CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 211097

Name: Teriparatide (injection), 0.6MG/2.4ML (0.25MG/ML)

Sponsor: Apotex Corp.

Approval Date: November 16, 2023

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA211097Orig1s000

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 211097

APPROVAL LETTER

ANDA 211097

ANDA APPROVAL

Apotex Corp.
U.S. Agent for Apotex Inc.
2400 North Commerce Parkway
Suite 400
Weston, FL 33326
Attention: Kiran Krishnan
Senior Vice President, Global Regulatory Affairs

Dear Kiran Krishnan:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on December 29, 2017, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Teriparatide Injection USP, 600 mcg/2.4 mL (250 mcg/mL) Single-Patient-Use Prefilled Pens.

Your product is a combination product as defined by 21 CFR 3.2(e) and is comprised of drug and device constituent parts.

Reference is also made to the tentative approval letter issued by this office on November 16, 2023, and to any amendments thereafter.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug meets the requirements for approval under the FD&C Act. Accordingly the ANDA is **approved**, effective on the date of this letter. We have determined your Teriparatide Injection USP, 600 mcg/2.4 mL (250 mcg/mL) Single-Patient-Use Prefilled Pens to be bioequivalent and therapeutically equivalent to the reference listed drug (RLD), Forteo Injection, 600 mcg/2.4 mL (250 mcg/mL), of Eli Lilly and Company (Lilly).

The reference listed drug (RLD) upon which you have based your ANDA, Lilly's Forteo Injection, 600 mcg/2.4 mL (250 mcg/mL), is subject to a period of patent protection. The following patent and expiration date is currently listed in the Agency's publication titled *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"):

U.S. Patent Number	Expiration Date
7,517,334 (the '334 patent)	March 25, 2025

Your ANDA contains a paragraph IV certification to the '334 patent under section 505(j)(2)(A)(vii)(IV) of the FD&C Act stating that the patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Teriparatide Injection USP, 600 mcg/2.4 mL (250 mcg/mL) Single-Patient-Use Prefilled Pens, under this ANDA. You have notified the Agency that Apotex Inc. (Apotex) complied with the requirements of section 505(j)(2)(B) of the FD&C Act. Litigation was initiated within the statutory 45-day period against Apotex for infringement of the '334 patent in the United States District Court for the Southern District of Indiana, Indianapolis Division [Eli Lilly and Company v. Apotex, Inc. and Apotex Corp., Civil Action No. 18-01037]. You have also notified the Agency that this case was dismissed. You have further notified the Agency that Apotex brought a declaratory judgment against Eli Lilly and Company in the United States District Court for the Southern District of Indiana, Indianapolis Division [Apotex, Inc. and Apotex Corp. v. Eli Lilly and Company, Civil Action No. 22-02342], and on January 27, 2023, the court decided "[t]he Apotex ANDA Product does not infringe the '334 patent."[1]

Please note that if FDA requires a Risk Evaluation and Mitigation Strategy (REMS) for a listed drug, an ANDA referencing that listed drug also will be required to have a REMS. See section 505-1(i) of the FD&C Act.

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standard for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website as https://www.uspnf.com/.

REQUIREMENTS AND RECOMMENDATIONS POST APPROVAL

Under applicable statutes, regulations, and guidances, your ANDA may be subject to certain requirements and recommendations post approval, including requirements regarding changes to approved ANDAs, postmarketing reporting, promotional materials, and annual facility fees, among others.

For information on post-approval requirements and recommendations for ANDAs and a list of resources for ANDA holders, we refer you to https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/requirements-and-resources-approved-andas.

Sincerely yours,

{See appended electronic signature page}

For Edward M. Sherwood
Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

[1] Consent Judgment, Apotex, Inc. and Apotex Corp. v. Eli Lilly and Company, Civil Action No. 22-02342 (Jan. 27, 2023).

John Ibrahim

Digitally signed by John Ibrahim
Date: 11/16/2023 03:12:23PM
GUID: 542af06d0124375c12e8c1d9fc86e87c

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 211097

OTHER ACTION LETTER(s)

ANDA 211097

ANDA TENTATIVE APPROVAL

Apotex Corp.
U.S. Agent for Apotex Inc.
2400 North Commerce Parkway
Suite 400
Weston, FL 33326
Attention: Kiran Krishnan
Senior Vice President, Global Regulatory Affairs

Dear Kiran Krishnan:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on December 29, 2017, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Teriparatide Injection USP, 600 mcg/2.4 mL (250 mcg/mL) Single-Patient-Use Prefilled Pens.

Reference is also made to the complete response letter issued by this office on June 14, 2021, and to any amendments thereafter.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug meets the requirements for approval under the FD&C Act. We have determined your Teriparatide Injection USP, 600 mcg/2.4 mL (250 mcg/mL) Single-Patient-Use Prefilled Pens to be bioequivalent and therapeutically equivalent to the reference listed drug (RLD), Forteo Injection, 600 mcg/2.4 mL (250 mcg/mL), of Eli Lilly and Company (Lilly).

However, we are unable to grant final approval to your ANDA at this time because of the exclusivity issue noted below. Therefore, the ANDA is **tentatively approved**. This determination is based upon information available to the Agency at this time (e.g., information in your ANDA and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacturing and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention.

The reference listed drug (RLD) upon which you have based your ANDA, Lilly's Forteo Injection, 600 mcg/2.4 mL (250 mcg/mL), is subject to a period of patent protection. The following patent and expiration date is currently listed in the Agency's publication titled *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"):

U.S. Patent Number	Expiration Date
7,517,334 (the '334 patent)	March 25, 2025

Your ANDA contains a paragraph IV certification to the '334 patent under section 505(j)(2)(A)(vii)(IV) of the FD&C Act stating that the patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Teriparatide Injection USP, 600 mcg/2.4 mL (250 mcg/mL) Single-Patient-Use Prefilled Pens, under this ANDA. You have notified the Agency that Apotex Inc. (Apotex) complied with the requirements of section 505(j)(2)(B) of the FD&C Act. Litigation was initiated within the statutory 45-day period against Apotex for infringement of the '334 patent in the United States District Court for the Southern District of Indiana, Indianapolis Division [Eli Lilly and Company v. Apotex, Inc. and Apotex Corp., Civil Action No. 18-01037]. You have also notified the Agency that this case was dismissed. You have further notified the Agency that Apotex brought a declaratory judgment against Eli Lilly and Company in the United States District Court for the Southern District of Indiana, Indianapolis Division [Apotex, Inc. and Apotex Corp. v. Eli Lilly and Company, Civil Action No. 22-02342], and on January 27, 2023, the court decided "[t]he Apotex ANDA Product does not infringe the '334 patent."[1]

However, we are unable to grant final approval to your ANDA at this time. Prior to the submission of your ANDA, another applicant or applicants submitted a substantially complete ANDA providing for Teriparatide Injection USP, 600 mcg/2.4 mL (250 mcg/mL) and containing a paragraph IV certification. Your ANDA will be eligible for final approval on the date that is 180 days after the commercial marketing date identified in section 505(j)(5)(B)(iv) of the FD&C Act.

Please note that if FDA requires a Risk Evaluation and Mitigation Strategy (REMS) for a listed drug, an ANDA referencing that listed drug also will be required to have a REMS. See section 505-1(i) of the FD&C Act.

REQUIREMENTS AND RECOMMENDATIONS POST APPROVAL

Under applicable statutes, regulations, and guidances, if your ANDA receives final approval, it may be subject to certain requirements and recommendations post approval, including requirements regarding changes to approved ANDAs, postmarketing reporting, promotional materials, and annual facility fees, among others. For information on post-approval requirements and recommendations for ANDAs and a list of resources for ANDA holders, we refer you to https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/requirements-and-resources-approved-andas.

RESUBMISSION

To request final approval, please submit an amendment titled "FINAL APPROVAL REQUESTED" with enough time to permit FDA review prior to the date you believe that

your ANDA will be eligible for final approval. A request for final approval that contains no new data, information, or other changes to the ANDA generally requires a period of 3 months for Agency review. Accordingly, such a request for final approval should be submitted no later than 3 months prior to the date on which you seek approval. A request for final approval that contains substantive changes to this ANDA or changes in the status of the manufacturing and testing facilities' compliance with cGMPs will be classified and reviewed according to OGD policy in effect at the time of receipt. Applicants should review available Agency guidance for industry related to amendments under the generic drug user fee program to determine the duration of Agency review needed to review the changes submitted. As part of this consideration, applicants should monitor any changes to the RLD that occur after tentative approval, including changes in labeling, patent or exclusivity information, or marketing status. The submission of multiple amendments prior to final approval may also result in a delay in the issuance of the final approval letter.

The amendment requesting final approval should provide the legal/regulatory basis for your request for final approval and should include a copy of a court decision, settlement or licensing agreement, or other information described in 21 CFR 314.107, as appropriate. It should also identify changes, if any, in the conditions under which the ANDA was tentatively approved, e.g., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made, and it should be designated clearly in your cover letter as a "FINAL APPROVAL REQUESTED."

In addition to the amendment requested above, the Agency may request, at any time prior to the date of final approval, that you submit an additional amendment containing information as specified by the Agency. Failure to submit either or, if requested, both types of amendments described above may result in a delay in the issuance of the final approval letter.

This drug product may not be marketed without final Agency approval under section 505(j) of the FD&C Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under section 301 of the FD&C Act. Also, until the Agency issues the final approval letter, this drug product will not be deemed approved for marketing under section 505(j) of the FD&C Act, and will not be listed in the Orange Book.

For further information on the status of this ANDA or upon submitting an amendment to the ANDA, please contact Kimberly McCullough, Regulatory Project Manager, at (240) 402 - 9021.

Sincerely yours,

{See appended electronic signature page}

For Edward M. Sherwood
Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

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[1] Consent Judgment, Apotex, Inc. and Apotex Corp. v. Eli Lilly and Company, Civil Action No. 22-02342 (Jan. 27, 2023).

