA's concerns in IR 22) used during Simulated Use Validation Testing (summative study) of Natpara.
- The pen, which is included in the starter-kit, will be delivered to the patient by the trainer during the first training visit, making it impossible for the patient to self-inject Natpara medication before being trained to proficiency on correct use of the Q-Cliq pen.

Revised training manual that addresses FDA's comments in IR 22

The Sponsor has revised the Training Manual (that will be used by the NPS nurses/health care providers to train each patient) to address each comment made by the CDRH reviewer in IR 22. The changes that have been made are as follows. During the training of the nurse/healthcare providers, these elements of the revised Training Manual will be emphasized and likewise incorporated during the training sessions of each patient.

Changes made to the Training Manual

- Provide clear instructions and reinforce to patients that they need to verify that the device components have been properly assembled prior to performing the priming and administration steps.
- Clearly communicate the specific device (tactile/auditory/visual) feedback in each of the preparatory steps
- Reinforce the availability of the 1-855-NATPARA number in case patients have any questions or need further assistance
- Emphasize the need to hold for 10 seconds after injection, and how important it is.
- Reinforce the importance of keeping the large needle cap for further recapping of the pen and demonstrate proper technique

In addition to the demonstrated training in the summative study, we have undertaken the following:

1. NPS is committed to providing a comprehensive support program for this orphan population once the product is available commercially.
2. To address the FDA's comments, we have revised our Training Manual to emphasize the specific areas of concern identified in IR 22.
3. In the risk management plan, NPS has revised the commercial support and risk mitigation strategy to include:
 - a. nurse (or healthcare provider) visiting the patient's home to deliver the pen and to train the patient on how to prepare and administer Natpara on Day 1.
 - b. a follow-up nursing visit on Day 15 to reinforce proper technique for changing the Natpara cartridge.
 - c. if after the Day 1 and 15 training sessions the patient does not demonstrate sufficient proficiency, the nurse (health care provider) can schedule additional daily training visits.
 - d. Elements of the revised Training Manual will be emphasized during each individual training session thus addressing specifically the concerns by the CDRH reviewer.
 - e. the availability (by phone) of a trained pen specialist 24/7.
 - f. each training nurse delivering the Natpara Q-Cliq to the patient during the first training session to ensure that no patient can self-inject Natpara unless they have been first trained to proficiency to safely and effectively use the Natpara Q-Cliq.
 - g. close monitoring for any adverse events of hypocalcemia/hypercalcemia via our post-marketing surveillance program.

The Sponsor believes that:

1. this proposed risk mitigation strategy provides a comprehensive real world assurance to ensure each patient can safely and effectively use the Natpara Q-Cliq, thus reducing as much as possible any opportunity for use errors that could result in possible hypocalcemia and/or needle stick injuries.
2. conducting another human factors (usability) study, as requested by the Agency, would not provide additional meaningful information about the safe and effective use of the Natpara Q-Cliq beyond the assurances of the currently proposed risk mitigation strategy.

Appendix 3: Device Related Information

Natpara Pen is delivery system for Natpara® (rhPTH[1-84]) for injection, a multi-dose injection device that consists primarily of Natpara in a disposable medication cartridge, a reusable injection pen (the Natpara Pen), and a reusable mixing device (the Natpara Mixing Device).

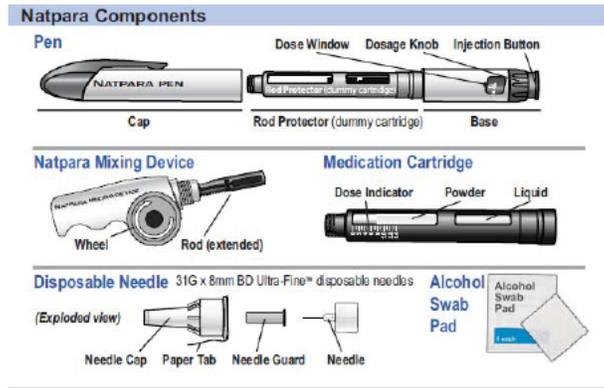


Figure 1: Device components

Changes were made to the IFU after the validation study was completed.

(b) (4)

No other changes are being made and these changes will not affect the layout, flow, or anything else that may impact the completion of tasks. These changes do not require any follow-up testing.

(b) (4)

Figure 2. Images a and c are from IFU version 04 March 2013, which was used in the current validation study (PAR-C12-003) and images b and d are from the revised IFU version 17 April 2013. The text regarding (b) (4) has been removed.

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

/s/

ELIZABETH R CHEN

09/09/2014

signing for QuynhNhu Nguyen (CDRH Human Factors reviewer)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Manufacturing Quality

DATE: August 27, 2014
TO: Meghna M. Jairath, CDER Division of Metabolic and Endocrine
Meghna.Jairath@fda.hhs.gov
Cc: Office of combination products at combination@fda.gov
Through: Francisco Vicenty, Chief, General Hospital Devices Branch,
Division of Manufacturing Quality, Office of Compliance, CDRH

Francisco Vicenty -S
2014.08.28 14:51:38 -04'00'

From: Viky Verna, MS BME, MS Pharm, Respiratory ENT General Hospital and Ophthalmology Devices Branch, Division of Manufacturing Quality, Office of Compliance, CDRH, WO66, Room 2628
Firm: NPS Pharmaceuticals, Incorporated
550 Hills Drive
3rd Floor
Bedminster, New Jersey 07921
Application # Original BLA 125511
Product Name: Natpara® (Recombinant Human Parathyroid Hormone (rDNA) or (rhPTH[1-84]))
Consult Instructions: NPS pharmaceuticals has submitted the BLA 125511 Natpara, a recombinant Human Parathyroid Hormone (rDNA) or (rhPTH[1-84]). This is biologic-device product. Please review the appropriate materials submitted in the EDR link.

Background

On October 31, 2013, the Office of Compliance at CDRH received a consult request from Meghna M. Jairath of CDER Division of Metabolic and Endocrine to evaluate the appropriate materials submitted by the applicant, NPS Pharmaceuticals, Incorporated for the Natpara®.

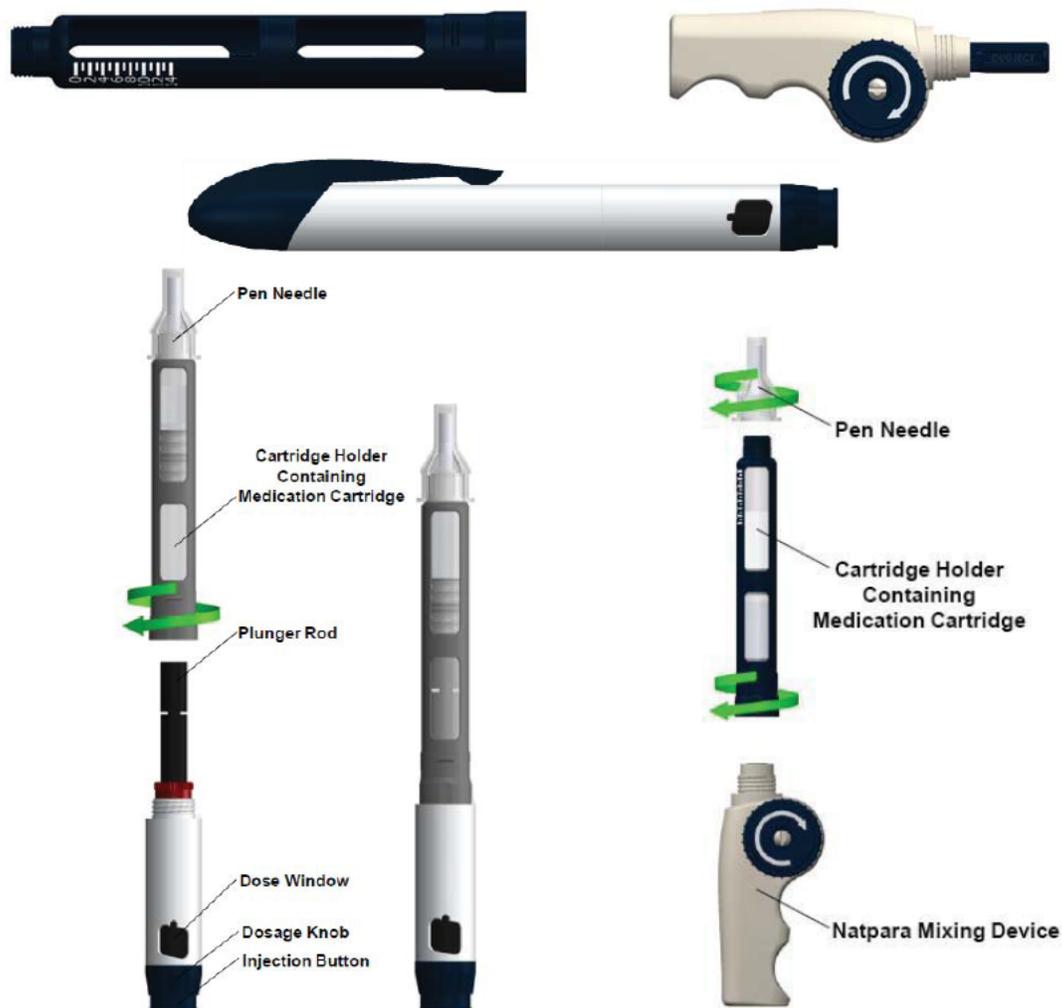
Combination Product Description

The Natpara® (rhPTH[1-84]) for injection is a replacement for endogenous parathyroid hormone (1-84) indicated for the long-term treatment of hypoparathyroidism. It is a

lyophilized formulation consisting of recombinant human parathyroid hormone, rhPTH(1-84), as the active ingredient which is formulated with the addition of various excipients.

The 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 drug product is supplied as a multiple dose glass dual-chamber cartridge. One chamber (designated as “Chamber 1”) contains a sterile lyophilized powder and the other chamber (designated as “Chamber 2”) contains a sterile diluent for reconstitution. The dual-chamber cartridge is provided in four different nominal dosage strengths (25, 50, 75, and 100 mcg/dose) that differ only in the concentration of the active ingredient. The disposable dual-chamber cartridge is designed for use with the pen injector with a targeted fixed-dose delivery volume of 71.4 μ L per dose. Using the pen injector, each dual-chamber cartridge is designed to deliver 14 doses; each dose containing 25, 50, 75, or 100 mcg of rhPTH(1-84), depending on the product dosage strength.



DOCUMENT REVIEW

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product.

In section 3.2.R2 of the application the firm provided information applicable to the medical devices and components associated with the Natpara® Reusable Pen (Haselmeier) “system,” which is used to reconstitute and deliver rhPTH(1-84) from the Natpara medication cartridge to treat hypoparathyroidism.

In the submission, the firm gave a description of each of the components and described the user assembly processes for the mixing and the injection operations. The firm also provided some key design, performance, and safety requirements for the cartridge holder, the mixing device, and the pen injector.

The cartridge holder is provided to the user pre-assembled with the Natpara medication cartridge. The Natpara Mixing Device and Natpara Reusable Pen are provided to the user packaged in separate individual folding cartons.

The manual assembly operations for the Natpara Mixing Device and the Natpara Reusable Pen are qualified through the inspection and expanded testing of assembled devices. The cartridge holders, Natpara Mixing Devices, and Natpara Reusable Pens are tested upon receipt at the sponsor’s secondary packaging site according to the release testing criteria below.

Multiple studies were conducted to verify the design of the Natpara Mixing Device and the Natpara Reusable Pen. The primary element of the design verification included demonstration of the safety and performance for the Natpara Reusable Pen in accordance with ISO 11608-1:20001. The pen was tested in conjunction with the Natpara Mixing Device and Natpara medication cartridge in the cartridge holder. Additional elements of the design verification also included a bioequivalence study and a biocompatibility assessment in accordance with ISO 10993-1. The firm provided summaries for the results of the different design verifications tests.

The firm explained that the Natpara Mixing Device, Natpara Reusable Pen, proposed commercial IFU, and training materials were developed and validated in accordance with IEC 62366:2007, Medical devices -- Application of usability engineering to medical devices and the FDA’s 2011 Draft Guidance for Industry and Food and Drug Administration Staff – Applying Human Factors and Usability Engineering to Optimize Medical Device Design. A “Human Factors and Usability Engineering Report” was prepared in accordance with Appendix A of the FDA draft guidance.

Deficiencies:

The following deficiencies were noted during the review:

1. The Applicant described and provided summarized results of the different tests conducted for the design verification and validation. However the firm did not provide its design control procedure covering the Design Input, Design output and Design Validation/Verification, including design changes, for the overall finished combination product in order to ensure that specified design requirements are met.

Therefore, the information provided by the firm has inadequately addressed the requirements of 21 CFR 820.30.

Response:

The applicant's response dated January 31, 2014, is adequate. The firm explained that the device constituent parts of this combination product were developed by Haselmeier (b)(4) over the last 6 years with input, oversight, and final approval by NPS Pharmaceuticals (NPS). NPS required that the design process be coordinated by Haselmeier under Haselmeier's established, formal quality systems and procedures developed as part of their conformance with ISO 13485 under NPS's oversight. The firm stated that the development process of the pen injector generated a documented Design History File that fully supports the entire combination product design. Under this Design and Development system the overall design plan that guided the project was initiated by Haselmeier and reviewed, accepted, and followed by all three companies (Haselmeier, (b)(4) and NPS). Design Input activities were initiated that resulted in the generation of documentation that included a Target Product Profile, an intended use, and a hazard analysis. From these documents, Haselmeier (with input from (b)(4) and NPS) developed a Product Design Specification. All of these documents were co-generated by the three parties, and were reviewed and approved by NPS. Throughout the project, Haselmeier performed and documented formal and informal design reviews in which NPS and (b)(4) participated. Once the design was complete, Haselmeier generated a Verification Matrix consistent with their procedures to verify all of the specifications in the final approved Product Design Specification (Design Output) for review and approval by NPS. Subsequently, Haselmeier created and executed NPS-approved Design Verification Protocols. Haselmeier performed the verification testing on the entire combination product with the results documented in reports which were reviewed by NPS and filed in the Design History File. NPS performed two elements of the design under its own procedures; Risk Management and Design Validation. Design validation was primarily accomplished through simulated use testing of all of the components of the combination product representative of the final system (medication cartridge, Natpara® Reusable Pen, and Natpara® Mixing Device) according to approved protocols. During the development process, NPS developed and implemented a formal Risk Management Program (RMP). The RMP contained a risk management plan, hazard analyses, risk analyses, and execution of risk mitigation/control. The process resulted in generation of a final Risk Management report addressing any remaining "residual" risks. Design Control procedures are available at Haselmeier and (b)(4) for review at the respective facilities.

2. The Applicant provided a table of the firms involved in the manufacturing of the combination product and the different device components, as well as their responsibilities. However, the sponsor firm did not provide a copy of the procedures for purchasing controls or supplier qualification. Also, the firm explained that the cartridge holders, Natpara Mixing Devices, and Natpara Reusable Pens are tested upon receipt at a secondary packaging site. However the firm did not provide the firm name and location of the secondary/final packaging site. The controls applicable to suppliers should be specified, and should include the requirement that the firm be notified of any changes made to the product

supplied that may impact the safety and effectiveness of the finished product. The procedures should describe the firm's supplier evaluation process and describe how it will determine type and extent of control it will exercise over suppliers. Therefore, the information provided by the firm has inadequately addressed the requirements of 21 CFR 820.50.

Response:

The applicant's response dated January 31, 2014, is adequate. The firm provided a Table in order to clarify the roles and responsibilities for all of the manufacturers responsible for Device Manufacturing operations. (b) (4) was added as a secondary drug packager/medical device packager. The firm provided detailed description of the responsibilities of (b) (4) and clarified that the components which are packaged are provided in separate packaging and are only combined by the end user. For supplier controls, the firm approves key suppliers on a review of the supplier's expertise and experience with the defined product or service requirements and past performance before executing a supplier agreement. All of the manufacturers listed in Table 17.1 were audited, and have signed Quality Agreements which at a minimum, require ongoing audits and change notification. These controls, as well as other elements such as oversight and approval by NPS on all batch release processes for Haselmeier, (b) (4) and (b) (4) (including final release of the product to intended markets) are required under NPS Supplier control procedures.

3. There was no information available for review regarding the establishment of a CAPA system compliant with 21 CFR 820.100.

Response:

The applicant's response dated January 31, 2014, is adequate. The firm confirmed that each of the firms involved with the manufacture of the device constituent parts of this combination product are registered medical device establishments, have CAPA procedures in conformance with 21 CFR Part 820.100, and are subject to oversight by NPS. NPS has recently updated its CAPA process to add the elements which are required to conform with the Medical Device CAPA requirements in Part 820.100. All of the procedures, including the NPS procedure will be available for review at the respective facilities.

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

Response:

The applicant's response dated January 31, 2014, is adequate. The firm further described the manufacturing activities of the finished combination product and provided diagrams to display the process flow. The device packaging facility and overview of the Device Quality System activities employed during device development were also described for the manufacturing activities of the finished combination product.

REGULATORY HISTORY

- NPS Pharmaceuticals, Incorporated
550 Hills Drive
3rd Floor
Bedminster, New Jersey 07921

No regulatory history could be found for the firm as it does not appear to be registered with the FDA.

Update:

A pre-approval baseline (Level 2 QSIT) inspection was initiated for Application#: Original BLA 125511, Natpara (Recombinant Human Parathyroid Hormone (rDNA)/(rhPTH[1-84])). The objective of the assignment was to inspect the firm's activities associated with the evaluation of the appropriate materials submitted by the applicant, NPS Pharmaceuticals, Inc. for the Natpara product. The inspection focused on management responsibility (21 CFR 820.20), design controls (21 CFR 820.30), corrective and preventive action (21 CFR 820.100), and purchasing controls (21 CFR 820.50). The inspection was performed from 4/28/2014 to 05/13/2014 and was classified as VAI on 06/14/2014.

(b) (4)
FEI: (b) (4)

The last inspection at (b) (4) which was completed on (b) (4), was classified NAI. The inspection covered quality subsystems Management, CAPA and Production/Process Controls. Design controls are not applicable to this site.

The previous inspection in (b) (4) (QSIT inspection) was also classified as NAI. The inspection noted no significant QSR issues; however, the following items were briefly discussed with management at the conclusion of the inspection: batch yield consistency, incomplete equipment usage logs, no cleaning SOP for (b) (4) equipment, and maintenance of employee training records.