John
Ibrahim

Digitally signed by John Ibrahim
Date: 11/16/2023 10:09:00AM
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ANDA 211097

COMPLETE RESPONSE

Apotex Corp.
U.S. Agent for Apotex Inc.
2400 North Commerce Parkway
Suite 400
Weston, FL 33326
Attention: Kiran Krishnan
Senior Vice President, Global Regulatory Affairs

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) received for review on December 29, 2017, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Teriparatide Injection, 600 mcg/2.4 mL (250 mg/mL) in prefilled delivery device (pen).

We acknowledge receipt of the October 15, 2020 submission, which constituted a complete response to our October 26, 2018 action letter, and to any amendments thereafter.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

(b) (4)

[redacted]

4 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

LABELING

1. CARTON/CONTAINER LABEL

   Revise your labels to be in accordance with the labeling for the reference listed drug (RLD), Forteo® (NDA 021318/S-054) approved on November 16, 2020 found on the Drugs@FDA website.

2. HIGHLIGHTS OF PRESCRIBING INFORMATION

   DOSAGE FORMS AND STRENGTHS: Revise to read, “Injection: 620 mcg/2.48 mL (250 mcg/mL) in a single-patient-use prefilled delivery device (pen) containing

28 daily doses of 20 mcg (b) (4)".

3. PRESCRIBING INFORMATION

   a. 3 DOSAGE FORMS AND STRENGTHS: Revise to read,
   "Injection: 620 mcg/2.48 mL (250 mcg/mL) clear, colorless solution in a single-patient-use prefilled delivery device (pen) containing 28 daily doses of 20 mcg."

   b. 11 DESCRIPTION: Revise the last sentence of the section to read,
   "Each prefilled delivery device (pen) delivers 20 mcg of teriparatide per dose for up to 28 days."

4. MEDICATION GUIDE

   Add "for subcutaneous use" under the established name and pronunciation in the title to be in line with the RLD.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

MICROBIOLOGY/FACILITY INSPECTION/BIOEQUIVALENCE/CLINICAL

There are no further questions for the above listed disciplines at this time. The comments provided in this communication are comprehensive as of the date the discipline review was completed. However, these comments are subject to revision if any scientific or regulatory division identifies additional concerns, as well as any concerns due to inspection results that may arise in the future. Additionally, the compliance status of each facility named in the application may be re-evaluated upon re-submission.

FDA publishes new and revised product-specific guidances describing the Agency's current recommendations on demonstrating bioequivalence and certain other approval requirements. To ensure you are aware of FDA's recommendations for the most accurate, sensitive, and reproducible methodology to demonstrate bioequivalence (21 CFR 320.24(a)), please continue to monitor for the availability of new and revised product-specific guidances in the *Federal Register* and on the FDA Web site at the following address: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

OTHER

The resubmission to this CR letter will be considered to represent a **MAJOR** AMENDMENT, given that the deficiencies have been classified as **MAJOR**.

Prominently identify the submission with the following wording in bold, capital letters at the top of the first page of the submission. If your submission includes gratuitous information in addition to the category or categories below, clearly identify the type of information submitted immediately following the wording below:

RESUBMISSION
MAJOR
COMPLETE RESPONSE AMENDMENT
DRUG SUBSTANCE/DRUG PRODUCT/PROCESS/FACILITIES/LABELING

Upon review of your amendment, FDA may identify information in the amendment that may require a change in classification and an adjustment to the goal date.

Within one year after the date of this letter, you are required to respond by taking one of the actions available under 21 CFR 314.110(b). If you do not take one of these actions, we may consider your lack of response as a request to withdraw the ANDA under 21 CFR 314.110(c)(1). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter does not fulfill the requirements in 21 CFR 314.110(b)(1) and therefore will not be processed as a resubmission and will not start a new review cycle.

The drug product may not be marketed without final Agency approval under section 505(j) of the FD&C Act.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[1] with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-

identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including by fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should

ensure your application addresses any changes to the RLD that occur after submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure you stay up to date with the Agency's current thinking on topics through guidances for industry, including product-specific guidances.

If you have any questions, call Kimberly McCullough, Regulatory Project Manager, Division of Project Management, at (240) 402 - 9021.

Sincerely yours,

{See appended electronic signature page}

For Denise P. Toyer McKan, PharmD
Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

[1] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

Aaron
Sigler

Digitally signed by Aaron Sigler
Date: 6/14/2021 05:25:47PM
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ANDA 211097

COMPLETE RESPONSE

Apotex Corp.
U.S. Agent for Apotex Inc
2400 North Commerce Parkway, Suite 400
Weston, FL 33326
Attention: Kiran Krishnan
Senior Vice President, Global Regulatory Affairs

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) received for review on December 29, 2017, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Teriparatide Injection, 600 mcg/2.4 mL (250 mg/mL) in prefilled delivery device (pen).

Reference is also made to any amendments submitted prior to the issuance of this letter.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

(b) (4)

[redacted]

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

11 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

LABELING

(b) (4)

d. DESCRIPTION

(b) (4)

ii. Include the statement "Teriparatide is manufactured chemical synthesis." prior to the sentence "Teriparatide injection, USP is supplied as a sterile, colorless, clear…"

(b) (4)

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

FACILITY INSPECTION/BIOEQUIVALENCE

There are no further questions for the above listed disciplines at this time. The comments provided in this communication are comprehensive as of the date the discipline review was completed. However, these comments are subject to revision if any scientific or regulatory division identifies additional concerns, as well as any concerns due to inspection results that may arise in the future. Additionally, the compliance status of each facility named in the application may be re-evaluated upon re-submission.

FDA publishes new and revised product-specific guidances describing the Agency's current recommendations on demonstrating bioequivalence and certain other approval requirements. To ensure you are using the most accurate, sensitive, and reproducible methodology to demonstrate bioequivalence, as required by FDA regulations (21 CFR320.24(a)), please continue to monitor for the availability of new and revised product specific guidances in the *Federal Register* and on the FDA Web site at the following address: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

OTHER

The resubmission to this CR letter will be considered to represent a **MAJOR** AMENDMENT, given that the deficiencies have been classified as **MAJOR**.

Prominently identify the submission with the following wording in bold, capital letters at the top of the first page of the submission:

RESUBMISSION
MAJOR
COMPLETE RESPONSE AMENDMENT
DRUG SUBSTANCE/DRUG PRODUCT/PROCESS/MICROBIOLOGY/CLINICAL/ LABELING

Upon review of your amendment, FDA may identify information in the amendment that may require a change in classification and an adjustment to the goal date.

Within one year after the date of this letter, you are required to respond by taking one of the actions available under 21 CFR 314.110(b). If you do not take one of these actions, we may consider your lack of response a request to withdraw the ANDA under 21 CFR 314.110(c)(1). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. Additionally, a partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

The drug product may not be marketed without final Agency approval under section 505(j) of the FD&C Act.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[1] with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts. All finished dosage forms or active pharmaceutical ingredients manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

If you have any questions, call Kimberly McCullough, Regulatory Project Manager, Division of Project Management, at (240) 402 - 9021.

Sincerely yours,

{See appended electronic signature page}

Aaron W. Sigler, PharmD, BCPS, PMP, CPH
CAPT, USPHS
Acting Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

[1] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

Aaron Sigler

Digitally signed by Aaron Sigler
Date: 10/26/2018 04:39:32PM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 211097

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TERIPARATIDE INJECTION safely and effectively. See full prescribing information for TERIPARATIDE INJECTION.

TERIPARATIDE injection for subcutaneous use
Initial U.S. Approval: 1987

----------INDICATIONS AND USAGE----------

Teriparatide injection is a parathyroid hormone analog, (PTH 1-34), indicated for:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture or patients who have failed or are intolerant to other available osteoporosis therapy (1)
- Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture or patients who have failed or are intolerant to other available osteoporosis therapy (1)
- Treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture or patients who have failed or are intolerant to other available osteoporosis therapy (1)

----------DOSAGE AND ADMINISTRATION----------

- Recommended dosage is 20 mcg subcutaneously once a day (2.1)
- Consider supplemental calcium and Vitamin D based on individual patient needs (2.1)
- Administer as a subcutaneous injection into the thigh or abdominal region (2.2)
- Administer initially under circumstances in which the patient can sit or lie down if symptoms of orthostatic hypotension occur (2.2)
- Use of teriparatide for more than 2 years during a patient's lifetime should only be considered if a patient remains at or has returned to having a high risk for fracture (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 600 mcg/2.4 mL (250 mcg/mL) in a single-patient-use prefilled delivery device (pen) containing 28 daily doses of 20 mcg (3)

----------CONTRAINDICATIONS----------

- Patients with hypersensitivity to teriparatide or to any of its excipients (4)

----------WARNINGS AND PRECAUTIONS----------

- Osteosarcoma: Avoid use in patients with increased risk of osteosarcoma including patients with open epiphyses, metabolic bone diseases including Paget's disease, bone metastases or history of skeletal malignancies, prior external beam or implant radiation therapy involving the skeleton, and hereditary disorders predisposing to osteosarcoma. (5.1)
- Hypercalcemia and Cutaneous Calcification: Avoid in patients known to have an underlying hypercalcemic disorder. Discontinue in patients developing worsening of previously stable cutaneous calcification. (5.2)
- Risk of Urolithiasis: Consider the risk/benefit in patients with active or recent urolithiasis because of risk of exacerbation (5.3)
- Orthostatic Hypotension: Transient orthostatic hypotension may occur with initial doses of teriparatide injection (5.4)

----------ADVERSE REACTIONS----------

Most common adverse reactions (>10%) include: arthralgia, pain, and nausea (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Apotex Inc. at 1-800-706-5575 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

Digoxin: Transient hypercalcemia may predispose patients to digitalis toxicity (5.5, 7.1)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Consider discontinuing when pregnancy is recognized (8.1)
- Lactation: Breastfeeding is not recommended (8.2)
- Pediatric Use: Safety and effectiveness not established. Avoid use due to increased baseline risk of osteosarcoma (5.1, 8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 01/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Teriparatide injection is indicated.