RECOMMENDATION

The Office of Compliance at CDRH has completed the evaluation of the Original BLA 12551.

The applicant's response dated January 31, 2014, is adequate and the pre-approval inspection of NPS Pharmaceuticals, Incorporated, was classified as VAI. Therefore, CDRH/OC recommends approval of Original BLA 125511.

Viky Verna -S
Digitally signed by Viky Verna -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
cn=Viky Verna -S,
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Date: 2014.08.28 15:11:36 -04'00'
Viky G. D. Verna, MS BME, MS Pharm

Prepared: VVerna: December 20, 2013
Revised: MITejero: December 24, 2013; 12/26/2013
Revised: Vverna: December 24, 2013; December 26, 2013
Updated: VVerna: August 27, 2014

cc:
WO66-2628 Viky Verna
WO22-3387 Meghna M. Jairath
combination@fda.gov (OCP)

BLA 125511
CTS: ICC1300560; ICC1400395

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

/s/

ELIZABETH R CHEN

09/08/2014

Signing for CDRH Reviewer, Viky Verna

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: August 21, 2014

TO: Naomi Lowy, M.D., Medical Officer
Dragos Roman, M.D., Medical Team Leader
Meghna M. Jairath, Pharm.D., Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

FROM: Cynthia F. Kleppinger, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA: 125511

APPLICANT: NPS Pharmaceuticals, Inc.

DRUG: NPSP558; Recombinant Human Parathyroid Hormone (rhPTH[1-84]);
Natpara[®]

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

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

CONSULTATION REQUEST DATE: December 20, 2013

CLINICAL INSPECTION SUMMARY GOAL DATE: August 22, 2014

DIVISION ACTION GOAL DATE: October 24, 2014

PDUFA DATE: October 24, 2014

I. BACKGROUND

NPS Pharmaceuticals, Inc. is seeking approval of Recombinant Human Parathyroid Hormone (rDNA) or (rhPTH[1-84]); Natpara[®], a biologic-device combination product for long-term treatment of hypoparathyroidism. The application is based on the results of a multicenter, randomized, double-blind, placebo-controlled Phase 3 trial CL1-11-040 entitled, “A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Investigate the Use of NPSP558, a Recombinant Human Parathyroid Hormone (rhPTH[1-84]; Natpara[®]) for the Treatment of Adults with Hypoparathyroidism (REPLACE).”

The first subject was consented on December 18, 2008 and the last subject completed on September 28, 2011. There were a total of 33 sites in eight countries (with 20 in the US); 29 sites randomized subjects. A total of 196 subjects were screened, 134 subjects were randomized, and 120 subjects completed the study.

The primary efficacy variable was the percentage of responders at Week 24, based on investigator-prescribed data relating to a composite endpoint of three components. A subject was considered a responder if he/she achieved:

- At least a 50% reduction from the baseline oral calcium supplementation dose and
- At least a 50% reduction from the baseline active vitamin D metabolite/analog dose and
- An albumin-corrected total serum calcium concentration that was maintained or normalized compared to the baseline value (≥ 7.5 mg/dL) and did not exceed the upper limit of the laboratory normal range.

The secondary objectives of the study were to demonstrate that 24 weeks of treatment with once daily NPSP558 across a dose range of 50 μ g, 75 μ g or 100 μ g SC is associated with improvements from Baseline measurements in urinary calcium excretion.

These inspections were conducted as part of the routine PDUFA pre-approval clinical investigation data validation in support of BLA 125511 in accordance with Compliance Programs 7348.810 and 7348.811. General instructions were also provided with this assignment.

II. RESULTS (by Site):

Name of CI/ Site #	Protocol 040 # of Subjects Randomized	Inspection Date	Preliminary Classification
John P. Bilezikian, M.D. Site 1002	10	3/25/- 4/14/2014	OAI
Tamara Vokes, M.D. Site 1010	8	3/04/- 3/14/2014	NAI
Nelson Watts, M.D. Site 1015	4	3/10/- 3/18/2014	VAI
NPS Pharmaceuticals Inc.	N/A	3/06/- 4/25/2014	VAI
(b) (4)	N/A	(b) (4)	VAI

Key to Classifications

NAI = No deviation from regulations

VAI = Deviation(s) from regulations

OAI = Significant deviations from regulations; data unreliable.

Pending = Preliminary classification based on information in 483, preliminary communication with the field, and review of EIR; final classification is pending letter to site.

1. John P. Bilezikian, M.D.
Columbia University Medical Center
630 W 168th St, Room 864
New York City, New York 10032

- a. **What was inspected:** The initial inspection focused on Study CL1-11-040. However, based upon findings, it was expanded to include two additional NPS studies performed under IND 76,514 and submitted under BLA 125511:
 - PAR-C10-007 “A Randomized, Dose-blinded Study to Investigate the Safety and Efficacy of NPSP558, a Recombinant Human Parathyroid Hormone (rhPTH[1-84]), at Fixed Doses of 25 µg and 50 µg for the Treatment of Adults with Hypoparathyroidism (RELAY)”
Study was completed September 23, 2011.
 - PAR-C10-008 “A Long-term Open-label Study Investigating the Safety and Tolerability of NPSP558, a Recombinant Human Parathyroid Hormone (rhPTH[1-84]), for the Treatment of Adults with Hypoparathyroidism – A Clinical Extension Study (RACE)”
Interim cut-off date for analyses was March 25, 2013. Study is still

ongoing.

The inspection included review of all study subjects comparing hospital charts to case report forms and data line listings provided by the sponsor, consents, correspondences with the IRB and sponsor, laboratory data, primary and secondary efficacy data, drug accountability, financial disclosure, 1572s, adverse events, and concomitant medications.

- b. General observations/commentary:** For Protocol CL1-11-040, there were 13 subjects screened, 10 subjects enrolled, and nine subjects who completed the study. For Protocol PAR-C10-007, there were six subjects screened, five subjects enrolled, and four subjects who completed the study. For Protocol PAR-C10-008, the study is still ongoing. Four subjects have been enrolled. During the inspection it was noted that there is study subject #1002-023 with no line data from the sponsor even though the monitor reviewed and collected data on this subject and Dr. Bilezikian's site followed this subject. Clarification was received by the FDA investigator at the sponsor site during the inspection. This subject came from Site #1008 and was Subject #1008-0004. When the subject transferred from Site 1008 to Site 1002, the subject retained the original subject number.

Dr. Bilezikian is the Primary Investigator of Study CL1-11-040. Dr. Bilezikian was a site investigator in Studies PAR-C10-007, PAR-C10-008, and CL1-11-040. In addition, he conducted his own investigator initiated trial (IIT), HEXT Study, also referred to as the "Bilezikian IIT". Data from the separate, investigator-initiated trail is also included in the BLA. The institutional review boards (IRBs) of record were (b) (4) and Columbia University.

During the review of Studies PAR-C10-007, PAR-C10-008, and CL1-11-040, it was found that the study coordinator forged Dr. Bilezikian's signature and the signature of the subinvestigator Dr. (b) (4) on several documents. The study coordinator attested to the fact of signing the names and/or initials and signed an affidavit to that effect. Dr. (b) (4) signed an affidavit attesting to the fact that it was not her signature on 127 prescriptions. The signing of the Affidavits was in the presence of Columbia University representatives. The study coordinator was terminated from employment on April 11, 2014.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued. Included were the following significant deficiencies:

For Study CL1-11-040:

1. The Study Coordinator was found to have forged the signature of Dr. John P. Bilezikian, PI on the Statement of the Investigator, FDA-1572, dated June 29, 2011.

OSI Reviewer Comment: Dr. Bilezikian responded to the findings in a letter dated May 2, 2014. He agreed with this observation.

- Two SAE reports for Subject 1002-0005 were forged by the same Study Coordinator using Dr. Bilezikian's name on June 1, 2011 and again on March 1, 2011.

OSI Reviewer Comment: Dr. Bilezikian agreed with this observation.

- Review of prescriptions and discussion with the Study Coordinator revealed that he forged the signatures and/or initials of Dr. [REDACTED]^{(b) (4)}, a Sub-Investigator on this study. Further, the Study Coordinator used the prescription pad which belonged to Dr. [REDACTED]^{(b) (4)}. These prescriptions were written for the test article, PTH, magnesium, vitamin D, calcitriol, and calcium citrate and were filled at Columbia's Research Pharmacy and provide to the study subjects. All of the above were used for the treatment of study subjects per the study protocol.

A review found that there were 150 prescriptions written from 2009 to 2011, inclusive of this study. It was found that 127 of these prescriptions were forged by the Study Coordinator, using Dr. [REDACTED]^{(b) (4)} signature and/or her initials. Additionally, there were two prescriptions where the Study Coordinator forged the signature of Dr. Bilezikian, using Dr. Bilezikian's prescription pad.

OSI Reviewer Comment: Dr. Bilezikian agreed with this observation.

- A review of the study charts for Subject 1002-0003 found that Dr. Bilezikian signed off on this subject's inclusion/exclusion criteria on 11/26/09. A review of Dr. Bilezikian's appointment book for 2009 found that 11/26/09 is Thanksgiving Day; his entry into this appointment book states "University Holidays" for 11/26/09 and 11/27/09.

OSI Reviewer Comment: Dr. Bilezikian agreed with this observation. He stated he frequently goes into the office on weekends and holidays. He did not confirm that had happened on November 26, 2009.

For Study PAR-C10-007:

- Record review of the Regulatory Binder for this study found that the Study Coordinator, selected by Dr. John P. Bilezikian to run the day-to-day operations for this study, forged Dr. Bilezikian's name on the Investigator's Agreement, dated June 7, 2011.

OSI Reviewer Comment: Dr. Bilezikian agreed with this observation.

For Study PAR-C10-008:

6. Record review of the Regulatory Binder for this study found that the Study Coordinator forged Dr. John P. Bilezikian's name on the Statement of the Investigator, FDA-1572, dated May 20, 2011.

OSI Reviewer Comment: Dr. Bilezikian agreed with this observation.

7. Record review of the Regulatory Binder for this study also found that the Study Coordinator forged Dr. John P. Bilezikian's name on the Investigator's Agreement dated June 28, 2011.

OSI Reviewer Comment: Dr. Bilezikian agreed with this observation.

There were also several findings for all three trials concerning not following the protocol and delayed or absent procedures.

OSI Reviewer Comment: Dr. Bilezikian responded to the 483 items in a letter dated May 2, 2014. He stated that the Columbia University IRB's Executive Committee placed restrictions on his active protocols:

- The enrollment of new subjects was suspended. Currently enrolled subjects are allowed to continue their participation in the studies.
- The Chair of the Department of Medicine picked an interim PI who meets the institutional criteria to serve as a PI and is qualified to manage the studies to assume the role of PI in his place.
- An experienced senior research coordinator was hired to manage the studies.
- Research coordinators who are currently members of the research team must undergo re-training in good clinical practice and clinical research coordination.
- Mandatory weekly research meetings will take place for the entire research staff.
- Columbia University's Human Research Protection Office has initiated an audit of all studies that involved the study coordinator and/or Dr. Bilezikian. Findings will be shared with the FDA, OHRP and other regulatory agencies.
- The forgery of prescriptions has been reported to the State of New York Office of Professional Discipline.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. The audit indicates serious deviations/findings that would impact the validity and reliability of the submitted data. The violations are significant and indicate that the clinical investigator lacked oversight and repeatedly submitted false information to FDA and the sponsor. In addition, the scope, severity, and pattern of

violations support a finding that subjects have been exposed to an unreasonable and significant risk of illness or injury, data integrity has been compromised, and subjects' rights have been seriously compromised. Data from this inspection are considered not reliable.

2. Tamara Vokes, M.D.

University of Chicago
5841 South Maryland Avenue
Room M247, MC 1027
Chicago, Illinois 60637-1447

- a. **What was inspected:** The inspection included review of correspondences with the IRB and sponsor, study monitoring logs, training records, delegation logs, informed consent forms, notes to file, laboratory data, drug accountability, financial disclosure, 1572s, adverse events, and concomitant medications. There were 12 subject records reviewed.
- b. **General observations/commentary:** There were 10 subjects screened (two subjects were repeats and assigned different subject IDs after they were rescreened so there were a total of 12 subject IDs); there were eight subjects randomized and six subjects who completed the study.

Records were legible and organized. There were instances where the subject ID number was not placed on each individual page. Corrections made in source records were also not always initialed and dated. There was no evidence of under-reporting of adverse events and the primary efficacy endpoint data was verifiable. [NOTE: A University of Chicago Internal Regulatory Audit of study files uncovered adverse events in source documents that were not recorded in the study database. The audit uncovered non-serious adverse events that were not correctly evaluated for potential entry onto the eCRFs. The CRO (b) (4) visited the site and confirmed the findings of the University of Chicago Internal Regulatory Audit. The adverse events that were not entered into the database were symptoms of the disease, which the investigator did not initially consider reportable, since they were related to the subjects' underlying condition. In addition, there were omissions of events of injection site reactions. Of the 45 adverse events identified from the University of Chicago Internal Regulatory Audit, 8 were confirmed as valid for entry onto the eCRFs and 37 were verified as not valid because they were symptoms of the disease that had not worsened. These findings led to additional monitoring of 10 sites, with additional adverse events found. NPS Clinical department along with Data Management made a decision to unlock the database on March 16, 2012 and update it with the additional non-serious AEs, as well as medical history and concomitant medications that were identified. The database was re-locked on 05 April 2012].

There were no stated issues/problems with the pen device and no unblinding

during the study reported.

OSI Reviewer Comment: This statement by the site was found later to be incorrect per the monitoring report found during the sponsor inspection. The July 26-28, 2010 monitoring report states that “The iPTH result was included in the e-mail unblinding Ms. (b) (6). Dr. Vokes was notified on 05 July 2010 by Ms. (b) (6) that she had been unblinded. Dr. Vokes was not unblinded.” The subject was eventually discontinued due to noncompliance. A corrective action was put in place so that the lab would not send the values to the site again.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. Monitoring visits had discovered and corrected the missing adverse events before the FDA inspection. Although the one unblinding episode was found to be reported to the sponsor, it had minimal impact on the data. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

3. Nelson Watts, M.D.
University of Cincinnati Bone Health
and Osteoporosis Center
University of Cincinnati Medical Center
222 Piedmont Avenue
Suite 6300
Cincinnati, Ohio 45219*

*Current address where actual FDA inspection occurred (Dr. Watts moved to his current location after completion of the study):

Nelson Watts, M.D.
Mercy Health Osteoporosis and Bone Health Services
4760 East Galbraith Road
Suite 212
Cincinnati OH 45236

- a. **What was inspected:** The inspection included review of correspondences with the IRB and sponsor, training records, delegation logs, informed consent forms, laboratory data, drug accountability, financial disclosure, 1572s, adverse events, randomization, drug temperature logs, and concomitant medications. All four subject records were reviewed.
- b. **General observations/commentary:** There were 19 subjects screened and four subjects enrolled into the study. All four subjects completed the study. All four subjects remained blinded during the study and there were no instances in which

a subject had to be unblinded.

The assignment asked to investigate the electronic subjects' diaries. They were called Invivodata™ Diary PRO®. It was reported that subjects were not happy with the diaries as information could not be entered 24/7 but only during certain times of the day. Documented training was provided for each subject.

The assignment asked to investigate any pen device complaints. The site had several subject complaints that were submitted to the sponsor. There were no unreported complaints. Complaints consisted of the daisy tip sticking and becoming jammed requiring a new pen and cartridge to be dispensed; the cartridge becoming empty sooner than anticipated; the dose indicator only going half way and stuck half green/half red requiring a new cartridge.

There were no issues regarding the primary efficacy endpoints and the data was verifiable. There were no serious adverse events at the site. All adverse events were captured except as noted in the findings for Subject 1015-0003.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for the following deficiencies:

OBSERVATION 1

Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation.

For Subject 1015-0004, there are four inclusion criteria with no corresponding verification in the source documents.

History of hypoparathyroidism for ≥ 18 months post-diagnosis, inclusive of historical biochemical evidence of hypocalcemia and concomitant serum intact PTH concentrations below the lower limit of the laboratory normal range of 2 test dates at least 21 days apart within 12 months prior to randomization.

Requirement for active vitamin D analog/metabolite therapy with Calcitriol ≥ 0.25 ug per day or alaphacalcidol ≥ 0.50 ug per day prior to randomization AND supplemental oral calcium treatment ≥ 1000 mg per day over and above normal dietary calcium intake prior to randomization.



Appears this Way on Original

The principal investigator and study nurse stated that there were no other documents available to substantiate the inclusion/exclusion criteria.

The paper source document screening visit (documenting that all inclusion/exclusion were met) has the statement “Signature of Principal investigator that all inclusion and exclusion criteria have been met”; it was never signed by the PI. However, the electronic case report form identifies that the subject met all inclusion/exclusion criteria.

For the other three subjects enrolled into the study, they were enrolled 1-2 months before the PI signed off that they met all inclusion/exclusion criteria.

[Of note, Protocol CL1-11-040 Version 8.1 amendment 7 identifies 12 inclusion criteria required for enrollment. The paper source for Visit 1 also identifies 12 inclusion criteria. However, the electronic case report form only identifies 10 inclusion criteria. The two missing are serum magnesium levels and serum 25-hydroxyvitamin D level].

For subject 1015-0003, there were three adverse events documented as moderate in the paper source but mild in the electronic case report form (nausea, vomiting, URI).

OSI Reviewer Comment: Dr. Watts responded to the findings in a letter dated April 1, 2014. He reviewed the records of the subjects and confirmed that all met the inclusion/exclusion criteria. He contended that the magnesium levels and vitamin D levels at the end of optimization could not be inclusion criteria as they were not available at screening and could not be known before randomization. However, this issue was not addressed with the sponsor. Regarding the adverse event data, he stated that it appears to be data entry error. Dr. Watts offered no corrective actions.

- c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Data from this site appear acceptable.