- For the treatment of postmenopausal women with osteoporosis at high risk for fracture (defined herein as having a history of osteoporotic fracture or multiple risk factors for fracture) or who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, teriparatide injection reduces the risk of vertebral and nonvertebral fractures.
- To increase bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture or who have failed or are intolerant to other available osteoporosis therapy.
- For the treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy (daily dosage equivalent to 5 mg or greater of prednisone) at high risk for fracture or who have failed or are intolerant to other available osteoporosis therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage is 20 mcg given subcutaneously once a day. Instruct patients to take supplemental calcium and vitamin D if daily dietary intake is inadequate.

2.2 Administration Instructions

- Administer teriparatide as a subcutaneous injection into the thigh or abdominal region. Teriparatide is not approved for intravenous or intramuscular use.
- Teriparatide injection should be administered initially under circumstances in which the patient can sit or lie down if symptoms of orthostatic hypotension occur *[see Warnings and Precautions (5.4)]*.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. (Teriparatide injection is a clear and colorless liquid). Do not use if solid particles appear or if the solution is cloudy or colored.
- Patients and/or caregivers who administer teriparatide injection should receive appropriate training and instruction on the proper use of the teriparatide injection prefilled delivery device (pen) from a qualified health professional.

2.3 Recommended Treatment Duration

Use of teriparatide injection for more than 2 years during a patient's lifetime should only be considered if a patient remains at or has returned to having a high risk for fracture *[see Warnings and Precautions (5.1)]*.

3 DOSAGE FORMS AND STRENGTHS

Injection: 600 mcg/2.4 mL (250 mcg/mL) clear, colorless solution in a single-patient-use prefilled delivery device (pen) containing 28 daily doses of 20 mcg.

4 CONTRAINDICATIONS

Teriparatide injection is contraindicated in patients with hypersensitivity to teriparatide or to any of its excipients. Hypersensitivity reactions have included angioedema and anaphylaxis *[see Adverse Reactions (6.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Osteosarcoma

An increase in the incidence of osteosarcoma (a malignant bone tumor) was observed in male and female rats treated with teriparatide. Osteosarcoma has been reported in patients treated with teriparatide in the post marketing setting; however, an increased risk of osteosarcoma has not been observed in observational studies in humans. There are limited data assessing the risk of osteosarcoma beyond 2 years of teriparatide use *[see*

Dosage and Administration (2.3), Adverse Reactions (6.3), and Nonclinical Toxicology (13.1)].

Avoid teriparatide use in patients with (these patients are at increased baseline risk of osteosarcoma):

- Open epiphyses (pediatric and young adult patients) (teriparatide is not approved in pediatric patients) *[see Use in Specific Populations (8.4)]*.
- Metabolic bone diseases other than osteoporosis, including Paget's disease of the bone.
- Bone metastases or a history of skeletal malignancies.
- Prior external beam or implant radiation therapy involving the skeleton.
- Hereditary disorders predisposing to osteosarcoma.

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5.2 Hypercalcemia and Cutaneous Calcification

Hypercalcemia

Teriparatide has not been studied in patients with pre-existing hypercalcemia. Teriparatide may cause hypercalcemia and may exacerbate hypercalcemia in patients with pre-existing hypercalcemia *[see Adverse Reactions (6.1, 6.3)]*. Avoid teriparatide in patients known to have an underlying hypercalcemic disorder, such as primary hyperparathyroidism.

Risk of Cutaneous Calcification Including Calciphylaxis

Serious reports of calciphylaxis and worsening of previously stable cutaneous calcification have been reported in the postmarketing setting in patients taking teriparatide. Risk factors for development of calciphylaxis include underlying autoimmune disease, kidney failure, and concomitant warfarin or systemic corticosteroid use. Discontinue teriparatide in patients who develop calciphylaxis or worsening of previously stable cutaneous calcification.

5.3 Risk of Urolithiasis

In clinical trials, the frequency of urolithiasis was similar in patients treated with teriparatide injection and patients treated with placebo. However, teriparatide injection has not been studied in patients with active urolithiasis. If teriparatide-treated patients have pre-existing hypercalciuria or suspected/known active urolithiasis, consider measuring urinary calcium excretion. Consider the risks and benefits of use in patients with active or recent urolithiasis because of the potential to exacerbate this condition.

5.4 Orthostatic Hypotension

Teriparatide injection should be administered initially under circumstances in which the patient can sit or lie down if symptoms of orthostatic hypotension occur. In short-term clinical pharmacology studies of teriparatide in healthy volunteers, transient episodes of symptomatic orthostatic hypotension were observed in 5% of volunteers. Typically, these events began within 4 hours of dosing and resolved (without treatment) within a few minutes to a few hours. When transient orthostatic hypotension occurred, it happened within the first several doses, it was relieved by placing the person in a reclining position, and it did not preclude continued treatment.

5.5 Risk of Digoxin Toxicity

Hypercalcemia may predispose patients to digitalis toxicity because teriparatide injection transiently increases serum calcium. Consider the potential onset of signs and symptoms of digitalis toxicity when teriparatide is used in patients receiving digoxin *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)].*

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Men with Primary or Hypogonadal Osteoporosis and Postmenopausal Women with Osteoporosis

The safety of teriparatide injection in the treatment of osteoporosis in men and postmenopausal women was assessed in two randomized, double-blind, placebo-controlled trials of 1382 patients (21% men, 79% women) aged 28 to 86 years (mean 67 years) *[see Clinical Studies (14.1, 14.2)].* The median durations of the trials were 11 months for men and 19 months for women, with 691 patients exposed to teriparatide injection and 691 patients to placebo. All patients received 1000 mg of calcium plus at least 400 IU of vitamin D supplementation per day.

The incidence of all-cause mortality was 1% in the teriparatide injection group and 1% in the placebo group. The incidence of serious adverse events was 16% in the teriparatide injection group and 19% in the placebo group. Early discontinuation due to adverse events occurred in 7% in the teriparatide injection group and 6% in the placebo group.

Table 1 lists adverse events from these two trials that occurred in ≥2% of teriparatide injection-treated and more frequently than placebo-treated patients.

Table 1. Percentage of Patients with Adverse Events Reported by at Least 2% of Teriparatide Treated Patients and in More Teriparatide Injection-Treated Patients than Placebo-Treated Patients from the Two Principal Osteoporosis Trials in Women and Men Adverse Events are Shown Without Attribution of Causality

	Teriparatide Injection N=691	**Placebo** N=691
Event Classification	**(%)**	**(%)**
Body as a Whole		
Pain	21.3	20.5
Headache	7.5	7.4
Asthenia	8.7	6.8
Neck pain	3	2.7
Cardiovascular		
Hypertension	7.1	6.8
Angina pectoris	2.5	1.6
Syncope	2.6	1.4
Digestive System		
Nausea	8.5	6.7
Constipation	5.4	4.5
Diarrhea	5.1	4.6
Dyspepsia	5.2	4.1
Vomiting	3	2.3
Gastrointestinal disorder	2.3	2
Tooth disorder	2	1.3
Musculoskeletal		
Arthralgia	10.1	8.4
Leg cramps	2.6	1.3
Nervous System		
Dizziness	8	5.4
Depression	4.1	2.7
Insomnia	4.3	3.6
Vertigo	3.8	2.7
Respiratory System		
Rhinitis	9.6	8.8
Cough increased	6.4	5.5
Pharyngitis	5.5	4.8
Dyspnea	3.6	2.6
Pneumonia	3.9	3.3
Skin and Appendages		
Rash	4.9	4.5
Sweating	2.2	1.7

Laboratory Findings

Serum Calcium — Teriparatide injection transiently increased serum calcium, with the maximal effect observed at approximately 4 to 6 hours post-dose. Serum calcium measured at least 16 hours post-dose was not different from pretreatment levels. In clinical trials, the frequency of at least 1 episode of transient hypercalcemia in the 4 to 6 hours after teriparatide injection administration was 11% of women and 6% of men treated with teriparatide compared to 2% of women and 0% of the men treated with placebo. The percentage of patients treated with teriparatide injection whose transient hypercalcemia was verified on consecutive measurements was 3% of

women and 1% of men.

Urinary Calcium — Teriparatide injection increased urinary calcium excretion, but the frequency of hypercalciuria in clinical trials was similar for patients treated with teriparatide injection and placebo *[see Clinical Pharmacology (12.2)]*.

Serum Uric Acid — Teriparatide injection increased serum uric acid concentrations. In clinical trials, 3% of teriparatide -treated patients had serum uric acid concentrations above the upper limit of normal compared with 1% of placebo-treated patients. However, the hyperuricemia did not result in an increase in gout, arthralgia, or urolithiasis.

Renal Function — No clinically important adverse renal effects were observed in clinical studies. Assessments included creatinine clearance; measurements of blood urea nitrogen (BUN), creatinine, and electrolytes in serum; urine specific gravity and pH; and examination of urine sediment.

Men and Women with Glucocorticoid-Induced Osteoporosis

The safety of teriparatide injection in the treatment of men and women with glucocorticoid-induced osteoporosis was assessed in a randomized, double-blind, active-controlled trial of 428 patients (19% men, 81% women) aged 22 to 89 years (mean 57 years) treated with ≥5 mg per day prednisone or equivalent for a minimum of 3 months *[see Clinical Studies (14.3)]*. The duration of the trial was 18 months with 214 patients exposed to teriparatide injection and 214 patients exposed to an oral daily bisphosphonate (active control). All patients received 1000 mg of calcium plus 800 IU of vitamin D supplementation per day.

There was no increase in mortality in the teriparatide group compared to the active control group. The incidence of serious adverse events was 21% in teriparatide injection patients and 18% in active control patients, and included pneumonia (3% teriparatide injection, 1% active control). Early discontinuation because of adverse events occurred in 15% of teriparatide injection patients and 12% of active control patients, and included dizziness (2% teriparatide injection, 0% active control).