4. NPS Pharmaceuticals, Inc.
550 Hills Drive, 3rd Floor
Bedminster, NJ 07921-1537

- a. **What was inspected:** Inspectional coverage of study protocol CL1-011-040 included the three sites that were inspected and one site chosen during the current inspection by the FDA investigator in support of BLA 125511 (Site 2001, Dr. Beckers). During the inspection, the following areas were reviewed: sponsor’s obligations, monitoring plans, monitoring reports, qualifications of clinical investigators and site monitors, electronic case reports forms (eCRF), selected inclusion/exclusion forms, selected informed consent forms, Clinical Study Agreements and financial disclosures of every clinical investigators, Data

Safety Monitoring Board, Standard Operating Procedures, training, adverse event reports, test article accountability, adequacy of monitoring and corrective actions taken by the sponsor/monitor/CRO, protocol deviations related to key safety and efficacy endpoints, and transfer of obligations to vendors. The firm registered the REPLACE study on ClinicalTrials.gov on August 8, 2008. The registration included all required information. Upon review of the registration at ClinicalTrials.gov, the purpose and description of the study reflected those stated in the protocol. The site was last updated on October 11, 2012 indicating that the study was completed

- b. General observations/commentary:** NPS (Natural Product Sciences) contracted out all activities for the study. During the inspection it was noted that many of the contracts were not signed until months after activities began and subjects had begun enrolling. After review of the SOPs which the firm supplied, most were not in effect until after the study had begun. Since the sponsor contracted out the majority of the study roles and responsibilities to CROs for the CL1-011-040 study, these CROs utilized their own SOPs. From the time of enrollment of the first subject on December 18, 2008, a fully executed Clinical Monitoring Plan (CMP) did not exist until June 16, 2009. The NPS Quality Assurance Unit did not have any SOPs when the study began.

Financial disclosure one year follow-up was missing for eight sites: 0002, 1004, 1007, 1019, 3001, 3002, 5001 and 8002. The sponsor staff stated that unsuccessful attempts were made to collect the information.

Inspection of records for the additional site (#2001, Dr. Beckers) found many issues with the completion and signing of paperwork, lack of oversight, and allowing study staff to make medical assessments. Screening at this site had been put on hold per NPS due to the multiple issues noted. Multiple issues continued due to Dr. Beckers' refusal to understand the protocol and receive training. The firm attempted to bring the site into compliance and decided to stop enrollment.

At the Bilezikian site (#1002), monitoring reports showed that throughout the study this site was continuously late completing logs, eCRF, drug accountability, etc. The pill counts were not used by the site to verify compliance or check accountability of subjects' supplies as the subjects progressed through the study. The site also did not perform procedures according to the time points specified in the protocol. Laboratory results were not reviewed in a timely manner and source documents were deficient. The monitor attempted to meet with Dr. Bilezikian but he was never available. The study coordinator had reported that he was responsible for 14 other active studies.

The FDA investigator was made aware of the falsified signatures at the Bilezikian site and was asked to investigate any sponsor knowledge of the

events. The Co-Monitoring Visit Report from September 19-26, 29 and October 1, 2011 states the following: “Upon review of all study source documentation applicable to PI or sub-investigator sign-off, further investigation is warranted to assure proper signature has been obtained from Dr. Bilezikian on such documents. Further investigation will commence as a sample of forms will be checked against the site signature log/delegation of authority log for further follow-up. This will include checking Dr. Bilezikian’s signatures on the following study documentation: FDA 1572’s, etiology forms, AESI’s, SAE’s randomization criteria forms, and internal chart source checks, when applicable. A follow-up visit will be made by NPS will commence to determine confirmation of a GCP violation.”

NPS Pharmaceuticals Study Contact Report dated January 5, 2012 documented a meeting between Dr. Bilezikian, the study coordinator, and NPS staff. The document states the following: “The rationale for this visit was to discuss findings noted from the September 26, 2011 to September 30, 2011 visit as due diligence”. During the visit Dr. Bilezikian attested to his signature on all forms presented to him.

On March 17, 2014, the FDA investigator was informed that the sponsor staff was performing inspection readiness training at Site 1002 (Dr. Bilezikian) and the study coordinator admitted during the preparation that he had signed Dr. Bilezikian’s signature to a number of documents involving studies CL1-011-040, PAR-C10-007, PAR-C10-008 and PAR-C10-008 extension study. Documents from study CL1-011-040 included approximately 150 study related prescriptions; Financial Disclosure by clinical investigator dated 5/1/12; two “Note to File” dated 9/1/11; One “Note to File” dated 9/21/11; and 12 “Primary Hypoparathyroidism Etiology Forms”.

During the inspection, the FDA investigator asked when the firm first knew that there was suspected forgery at Site 1002 and was told not until March 2014. The FDA investigator attempted to have affidavits signed but was told that the firm does not allow anyone to sign an affidavit or to listen to one. The FDA investigator requested and was provided with a copy of the QA Regulatory Authority Inspection Readiness Report, dated March 11-12, 2014. The report documents what the consultants covered during their inspection readiness training and provides a list of documents in question that the study coordinator confirmed he signed.

The FDA investigator requested the correspondences between the CRO (b) (4) and NPS and reviewed the documents. From the review of the correspondence, the FDA investigator did not identify any issues related to the misconduct at Site 1002.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for the following deficiencies:

1. An investigator who did not comply with the signed agreement and general investigational plan was not promptly brought into compliance.
2. Failure to ensure proper monitoring of the study and ensure the study is conducted in accordance with the protocol and/or investigational plan.

OSI Reviewer Comment: NPS Pharmaceuticals, Inc. responded to the findings in a letter dated May 29, 2014. The response is acceptable. NPS acknowledged it did not take adequate action to address repeated non-compliance at Site 1002. Numerous corrective actions were implemented to improve oversight, including revisions of the NPS Standard Operating Procedure (SOP) CDO-0524, Monitoring Plans, NPS SOP-CDO-0516, Monitoring Visits, SOP-CDO-0501, Selection and Oversight of Clinical, Biostatistical, and Data Management Vendors, NPS SOP-CDO-0507, Selection of Phase II-IV Investigational Sites, and revision of the Clinical Operations Manual. NPS has also initiated a Corrective and Preventive Action Plan, CAPA #2014-017, to conduct a comprehensive, systemic evaluation of IP accountability procedures for clinical studies. Within two weeks after each corrective action commitment date in the response, NPS Clinical QA will verify and document completion.

- NPS Quality Assurance and Clinical Operations are developing additional metrics aligned with the responses to this 483 to assess compliance with study requirements for current and future studies. By September 30, 2014, NPS Quality Assurance will begin reporting the results of site compliance audits quarterly to the Chief Medical Officer, a newly established Clinical Oversight Committee.
- NPS will provide FDA with regulator updates and copies of new and revised procedures, as well as other documentation of corrective actions promised in their response, within 60 days of the date of completion and/or implementation beginning August 31, 2014.

- c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Although regulatory violations were noted as described above, the audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

5. [REDACTED] (b) (4)

* [REDACTED] (b) (4)

The mailing address remains the same.

- a. What was inspected:** Five clinical investigator site files were reviewed, three that were inspected and two chosen during the current inspection by the FDA investigator in support of BLA 125511 (sites 1002, 1010, 1015, 1006 and 1023).

The following were evaluated for the five sites: adequacy of monitoring and corrective actions taken by the monitor/CRO, protocol deviations related to key safety and efficacy endpoints, training and experience of staff, communications between the CRO, sites, and sponsor, contractual agreements and transfer of obligations to vendors, and general site monitoring practices. Since the Trial Master File was transferred to the sponsor, study drug accountability, monitor sign-in logs, and case report forms were not evaluated during this inspection. Review of the records was performed using electronic records (scanned copies of original documents, database logs, electronic mail messages, etc.) which were provided. These included monitoring plans, monitoring reports for each clinical site chosen, Standard Operating Procedures (SOPs), training records, site reports, site visits, site personnel, study newsletters, site and sponsor communication logs, deviation logs, screening and enrollment information, payments to sites, SAE management, regulatory documents (1572s, IRB approvals, CVs for site personnel, IRB membership, medical license, protocol approval page, financial disclosure forms, laboratory director's license, laboratory certification, laboratory normal, and confidentiality agreements), and electronic mail correspondences.

- b. General observations/commentary:** (b) (4) was contracted by NPS Pharmaceuticals Inc. to provide monitoring of clinical study sites within the USA with some oversight of the firms contracted to perform the tasks outside of the USA. Since (b) (4) purchased (b) (4) after the close of the study, only a few employees remain who also worked for (b) (4). All of the employees who had responsibility for study CL1-11-040 no longer work at the firm and only one that performed monitoring visits as a (b) (4) contractor currently works for (b) (4).

Review of the curriculum vitae showed that all principal and sub investigators from the five sites evaluated were qualified by education, training and experience to fulfill the requirements of the study. (b) (4) was involved in the identification of investigators; however, the sponsor had the responsibility for the final approval.

(b) (4) was responsible for the selection and training of the monitors who performed the site visits. Many of the monitors were subcontractors that were hired by (b) (4) to perform the monitoring of the study. Historically, Quality Assurance (QA) at (b) (4) was managed by Regulatory Affairs. However, at the time of the acquisition by (b) (4), (b) (4) had a contractor who was responsible for Quality Management who did not have a background in QA.

Concerning Site 1002, many issues were identified during review of the monitoring reports. Throughout the study this site was continuously late in completing logs, eCRF, IP accountability, etc. They also did not perform procedures according to the time points specified in the protocol. Additionally, Dr. Bilezikian was not available for 31 of 47 visits as documented on the monitoring visit reports.

During the inspection, the communication logs and the electronic mail messages between (b) (4) and the sponsor and (b) (4) and Site 1002 were reviewed. It could not be determined if (b) (4) had any knowledge of the issues identified during the clinical investigator and sponsor inspections at Site 1002. All staff denied any knowledge of the issues identified at Site 1002. All of the (b) (4) employees who worked on the CL1-11-040 study were no longer employees of (b) (4). Thus the FDA investigators were unable to ascertain if, at the time of the study, (b) (4) had any knowledge of the improprieties that had occurred at Site 1002.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for the following deficiencies:

1. Failure to ensure proper monitoring of the study and ensure the study is conducted in accordance with the protocol and/or investigational plan

The CRO (b) (4) responded to the findings in a letter dated July 21, 2014. The response is acceptable. (b) (4) QA and Senior Management outlined how (b) (4) approach to the conduct of clinical trials differs from (b) (4) approach. As noted, CL1-11-040 was not managed by (b) (4) and had already been completed and handed over to the sponsor more than a year prior to (b) (4) acquisition of (b) (4). The transaction took place on (b) (4). The Trial Master File (TMF) with all documents relating to the study had been returned to the sponsor before the (b) (4) acquisition and (b) (4) had been unaware of any of the issues in the study.

As a precaution to ensure that there is no risk of repetition of the findings identified in the FDA inspection and related 483, (b) (4) QA started working on additional QA audits in order to ascertain that there is no risk that the type of issues identified in the FDA 483 report could be repeated in any other studies initiated by (b) (4) pre-acquisition. The audits are not limited to monitoring but will cover all activities currently managed by (b) (4).

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Although regulatory violations were noted as described above, the audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this BLA consisted of three domestic clinical sites as well as the sponsor and contract research organization (CRO).

Observations noted above for all three site inspections, the sponsor, and the CRO are based on

the preliminary review of the Establishment Inspection Reports. An inspection summary addendum will be generated if conclusions change upon OSI final classification.

One site, Dr. Bilezikian (#1002) was issued a Form FDA-483 citing inspectional observations and classification is Official Action Indicated (OAI). The data at this site has been determined to be unreliable. This had been communicated previously to the review division. The sponsor is aware of the issues found, Dr. Bilezikian has been removed from his role as clinical investigator, and the sponsor has been asked to re-analyze the data submitted to the application with the exclusion of this site.

One clinical site inspected, Drs. Watts (#1015), the sponsor (NPS) and the CRO (b)(4) were issued a Form FDA-483, citing inspectional observations and classification for these inspections is Voluntary Action Indicated (VAI). Although regulatory violations were noted as described above for the site, sponsor and CRO, they are unlikely to significantly impact primary safety and efficacy analyses. Reliability of data from this site, sponsor and CRO is acceptable for use in support of the indication for this application.

Dr. Vokes (#1010) was not issued a Form FDA 483; the classification for this site inspection is NAI (No Action Indicated). Data from this site is considered reliable based on the available information.

In general, with removal of the data from Dr. Bilezikian's site and based on the inspections of the two clinical sites, the sponsor, and the CRO, the inspectional findings support validity of data as reported by the sponsor under this BLA.

{See appended electronic signature page}

Cynthia F. Kleppinger, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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

/s/

CYNTHIA F KLEPPINGER
08/22/2014

JANICE K POHLMAN
08/23/2014

KASSA AYALEW
08/24/2014



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: June 9, 2014

From: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER
For the CDER DCRP QT Interdisciplinary Review Team

To: Elizabeth Chen, DMEP

Subject: QT-IRT Consult to BLA 125511

This memo responds to your consult to us dated 6 May 2014 regarding the sponsor's integrated cardiovascular safety report. The QT-IRT received and reviewed the following materials:

- NATPARA Integrated Cardiovascular Safety Report dated 13 September 2013

Natpara is a form of recombinant human parathyroid hormone (first 84 amino acids). IRT previously recommended that the sponsor summarize QT and other cardiovascular safety data from clinical studies rather than conduct a specific QT study.

The best data were obtained in study CL1-111-040, in which 134 subjects (randomized 2:1) received either Natpara (doses up to 100 mcg/day) or placebo for 24 weeks. This study sufficed to rule out clinically relevant effects on vital signs, and PR and QRS intervals.

QTc declined by about 10 ms, more or less paralleling the rise in serum calcium that was seen. I also do not think that this effect is clinically relevant.

Various conduction abnormalities were reported, but were no more frequent on drug than on placebo.

The next best data are from study PAR-C10-007, in which 45 subjects received 25 or 50 mcg for 8 weeks. There was no placebo group. The results are compatible with the placebo-controlled data. Also described are 77 subjects in two uncontrolled studies (PAR-C10-008 and PAR-C10-009), also showing no signal.

Given the relatively benign profile expected, I think these data, sparse as they are, suffice to reassure me about the cardiovascular safety profile.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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

/s/

NORMAN L STOCKBRIDGE
06/09/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES MEMORANDUM

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: June 6, 2014
From: Lana Shiu, M.D.
General Hospital Devices Branch, DAGRID, ODE, CDRH
To: Elizabeth Chen, Meghana Jairath
Project Manager, Division of Metabolism and Endocrine Products, CDER
Via: Keith Marin
Combination Products Team Leader, GHDB, DAGRID, CDRH

Rick Chapman
Branch Chief, General Hospital Devices Branch, DAGRID, ODE, CDRH

Subject: BLA 125511(Natpara – Recombinant human parathyroid hormone)
Applicant: NPS Pharmaceuticals, Inc.

CDRH Tracking: ICC1300665

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

Device Description

Medical device constituent of this combination product consists of 3 components:

- The cartridge holder manufactured by Haselmeier GmbH (Haselmeier).
- The Natpara Mixing Device manufactured by (b) (4)
- The Natpara Reusable Pen manufactured by Haselmeier.

Cartridge Holder (available in four dosage strengths/colors)



The cartridge holder is disposable and is provided to the user pre-assembled with each medication cartridge. It is intended to ensure that the cartridge can be safely and effectively interfaced with the Natpara Mixing Device and pen needle for reconstitution, and then with the Natpara Reusable Pen for injection. The cartridge holder is discarded with the empty cartridge.

Natpara Mixing Device



The Natpara Mixing Device is designed to provide the user with a convenient means of reconstituting the Natpara Drug Product and preparing the medication cartridge for subsequent use with the Natpara Reusable Pen. The mixing device is reusable and designed to reconstitute up to six medication cartridges (typically, a new medication cartridge is reconstituted every 14 days). A new mixing device will be provided to the user with each shipment of medication cartridges

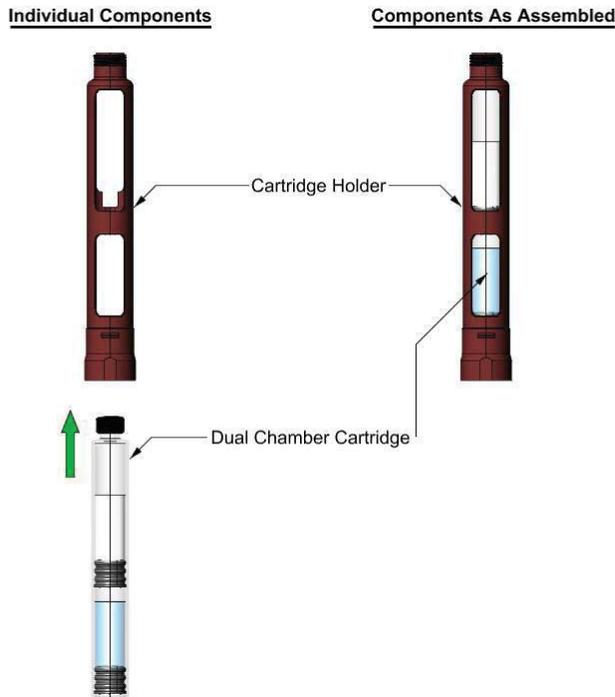
Natpara Reusable Pen



The Natpara Reusable Pen is intended to deliver a daily subcutaneous dose of the Natpara Drug Product (with a targeted fixed-dose delivery volume of 71.4 μL per dose) for the treatment of hypoparathyroidism. The rhPTH(1-84) is contained in a prefilled multiple dose glass dual-chamber cartridge and is injected through a commercially available pen needle.

The pen is intended for use on a single patient for self-administration, administration by a nonprofessional caregiver, or professional use in a health care setting. It is intended for up to two years of daily dosing.

Cartridge/Cartridge Holder Assembly (shown before and after assembly during secondary packaging)



The cartridge holder is considered to be a nonfunctional secondary packaging component and it is a simple plastic component with threaded fittings at each end that allows the drug product cartridge to be interfaced with the Natpara® Mixing Device (for reconstitution) and the Natpara® Reusable Pen (for drug delivery).

For each of the four Natpara Drug Product dosage strengths, the Sponsor intends to commercialize a 2-count kit configuration which contains 2 medication cartridges (equivalent to 28 days of therapy).

The multiple dose glass dual-chamber medication cartridge is provided to the user preassembled within the disposable plastic cartridge holder. The cartridge holder is manufactured in four colors and also is labeled to differentiate the four drug product dosage strengths.

Product Dosage Strength	Cartridge Holder Color	Cartridge Holder Print Color
25 mcg/dose	Purple	White
50 mcg/dose	Red	White
75 mcg/dose	Gray	Black
100 mcg/dose	Blue	White

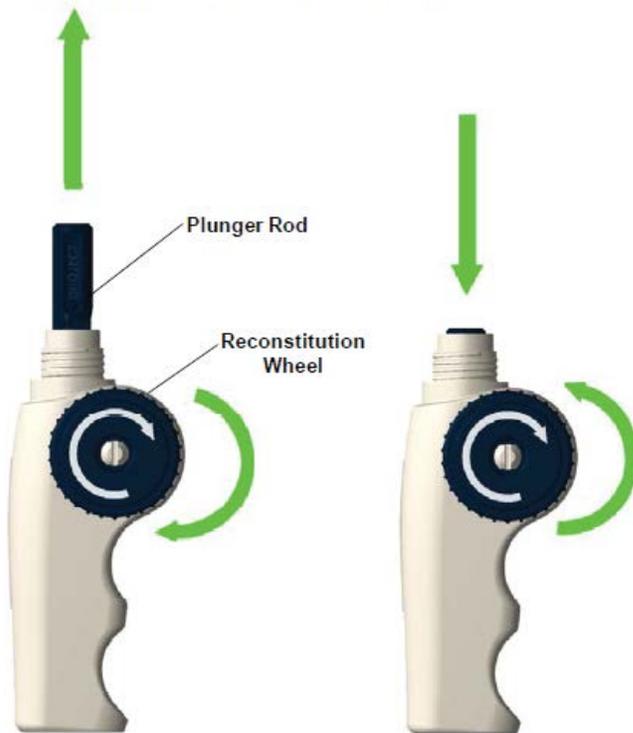
The cartridge holder has cut-out portions, or “windows”, to allow examination of the drug before use and a visual check for drug product reconstitution. Graduation marks on the cartridge holder provide a visual indication of the approximate number of product doses remaining within the medication cartridge.

Interface of Cartridge Holder with Natpara Mixing Device and Pen Needle



(b) (4) designed the reusable mixing device to work in conjunction with the cartridge holder and Natpara medication cartridge. Prior to attaching the cartridge holder to the reusable pen injector, the Natpara Mixing Device is used to reconstitute the drug product (ie, mixing the diluent in Chamber 2 with the lyophilized drug product formulation in Chamber 1 of the multiple dose glass dual-chamber medication cartridge) to prepare it for injection. The mixing device is a simple unit consisting of a plastic, manually-rotated reconstitution wheel that can be rotated clockwise or counterclockwise to extend or retract the plastic plunger rod, respectively.

Extending and Retracting the Plunger Rod



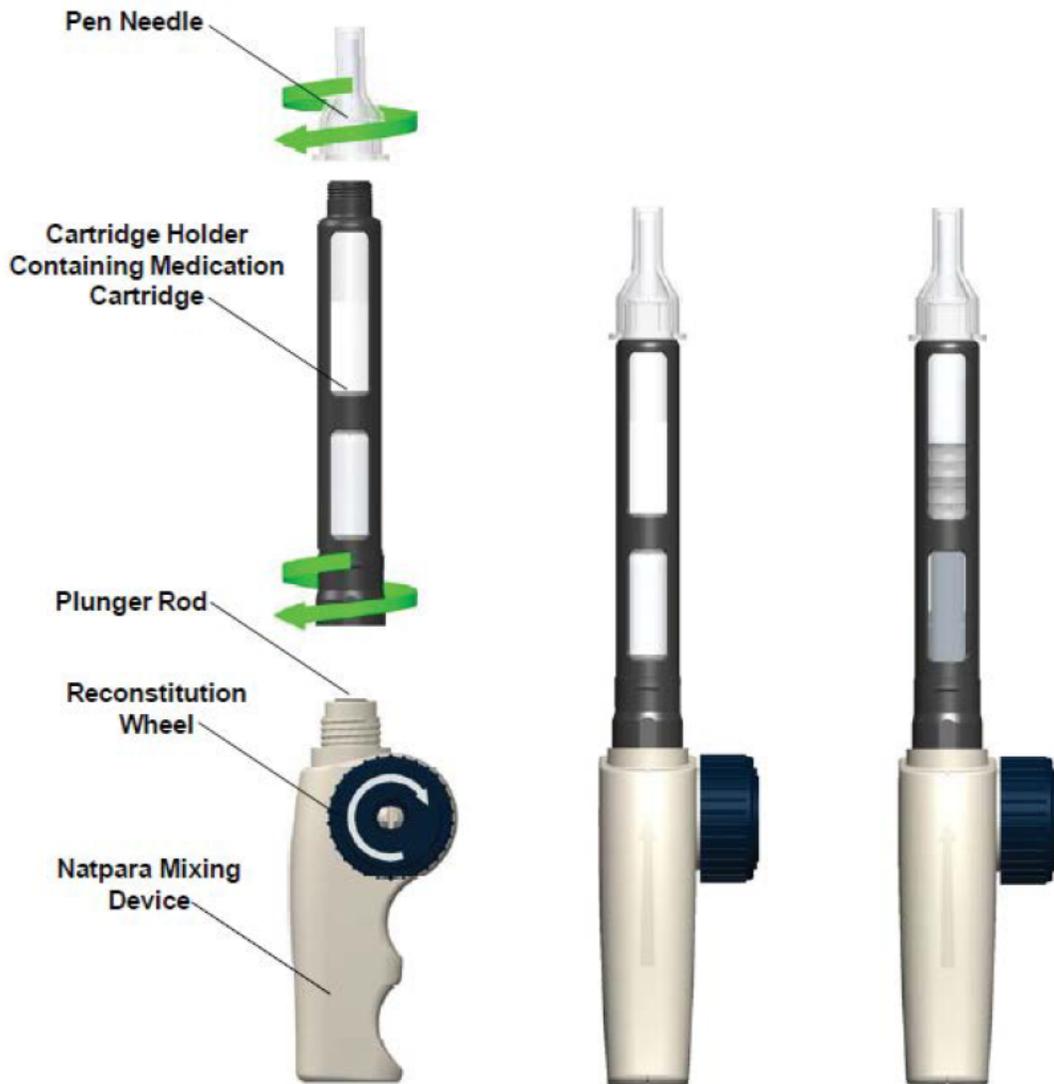
To reconstitute the drug product, a pen needle is screwed onto the cartridge holder, which is then screwed onto the mixing device. When the wheel of the mixing device is turned clockwise, the plunger rod extends to transfer the diluent from Chamber 2 to Chamber 1 to reconstitute the lyophilized drug product. The user can then visually confirm the successful reconstitution. Once the medication cartridge has been reconstituted, it is ready to be transferred to the pen.

Exploded View of Natpara Mixing Device

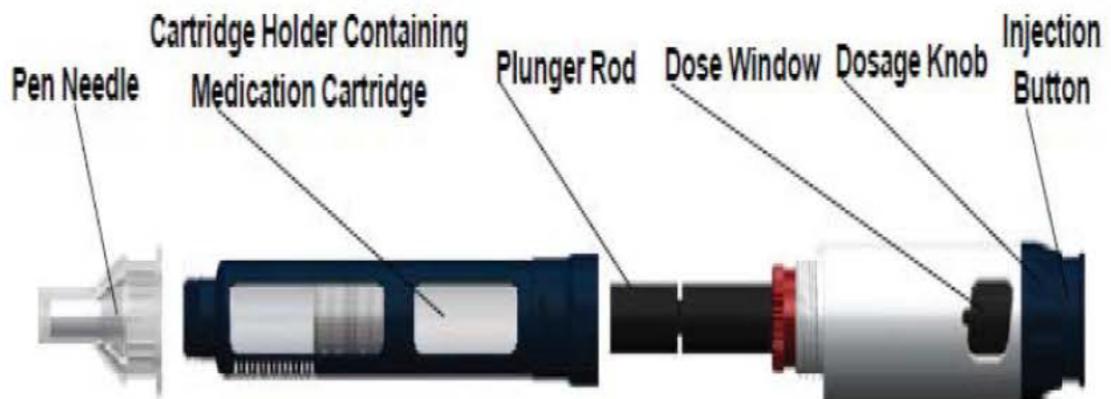


Natpara Mixing Device Materials of Construction

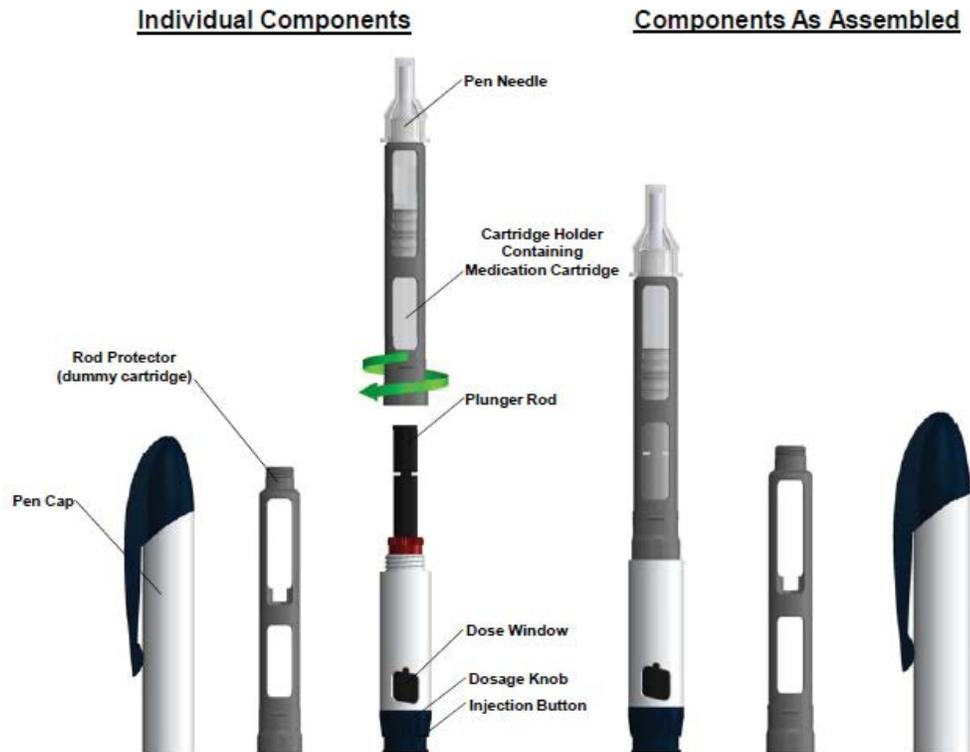
Component Number (Refer to Figure 3.2.R.2-11)	Part Name	Material
1 and 2	Housing	(b) (4)
3	Plunger Rod	
4	Reconstitution Wheel	
5	Reconstitution Wheel Arrow	



Interface of Cartridge Holder with Natpara Reusable Pen and Pen Needle



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



The Natpara Reusable Pen is initially supplied to the user with an attached outer rod protector (also identified as a “dummy cartridge”) that protects the pen injector rod during transport which should be removed from the pen to prepare for attachment of the reconstituted medication cartridge. The cartridge holder is unscrewed from the mixing device and screwed onto the pen base. To prime the pen for delivery, the dosage knob is turned to “GO” and the injection button is pressed.

The Natpara Reusable Pen has a dosage knob with two settings (“0” and “GO”) that enable users to easily identify when the dose has been set correctly. For each injection, the dosage knob at the end of the pen injector is rotated clockwise from a starting point where “0” is displayed in the dose window to a hard stop where the word “GO” is displayed in the dose window. The dosage knob also extends away from the end of the pen during dose-setting.

The dose window on the Natpara Reusable Pen returns to the “0” setting after depression of the injection button to its original position and delivery of the dose. Both the dose window and the dose indicator can be used as visual indicators to confirm successful delivery of individual doses. After 14 doses, the medication cartridge will be empty. At this point, the dosage knob can no longer be turned to “GO” and the depleted cartridge must be replaced with a new reconstituted cartridge. After the medication cartridge is removed, the Natpara Reusable Pen’s plunger rod is manually retracted to the starting position by rotating the red ring at the base of the pen module in a counter-clockwise direction.

Without the medication cartridge, the Natpara Reusable Pen may be stored at room temperature. When assembled with the cartridge holder containing the reconstituted medication cartridge, however, the pen must be refrigerated between injections. After 14 doses, the medication cartridge will be empty and must be replaced by unscrewing and disposing of the empty cartridge holder and medication cartridge. A new medication cartridge will be reconstituted using the mixing device and transferred to the Natpara Reusable Pen for dosing.

Shelf Life

According to the Sponsor, “the cartridge holder, mixing device, and pen injector are each designed for a shelf life of at least (b) (4) months” and “testing to date has been completed after 12 months and 24 months of storage under ambient conditions (PD-TEM-PTH-0302).” However, we are unable to find a report titled PD-TEM-PTH-0302.

Biocompatibility

The cartridge holder, mixing device and reusable pen injector were all evaluated based on limited contact duration (ie, less than 24 hours) with intact skin. The required tests include cytotoxicity (ISO 10993-5), sensitization (ISO 10993-10), and irritation testing (ISO 10993-10) which were passed by all components of the device system. The results of these studies showed that the cartridge holder, the Natpara Mixing Device, and the Natpara Reusable Pen are biocompatible for limited exposure to intact skin.

Functional Performance Testing

Reconstitution Mixing Device

Protocol and engineering report reference	Test description/ Acceptance Criteria	Summarized results
DHF-DHD-TP-104 DHF-DHD-ER-231	<p>Free fall testing: After the three drops are completed, the Reconstitution Devices will be:</p> <ol style="list-style-type: none"> visually inspected for significant defects, no detachment of wheel: Pass or Fail Reconstitution without failure : Pass or Fail Final plunger positioning: (b) (4) Deliverable volume (b) (4) mL 	<ol style="list-style-type: none"> 30/30 Pass 30/30 Pass 30/30 within limit 30/30 within limit
Protocol and engineering report reference	Test description/ Acceptance Criteria	Summarized results
DHF-DHD-TP-107 DHF-DHD-ER-232	<p>Wheel Detachment force Force to disassemble wheel from Reconstitution Device housing shall be (b) (4)</p>	30/30 within limits

Protocol and engineering report reference	Test description/ Acceptance Criteria	Summarized results
DHF-DHD-TP-105 DHF-DHD-ER-233	Verification of performance after pre-conditioning - 4 hours at 18 to 28 °C (25 to 75% relative humidity) 6 Reconstitutions per device 1) Reconstitution without failure : Pass or Fail 2) Final plunger positioning: (b) (4) 3) Deliverable volume: (b) (4) mL	1) 90/90 Pass 2) 90/90 within limit 3) 90/90 within limit
DHF-DHD-TP-105 DHF-DHD-ER-233	Verification of performance after pre-conditioning 4 hours at 2 to 8 °C (ambient relative humidity) 2 Reconstitutions per device 1) Reconstitution without failure : Pass or Fail 2) Final plunger positioning: (b) (4) mm 3) Deliverable volume (b) (4) mL	1) 30/30 Pass 2) 30/30 within limit 3) 30/30 within limit
DHF-DHD-TP-105 DHF-DHD-ER-233	Verification of performance after pre-conditioning 4 hours at 38 to 42 °C (40 to 60% relative humidity) (b) (4)	1) 30/30 Pass 2) 30/30 within limit
(b) (4)	2 Reconstitutions per device 1) Reconstitution without failure : Pass or Fail 2) Final plunger positioning: (b) (4) mm 3) Deliverable volume: (b) (4) mL	3) 30/30 within limit

Mixing Device Life Time Test-Per ISO11608-1 requires that the reusable device performs its function throughout its intended lifetime, with an additional security factor of 150%. Since this device is intended to be replaced after 6 uses, the device was functionally evaluated after it was used 18 times (300% of intended use life to provide and even greater safety margin).

Protocol and engineering report reference	Test description/ Acceptance Criteria	Summarized results
DHF-DHD-TP-109 DHF-DHD-ER-236	Device lifetime 18 Reconstitutions per device and measure for last 12 reconstitutions: 1) Reconstitution without failure : Pass or Fail 2) Final plunger positioning: (b) (4) mL 3) Deliverable volume : [(b) (4)] mL	1) 60/60 Pass 2) 60/60 within limit 3) 60/60 within limit

Protocol and engineering report reference	Test description/ Acceptance Criteria	Summarized results
DHF-DHD-TP-106 DHF-DHD-ER-234	Total time to perform reconstitution Time recorded for standard reconstitution process (seconds)	MEAN 97.8 sec

Protocol and engineering report reference	Test description/ Acceptance Criteria	Summarized results
DHF-DHD-TP-108 DHF-DHD-ER-235	Continuous turning of the wheel After 50 turning cycles of the wheel, the Reconstitution Devices will be: 1) visually inspected for significant defects: Pass or Fail 2) Reconstitution without failure : Pass or Fail 3) Final plunger positioning: (b) (4) mm 4) Deliverable volume : (b) (4) mL	1) 15/15 Pass 2) 15/15 Pass 3) 15/15 within limit 4) 15/15 within limit

Protocol and engineering report reference	Test description/ Acceptance Criteria	Summarized results
DHF-DHD-TP-110 DHF-DHD-ER-237	Reconstitution Feedback Standard reconstitution process 1) Visually inspected; good admixture/ plungers position to the 14 mark. Pass or Fail 2) audible feedback; Pass or Fail 3) tactile feedback/ reduction of resistance; Pass or Fail	1) 30/30 Pass 2) 30/30 Pass 3) 30/30 Pass
DHF-DHD-TP-111 DHF-DHD-ER-238	Reconstitution device compatibility with the cartridge holder thread Attachment of cartridge socket ; Pass or Fail	1) 30/30 Pass
DHF-DHD-TP-105 DHF-DHD-ER-240	Storage testing – dry heat 2 Reconstitutions per device 1) Visually inspected for significant defects: Pass or Fail 2) Reconstitution without failure : Pass or Fail 3) Final plunger positioning: (b) (4) 4) Deliverable volume : (b) (4) mL	1) 30/30 Pass 2) 30/30 Pass 3) 30/30 within limit 4) 30/30 within limit
DHF-DHD-TP-105 DHF-DHD-ER-240	Storage Testing - cold 2 Reconstitutions per device 1) Visually inspected for significant defects: Pass or Fail 2) Reconstitution without failure : Pass or Fail 3) Final plunger positioning: (b) (4)mm 4) Deliverable volume : (b) (4) mL	1) 30/30 Pass 2) 30/30 Pass 3) 30/30 within limit 4) 30/30 within limit
DHF-DHD-TP-105 DHF-DHD-ER-240	Storage Testing – dry heat and cold cycles 2 Reconstitutions per device 1) Visually inspected for significant defects: Pass or Fail 2) Reconstitution without failure : Pass or Fail 3) Final plunger positioning: (b) (4)mm 4) Deliverable volume : (b) (4) mL	1) 30/30 Pass 2) 30/30 Pass 3) 30/30 within limit 4) 30/30 within limit
DHF-DHD-TP-105 DHF-DHD-ER-233	Verification of performance after pre-conditioning - 4 hours at 18 to 28 °C (25 to 75% relative humidity) 2 Reconstitutions per device 1) Reconstitution without failure: Pass or Fail 2) Final plunger positioning: (b) (4)mm 3) Deliverable volume using Haselmeier push rod: > (b) (4) mL	1) 30/30 Pass 2) 30/30 within limit 3) 30/30 within limit