Adverse events reported at a higher incidence in the teriparatide injection group and with at least a 2% difference in teriparatide injection-treated patients compared with active control-treated patients were: nausea (14%, 7%), gastritis (7%, 3%), pneumonia (6%, 3%), dyspnea (6%, 3%), insomnia (5%, 1%), anxiety (4%, 1%), and herpes zoster (3%, 1%), respectively.

6.2 Immunogenicity

As with all peptides, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other teriparatide products may be misleading.

In the clinical trial of postmenopausal women with osteoporosis *[see Clinical Studies (14.1)]*, antibodies that cross reacted with teriparatide were detected in 3% of women (15/541) who received teriparatide. Generally, antibodies were first detected following 12 months of treatment and diminished after withdrawal of therapy. There was no evidence of hypersensitivity reactions among these patients. Antibody formation did not appear to have effects on serum calcium, or on bone mineral density (BMD) response.

6.3 Postmarketing Experience

Adverse Reactions from Postmarketing Spontaneous Reports

The following adverse reactions have been identified during postapproval use of teriparatide injection. 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.

- Cases of bone tumor and osteosarcoma have been reported rarely in the postmarketing period [*see Warnings and Precautions (5.2)*].
- Hypercalcemia greater than 13 mg/dL has been reported with teriparatide injection use.

Adverse events reported since market introduction that were temporally related to teriparatide injection therapy include the following:

- Allergic Reactions: Anaphylactic reactions, drug hypersensitivity, angioedema, urticaria

- Investigations: Hyperuricemia
- Respiratory System: Acute dyspnea, chest pain
- Musculoskeletal: Muscle spasms of the leg or back
- Other: Injection site reactions including injection site pain, swelling and bruising; oro-facial edema

Adverse Reactions from Observational Studies to Assess Incidence of Osteosarcoma

Two osteosarcoma surveillance safety studies (U.S. claims-based database studies) were designed to obtain data on the incidence rate of osteosarcoma among teriparatide-treated patients. In these two studies, three and zero osteosarcoma cases were identified among 379,283 and 153,316 teriparatide users, respectively. The study results suggest a similar risk for osteosarcoma between teriparatide users and their comparators. However, the interpretation of the study results calls for caution owing to the limitations of the data sources which do not allow for complete measurement and control for confounders.

7 DRUG INTERACTIONS

7.1 Digoxin

Sporadic case reports have suggested that hypercalcemia may predispose patients to digitalis toxicity. Teriparatide injection may transiently increase serum calcium. Consider the potential onset of signs and symptoms of digitalis toxicity when teriparatide injection is used in patients receiving digoxin *[see Warnings and Precaution (5.5) and Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on teriparatide injection use in pregnant women to evaluate for drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Consider discontinuing teriparatide injection when pregnancy is recognized.

In animal reproduction studies, teriparatide increased skeletal deviations and variations in mouse offspring at subcutaneous doses equivalent to more than 60 times the recommended 20 mcg human daily dose (based on body surface area, mcg/m^2), and produced mild growth retardation and reduced motor activity in rat offspring at subcutaneous doses equivalent to more than 120 times the human dose *(see Data)*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. The background risk in the US general population of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Data

Animal Data

In animal reproduction studies, pregnant mice received teriparatide during organogenesis at subcutaneous doses equivalent to 8 to 267 times the human dose (based on body surface area, mcg/m^2). At subcutaneous doses ≥60 times the human dose, the fetuses showed an increased incidence of skeletal deviations or variations (interrupted rib, extra vertebra or rib). When pregnant rats received teriparatide during organogenesis at subcutaneous doses 16 to 540 times the human dose, the fetuses showed no abnormal findings.

In a perinatal/postnatal study in pregnant rats dosed subcutaneously from organogenesis through lactation, mild growth retardation was observed in female offspring at doses ≥120 times the human dose. Mild growth retardation in male offspring and reduced motor activity in both male and female offspring were observed at maternal doses of 540 times the human dose. There were no developmental or reproductive effects in mice or rats at doses 8 or 16 times the human dose, respectively.

8.2 Lactation

Risk Summary

It is not known whether teriparatide is excreted in human milk, affects human milk production, or has effects on the breastfed infant. Avoid teriparatide use in women who are breastfeeding.

8.4 Pediatric Use

The safety and effectiveness of teriparatide injection have not been established in pediatric patients. Pediatric patients are at higher baseline risk of osteosarcoma because of open epiphyses *[see Warnings and Precautions (5.1)]*.

8.5 Geriatric Use

Of the patients who received teriparatide injection in the osteoporosis trial of 1637 postmenopausal women, 75% were 65 years of age and older and 23% were 75 years of age and older. Of the patients who received teriparatide injection in the trial of 437 men with primary or hypogonadal osteoporosis, 39% were 65 years of age and over and 13% were 75 years of age and over. Of the 214 patients who received teriparatide injection in the glucocorticoid induced osteoporosis trial, 28% were 65 years of age and older and 9% were 75 years of age and older. No overall differences in safety or effectiveness of teriparatide injection have been observed between patients 65 years of age and older and younger adult patients.

8.6 Hepatic Impairment

No studies have been performed in patients with hepatic impairment. *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

In 5 patients with severe renal impairment (CrCl<30 mL/minute), the AUC and $T_{1/2}$ of teriparatide were increased by 73% and 77%, respectively. Maximum serum concentration of teriparatide was not increased. It is unknown whether teriparatide injection alters the underlying metabolic bone disease seen in chronic renal impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

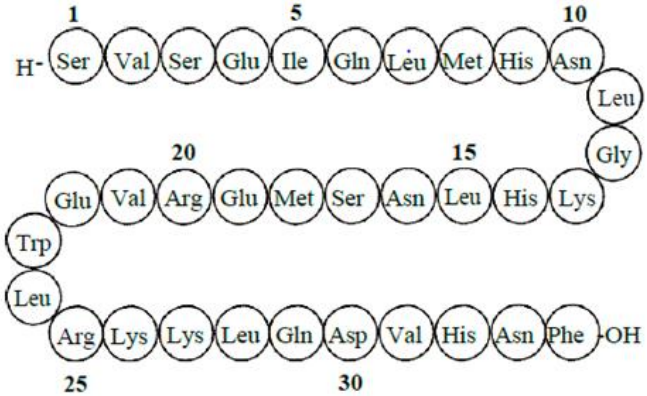
In postmarketing spontaneous reports, there have been cases of medication errors in which the entire contents (up to 800 mcg) (40 times the recommended dose) of the teriparatide injection prefilled delivery device (pen) have been administered as a single dose. Transient events reported have included nausea, weakness/lethargy and hypotension. No fatalities associated with overdose have been reported. Additional signs, symptoms, and complications of teriparatide injection overdosage may include a delayed hypercalcemic effect, vomiting, dizziness, and headache.

Overdose Management — There is no specific antidote for a teriparatide overdosage. Treatment of suspected overdosage should include discontinuation of teriparatide injection, monitoring of serum calcium and phosphorus, and implementation of appropriate supportive measures, such as hydration.

11 DESCRIPTION

Teriparatide injection, USP contains chemically synthesized human parathyroid hormone (1-34), and is also called hPTH (1-34). It has an identical sequence to the 34 N-terminal amino acids (the biologically active region) of the 84-amino acid human parathyroid hormone.

The molecular formula of teriparatide is $C_{181}H_{291}N_{55}O_{51}S_2$ and a molecular weight of 4117.8 daltons and its amino acid sequence is shown below:



Teriparatide is manufactured chemical synthesis. Teriparatide injection, USP is supplied as a sterile, colorless, clear, isotonic solution in a glass cartridge which is pre-assembled into a disposable delivery device (pen) for subcutaneous injection. Each prefilled delivery device is filled with 2.7 mL to deliver 2.4 mL. Each mL contains 250 mcg teriparatide (corrected for acetate, chloride, and water content), 0.41 mg glacial acetic acid, 0.1 mg sodium acetate (anhydrous), 45.4 mg mannitol, 3 mg Metacresol, and Water for Injection. In addition, hydrochloric acid solution 10% and/or sodium hydroxide solution 10% may have been added to adjust the product to pH 4.

Each prefilled delivery device (pen) delivers 20 mcg of teriparatide per dose for up to 28 days.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Endogenous 84-amino acid parathyroid hormone (PTH) is the primary regulator of calcium and phosphate metabolism in bone and kidney. Physiological actions of PTH include regulation of bone metabolism, renal tubular reabsorption of calcium and phosphate, and intestinal calcium absorption. The biological actions of PTH and teriparatide are mediated through binding to specific high-affinity cell-surface receptors. Teriparatide and the 34 N-terminal amino acids of PTH bind to these receptors with the same affinity and have the same physiological actions on bone and kidney. Teriparatide is not expected to accumulate in bone or other tissues.

The skeletal effects of teriparatide depend upon the pattern of systemic exposure. Once-daily administration of teriparatide stimulates new bone formation on trabecular and cortical (periosteal and/or endosteal) bone surfaces by preferential stimulation of osteoblastic activity over osteoclastic activity. In monkey studies, teriparatide improved trabecular microarchitecture and increased bone mass and strength by stimulating new bone formation in both cancellous and cortical bone. In humans, the anabolic effects of teriparatide manifest as an increase in skeletal mass, an increase in markers of bone formation and resorption, and an increase in bone strength. By contrast, continuous excess of endogenous PTH, as occurs in hyperparathyroidism, may be detrimental to the skeleton because bone resorption may be stimulated more than bone formation.

12.2 Pharmacodynamics

Pharmacodynamics in Men with Primary or Hypogonadal Osteoporosis and Postmenopausal Women with Osteoporosis

Effects on Mineral Metabolism — Teriparatide affects calcium and phosphorus metabolism in a pattern consistent with the known actions of endogenous PTH (e.g., increases serum calcium and decreases serum phosphorus).

Serum Calcium Concentrations — When teriparatide 20 mcg was administered once daily, the serum calcium concentration increased transiently, beginning approximately 2 hours after dosing and reaching a maximum concentration between 4 and 6 hours (median increase, 0.4 mg/dL). The serum calcium concentration began to decline approximately 6 hours after dosing and returned to baseline by 16 to 24 hours after each dose.

In a clinical study of postmenopausal women with osteoporosis, the median peak serum calcium concentration measured 4 to 6 hours after dosing with teriparatide injection (20 mcg subcutaneous once daily) was 9.68 mg/dL at 12 months. The peak serum calcium remained below 11 mg/dL in >99% of women at each visit. Sustained hypercalcemia was not observed.

In this study, 11.1% of women treated with teriparatide injection had at least 1 serum calcium value above the upper limit of normal (ULN) (10.6 mg/dL) compared with 1.5% of women treated with placebo. The percentage of women treated with teriparatide injection whose serum calcium was above the ULN on consecutive 4- to 6-hour post-dose measurements was 3% compared with 0.2% of women treated with placebo. In these women, calcium supplements and/or teriparatide injection doses were reduced. The timing of these dose reductions was at the discretion of the investigator. Teriparatide injection dose adjustments were made at varying intervals after the first observation of increased serum calcium (median 21 weeks). During these intervals, there was no evidence of progressive increases in serum calcium.

In a clinical study of men with either primary or hypogonadal osteoporosis, the effects on serum calcium were similar to those observed in postmenopausal women. The median peak serum calcium concentration measured 4 to 6 hours after dosing with teriparatide injection was 9.44 mg/dL at 12 months. The peak serum calcium remained below 11 mg/dL in 98% of men at each visit. Sustained hypercalcemia was not observed.

In this study, 6% of men treated with teriparatide injection daily had at least 1 serum calcium value above the ULN (10.6 mg/dL) compared with none of the men treated with placebo. The percentage of men treated with teriparatide injection whose serum calcium was above the ULN on consecutive measurements was 1.3% (2 men) compared with none of the men treated with placebo. Calcium supplementation was reduced in these men *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*.

In a clinical study of women previously treated for 18 to 39 months with raloxifene (n=26) or alendronate (n=33), mean serum calcium >12 hours after teriparatide injection treatment was increased by 0.36 to 0.56 mg/dL, after 1 to 6 months of teriparatide injection treatment compared with baseline. Of the women pretreated with raloxifene, 3 (11.5%) had a serum calcium >11 mg/dL, and of those pretreated with alendronate, 3 (9.1%) had a serum calcium >11.mg/dL. The highest serum calcium reported was 12.5 mg/dL. None of the women had symptoms of hypercalcemia. There were no placebo controls in this study.

In the study of patients with glucocorticoid-induced osteoporosis, the effects of teriparatide injection on serum calcium were similar to those observed in postmenopausal women with osteoporosis not taking glucocorticoids.

Urinary Calcium Excretion — In a clinical study of postmenopausal women with osteoporosis who received 1000 mg of supplemental calcium and at least 400 IU of vitamin D, daily teriparatide injection increased urinary calcium excretion. The median urinary excretion of calcium was 190 mg/day at 6 months and 170 mg/day at 12 months. These levels were 30 mg/day and 12 mg/day higher, respectively, than in women treated with placebo. The incidence of hypercalciuria (>300 mg/day) was similar in the women treated with teriparatide injection or placebo.

In a clinical study of men with either primary or hypogonadal osteoporosis who received 1000 mg of supplemental calcium and at least 400 IU of vitamin D, daily teriparatide injection had inconsistent effects on urinary calcium excretion. The median urinary excretion of calcium was 220 mg/day at 1 month and 210 mg/day at 6 months. These levels were 20 mg/day higher and 8 mg/day lower, respectively, than in men treated with placebo. The incidence of hypercalciuria (>300 mg/day) was similar in the men treated with teriparatide injection or placebo.

Phosphorus and Vitamin D — In single-dose studies, teriparatide produced transient phosphaturia and mild transient reductions in serum phosphorus concentration. However, hypophosphatemia (<2.4 mg/dL) was not observed in clinical trials with teriparatide injection.

In clinical trials of daily teriparatide injection, the median serum concentration of 1,25-dihydroxyvitamin D was increased at 12 months by 19% in women and 14% in men, compared with baseline. In the placebo group, this concentration decreased by 2% in women and increased by 5% in men. The median serum 25-hydroxyvitamin D concentration at 12 months was decreased by 19% in women and 10% in men compared with baseline. In the placebo group, this concentration was unchanged in women and increased by 1% in men.

In the study of patients with glucocorticoid-induced osteoporosis, the effects of teriparatide injection on serum phosphorus were similar to those observed in postmenopausal women with osteoporosis not taking glucocorticoids.

Effects on Markers of Bone Turnover — Daily administration of teriparatide injection to men and postmenopausal women with osteoporosis in clinical studies stimulated bone formation, as shown by increases in the formation markers serum bone-specific alkaline phosphatase (BSAP) and procollagen I carboxy-terminal propeptide (PICP). Data on biochemical markers of bone turnover were available for the first 12 months of treatment. Peak concentrations of PICP at 1 month of treatment were approximately 41% above baseline, followed by a decline to near-baseline values by 12 months. BSAP concentrations increased by 1 month of treatment and continued to rise more slowly from 6 through 12 months. The maximum increases of BSAP were 45% above baseline in women and 23% in men. After discontinuation of therapy, BSAP concentrations returned toward baseline. The increases in formation markers were accompanied by secondary increases in the markers of bone resorption: urinary N-telopeptide (NTX) and urinary deoxypyridinoline (DPD), consistent with the physiological coupling of bone formation and resorption in skeletal remodeling. Changes in BSAP, NTX, and DPD were lower in men than in women, possibly because of lower systemic exposure to teriparatide in men.

In the study of patients with glucocorticoid-induced osteoporosis, the effects of teriparatide injection on serum markers of bone turnover were similar to those observed in postmenopausal women with osteoporosis not taking glucocorticoids.

12.3 Pharmacokinetics

Absorption — Teriparatide is absorbed after subcutaneous injection; the absolute bioavailability is approximately 95% based on pooled data from 20-, 40-, and 80- mcg doses (1-, 2-, and 4-times the recommended dosage, respectively). The peptide reaches peak serum concentrations about 30 minutes after subcutaneous injection of a 20-mcg dose and declines to non-quantifiable concentrations within 3 hours.

Distribution — Volume of distribution following intravenous injection is approximately 0.12 L/kg.

Elimination — Systemic clearance of teriparatide (approximately 62 L/hour in women and 94 L/hour in men) exceeds the rate of normal liver plasma flow, consistent with both hepatic and extra-hepatic clearance. The half-life of teriparatide in serum was approximately 1 hour when administered by subcutaneous injection. No metabolism or excretion studies have been performed with teriparatide. Peripheral metabolism of PTH is believed to occur by non-specific enzymatic mechanisms in the liver followed by excretion via the kidneys.

Specific Populations

Geriatric Patients — No age-related differences in teriparatide pharmacokinetics were detected (range 31 to 85 years).

Male and Female Patients — Although systemic exposure to teriparatide was approximately 20% to 30% lower in men than women, the recommended dosage for men and women is the same.

Racial Groups —The influence of race has not been determined.

Patients with Renal Impairment — No pharmacokinetic differences were identified in 11 patients with creatinine clearance (CrCl) 30 to 72 mL/minute administered a single dose of teriparatide. In 5 patients with severe renal impairment (CrCl<30 mL/minute), the AUC and $T_{1/2}$ of teriparatide were increased by 73% and 77%, respectively. Maximum serum concentration of teriparatide was not increased. No studies have been performed in patients undergoing dialysis for chronic renal failure.

Patients with Hepatic Impairment — No studies have been performed in patients with hepatic impairment. Non-specific proteolytic enzymes in the liver (possibly Kupffer cells) cleave PTH(1-34) and PTH(1-84) into fragments that are cleared from the circulation mainly by the kidney.

Drug Interaction Studies

Digoxin — In a study of 15 healthy people administered digoxin daily to steady state, a single teriparatide injection dose did not alter the effect of digoxin on the systolic time interval (from electrocardiographic Q-wave onset to aortic valve closure, a measure of digoxin's calcium-mediated cardiac effect).

Hydrochlorothiazide — In a study of 20 healthy people, the coadministration of hydrochlorothiazide 25 mg with

40 mcg of teriparatide (2 times the recommended dose) did not affect the serum calcium response to teriparatide injection. The 24-hour urine excretion of calcium was reduced by a clinically unimportant amount (15%). The effect of coadministration of a higher dose of hydrochlorothiazide with teriparatide on serum calcium levels has not been studied.

Furosemide — In a study of 9 healthy people and 17 patients with CrCl 13 to 72 mL/minute, coadministration of intravenous furosemide (20 to 100 mg) with teriparatide 40 mcg (2 times the recommended dose) resulted in small increases in the serum calcium (2%) and 24-hour urine calcium (37%); however, these changes did not appear to be clinically important.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis — Two carcinogenicity bioassays were conducted in Fischer 344 rats. In the first study, male and female rats were given daily subcutaneous teriparatide injections of 5, 30, or 75 mcg/kg/day for 24 months from 2 months of age. These doses resulted in rat systemic exposures that were 3, 20, and 60 times higher than the systemic exposure observed in humans, respectively, following a subcutaneous dose of 20 mcg (based on AUC comparison). Teriparatide treatment resulted in a marked dose-related increase in the incidence of osteosarcoma, a rare malignant bone tumor, in both male and female rats. Osteosarcomas were observed at all doses and the incidence reached 40% to 50% in the high-dose groups. Teriparatide also caused a dose-related increase in osteoblastoma and osteoma in both sexes. No osteosarcomas, osteoblastomas or osteomas were observed in untreated control rats. The bone tumors in rats occurred in association with a large increase in bone mass and focal osteoblast hyperplasia.