DHF-DHD-TP-105 DHF-DHD-ER-233	Verification of performance after pre-conditioning 4 hours at 2 to 8°C (ambient relative humidity) 2 Reconstitutions per device 1) Reconstitution without failure : Pass or Fail 2) Final plunger positioning: (b) (4) mm 3) Deliverable volume using Haselmeier push rod: > (b) (4) mL	1) 30/30 Pass 2) 30/30 within limit 3) 30/30 within limit
DHF-DHD-TP-105 DHF-DHD-ER-233	Verification of performance after pre-conditioning 4 hours at 38 to 42°C (40 to 60% relative humidity) 2 Reconstitutions per device 1) Reconstitution without failure : Pass or Fail 2) Final plunger positioning: (b) (4) mm 3) Deliverable volume using Haselmeier push rod: > (b) (4) mL	1) 30/30 Pass 2) 30/30 within limit 3) 30/30 within limit
Protocol and engineering report reference	Test description/ Acceptance Criteria	Summarized results
DHF-DHD-TP-127 DHF-DHD-ER-258	IFU misuse – cartridge holder and pen thread engagement Visual inspection: note any significant defect. After the reconstitution process, and after having engaged the cartridge holder on the pen injector, observe if the upper plunger is well positioned at the “14 doses graduation mark” on the cartridge holder. Performance: - complete reconstitution and note any observations during the process (loss of product, product not well mixed, ...) - complete attachment of the cartridge holder containing the reconstituted cartridge on the pen injector and note any observations during the process (loss of product, force to screw the cartridge to the pen injector)	Pass
(b) (4) DHF-DHD-TP-128 DHF-DHD-ER-259	IFU misuse - Continuous reconstitution process Visual inspection: note any significant defect. After the reconstitution process, and after having engaged the cartridge holder on the pen injector, observe if the upper plunger is well positioned at the “14 doses graduation mark” on the cartridge holder. Performance: - complete reconstitution and note any observations during the process (loss of product, product not well mixed, ...) - complete attachment of the cartridge holder containing the reconstituted cartridge on the pen injector and note any observations during the process (loss of product, force to screw the cartridge to the pen injector)	Pass

Pen-Injection Performance Testing

According to the sponsor (see below), but we are unable to locate report TP-10206, TP-1030, Protocol B87000-00, DE_Form 3.3.4NPS-00 and DE_Form 3.3.5NPS-02 to assess the performance details.

No deviations have been occurred during the Testing of the NPS Pen LOT 14865 has been observed. The following dose accuracy test and outpost tests have been carried out and passed successfully

- TP-10206
 - standard atmosphere
 - cool atmosphere
 - hot atmosphere
- TP-1029
 - dry heat atmosphere Pre Conditioned
 - cold storage atmosphere Pre Conditioned
 - cyclical atmosphere Pre Conditioned
- TP-1030
 - Free Fall
 - Lifetime
- Outgoing Test
 - Protocol B87000-00
 - DE_Form 3.3.4NPS-00 Measurement Protocol Torque
 - DE_Form 3.3.5NPS-02 Measurement Protocol Dose Accuracy

Review and Comments:

1. The Halsemier reusable pen-injector performance testing you have provided as the 8 page document in 3.2.R (TR-1031-0049-00) is devoid of basic device specification details (for example, activation force, dispensing time and etc.) which is unacceptable to the Agency. For dose accuracy of a biologic-device combination product, the testing should be performed using final-finished product (device with needle fully assembled with the biologic) actually dispensing the subject biologic. Please provide the actual test reports and accompanying clear concise write-up to include test objective, protocol, actual sample size, pass/fail criteria, results and conclusion for each of the test performed (9.2.2 to 9.2.5 and 10.1).

2. We are unable to locate the reports of TP-10206, TP-1030, Protocol B87000-00, DE_Form 3.3.4NPS-00 and DE_Form 3.3.5NPS-02 mentioned on Page 8 of TR-1031-0049-00 to assess the performance details. Please provide all of these reports.

3. Your re-usable pen is intended for 2 years of daily injection use. During the 2 years, the pen assembled with the biologic cartridge is refrigerated except for the few minutes each day when the injector takes place. Please provide realistic pen-injector device lifetime testing simulating long term refrigerator (96 hours is inadequate) using devices near the end-of-shelf-life that your device can accurately dispense the prescribed biologic dose daily for 3 years (1.5 times of the intended 2 years) without medication error, device malfunction /breakage or adverse events.

4. Many users use alcohol pads to clean their medical devices and alcohol has been known to degrade plastic leading to cracking. Your re-usable pen-injector is intended for daily use over 2 years of time. Will your pen-injector withstand 730 days of alcohol wiping or will there be a warning statement in your labeling to advise them otherwise?

5. Figure 3.2.R.2-18 Injection Time to Deliver Dose (page 25 of 27) is a blank. Please re-submit the appropriate graph.

6. Warning to the patients in the labeling that if the needle is removed before counting to 10 seconds after the counter is reset to zero, then under-dosing will occur and may require additional or increased parathyroid administration.
-

The sponsor responded to Agency's Information Request #24 on 5/30/14 for above 6 questions:

1. Testing for this manual, reusable injection system was performed per ISO11608-1.

- [Attachment 1a \(Haselmeier Protocol TP-1026-04\)](#) which describes the ISO 11608-1 testing plan associated with “standard”, “cool”, and “hot” atmospheres. This protocol corresponds with dose accuracy verification testing using the sample size and statistical acceptance criteria as required by ISO 11608-1 for these three conditions.
- [Attachment 1b \(Haselmeier Report TF-1026-03\)](#) which provides the ISO 11608-1 testing results associated with standard, cool, and hot atmospheres for pen lot 14865. The results meet the statistical requirements set forth in ISO 11608-1 and are presented in three 3-page forms. The first three pages are for the standard atmosphere testing, the next three pages are for the cool atmosphere testing, and the last three pages are for the hot atmosphere testing.
- [Attachment 1c \(Haselmeier Protocol TP-1029-03\)](#) which describes the ISO 11608-1 testing plan associated with “dry heat”, “cold storage”, and “cyclical” atmosphere preconditioning. This protocol corresponds with dose accuracy verification testing using the sample size and statistical acceptance criteria as required by ISO 11608-1 for these three “preconditions”.
- [Attachment 1d \(Haselmeier Report TF-1029-02\)](#) which describes the ISO 11608-1 testing results associated with dry heat, cold storage, and cyclical atmosphere preconditioning for pen lot 14865. The results meet the statistical requirements set forth in ISO 11608-1 and are presented in three 3-page forms. The first three pages are for the dry heat preconditioning, the next three pages are for the cold storage preconditioning, and the last three pages are for the cyclical preconditioning.
- [Attachment 1e \(Haselmeier Protocol TP-1030-03\)](#) which describes the ISO 11608-1 testing plan associated with “free fall” and “lifetime” preconditioning. This protocol corresponds with dose accuracy verification testing using the sample size and statistical acceptance criteria as required by ISO 11608-1 for these two “preconditions”.
- [Attachment 1f \(Haselmeier Report TF-1030-02\)](#) which describes the ISO 11608-1 testing results associated with “free fall” and “lifetime” preconditioning for pen lot 14865. The results meet the statistical requirements set forth in ISO 11608-1 and are presented in two 4-page forms. The first four pages are for the free fall preconditioning and the last four pages are for the lifetime preconditioning.
- [Attachment 1g \(Haselmeier Document B87000-00\)](#) represents the routine supplier release testing required for each batch of manufactured pens. The completed testing summary for pen lot 14865 is provided in this 2-page form. This document cross-refers to two additional forms which are also provided as part of Attachment 1g.
 - Haselmeier DE Form 3.3.4 NPS-02 represents the form on which the torque measurements are recorded for lot release. The completed DE Form 3.3.4 NPS-02 (1 page) for pen lot 14865 is included.
 - Haselmeier DE Form 3.3.5 NPS-02 represents the form on which the dose accuracy measurements and confirmation of dose indicator performance are recorded for lot release. The completed DE Form 3.3.5 NPS-02 (1 page) for pen lot 14865 is included.

Figure 3.2.R.2-18 Injection Time to Deliver Dose³

(b) (4)



The injection time prescribed in the IFU, which requires the patient to keep the needle in the skin for 10 seconds after pressing the injection button, is adequate to avoid an underdose.

CDRH Reviewer Comments for #1:

[Attachment 1g \(Haselmeier Document B87000-00\)](#) represented by pages 64-67 of this document are NOT IN ENGLISH and thus we cannot confirm whether Haselmeier DE Form 3.3.5 NPS-02 and Haselmeier DE Form 3.3.4 NPS-02 are present or has appropriate content for review.

The sponsor argued that with regards to activation force and dispensing time, these criteria are not appropriate or relevant for this type of delivery device. The Haselmeier reusable pen is a manual injection system (as contrasted to an “autoinjector”). The injection force is variable and dependent on the end user. Once the injection button is fully depressed, the dispensing time is defined by the system dimensions and fluid dynamics associated with the product as it is delivered from the medication cartridge through the pen needle. CDRH would like the sponsor to define the internal resistances of the Haselmeier Pen, which in turn would result in the force required to press down the dose button. Please define the force required during injection which should be a combination of the internal resistance to the injection movement of the device and the resistance to movement of the rubber stopper within the cartridge.

The sponsor has not submitted the fundamental device performance design specifications as outlined in the FDA published finalized Injector Guidance.

<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM147095.pdf>

Examples of type of information that would be submitted would include:

Functional

System injection activation sequence

Inspection window shall allow visibility of drug product and injection progress

Needle insertion depth

Needle:

- Limits for acidity or alkalinity

- Limits for extractable metals

- Visual inspection for lubricants

- Patency of lumen

- Needle bond strength

Primary container:

- Container closure integrity

- Gliding forces for plunger

Performance

Deliverable volume

Injection time

Force to compress the needle shield (unlock) into compressed position

Force to depress the activation button

Plunger spring force

Auditory and/or visual notification after completion of full dose delivery

Drug compatibility:

- Meet drug product specification after delivery through AI (drug product injected through device, collected and evaluated to drug product specification)

Drop (free fall testing and acceptance)

Physical Hold up volume
 Dimensions:
 Device (diameter, length)
 Needle size
 Inspection window (width, length)
Weight

2. The sponsor did provide the following:

Attachment 1a (Haselmeier Protocol TP-1026-04)

Attachment 1b (Haselmeier Report TF-1026-03)

Attachment 1c (Haselmeier Protocol TP-1029-03)

Attachment 1d (Haselmeier Report TF-1029-02)

Attachment 1e (Haselmeier Protocol TP-1030-03)

Attachment 1f (Haselmeier Report TF-1030-02)

Attachment 1g (Haselmeier Document B87000-00) represented by pages 64-67 of this document are NOT IN ENGLISH and thus we cannot confirm whether Haselmeier DE Form 3.3.5 NPS-02 and Haselmeier DE Form 3.3.4 NPS-02 are present or has appropriate content for review.

3. The sponsor argues that the warehouse storage of these pens occurs at ambient temperature, a stability storage condition of 25°C was selected for the device stability study. As described in Section 3.2.R.2.10, stability testing after 12 months and 24 months of storage at 25°C was completed and met the pre-established specifications with no significant differences observed when compared with the initial results after the pens were originally manufactured by Haselmeier. The stability program included full ISO 11608-1 testing, including a repeat of the lifetime testing to demonstrate that as the pens aged over time, they still met the same rigorous criteria that they had met when they were originally manufactured.

The sponsor further argues the 25°C condition can be considered a worst case accelerated storage condition for the pens. Two years at 25°C represents an accelerated aging of 8 years at refrigerated conditions (2-8°C) per ASTM F1980 – 07. The materials of construction [REDACTED] (b) (4)

[REDACTED] as they are specifically selected by the manufacturer (Haselmeier) to perform under these conditions.

CDRH Reviewer Comments on #3:

The pen is not totally made of aluminum. In fact, the construction of the Haselmeier Pen is a combination of metal and plastic. The outer body parts are aluminum and plastic, and the internal mechanism is plastic with a steel spring. ISO 11608-1 is not written for injectors which are stored in refrigeration for prolonged periods of time (which for this combination product is about 23.75 hours per day except for the 5-15 minutes of injection per day). While tests can be done on the injector device (devoid of the biologics in the cartridge) using accelerated aging, once the cartridge containing the biologic is assembled to the device, the whole combination product will be refrigerated for approximately 2 years while in use. Plastic components can become brittle

with prolonged refrigeration and lead to device malfunctions such as cracking or resulting in leaking. CDRH recommends that you send the following question to the sponsor for real-life data:

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

4. The Natpara Reusable Pen is not intended to be cleaned with alcohol. The Natpara Instructions For Use (IFU) include the following text under “Frequently Asked Questions”:

“If necessary, clean the pen and mixing device by wiping them with a damp cloth. Do NOT place the pen and mixing device in water or wash them with any liquid.”

CDRH Reviewer Comment for #4:

Please have the sponsor consider including a caution statement in their labeling: Alcohol should not be used with the injector because repeated prolonged exposure may lead to degradation of the plastic.

5. Injection Time to Deliver Dose Graph has been obtained showing that almost of 100% of the dose is delivered by the (b) (4) mark during bench test so the labeling states that the pen-injector should be held until 10 seconds have elapsed.

CDRH Reviewer Comment for #5: Adequate response.

6. The Natpara Instructions For Use (IFU) includes the following text under “Giving the Injection”:

(b) (4) *keep the needle in the skin for 10 seconds AFTER pressing the injection button.”*

On the same page of the IFU, it is made clear what should be done if the patient believes that (s)he did not inject a full dose:

(b) (4) *, call your heathcare provider. You may need to take calcium and active vitamin D.”*

CDRH Reviewer Comment for #6: Adequate response.

Recommendation:

Request for further information on #1 to #4.

We received IR 24 Clarifications on 6/11/2014 after the teleconference with the sponsor on 6/5/2014:

FDA Clarification Request #1

What is the Haselmeier reusable pen-injector activation force, that is a resistance number to activate the cartridge or a total force of the system, such as maximum force to dispense medication or to push the button. Please consider the FDA’s 2013 Injector Guidance for design specifications on system activation sequence.

NPS Response #1:

The Natpara Reusable Pen (manufactured by Haselmeier) used in conjunction with the Natpara medication cartridge in the cartridge holder has been tested as a complete system in accordance with the FDA-recognized ISO Standards 11608. In consideration of Injector Guidance that FDA recommended, the Sponsor has identified several additional use-related parameters, where functional force testing has been performed, as summarized below:

Parameter	Method	Accept/Reject Criteria	Results	
<ul style="list-style-type: none"> • Force required to actuate the injector (Dispense Force) <ul style="list-style-type: none"> ○ Maximum injection force without product cartridge ○ Maximum injection force with product cartridge 	Force gauge		(b) (4)	
<ul style="list-style-type: none"> • Minimum and maximum torque to dial a set dose 	Torque gauge			
<ul style="list-style-type: none"> • Needle compatibility <ul style="list-style-type: none"> ○ Dose accuracy ○ Maximum removal torque 	ISO 11608-1 & 2			
	ISO 11608-2			
N = Newton; Ncm = Newton-centimeter; µL = microliter				

Sponsor has completed Human Factors Testing of this design with no reported issues regarding the forces required to use the device. Additionally, there have been no complaints related to the forces required to use the device during clinical use of the Haselmeier pen.

FDA Clarification Request #2

Please provide an English language translation for [Attachment 1g of Response to Request #1 of IR 24](#).

NPS Response #2:

Attachment 1g from Response 1 of BLA 125511 IR 24 included three Haselmeier documents that were issued in German (“Haselmeier Document B87000-00”, “Haselmeier DE Form 3.3.4 NPS-00”, and “Haselmeier DE Form 3.3.5 NPS-02”). An English translation of these three documents is provided in [Attachment 1g_English.pdf](#).

<input checked="" type="checkbox"/> NPS	801-012	<input checked="" type="checkbox"/> OK <input type="checkbox"/> Nok	25-01-11 Signed
	Testing device no.	Result	
<input type="checkbox"/> *	14865	25-01-11, Signed	
Project (* Enter project)	Batch	Date, sign of Tester	Date, sign QA

Limit (b) (4)

No.	Torque (Ncm)
1	(b) (4)
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	
21	
22	
23	
24	
25	

No.	Torque (Ncm)
26	(b) (4)
27	
28	
29	
30	
31	
32	
33	
34	
35	
36	
37	
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39	
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FDA Clarification Request #4:

Since many users employ alcohol pads to clean their medical devices, you should consider a warning statement in your IFU to advise them otherwise.

NPS Response #4:

Sponsor acknowledges the Agency’s concerns expressed during the June 5, 2014 teleconference and has agreed to update the text in the “Frequently Asked Questions” section of the Natpara Instructions For Use (IFU). The following change (in red text) will be incorporated:

“If necessary, clean the pen and mixing device by wiping them with a damp cloth. Do NOT place the pen and mixing device in water or wash them with any liquid such as alcohol.”

The IFU will be modified accordingly when it will be updated in the next available time.

CDRH/GHDB Reviewer Comments and Recommendations

Sponsor's responses to #1, #2 and #4 are adequate but we still need the real-life use during the clinical trial to see if the pen-injector can hold up to 2 years of refrigerations as requested in #3.

CDRH/GHDB received response from the Sponsor on 6/13/2014 regarding CDRH question in the IR 25 request on "pen-leaking" as noted during clinical trial and whether this may be due to prolonged refrigeration of the device which can cause some materials/components of the device to become brittle or shrink.

NPS Response #3:

NPS has received a total of 8 complaint reports of leaking medication for the Haselmeier pen device during the ongoing PAR-C10-008₁ clinical trial which encompasses 49 subjects with a mean duration of use of 726 days; of these subjects 43 subjects had ≥ 2 years of use. Each complaint was thoroughly investigated and standard functional testing was performed on the returned pen devices. It was determined in each case that the pen was functioning as expected. Due to the number of complaints received, further investigation was conducted under NPS CAPA 2013-007.

The leaking complaints are related to two types of observations from patients: 1) patients noticed droplets from the tip of the patient-attached commercially available needle during the injection process and 2) patients observed a small amount of residual product which can be released from the cartridge bypass (the molded channel in the wall of the glass cartridge).

These two types of complaints are not a product "leak" in the sense of a product failure or device malfunction.

1) Droplets of medication observed at the needle tip during mixing or an injection is addressed in our [Instructions for Use, Module 1, page 19 and 25](#).

2) In addition, there can be a migration of residual product observable as the stoppers cross the by-pass channel of the 14-dose Natpara medication cartridge. This migrated material may appear with normal use as either wetness between the glass and the pen's plunger rod, or as a small amount of dried white material on the inside of the cartridge or on the piston rod. It may be observed either during cartridge use or while the patient changes cartridges.

All of the pen leakage complaints received to date are due to these two known outcomes of normal pen use which are not related to the refrigerated storage conditions.

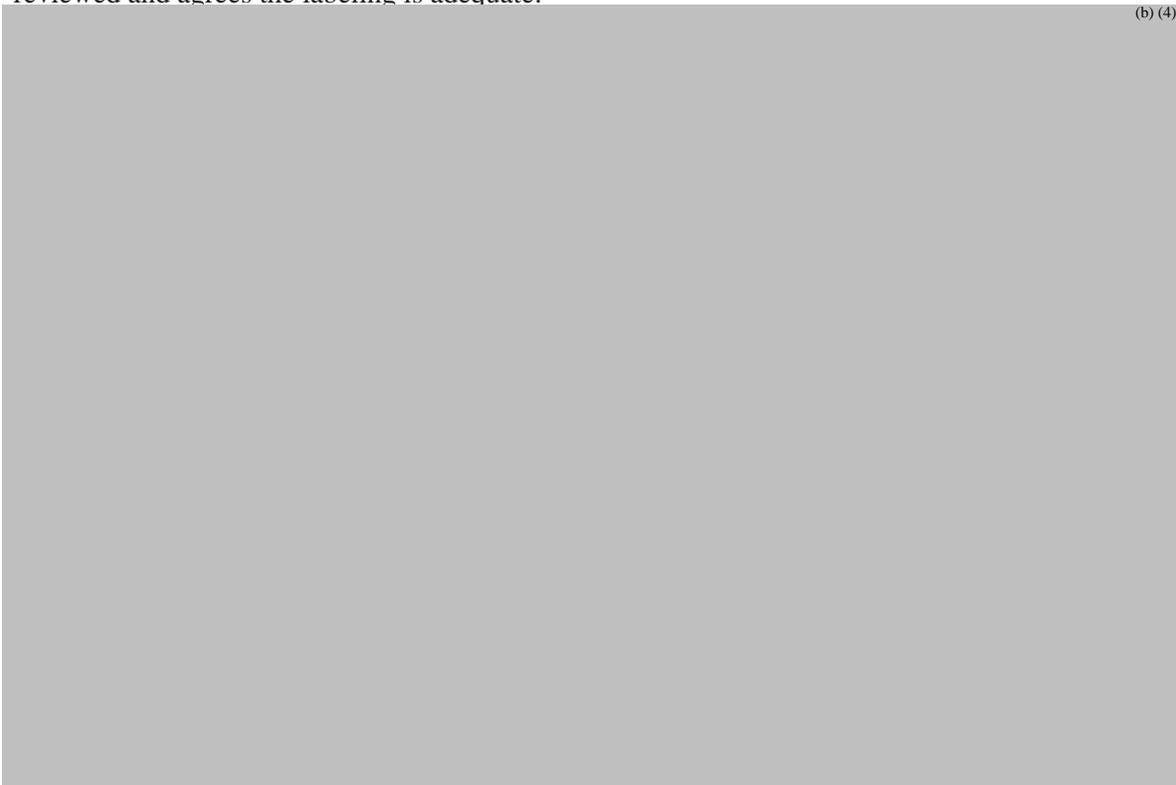
It should also be noted that the clinical experience in the on-going PAR-C10-008₁ clinical trial (49 patients with a mean duration of use of 726 days) using refrigerated storage conditions according to the IFU as well as the ISO 11608-1 testing at cold and cold cycled pre-conditions; refrigeration does not impact the device function.

Date of Occurrence	Site Number	Subject Number	Narrative of Complaint Report	Complaint Status	Supplies collected and provided for standard functional testing	Investigation
5/16/2012	1010	0008	Injection pen leaked medication as subject prepared the pen for injection.	Closed	Yes	Standard Functional Testing Performed
6/20/2012	1010	0012	Injection Pen leaked medication as subject prepared the pen for injection.	Closed	Yes	Standard Functional Testing Performed
1/30/2013	1012	0004	Subject was giving herself dose when noticed leaking around the base of the needle;	Closed	Yes	Standard Functional Testing Performed
1/20/2013	1010	0008	Reported leaking medication due to observing small amounts of white crystallized powder found on the pen's piston rod.	Closed	Yes	Standard Functional Testing Performed
4/23/2013	1012	0004	Complaining of pen cartridges leaking when using and storing the device.	Closed	No	No component available for return; batch record review conducted
8/2/2013	1010	0008	Reported leaking medication due to observing small amounts of white crystallized powder found on the pen's piston rod.	Closed	Yes	CAPA Investigation
8/2/2013	1010	0008	Reported leaking medication due to observing small amounts of white crystallized powder found on the pen's piston rod.	Closed	Yes	CAPA Investigation
12/1/2013	1018	0010	Reported leaking medication during the dose preparation stage	Closed	Yes	Standard Functional Testing Performed

CDRH/GHDB Reviewer Comments:

It is noted that out of the 8 pen-leak complaints 4 of these complaints were from the same person (subject #8). We also agree that droplet of medication can be observed at the needle tip after injection or during needle attachment process which does not represent device failure if the medication is not observed at the needle attachment point to the injector after injection.

Sponsor has modified the labeling with the following explanation which CDRH/GHDB has reviewed and agrees the labeling is adequate:



CDRH/GHDB received response from the Sponsor as and IR 31 and IR 32 on 6/16/2014 regarding CDRH/GHDB's question to #3 requesting real-life data of patient use of pen-injector to support the 2 year pen-injector use-life as claimed by the sponsor with prolonged refrigeration:

Listing 1a Duration of Use of Haselmeier Pen – Safety Population
PAR-C10-008

Subject ID	Duration (Days) as of 30SEP2013	Duration (Days) as of 31MAY2014
CL1-11-040-1014-0005	0	0
CL1-11-040-1015-0001	567	810
CL1-11-040-1015-0003	592	835
CL1-11-040-1015-0004	592	835
CL1-11-040-1018-0003	578	821
CL1-11-040-1018-0005	581	824
CL1-11-040-1018-0010	585	828
CL1-11-040-1018-0011	574	817
CL1-11-040-1020-0004	347	347
PAR-C10-007-1002-0017	532	775
PAR-C10-007-1002-0019	516	759
PAR-C10-007-1002-0021	533	776
PAR-C10-007-1003-0005	561	804
PAR-C10-007-1003-0006	531	774
PAR-C10-007-1006-0009	57	57
PAR-C10-007-1006-0010	557	800
PAR-C10-007-1006-0011	557	800
PAR-C10-007-1006-0012	523	766
PAR-C10-007-1012-0011	558	801
PAR-C10-007-1014-0007	578	821
PAR-C10-007-1014-0008	544	787
PAR-C10-007-1014-0009	561	804
PAR-C10-007-1015-0005	593	593
PAR-C10-007-1018-0012	592	835
PAR-C10-007-1020-0006	0	0

Listing 1a Duration of Use of Haselmeier Pen – Safety Population
PAR-C10-008

Subject ID	Duration (Days) as of 30SEP2013	Duration (Days) as of 31MAY2014
C09-002-001-003	579	822
C09-002-001-005	98	98
C09-002-001-006	579	822
CL1-11-040-1001-0003	505	748
CL1-11-040-1001-0004	505	748
CL1-11-040-1003-0003	560	803
CL1-11-040-1003-0004	546	789
CL1-11-040-1004-0003	564	807
CL1-11-040-1004-0007	561	804
CL1-11-040-1006-0001	559	802
CL1-11-040-1006-0003	539	782
CL1-11-040-1006-0006	560	803
CL1-11-040-1006-0007	553	796
CL1-11-040-1007-0001	574	817
CL1-11-040-1007-0003	574	817
CL1-11-040-1008-0004	533	776
CL1-11-040-1010-0004	536	779
CL1-11-040-1010-0008	558	801
CL1-11-040-1010-0009	532	775
CL1-11-040-1010-0010	557	800
CL1-11-040-1010-0011	558	801
CL1-11-040-1010-0012	558	801
CL1-11-040-1011-0004	579	822
CL1-11-040-1012-0002	560	803
CL1-11-040-1012-0003	537	780
CL1-11-040-1012-0004	523	766
CL1-11-040-1014-0001	574	817
CL1-11-040-1014-0004	544	787

Listing 1b Duration of Use of Haselmeier Pen – Safety Population
PAR-C10-008 Excluding Dr. Bilezikian's Site (1002)

Subject ID	Duration (Days) as of 30SEP2013	Duration (Days) as of 31MAY2014
C09-002-001-003	579	822
C09-002-001-005	98	98
C09-002-001-006	579	822
CL1-11-040-1001-0003	505	748
CL1-11-040-1001-0004	505	748
CL1-11-040-1003-0003	560	803
CL1-11-040-1003-0004	546	789
CL1-11-040-1004-0003	564	807
CL1-11-040-1004-0007	561	804
CL1-11-040-1006-0001	559	802
CL1-11-040-1006-0003	539	782
CL1-11-040-1006-0006	560	803
CL1-11-040-1006-0007	553	796
CL1-11-040-1007-0001	574	817
CL1-11-040-1007-0003	574	817
CL1-11-040-1010-0004	536	779
CL1-11-040-1010-0008	558	801
CL1-11-040-1010-0009	532	775
CL1-11-040-1010-0010	557	800
CL1-11-040-1010-0011	558	801
CL1-11-040-1010-0012	558	801
CL1-11-040-1011-0004	579	822
CL1-11-040-1012-0002	560	803
CL1-11-040-1012-0003	537	780
CL1-11-040-1012-0004	523	766
CL1-11-040-1014-0001	574	817
CL1-11-040-1014-0004	544	787
CL1-11-040-1014-0005	0	0

The sponsor provided data to show 49 of the patients that used the Haselmeier pen-injector during the clinical trial had over 2 year of use-life with out significant number of device complaints and malfunctions.

CDRH/GHDB Final Review Comments: Response is adequate, we have no further issues from the device engineering perspective.

Lana Shiu, M.D.

Lana L. Shiu -S

Digitally signed by Lana L. Shiu -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Lana L. Shiu -S,
0.9.2342.19200300.100.1.1=1300389268
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Team Leader

**Ryan J.
Mcgowan -S**

Digitally signed by Ryan J. McGowan -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
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62, cn=Ryan J. McGowan -S
Date: 2014.07.02 17:08:11 -04'00'

Branch Chief



Digitally signed by
Richard C. Chapman -S
Date: 2014.07.02
17:10:12 -04'00'

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

/s/

ELIZABETH R CHEN

09/08/2014

Signing for CDRH Reviewer (Engineering), Lana Shiu

LABEL AND LABELING, HUMAN FACTORS AND USABILITY REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: April 18, 2014
Requesting Office or Division: Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number: BLA 125511
Product Name and Strength: Natpara (Recombinant Human Parathyroid Hormone[1-84])
for Injection, 25 mcg, 50 mcg, 75 mcg, and 100 mcg
Product Type: Drug-Device Combination
Rx or OTC: Rx
Applicant/Sponsor Name: NPS Pharmaceuticals
Submission Date: October 23, 2013
OSE RCM #: 2013-2499, 2013-2504
DMEPA Primary Reviewer: Tingting Gao, PharmD
DMEPA Team Leader: Yelena Maslov, PharmD

1 REASON FOR REVIEW

This review evaluates the Human Factors/Usability Study results, proposed container labels, carton and insert labeling, and instructions for use (IFU) for Natpara (Recombinant Human Parathyroid Hormone[1-84]), BLA 125511 for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B – N/A
Previous DMEPA Reviews	C
Human Factors Study (if applicable)	D
ISMP Newsletters	E – N/A
Other (if applicable)	F – N/A
Container Label, Carton Labeling, and Instructions for Use or Medication Guide (if applicable)	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

NPS Pharmaceuticals conducted a HF study that included two components: dose identification and usability of the product.

The dose identification study was conducted with 49 consumers and the results demonstrated that 49 of 49 participants identified the correct Natpara medication cartridge based on the prescribed dose. Only one participant had a difficulty identifying the correct cartridge because she did not bring her reading glass when she pulled the cartridge out of the tray in the refrigerator. However, in clinical practice, patients do not typically identify their dose since dose selection occurs at the dispensing process. Therefore, no additional modifications are needed to the delivery system packaging, IFU and the labeling to mitigate this type of error.

The Human Factors Study usability results demonstrated that although the product is not intuitive for use, it could be used safely and effectively with proper training and disease monitoring.

The Human Factors Study results demonstrated some users encountered difficulties while administering this product despite initial training and follow-up phone training on day 15. Some errors occurred with tasks that are common to many of injection pen devices and are not unique to the proposed product. Six types of errors occurred in this category: 1) Misinterpreting the “Discard on” date on the medication cartridge tracker in the IFU, 2) Failing to ensure that the dose window on the pen is set to zero position, 3) Failing to prime the pen, 4) Not pressing the injection button all the way down until it stops (i.e., until 0 is visible in the display window), 5) Failing to counts to at least 10 after pressing the injection button before removing the pen from the foam injection pad, and 6) Not recognizing the medication cartridge is empty or checks the Medication Cartridge Tracker in the IFU to recognize that the cartridge needs to be changed.

1. Errors associated with misinterpreting the “Discard on” date on the medication cartridge tracker in the IFU occurred with one lay person participant. The patient misinterpreted the statement “discard on” date and thought she delivers her last dose on the “discard on” date and mix the next day. Attempting to deliver a dose on the “discard on” date may result in underdose or dose omission since the medication cartridge will be empty two weeks later. As a result, we recommend revising the instructions on the IFU to clarify “discard on” date to help mitigate this type of error.
2. Errors associated with failure to ensure that the dose window on the pen is set to zero position before attaching a newly mixed medication cartridge occurred with two health care providers and four lay person participants. We attribute this error to the fact that in practice, users do not frequently check to see the dose window is set to zero position because they assume the dose window is already set to zero. Additionally, even if the dose window is not set to zero, it has no impact on the product’s efficacy and does not result in any dosing errors. Therefore, no additional modifications are needed to the delivery system packaging, IFU and the labeling to mitigate this type of error.
3. Errors associated with failure to prime the pen prior to first injection occurred with lay person participants after they changed medication cartridge. We attribute this error to the fact that some participants who made this error did not use the IFU and were used to injecting themselves for 13 days on their last medication cartridge, and thus simply forgot to prime. Additionally, some participants stated that when they turned the knob to “GO”, they thought it means ready to inject and therefore they moved on to injecting. Although priming did not occur, this error would only result in a single underdose per cartridge. A single underdose is clinically acceptable and would not decrease in product’s efficacy because this pen needs to be primed only once for the entire 14 days of pen use. However, we still recommend increasing the prominence of the priming step in the IFU to help mitigate this type of error.

4. Errors associated with not pressing the injection button all the way down until it stops (i.e., until 0 is visible in the display window) occurred with one participant who admitted to reading the instructions too quickly and may have missed the instruction to press the button all the way. The participant stated that the button moved but then provided resistance, giving the impression that the device functioned. Not pressing the button all the way may result in chronic underdosing which may affect calcium levels. This type of error can be detected during monitoring when the patient is monitored for serum calcium as stated in the labeling. Additionally, the IFU clearly states to (b) (4) with a graphic demonstrating the step in step (b) (4). As a result, we recommend adding a statement in the PI in the Dosage and Administration to instruct healthcare practitioners to ensure patient uses the device correctly if the serum calcium levels are not within the desired range.
5. Errors associated with failure to counts to at least 10 after pressing the injection button before removing the pen from the foam injection pad occurred with one lay person participant. The lay person participant did not verbally count to 10 and only had it in the pad for 6 seconds. However, the Applicant conducted a study and confirmed that a complete dose is achieved within (b) (4), and this participant did hold it for (b) (4). Lastly, the IFU clearly states “(b) (4) keep (b) (4) the needle in the skin for 10 seconds AFTER pressing the injection button” with a picture of a clock demonstrating the step on page (b) (4). Therefore, no additional modifications are needed to the delivery system packaging, IFU and the labeling to mitigate this type of error.
6. Errors associated with not recognizing the medication cartridge is empty or checking the Medication Cartridge Tracker in the IFU to recognize that the cartridge needs to be changed occurred with two participants. Two lay person participants threw out the cartridges with 13 doses remaining during Day 2 testing because one of them did not check to see if there were doses in the cartridge, and the other could not distinguish between rod protectors, and could not identify whether the cartridge is empty or full. Throwing out the cartridge prematurely will not result in dosing errors (i.e., underdose or overdose). Therefore, no additional modifications are needed to the delivery system packaging, IFU and the labeling to mitigate this type of error.

Additionally, four types of errors occurred with some tasks that are unique to the proposed pen: 1) Not turning the wheel on the Mixing Device until the two stoppers no longer move and the wheel turns freely, 2) Not ensuring that the rod on the Q-Cliq pen is extended before attaching a new cartridge, 3) Difficulty in screwing the medication cartridge onto the pen, and 4) Not inverting the pen with needle cap pointing down and taps air bubbles that may be present away from the needle end of the medication cartridge before each daily injection.

1. Errors associated with not turning the wheel on the Mixing Device until the two stoppers no longer move and the wheel turns freely occurred with three lay person participants on Day 29 (i.e., the day participants started a new pen and did not receive

training, See Appendix D.3 for details). Not turning the wheel all the way will result in the stoppers being in an incorrect position and will lead to difficulty in attaching the cartridge and multiple under doses. We contribute this error to the fact that all participants may have only read the first part of the IFU statement, which states “With the needle pointing up, turn the wheel slowly” and overlooked the remaining instructions (e.g., “until the stoppers no longer move and the wheel turns (b) (4)”). Therefore, we recommend revising the instructions to increase the prominence of the reconstitution step in the IFU to help mitigate this type of error.