The second 2-year study was carried out in order to determine the effect of treatment duration and animal age on the development of bone tumors. Female rats were treated for different periods between 2 and 26 months of age with subcutaneous teriparatide doses of 5 and 30 mcg/kg (equivalent to 3 and 20 times the human exposure at the 20-mcg dose, respectively, based on AUC comparison). The study showed that the occurrence of osteosarcoma, osteoblastoma and osteoma was dependent upon dose and duration of teriparatide exposure. Bone tumors were observed when immature 2-month old rats were treated with 30 mcg/kg/day of teriparatide for 24 months or with 5 or 30 mcg/kg/day of teriparatide for 6 months. Bone tumors were also observed when mature 6-month old rats were treated with 30 mcg/kg/day of teriparatide for 6 or 20 months. Tumors were not detected when mature 6-month old rats were treated with 5 mcg/kg/day of teriparatide for 6 or 20 months. The results did not demonstrate a difference in susceptibility to bone tumor formation, associated with teriparatide treatment, between mature and immature rats.

No bone tumors were detected in a long-term monkey study *[see Nonclinical Toxicology (13.2)].*

Mutagenesis

Teriparatide was not genotoxic in any of the following test systems: the Ames test for bacterial mutagenesis; the mouse lymphoma assay for mammalian cell mutation; the chromosomal aberration assay in Chinese hamster ovary cells, with and without metabolic activation; and the *in vivo* micronucleus test in mice.

Impairment of Fertility

No effects on fertility were observed in male and female rats given subcutaneous teriparatide doses of 30, 100, or 300 mcg/kg/day prior to mating and in females continuing through gestation Day 6 (16 to 160 times the human dose of 20 mcg based on surface area, mcg/m^2).

13.2 Animal Toxicology

In single-dose rodent studies using subcutaneous injection of teriparatide, no mortality was seen in rats given doses of 1000 mcg/kg (540 times the human dose based on surface area, mcg/m^2) or in mice given 10,000 mcg/kg (2700 times the human dose based on surface area, mcg/m^2).

In a long-term study, skeletally mature ovariectomized female monkeys (N=30 per treatment group) were given either daily subcutaneous teriparatide injections of 5 mcg/kg or vehicle. Following the 18-month treatment

period, the monkeys were removed from teriparatide treatment and were observed for an additional 3 years. The 5 mcg/kg dose resulted in systemic exposures that were approximately 6 times higher than the systemic exposure observed in humans following a subcutaneous dose of 20 mcg (based on AUC comparison). Bone tumors were not detected by radiographic or histologic evaluation in any monkey in the study.

14 CLINICAL STUDIES

14.1 Treatment of Osteoporosis in Postmenopausal Women

The safety and efficacy of once-daily teriparatide injection, median exposure of 19 months, were examined in a double-blind, multicenter, placebo-controlled clinical study of 1637 postmenopausal women with osteoporosis. In this study 541 postmenopausal women were treated with 20 mcg teriparatide injection subcutaneously once daily.

All women received 1000 mg of calcium and at least 400 IU of vitamin D per day. Baseline and endpoint spinal radiographs were evaluated using the semiquantitative scoring. Ninety percent of the women in the study had 1 or more radiographically diagnosed vertebral fractures at baseline. The primary efficacy endpoint was the occurrence of new radiographically diagnosed vertebral fractures defined as changes in the height of previously undeformed vertebrae. Such fractures are not necessarily symptomatic.

Effect on Fracture Incidence

New Vertebral Fractures — Teriparatide injection, when taken with calcium and vitamin D and compared with calcium and vitamin D alone, reduced the risk of 1 or more new vertebral fractures from 14.3% of women in the placebo group to 5% in the teriparatide injection group (444 of the 541 patients treated with 20 mcg once daily of teriparatide injection were included in this analysis). This difference was statistically significant ($p<0.001$); the absolute reduction in risk was 9.3% and the relative reduction was 65%. Teriparatide injection was effective in reducing the risk for vertebral fractures regardless of age, baseline rate of bone turnover, or baseline BMD (*see* Table 2).

Table 2: Effect of Teriparatide Injection on Risk of Vertebral Fractures in Postmenopausal Women with Osteoporosis

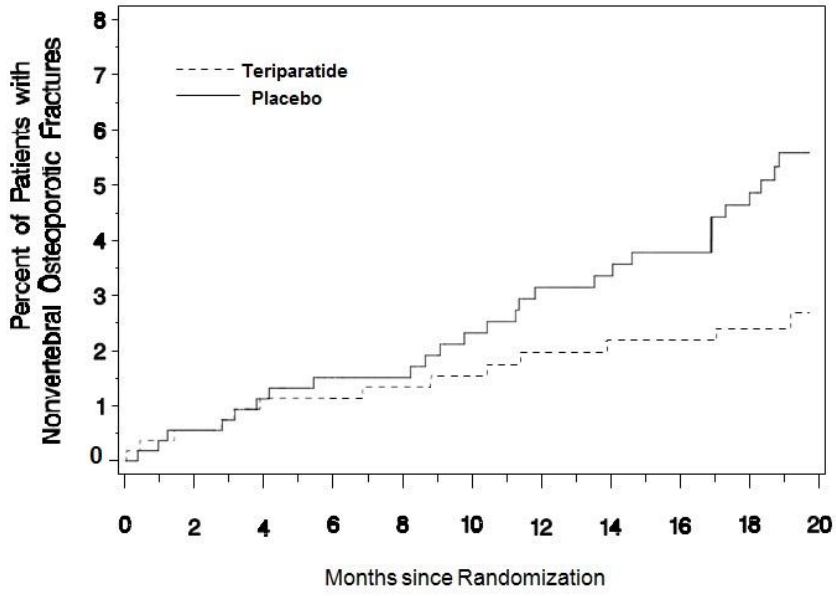
	Percent of Women With Fracture			
	Teriparatide Injection (N=444)	**Placebo (N=448)**	**Absolute Risk Reduction (%, 95% CI)**	**Relative Risk Reduction (%, 95% CI)**
New fracture (≥1)	5[a]	14.3	9.3 (5.5-13.1)	65 (45-78)
1 fracture	3.8	9.4		
2 fractures	0.9	2.9		
≥3 fractures	0.2	2		

[a] $p \leq 0.001$ compared with placebo.

New Nonvertebral Osteoporotic Fractures — Teriparatide injection significantly reduced the risk of any nonvertebral fracture from 5.5% in the placebo group to 2.6% in the teriparatide injection group ($p<0.05$). The absolute reduction in risk was 2.9% and the relative reduction was 53%. The incidence of new nonvertebral fractures in the teriparatide injection group compared with the placebo group was ankle/foot (0.2%, 0.7%), hip (0.2%, 0.7%), humerus (0.4%, 0.4%), pelvis (0%, 0.6%), ribs (0.6%, 0.9%), wrist (0.4%, 1.3%), and other sites (1.1%, 1.5%), respectively.

The cumulative percentage of postmenopausal women with osteoporosis who sustained new nonvertebral fractures was lower in women treated with teriparatide injection than in women treated with placebo (*see* Figure 1).

Figure 1: Cumulative Percentage of Postmenopausal Women with Osteoporosis Sustaining New Nonvertebral Osteoporotic Fractures



Effect on Bone Mineral Density (BMD)

Teriparatide injection increased lumbar spine BMD in postmenopausal women with osteoporosis. Statistically significant increases were seen at 3 months and continued throughout the treatment period. Postmenopausal women with osteoporosis who were treated with teriparatide injection had statistically significant increases in BMD from baseline to endpoint at the lumbar spine, femoral neck, total hip, and total body (*see* Table 3).

Table 3: Mean Percent Change in BMD from Baseline to Endpoint[a] in Postmenopausal Women with Osteoporosis, Treated with Teriparatide Injection or Placebo for a Median of 19 Months

	Teriparatide Injection N=541	**Placebo N=544**
Lumbar spine BMD	9.7[b]	1.1
Femoral neck BMD	2.8[c]	-0.7
Total hip BMD	2.6[c]	-1
Trochanter BMD	3.5[c]	-0.2
Intertrochanter BMD	2.6[c]	-1.3
Ward's triangle BMD	4.2[c]	-0.8
Total body BMD	0.6[c]	-0.5
Distal 1/3 radius BMD	-2.1	-1.3
Ultradistal radius BMD	-0.1	-1.6

[a] Intent-to-treat analysis, last observation carried forward.
[b] p<0.001 compared with placebo.
[c] p<0.05 compared with placebo.

Teriparatide injection treatment increased lumbar spine BMD from baseline in 96% of postmenopausal women treated.

Seventy-two percent of patients treated with teriparatide injection achieved at least a 5% increase in spine BMD, and 44% gained 10% or more.

Both treatment groups lost height during the trial. The mean decreases were 3.61 and 2.81 mm in the placebo and teriparatide injection groups, respectively.

Bone Histology

The effects of teriparatide on bone histology were evaluated in iliac crest biopsies of 35 postmenopausal women treated for 12 to 24 months with calcium and vitamin D and teriparatide. Normal mineralization was observed with no evidence of cellular toxicity. The new bone formed with teriparatide was of normal quality (as evidenced by the absence of woven bone and marrow fibrosis).

14.2 Treatment to Increase Bone Mass in Men with Primary or Hypogonadal Osteoporosis

The safety and efficacy of once-daily teriparatide injection, median exposure of 10 months, were examined in a double-blind, multicenter, placebo-controlled clinical study of 437 men with either primary (idiopathic) or hypogonadal osteoporosis. In this study, 151 men received 20 mcg of teriparatide given subcutaneously once daily. All men received 1000 mg of calcium and at least 400 IU of vitamin D per day. The primary efficacy endpoint was change in lumbar spine BMD.

Teriparatide injection increased lumbar spine BMD in men with primary or hypogonadal osteoporosis. Statistically significant increases were seen at 3 months and continued throughout the treatment period. Teriparatide injection was effective in increasing lumbar spine BMD regardless of age, baseline rate of bone turnover, and baseline BMD. The effects of teriparatide injection at additional skeletal sites are shown in Table 4.