2. Error associated with failure to ensure that the rod on the Q-Cliq pen for Natpara is not extended before attaching a new cartridge occurred with one lay person participant. The participant was following the instructions in IFU and tried not to over-tighten the cartridge and thought she had successfully positioned the cartridge with a small gap like the picture in IFU (b) (4). We attribute this error to the fact that the instructions aren’t clear and we recommend revising the instructions in the IFU to help mitigate this type of error.
3. Error associated with difficulty in screwing the medication cartridge onto the pen occurred with three lay person participants. All three participants misread the cartridge and said the cartridge felt snug and looked to be on straight. A partial attachment of the medication cartridge to the pen base will result in missed doses and/or underdoses for one cartridge only. This error can be detected during monitoring when the patient is monitored for serum calcium as stated in the labeling. The IFU currently has a statement that says (b) (4). We recommend revising this instruction in the IFU to improve clarity and to help mitigate this type of error. As a result, we recommend adding a statement in the PI in the Dosage and Administration to instruct healthcare practitioners to ensure patient uses the device correctly if the serum calcium levels are not within the desired range.
4. Errors associated with not inverting the pen with needle cap pointing down and tapping air bubbles before each daily injection occurred with two health care providers and three lay person participants on Day 2. Two participants tapped with the needle cap pointing up, one participant did not tap, and two participants held the pen past horizontal after tapping. We attribute this error to the fact that in practice, both health care providers and patients are accustomed to priming and removing needle cap with the needle cap pointing up. Therefore, tapping with the need cap pointing up will result in single or multiple underdoses. The clinical likelihood that patients will experience low serum calcium as a result of this error is largely dependent on where the patient’s serum calcium is stored in the body. The patient should be monitored for serum calcium levels as stated in the PI labeling. However, we still recommend increasing the prominence of this step in the IFU to help mitigate this type of error. Additionally, we recommend adding a statement in the Prescribing Information labeling to ensure that if the patients’ serum calcium levels are not within the desired range, the patients should also be monitored for the correct use of the device.

The Human Factors Study demonstrated that the device is not intuitive for use and some users encountered difficulties while using it. Despite these difficulties, we believe that the device is approvable for the following reasons:

1. NPS Pharmaceuticals proposed a commercialization plan to provide support for patients for whom Natpara is prescribed for securing access to Natpara and providing training on the proper use of Q-Cliq pen. The NPS Advantage support program will ensure that patients are properly trained on the use of Natpara and the delivery device by a trained HCP or a member of the NPS support program before the product is shipped to the patient. Upon shipment of the first dose of Natpara, NPS Advantage or the Specialty Pharmacy will schedule a follow-up training session for the date when the second cartridge (Day 15) has to be reconstituted. At that point the patient will be contacted by phone and go over the steps to reconstitute Natpara as the patient performs these steps simultaneously. In case of any specific need not being able to be addressed over the phone, an in-person session will be scheduled. Additionally, we still recommend revisions to the Instructions for Use (IFU) to include information regarding to providing training to patients prior to first use.
2. When starting this product or changing the dose, patients will be monitored by their physician on a weekly basis for serum calcium levels during the titration period. If their calcium levels are not within the normal ranges, patients will be evaluated for possible chronic underdosing. As part of the monitoring program, we recommend revision to the Prescribing Information labeling to include information to monitor the patient for correct use of the device if the patients' serum calcium levels are not within the desired range.

(b) (4)

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the NPS Pharmaceuticals's proposal for proper education and training prior to first injection of Natpara pen, and a follow up training on Day 15 is acceptable in order for the product to be used safely and effectively. Additionally, DMEPA concludes patients should also be monitored for appropriate use technique if their serum calcium is not within desired ranges.

We also conclude that the proposed Instructions for Use (IFU), container label, and carton labeling can be improved to increase the readability, clarity and prominence of important information on the label to promote the safe use of the product, to mitigate any confusion, and to clarify information.

4.1 RECOMMENDATIONS FOR THE DIVISION

DMEPA provides the following comments for consideration by the review Division prior to the approval of this BLA:

Human Factors Validation Study results demonstrated that some patients encountered difficulties during mixing and injecting Natpara. As a result, we recommend the following revisions regarding training and counseling be added to the appropriate sections of the Prescribing Information labeling to further mitigate potential medication errors.

(b) (4)

4.2 RECOMMENDATIONS FOR THE APPLICANT/SPONSOR

A. Instructions for Use (IFU)

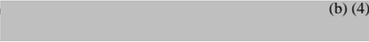
- a. [REDACTED] (b) (4)
- b. Delete page [REDACTED] (b) (4) in the IFU because this information is repeated in page 6 and 7.
- c. Since disposable needles, alcohol swap pad, and puncture-resistant container represents additional supplies and not part of the components for use with Natpara, add a subtitle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

B. All container labels and carton labeling

- a.  (b) (4)
- b. Revise the presentation of the proprietary name from all upper case letters “NATPARA” to mixed case letters “Natpara” to improve readability. Words set in upper and lower case form recognizable shapes, making them easier to read than the rectangular shape that is formed by words set in all capital letters.¹

C. Carton labeling

a. Medication cartridge, all strengths

- i. Add the following statement “Use only after training by your health care provider” to the principal display panel to ensure that patients are trained prior to first use of Natpara.
- ii. Revise the statement “ (b) (4)” to “Must be refrigerated, store at 36°F to 46°F (2°C to 8°C)” to increase the prominence of this important information and to minimize the risk of the storage information being overlooked.
- iii. As currently presented, the net quantity statement “Contains: Two 14-dose medication cartridges of Natpara (rhPTH [1-84]) for injection” is located in the back panel. If space permits, repeat this statement on the principal display panel to increase the prominence of this net quantity statement.¹

Additionally, there is a picture of the two medication cartridges on the principal display panel with no explanation of what the picture represents. Therefore, adding the net quantity statement below this picture will help to explain what the picture represents and minimize confusion.

b. Q-Cliq pen

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

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

essential to ensure safe use of this product and to minimize the risk of medication errors.

c. Mixing Device

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

If you have further questions or need clarifications, please contact Terrolyn Thomas, project manager, at 240-402-3981.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Natpara that NPS Pharmaceuticals submitted on October 23, 2013.

Table 2. Relevant Product Information for Natpara	
Active Ingredient	Recombinant Human Parathyroid Hormone
Indication	Replacement for endogenous parathyroid hormone (1-84) indicated for the long-term treatment of hypoparathyroidism
Route of Administration	Subcutaneous injection
Dosage Form	Powder for injection
Strength	25 mcg/dose, 50 mcg/dose, 75 mcg/dose, and 100 mcg/dose
Dose and Frequency	Starting dose of Natpara is 50 mcg once daily. Based on calcemic response, titrate Natpara doses at 2 to 4 week intervals upward to doses of 75 mcg and then 100 mcg. Downward titration to a minimum dose of 25 mcg can occur at any time.
How Supplied	Q-Cliq pen Mixing Device Dose-specific medication cartridge (one medication cartridge for each strength)
Storage	Refrigerated, 36° to 46°F (2° to 8°C) Discard reconstituted medication cartridges after 14 days
Container Closure	Multiple dose glass dual-chamber cartridge with lyophilized powder and reconstitution diluent

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L:Drive on March 6, 2014 using the terms, Natpara to identify reviews previously performed by DMEPA.

C.2 Results

DMEPA has reviewed Natpara in the following OSE reviews:

- 2012-746 NPSP558 HF and IFU Review

APPENDIX D. HUMAN FACTORS STUDY

Using the principles of human factors and Failure Mode and Effects Analysis², along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Validation study results entitled “Simulated Use Validation Testing of Natpara®, Report PAR-C12-003,” submitted on October 23, 2013.
- Validation study results entitled “NATPARA dose identification study: summary and testing results,” Version 1.0, dated October 1, 2013
- Validation study results entitled “Qualitative Research to Evaluate the Natpara® (rhPTH[1-84]) for Injection Medication Guide: Final Report,” dated September 13, 2013

An Information Request (IR) was sent on January 6, 2014, requesting the Applicant to submit a breakdown of the user tasks observed at the end of each training session for each user group (e.g. HCP, Day 1 LPs, Day 15 LPs, and Day 29 LPs) that were scored as resolved or incorrect and a detailed description of the user tasks that two lay people were determined not proficient at and a root cause analysis of their incompetence after two training sessions. The sponsor provided their response to our IR request on January 21, 2014.

- NPS Pharmaceutical’s response titled “Response to FDA for Request for Information: Request #'s 9, 11, 12, and 13 Contained in Filing Communication (74-Day) Letter Dated January 6, 2014”, received on January 21, 2014.

The study design and results for “Simulated Use Validation Testing of Natpara®, Report PAR-C12-003,” are described in sections D.1 to D. 4 below:

D.1 Study Objective

The purpose of this study is to demonstrate that the hazards associated with use of the product (i.e., the component devices, instructions, and training) have been successfully controlled such that the product is reasonably safe and effective for the intended users, uses and use environments.

D.2 Study Population

To represent the intended user population, the study included three groups: health care providers (HCP), experienced lay people (ELP), and inexperienced lay people (ILP).

² Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Study size	n	How Participants Are Representative of Users
Experienced lay people (ELP)	19	They have hypoparathyroidism and use the product to self-administer treatment ³ ; in contrast to HCPs, they are not professionally trained/educated to administer injections, but have prior experience with self-injection of other medications; they may have vision, dexterity, and cognitive deficits, but are deemed by their HCP as fit to self-inject; they are a mix of men and women.
Inexperienced lay people (ILP)	20	They have hypoparathyroidism and use the product to self-administer treatment ³ ; in contrast to ELPs, they do not have prior experience with self-injection; they may have vision, dexterity, and cognitive deficits, but are deemed by their HCP as fit to self-inject; they are a mix of men and women.
Health care providers (HCP)	15	They are typically nurses; they provide care for their patients who have hypoparathyroidism, and train those in their care to self-administer treatment; they are professionally trained/educated to administer injections and typically have experience using a range of injection devices; they typically do not have uncorrected vision, dexterity, or cognitive deficits; as a group, they are 80- 90% women.

D.3 Study Design

The study design is summarized in Table 3. HCPs were given one one-hour training session and LPs received one-hour training session plus an additional 30-minute training session if they were determined not proficient after one training session. Additionally, HCPs participated in a single testing session, while LPs participated in three testing sessions: “Day 2”, “Day 15”, and “Day 29”.

#	Sessions	HCP	LP (ELP and ILP)
1	Day 1	One-hour training	One-hour training
2	Day 1, continued	n/a	Additional 30-minute training, if needed
3	Day 2	Device Preparation Dose Administration Labeling Comprehension	Dose Administration

³ Participants in this study will not actually have hypoparathyroidism, but will be representative of the key characteristics of this patient group.

Table 3. Study sessions per group			
#	Sessions	HCP	LP (ELP and ILP)
4	Day 15	n/a	Device Preparation with phone call <i>Dose Administration (not observed)</i>
5	Day 29	n/a	Device Preparation (Cartridge Empty) Labeling Comprehension

- **HCP, Device Preparation and Dose Administration, clinic setting:** HCP participants were provided a demo device and the instructions. They need to show the moderator how to use the device for the first time, as if the moderator were a new patient learning how to do daily injections. HCP also need to demonstrate how to use this device to self-administer an injection into the injection pad in a clinic setting.
- **LP, Day 2 Dose Administration, home setting:** Since the participants received their first daily injection yesterday in a clinic setting (Day 1 training), they need to demonstrate giving themselves a second daily injection in a home setting. (Note: Participants self-administer the second daily injection into an injection pad under the moderator's observation.)
- **LP, Day 15 Device Preparation, home setting:** The participants were given a pen with an empty cartridge. The participants receive a phone call from the company (moderator 2) to walk through the participant on how to change their cartridges. After changing the cartridge, the participants self-administer their daily injection, and may either proceed on their own or ask the company representative to stay on the line with them while they perform their daily injection.
- **LP, Day 29 Device Preparation, home setting:** The participants were given a pen with empty cartridge and a Medication Cartridge Tracker filled out with disposal date of today. Participants self-administer their daily injection into the injection pad.

D.4 Results

Training

Fifteen HCPs completed one-hour training session and were found proficient. Forty-one LPs were trained for one hour each and if it was determined by the trainer that they needed additional training they received another 30 minutes the next day. Twenty-one LPs were proficient after one training session. Eighteen LPs were proficient after 2 training sessions. Two participants were determined at the end of their second training session not to be proficient. They would subsequently require additional training in real life and were dismissed from the study (per the study protocol) due to scheduling limitations (See Table 4).

Table 4. Groups that completed training			
	Training Session 1 (1 hour)	Training Session 2 (30 minutes)	excluded
HCP (n=15)	15	n/a	n/a
LP (n=41)	21	18	2

Following are descriptions of the performance of the two LPs who were determined not to be proficient at the end of their second training sessions:

- LP407, when asked to use the product on her own (without direct guidance from the trainer) at the end of her second training session, successfully mixed the cartridge, but then
 - attempted to keep the cartridge attached to the mixing device;
 - was not sure what “pen base” referred to; and
 - when the IFU mentioned and depicted the “rod protector,” she attempted to interact with the cartridge.
- LP419, when asked to use the product on her own (without direct guidance from the trainer) at the end of her second training session,
 - did not use the IFU,
 - did not fill in the medication tracker,
 - did not lower pen rod or
 - did not check that it was at 0 before attaching the cartridge, and
 - did not tap the cartridge.

Testing Session

HCPs participated in a single testing session, while LPs participated in 3 testing sessions: “Day 2”, “Day 15”, and “Day 29”.

Figure 1 provides a summary of scenario scoring by testing session. Each testing session was scored overall as incorrect, resolved (some difficulty, but successfully use the product in the end), or successful, based on the tasks necessary for product use. If a participant had no use events, then the session was scored as successful.

Figure 1. Summary of Scenario Scoring by Testing Session

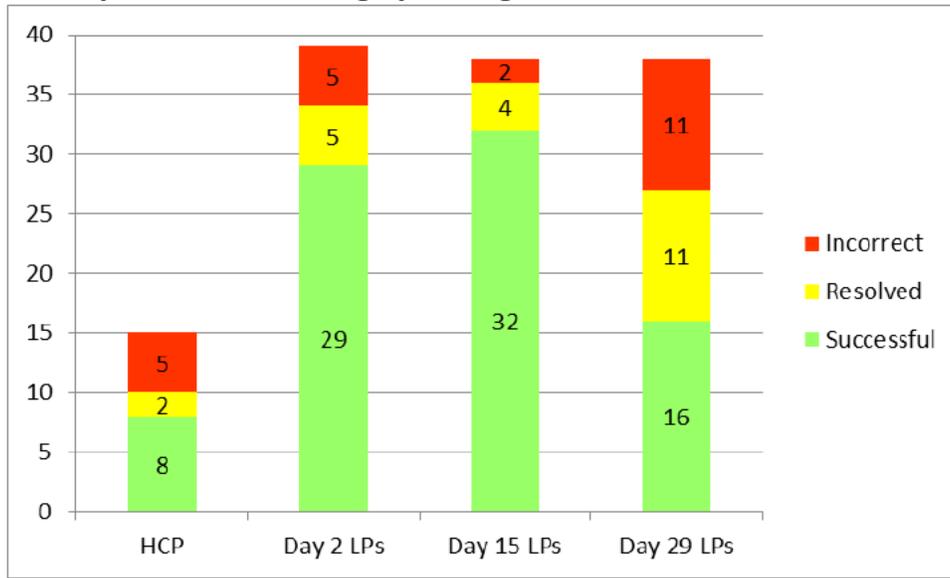


Table 5 provides a summary of user tasks and their use related hazards based on harm as defined by the Applicant. There were no use events observed or reported with catastrophic harm or critical harm.

Table 5. User tasks and their use related hazards based on harm				
User event	Risk	HCP	ILP	ELP
No user events	Catastrophic	0	0	0
No user events	Critical	0	0	0
Multiple missed doses/underdoses per cartridge <ul style="list-style-type: none"> 2 HCPs did not attach needles before attempting to mix 2 ILPs and 1 ELP turned the wheel until the stoppers came together but not until the wheel turned freely. They all had difficulty getting the cartridge onto the pen base. 1 ILP and 1 ELP tapped the cartridge with the needle pointing up (supposed to point down to tap air bubbles away from the needle end of the cartridge) 1 ILP and 1 HCP did not count to 10 before removing the pen 	Slight	3	4	2

Table 5. User tasks and their use related hazards based on harm				
User event	Risk	HCP	ILP	ELP
Single missed dose/under dose per cartridge <ul style="list-style-type: none"> • 2 ILPs said they could still use the medication on the “Discard on” date. • 1 HCP checked to ensure the pen was set in the 0 position after attaching the cartridge, instead of before. • 3 ILP, 2 ELP, 1 HCP did not check to see if their pens were set to 0 before attaching the cartridge. • 1 ELP did not retract the rod fully, resulting in leakage during priming. • 2 ILPs and 2 ELPs did not prime and 1 HCP indicated confusion about how to complete the priming step. • 1 participant removed the needle during priming and then reattached it. (*unknown participant category) • 1 HCP did not tap the cartridge for air bubbles and 1 ELP and 1 ILP raised the pen past horizontal after tapping. • 3 ILPs and 1 ELP attached needles to empty cartridges and tried to turn the dosage knob to “GO.” They felt resistance, stopped, and then mixed new cartridges. • 1 ELP was not sure if the medication cartridge was empty on “Day 29” and called 1-800 phone support. • 1 ILP turned the dosage knob most of the way to “GO” and then attempted dose delivery with an empty cartridge. 	Slight	4*	12*	8*
Missed doses/underdoses during initial use of the 1st cartridge or only affecting one cartridge <ul style="list-style-type: none"> • 3 ILP failed to fully attach the cartridge to the pen base. • 1 ILP and 1 ELP resolved an initial difficulty of attaching the cartridge onto the pen base by pushing hard and repeatedly screwing and unscrewing the cartridge until it was fully attached. • 2 HCP did not turn the knob to "GO," but self-corrected the mistake before delivering a dose. • 1 ELP pressed the injection button only part of the way. 	Slight	2	4	2
Needlestick <ul style="list-style-type: none"> • 2 ILP discarded the large needle cap before recapping their needle. 	Slight	0	2	0

Table 5. User tasks and their use related hazards based on harm				
User event	Risk	HCP	ILP	ELP
Missed dose due to not having an available cartridge <ul style="list-style-type: none"> 1 ELP and 1 ILP did not recognize that their cartridges were not empty, but had 13 doses left. They threw out the cartridge during “Day 2” testing and therefore would run out of cartridges before new ones arrived. 	Irrelevant	0	1	1

Tables 6 identify the tasks that were performed incorrectly by the participants.