Teriparatide injection treatment for a median of 10 months increased lumbar spine BMD from baseline in 94% of men treated. Fifty-three percent of patients treated with teriparatide injection achieved at least a 5% increase in spine BMD, and 14% gained 10% or more.

Table 4: Mean Percent Change in BMD from Baseline to Endpoint[a] in Men with Primary or Hypogonadal Osteoporosis, Treated with Teriparatide Injection or Placebo for a Median of 10 Months

	Teriparatide Injection N=151	Placebo N=147
Lumbar spine BMD	5.9[b]	0.5
Femoral neck BMD	1.5[c]	0.3
Total hip BMD	1.2	0.5
Trochanter BMD	1.3	1.1
Intertrochanter BMD	1.2	0.6
Ward's triangle BMD	2.8	1.1
Total body BMD	0.4	-0.4
Distal 1/3 radius BMD	-0.5	-0.2
Ultradistal radius BMD	-0.5	-0.3

[a] Intent-to-treat analysis, last observation carried forward.

[b] $p<0.001$ compared with placebo.

[c] $p<0.05$ compared with placebo.

14.3 Treatment of Men and Women with Glucocorticoid-Induced Osteoporosis

The efficacy of teriparatide injection for treating glucocorticoid-induced osteoporosis was assessed in a randomized, double-blind, active-controlled trial of 428 patients (19% men, 81% women) aged 22 to 89 years (mean 57 years) treated with ≥5 mg/day prednisone or equivalent for a minimum of 3 months. The duration of the trial was 18 months. In the trial 214 patients were treated with teriparatide injection 20 mcg given subcutaneously once daily. In the teriparatide injection group, the baseline median glucocorticoid dose was 7.5 mg/day and the baseline median duration of glucocorticoid use was 1.5 years. The mean (SD) baseline lumbar spine BMD was 0.85 ± 0.13 g/cm^2 and lumbar spine BMD T-score was –2.5 ± 1 (number of standard deviations below the mean BMD value for healthy adults). A total of 30% of patients had prevalent vertebral fracture(s) and 43% had prior non-vertebral fracture(s). The patients had chronic rheumatologic, respiratory or other diseases that required sustained glucocorticoid therapy. All patients received 1000 mg of calcium plus 800 IU of vitamin D supplementation per day.

Because of differences in mechanism of action (anabolic vs. anti-resorptive) and lack of clarity regarding differences in BMD as an adequate predictor of fracture efficacy, data on the active comparator are not presented.

Effect on Bone Mineral Density (BMD)

In patients with glucocorticoid-induced osteoporosis, teriparatide injection increased lumbar spine BMD

compared with baseline at 3 months through 18 months of treatment. In patients treated with teriparatide injection, the mean percent change in BMD from baseline to endpoint was 7.2% at the lumbar spine, 3.6% at the total hip, and 3.7% at the femoral neck (p <0.001 all sites). The relative treatment effects of teriparatide injection were consistent in subgroups defined by gender, age, geographic region, body mass index, underlying disease, prevalent vertebral fracture, baseline glucocorticoid dose, prior bisphosphonate use, and glucocorticoid discontinuation during trial.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Teriparatide Injection is a clear and colorless solution, available as single-patient-use prefilled delivery device (pen) in the following package size:

- 600 mcg/2.4 mL (250 mcg/mL) [containing 28 daily doses of 20 mcg] NDC 60505-6188-0.

16.2 Storage and Handling

- Store teriparatide injection, USP under refrigeration at 2°C to 8°C (36°F to 46°F) at all times except when administering the product.
- Recap the delivery device (pen) when not in use to protect the cartridge from physical damage and light.
- When using teriparatide injection, minimize the time out of the refrigerator; deliver the dose immediately following removal from the refrigerator.
- Do not freeze. Do not use teriparatide injection, USP if it has been frozen.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and the User Manual) before starting teriparatide and each time the prescription is renewed. Failure to follow the instructions may result in inaccurate dosing.

Osteosarcoma

Patients should be made aware that in rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor). Although cases of osteosarcoma have been reported in patients using teriparatide injection no increased risk of osteosarcoma was observed in adult humans treated with teriparatide injection *[see Warnings and Precautions (5.1)]*.

Hypercalcemia

Instruct patients taking teriparatide injection to contact a health care provider if they develop persistent symptoms of hypercalcemia (e.g., nausea, vomiting, constipation, lethargy, muscle weakness) *[see Warnings and Precautions (5.2)]*.

Orthostatic Hypotension

When initiating teriparatide injection treatment, instruct patients to be prepared to immediately sit or lie down during or after administration in case they feel lightheaded or have palpitations after the injection. Instruct patients to sit or lie down until the symptoms resolve. If symptoms persist or worsen, instruct patients to consult a healthcare provider before continuing treatment *[see Warnings and Precautions (5.4)]*.

Other Osteoporosis Treatment Modalities

Patients should be informed regarding the roles of supplemental calcium and/or vitamin D.

Use of the Prefilled Delivery Device (Pen)

Instruct patients and caregivers who administer teriparatide injection on how to properly use the delivery device (refer to *User Manual*), to properly dispose of needles, and not to share their prefilled delivery device with other patients. Instruct patients and caregivers who administer teriparatide injection that the contents of the delivery device should not be transferred to a syringe.

Inform patients that each teriparatide injection delivery device can be used for up to 28 days. After the 28-day use period, instruct patients to discard the teriparatide injection delivery device, even if it still contains some unused solution. Instruct patients not to use teriparatide injection after the expiration date printed on the delivery device and packaging.

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Medication Guide
Teriparatide Injection, USP
(ter" i par' a tide)
for subcutaneous use

Read this Medication Guide before you start using teriparatide injection and each time you get a refill. There may be new information. Also, read the User Manual that comes with the teriparatide injection delivery device (pen) for information on how to use the device to inject your medicine the right way. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about teriparatide injection?

Possible bone cancer. During drug testing, the medicine in teriparatide injection caused some rats to develop a bone cancer called osteosarcoma. Studies in people have not shown that teriparatide injection increases your chance of getting osteosarcoma. There is little information about the chance of getting osteosarcoma in patients using teriparatide injection beyond 2 years.

What is teriparatide injection?

Teriparatide injection is a prescription medicine used to:

- treat postmenopausal women who have osteoporosis who are at high risk for having broken bones (fractures) or who cannot use other osteoporosis treatments. Teriparatide injection can lessen the chance of broken bones (fractures) in the spine and other bones in postmenopausal women with osteoporosis.
- increase the bone mass in men with primary or hypogonadal osteoporosis who are at high risk for having broken bones (fractures) or who cannot use other osteoporosis treatments.
- treat both men and women with osteoporosis due to use of glucocorticoid medicines, such as prednisone, for several months, who are at high risk for having broken bones (fractures) or who cannot use other osteoporosis treatments.

It is not known if teriparatide injection is safe and effective in children.
Teriparatide injection should not be used in children and young adults whose bones are still growing.

Who should not use teriparatide injection?

Do not use teriparatide injection if you:

- are allergic to any of the ingredients in teriparatide injection. See the end of this Medication Guide for a complete list of the ingredients in teriparatide injection.

Symptoms of a serious allergic reaction of teriparatide injection may include swelling of the face, lips, tongue or throat that may cause difficulty in breathing or swallowing. Call your healthcare provider right away or get emergency medical help if you get any of these symptoms.

What should I tell my healthcare provider before using teriparatide injection?

Before you use teriparatide injection, tell your healthcare provider about all of your medical conditions, including if you:

- have a certain bone disease called Paget's disease or other bone disease.
- have bone cancer or have had a history of bone cancer.
- are a young adult whose bones are still growing.
- have had radiation therapy.
- are affected with a condition that runs in your family that can increase your chance of getting cancer in your bones.
- have or have had too much calcium in your blood (hypercalcemia).
- have or have had a skin condition with painful sores or wounds caused by too much calcium.
- have or have had kidney stones.
- take medicines that contain digoxin.
- are pregnant or plan to become pregnant. It is not known if teriparatide injection will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if teriparatide injection passes into your breastmilk. You should not breastfeed while taking teriparatide injection.

Tell your healthcare provider about all the medicines you take including prescription and over-the-counter medicines, vitamins, and herbal supplements.
Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use teriparatide injection?

- Read the detailed Instructions for Use (User Manual) included with your teriparatide injection delivery device.
- Use teriparatide injection exactly as your healthcare provider tells you to. Your healthcare provider will tell you how much teriparatide injection to use and when to use it.
- Before you try to inject teriparatide injection yourself, a healthcare provider should teach you how to use the teriparatide injection delivery device to give your injection the right way.
- Inject teriparatide injection 1 time each day in your thigh or abdomen (lower stomach area). Do not inject into a vein or a muscle. Talk to a healthcare provider about how to rotate injection sites.
- The teriparatide injection delivery device has enough medicine for 28 days. It is set to give a 20-microgram dose of medicine each day. Do not inject all the medicine in the teriparatide injection delivery device at any one time.
- Do not transfer the medicine from the teriparatide injection delivery device to a syringe. This can result in taking the wrong dose of teriparatide injection. If you do not have pen needles to use with your teriparatide injection delivery device, talk with your healthcare provider.
- Teriparatide injection should look clear and colorless. Do not use teriparatide injection if it has particles in it, or if it is cloudy or colored.
- Inject teriparatide injection right away after you take the delivery device out of the refrigerator.
- After each use, safely remove the needle, recap the delivery device, and put it back in the refrigerator right away.
- When you inject the first few doses of teriparatide injection, make sure you are in a place where you can sit or lie down right away in case you feel dizzy or have an abnormal heartbeat after the injection.
- Do not take more than 1 injection in the same day.
- Do not share your teriparatide injection delivery device with other people.
- If you take more teriparatide injection than prescribed, call your healthcare provider. If you take too much teriparatide injection, you may have nausea, vomiting, weakness, or dizziness.
- You should not use teriparatide injection for more than 2 years over your lifetime unless your healthcare provider finds that you need longer treatment because you have a high chance of breaking your bones.