Step	User Task and Error description	HCP (n=15)	Day 2 LPs (n=39)		Day 15 LPs (n=38)		Day 29 LPs (n=38)	
			ILP	ELP	ILP	ELP	ILP	ELP
2	Fills in Medication Cartridge Tracker <i>Misinterpreting the Medication Cartridge Tracker. (Slight)</i>	0	0	0	0	0	1	0
8	Turns the wheel until the 2 stoppers no longer move and the wheel turns freely <i>Insufficiently turning the wheel will result in the stoppers being in an incorrect position and will lead to difficulty in attaching the cartridge and multiple under doses. (Slight)</i>	0	0	0	0	0	2	1
15	Ensures that the dose window on the pen is set to the zero position (0 mark) <i>Pressing cocked injection button while attaching cartridge may prematurely prime device and result in a single under dose per 14 days of use of medication cartridge. (Slight)</i>	2	0	0	0	0	3	1
16	Ensures the rod on the pen is not extended <i>Attaching cartridge while rod extended may prematurely prime device and result in loss of multiple doses. (Slight)</i>	0	0	0	0	0	0	1
18	Screws the medication cartridge onto the pen <i>Not fully attaching the cartridge to the pen base will result in multiple under doses. (Slight)</i>	0	0	0	2	0	1	0
20	While holding the pen with the needle pointing up, presses the injection button on a flat surface, such as a table top, all the way until it stops and the 0 mark becomes visible in the dose window <i>Not priming will result in a single under dose per 14-day cartridge. (Slight)</i>	0	0	0	0	0	2	2

Step	User Task and Error description	HCP (n=15)	Day 2 LPs (n=39)		Day 15 LPs (n=38)		Day 29 LPs (n=38)	
			ILP	ELP	ILP	ELP	ILP	ELP
23	Inverts pen with needle cap pointing down and taps air bubbles that may be present away from the needle end of the medication cartridge <i>Presence of bubbles near needle during injection may result in a single under dose. (Slight)</i> <i>Tapping the cartridge with the needle pointing up results in multiple under doses. (Slight)</i> <i>Tapping with the needle pointing down and then raising the needle up may result in a single under dose. (Slight)</i>	2	2	1	0	0	0	0
30	Presses the blue injection button all the way down until it stops (i.e., until 0 is visible in the display window) <i>Not pressing button until "0" mark may result in under dose each time. (Slight)</i>	0	0	1	0	0	0	0
31	Counts to at least 10 after pressing the injection button before removing the pen from the foam injection pad (i.e., simulated skin) <i>Not counting to at least 10 before removing the needle after starting to push the button may result in under dose each time. (Slight)</i>	1	1	0	0	0	0	0
37	Recognizes on the empty medication cartridge that the upper edge of the stopper in the chamber will have reached 0, or proceeds to turn the dosage knob to "GO" and recognizes that it is not possible, or checks the Medication Cartridge Tracker and recognizes the cartridge needs to be changed <i>Removed cartridge with doses remaining results in missed dose. (Slight)</i> <i>Attempted dose delivery with empty cartridge will result in missed dose each time if not detected. (Slight)</i>	0	1	1	0	0	1	0

HCP = health care providers, ILP = inexperienced lay people, ELP = experienced lay people

The user tasks are detailed below:

- 1. Step 2: Fills in Medication Cartridge Tracker (n = 1 incorrect)**
 - LP Day 29: ILP439 reported that she thought she delivers her last dose on the discard on date and mix the next day.
- 2. Step 8: Turns the wheel until the 2 stoppers no longer move and the wheel turns freely (n = 3 incorrect)**
 - LP Day 29: ILP411, ELP424, ILP438 turned the wheel until the stoppers came together, but not until the wheel turned freely. They then had difficulty getting the cartridge on to the pen base.
- 3. Step 15: Ensures that the dose window on the pen is set to the zero position (0 mark) (n = 2 HCP incorrect, 4 LP Day 29 incorrect)**
 - HCP: HCP449 only checked for the pen to be set in the “0” position after attaching the cartridge (it was).
 - HCP: HCP454 did not check to see if the pen was set to “0” before they attached the cartridge (it was).
 - LP Day 29: Four participants (ELP415, ILP418, ILP435, ILP437) did not check to see if the pen was set to “0” before they attached the cartridge (it was).
- 4. Step 16: Ensures the rod on the pen is not extended (n = 1 incorrect)**
 - LP day 29: ELP421 did not retract the rod fully, resulting in leakage during priming.
- 5. Step 18: Screws the medication cartridge onto the pen (n = 2 LP day 15 incorrect, 1 LP Day 29 incorrect)**
 - LP Day 15: Two participants (ILP432 and ILP433) failed to completely attach the cartridge to the pen on Day 15.
 - LP Day 29: ILP438 failed to completely attach the cartridge onto the pen base because the stoppers were not in the correct position.
- 6. Step 20: While holding the pen with the needle pointing up, presses the injection button on a flat surface, such as a table top, all the way until it stops and the 0 mark becomes visible in the dose window (n = 4 incorrect)**
 - LP Day 29: ELP415, ELP446, ILP432, ILP435 did not prime.
- 7. Step 23: Inverts pen with needle cap pointing down and taps air bubbles that may be present away from the needle end of the medication cartridge (n = 2 HCP incorrect, 3 LP Day 2 incorrect)**
 - HCP: HCP450 did not tap.
 - HCP: HCP452 tapped with the needle pointing up. HCP452 then said you should tap with the needle pointing down but never did it.
 - LP Day 2: ILP413 tapped with the needle pointing up.
 - LP Day 2: ELP427 held the pen past horizontal after tapping and did not re-tap.
 - LP Day 2: ILP414 tapped with the needle pointing down, but then placed the pen on the table with the needle pointing up.

- 8. Step 30: Presses the blue injection button all the way down until it stops (i.e., until 0 is visible in the display window) (n = 1 incorrect)**
 - LP Day 2: ELP430 did not press the injection button all the way ("GO" was still visible in the dose window after the injection).
- 9. Step 31: Counts to at least 10 after pressing the injection button before removing the pen from the foam injection pad (i.e., simulated skin) (n = 1 HCP incorrect, 1 LP Day 2 incorrect)**
 - HCP: HCP451 did not count to ten after injecting. HCP451 did not count to 10. She said she skipped this step in the IFU as her mind was on getting the injection going. She indicated that she knows it is important to hold it in to avoid an under dose. Timing from the video she did have the needle in the thigh pad for 12 seconds.
 - LP Day 2: ILP414 did not count to ten after injecting. Timing from the video shows he had the needle in the thigh pad for 6 seconds.
- 10. Step 37: Recognizes on the empty medication cartridge that the upper edge of the stopper in the chamber will have reached 0, or proceeds to turn the dosage knob to "GO" and recognizes that it is not possible, or checks the Medication Cartridge Tracker and recognizes the cartridge needs to be changed (n = 2 LP Day 2 incorrect, 1 LP Day 29 incorrect)**
 - LP Day 2: 2 participants (ILP413 and ELP426) threw out cartridges with 13 doses remaining during "Day 2" testing.
 - LP Day 29: ILP439 attempted dose delivery with an empty cartridge. She turned the dosage knob most of the way to "GO" but did not force it, then inserted the needle into the pad and pressed the injection button.

APPENDIX G. CONTAINER LABEL, CARTON LABELING, INSTRUCTIONS FOR USE, MEDICATION GUIDE

G.1 List of Label and Labeling Reviewed

We reviewed the following Natpara labels and labeling submitted by NPS Pharmaceuticals on October 23, 2013.

- Container Label submitted on October 23, 2013
 - Q-Cliq™ pen
 - Natpara cartridge
 - Mixing Device
 - Rod Protector
 - Cartridge sticker entitled “Attach Needle Before Mixing See Instructions”
- Carton Labeling submitted on October 23, 2013
 - Q-Cliq™ pen
 - Natpara cartridge
 - Mixing Device
- Insert Labeling submitted on October 23, 2013
- Natpara® Medication Guide submitted on October 23, 2013
- Instructions for Use (IFU) submitted on October 23, 2013

G.2 Label and Labeling Images

10 Page(s) of Draft Labeling 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/

TINGTING N GAO
04/18/2014

YELENA L MASLOV
04/21/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # BLA# 125511/0	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Natpara Established/Proper Name: Recombinant Human Parathyroid Hormone (rDNA) or (rhPTH[1-84]) Dosage Form: lyophilized for reconstitution for injection Strengths: subcutaneous injection 25, 50, 75 and 100 mcg/doses		
Applicant: NPS Pharmaceuticals Inc. Agent for Applicant (if applicable): n/a		
Date of Application: October 23, 2013 Date of Receipt: October 24, 2013 Date clock started after UN:		
PDUFA Goal Date: October 24, 2014		Action Goal Date (if different):
Filing Date: December 23, 2013		Date of Filing Meeting: December 17, 2013
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): Replacement for endogenous parathyroid hormone (1-84) for the long-term treatment of hypoparathyroidism		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input checked="" type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): 076514				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	<input type="checkbox"/>	<input type="checkbox"/>	X	
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Jehand Rowlands is listed as the authorized agent but someone named Robert Ashworth (vice president)

					signed the form.	
User Fee Status <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>			Payment for this application: <input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government)- Orphan status <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>			Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
505(b)(2)			YES	NO	NA	Comment
(NDAs/NDA Efficacy Supplements only)						
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].			<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?			<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i>						
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?			<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm						
If yes, please list below:						
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration			
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>						
Exclusivity			YES	NO	NA	Comment
Does another product (same active moiety) have orphan			<input type="checkbox"/>	<input checked="" type="checkbox"/>		

exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/ood/index.cfm</i>				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Applicant requested for 7 yrs market exclusivity for Orphan designation and reference product exclusivity for 12 yrs.
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index : Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

(NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: <input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only) If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	One patent submitted 5,496,801
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>				
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Reworded to following: "NPS pharmaceuticals certifies that the services of any person debarred under subsection 306(a) or 306(b) of the Federal, Food, Drug and Cosmetic Act has not, nor will be, used in any capacity in connection with the BLA"
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<p>PREA</p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Has an Orphan designation.

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<i>routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Applicant got a conditional approval of "Natpara" on 11/7/2011.
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Risk Management plan submitted. OSE/DRISK consult sent.
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

format?				
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Consult sent on 10/31/13
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Consult sent on 10/31/13
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Sent to both OSE/DMEPA and OBP 10/31/13
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<p><i>If yes, specify consult(s) and date(s) sent:</i></p> <p>1. CDRH human factors (10/31/13), compliance(10/31/13) and engineering (12/7/13)</p> <p>2. OBP-1/6/13</p> <p>3. OSI (clinical)- 12/20/13</p> <p>4. DMPP (Med Guide and IFU)- 10/31/13</p>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
<p>End-of Phase 2 meeting(s)?</p> <p>Date(s):</p> <p><i>If yes, distribute minutes before filing meeting</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</p> <p>Date(s): May 15, 2012</p> <p><i>If yes, distribute minutes before filing meeting</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<p>Any Special Protocol Assessments (SPAs)?</p> <p>Date(s): 3/1/01 (Carcinogenicity)</p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 17, 2013

BLA/NDA/Supp #: BLA 125511/0

PROPRIETARY NAME: Natpara

ESTABLISHED: Recombinant Human Parathyroid Hormone (rDNA) or (rhPTH[1-84])

DOSAGE FORM/STRENGTH: lyophilized for reconstitution for injection; subcutaneous injection 25, 50, 75 and 100 mcg/doses

APPLICANT: NPS Pharmaceuticals Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Replacement for endogenous parathyroid hormone (1-84) for the long-term treatment of hypoparathyroidism

BACKGROUND: NPS pharmaceuticals is producing recombinant Human Parathyroid Hormone (rDNA) or (rhPTH[1-84]) by manufacturing using a strain of Escherichia coli modified by recombinant deoxyribonucleic acid (rDNA) technology. The amino acid sequence of this synthesized rhPTH(1-84) is identical to that of native (endogenous) human parathyroid hormone.

In 2007, FDA granted Orphan Drug Designation for NPSP558 (rhPTH [1-84]) for the treatment of replacement for endogenous parathyroid hormone (1-84) for the long-term treatment of hypoparathyroidism. On November 7, 2011, a proprietary name, Natpara, was conditionally accepted.

NPS submitted this BLA application as a biologic-device combination. The review timeline will be twelve month review clock under “the Program” PDUFA V.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Meghna M. Jairath; Elizabeth Hanan	Y
	CPMS/TL:	Pam Lucarelli	N
Cross-Discipline Team Leader (CDTL)	Jean-Marc Guettier		Y
Clinical	Reviewer:	Naomi Lowy	Y
	TL:	Dragos Roman	Y

Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Manoj Khurana	Y
	TL:	Immo Zadezensky	Y
Biostatistics	Reviewer:	Jennifer Clark	Y
	TL:	Mark Rothman	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Karen Davis-Bruno	Y
	TL:	Robert Maher	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	Daniela Verthelyi	N
	TL:		
Product Quality (CMC)	Reviewer:	Su Tran/Joseph Leginus/Muthukumar Ramaswamy	Y
	TL:	Danae Christodoulou	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Jessica Cole	Y
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Tingting Gao	Y
	TL:	Yelena Maslov	N
OSE/DRISK (REMS)	Reviewer:	Amrilys Vega	Y
	TL:	Cynthia LaCivita	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:	Cynthia Kleppinger	Y
	TL:	Jan Pohlman	N

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	OCP: Patricia Love, Bindi Nikhar OPDP: Kendra Jones CDRH (human factor): Quynh Nguyen CDRH (compliance): Viky Verna CMC: Priyanka Kumar (RPM) OMPI/DMPP: Shawana Hutchins OSE: Terrolyn Thomas (RPM) Safety: Suchitra Balkrishnan (Deputy Safety) OSE/DPV: Selena Ready (SE), Ali Niak (MO)		Y
Other attendees	ADRA: Sara Stradley ODEII Deputy Director: Mary Parks		

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies): 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? If no, explain:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments List comments:	<input type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable

<p>Comments:</p>	<input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? If no, explain: 3 sites identified 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? Comments: <i>If no, for an NME NDA or original BLA , include the reason. For example:</i> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input checked="" type="checkbox"/> YES Date if known: July 2014 <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential Comments: 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments: 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter

<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments: Reviewer assignment made after the filing meeting.</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO If no, was a complete EA submitted? <input type="checkbox"/> YES <input type="checkbox"/> NO If EA submitted, consulted to EA officer (OPS)? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <p>Comments:</p>	
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <p>Comments: Jessica Cole was not present at the filing meeting. Assignment made after the meeting.</p>	<input type="checkbox"/> Not Applicable

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments: No reviewer present</p>	<p><input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<p><input type="checkbox"/> N/A</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	<p>Sponsor submitted an amendment on 11/11/13 for case report forms (CRFs) which were left out in the original BLA submission.</p>
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>

<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Curt Rosebraugh, M.D. (ODEII Director)/Mary Parks, M.D.</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): March 19, 2014</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments: Application maybe going to an AC.</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input checked="" type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter

<input type="checkbox"/>	
<input type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input checked="" type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at:</p> <p>http://erom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]</p>
<input type="checkbox"/>	Other

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

/s/

MEGHNA M JAIRATH
01/08/2014

**Selected Requirements of Prescribing Information
REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION**

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: 125511/0

Application Type: New BLA

Name of Drug/Dosage Form: Natpara [Recombinant Human Parathyroid Hormone (rDNA) or (rhPTH[1-84])]; Lyophilized for reconstitution for injection; subcutaneous injection 25, 50, 75 and 100 mcg/doses

Applicant: NPS Pharmaceuticals Inc.

Receipt Date: October 24, 2013

Goal Date: October 24, 2014

1. Regulatory History and Applicant's Main Proposals

NPS pharmaceuticals is producing recombinant Human Parathyroid Hormone (rDNA) or (rhPTH[1-84]) by manufacturing using a strain of Escherichia coli modified by recombinant deoxyribonucleic acid (rDNA) technology. The amino acid sequence of this synthesized rhPTH(1-84) is identical to that of native (endogenous) human parathyroid hormone.

In 2007, FDA granted Orphan Drug Designation for NPSP558 (rhPTH [1-84]) for the treatment of replacement for endogenous parathyroid hormone (1-84) for the long-term treatment of hypoparathyroidism. On November 7, 2011, a proprietary name, Natpara, was conditionally accepted.

NPS submitted this BLA application as a biologic-device combination. The review timeline will be twelve month review clock under "the Program" PDUFA V.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

In addition, the following labeling issues were identified:

Highlights

1. Highlights Limitation Statement

Selected Requirements of Prescribing Information

The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**” The name of drug product should appear in UPPER CASE letters.

Comment: Please change the name of the drug product to **UPPER CASE letters**.

Highlights Details

2. Initial U.S. Approval in Highlights

Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment: Please change [year] to **xxxx**.

3. Patient Counseling Information Statement in Highlights

The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment: Applicant submitted a medguide and IFU.

Please **delete** “*See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling*” and **add** “*See 17 for PATIENT COUNSELING INFORMATION and Medication Guide*”.

The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by January 27, 2014. The resubmitted PI will be used for further labeling review.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

- YES**
1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Selected Requirements of Prescribing Information

Comment:

- YES** 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment:

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI

Selected Requirements of Prescribing Information

• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

- NO** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**” The name of drug product should appear in UPPER CASE letters.

Comment: Please change the name of the drug product to UPPER CASE letters..

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- NO** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment: After Initial U.S. approval no 4-digit year follows. Change from [year] to xxxx.

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

Selected Requirements of Prescribing Information

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

Selected Requirements of Prescribing Information

- NO** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment: Applicant included a web address after phone number. Delete www.NATPARA.com after 1-855-NATPARA.

Patient Counseling Information Statement in Highlights

- NO** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment: Applicant included IFU and Medication Guide. Please delete “See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling” and add “See 17 for PATIENT COUNSELING INFORMATION and Medication Guide”

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment:

Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- N/A** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

- [text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

MEGHNA M JAIRATH
01/07/2014