If your healthcare provider recommends calcium and vitamin D supplements, you can take them at the same time you take teriparatide injection.

What are the possible side effects of teriparatide injection?

Teriparatide injection may cause serious side effects including:

- See "**What is the most important information I should know about teriparatide injection?**"
- **Bone cancer (osteosarcoma):** Tell your healthcare provider right away if you have pain in your bones, pain in any areas of your body that does not go away, or any new or unusual lumps or swelling under your skin that is tender to touch.
- **Increased calcium in your blood.** Tell your healthcare provider if you have nausea, vomiting, constipation, low energy, or muscle weakness. These may be signs there is too much calcium in your blood.
- **Worsening of your kidney stones.** If you have or have had kidney stones your healthcare provider may check the calcium levels in your urine while you use teriparatide injection to see if there is worsening of this condition.
- **Decrease in blood pressure when you change positions.** Some people may feel dizzy, get a fast heartbeat, or feel light-headed right after the first few doses of teriparatide injection. This usually happens within 4 hours of taking teriparatide injection and goes away within a few hours. For the first few doses, give your injections of teriparatide injection in a place where you can sit or lie down right away if you get these symptoms. If your symptoms get worse or do not go away, contact your healthcare provider before you continue using teriparatide injection.

The most common side effects of teriparatide injection include:

- pain
- nausea

- joint aches

These are not all the possible side effects of teriparatide injection. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store teriparatide injection?

- Store teriparatide injection in the refrigerator between 36°F to 46°F (2°C to 8°C) until ready to use. Use teriparatide injection right away after you remove it from the refrigerator.
- Do not freeze the teriparatide injection delivery device. Do not use teriparatide injection if it has been frozen.
- Throw away the teriparatide injection delivery device after 28 days even if it has medicine in it (see the User Manual).
- Do not use teriparatide injection after the expiration date printed on the delivery device and packaging.
- Recap teriparatide injection when not in use to protect it from physical damage and light.

Keep teriparatide injection and all medicines out of the reach of children.

General information about the safe and effective use of teriparatide injection.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use teriparatide injection for a condition for which it was not prescribed. Do not give teriparatide injection to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about teriparatide injection that is written for health professionals.

What are the ingredients in teriparatide injection?

Active ingredient: teriparatide

Inactive ingredients: glacial acetic acid, sodium acetate (anhydrous), mannitol, metacresol, and water for injection. In addition, hydrochloric acid solution 10% and/or sodium hydroxide solution 10% may have been added to adjust the product to pH 4.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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Medication Guide revised: January 2023

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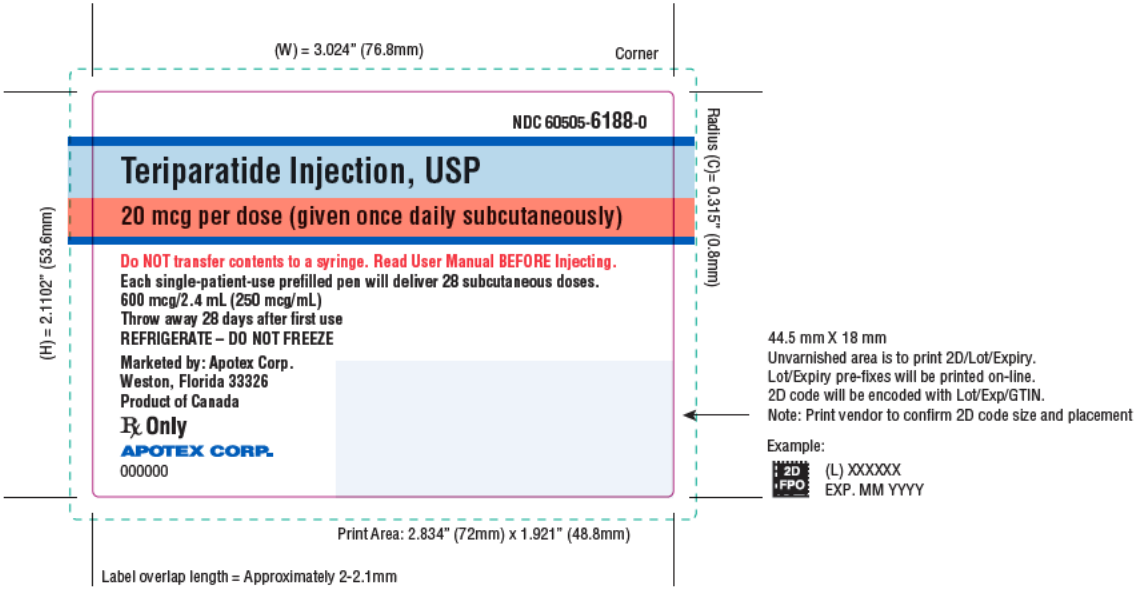
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Corner
NDC 60505-6188-0
Teriparatide Injection, USP
20 mcg per dose (given once daily subcutaneously)
Do NOT transfer contents to a syringe. Read User Manual BEFORE Injecting.
Each single-patient-use prefilled pen will deliver 28 subcutaneous doses.
600 mcg/2.4 mL (250 mcg/mL)
Throw away 28 days after first use
REFRIGERATE – DO NOT FREEZE
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Weston, Florida 33326
Product of Canada
℞ Only
APOTEX CORP.
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(H) = 2.1102" (53.6mm)
Radius (C)= 0.315" (0.8mm)
Print Area: 2.834" (72mm) x 1.921" (48.8mm)
Label overlap length = Approximately 2-2.1mm
44.5 mm X 18 mm
Unvarnished area is to print 2D/Lot/Expiry.
Lot/Expiry pre-fixes will be printed on-line.
2D code will be encoded with Lot/Exp/GTIN.
Note: Print vendor to confirm 2D code size and placement
Example:
2D
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EXP. MM YYYY

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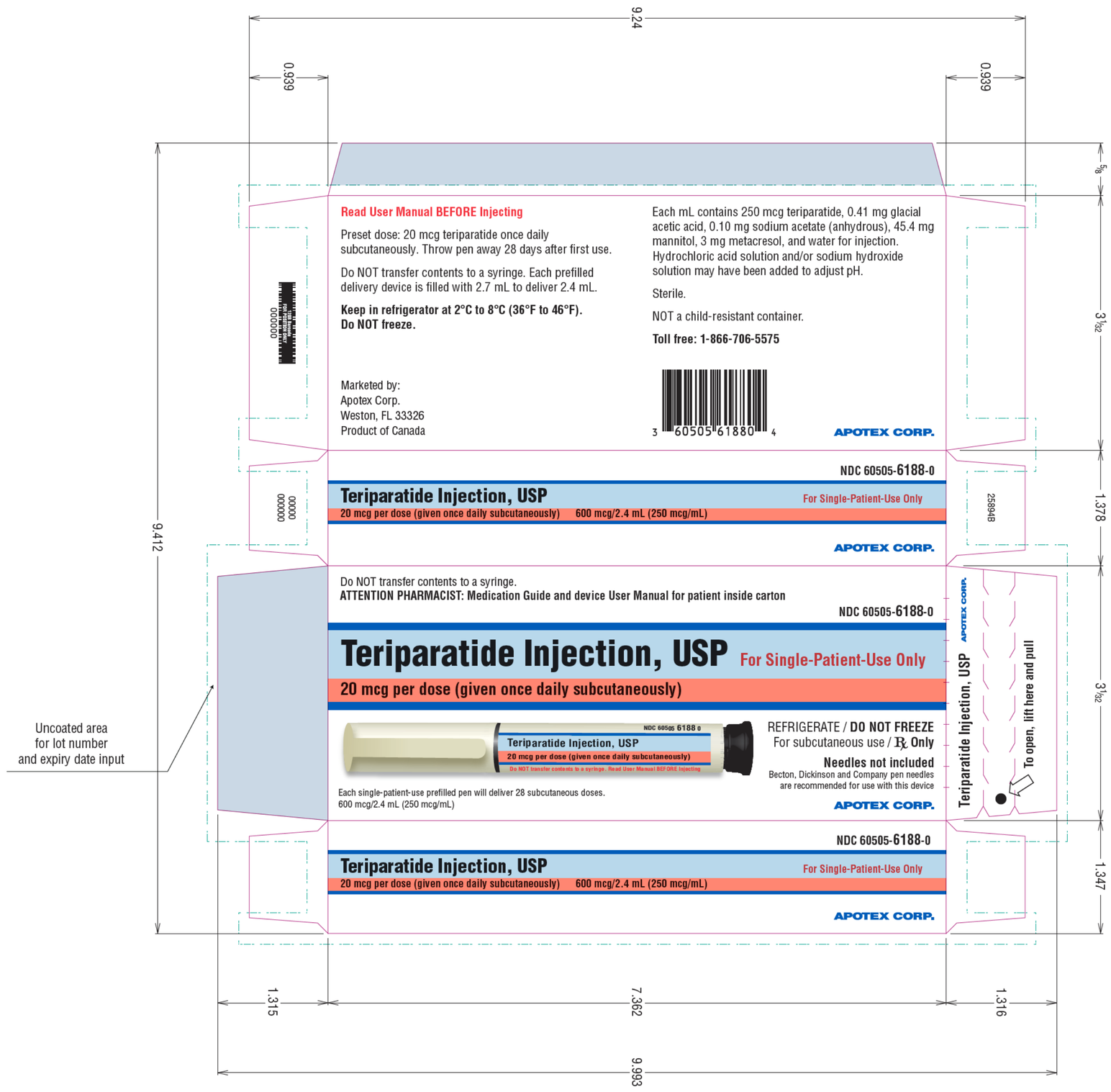
9.24
0.939
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1.315
7.362
1.316
9.993
Uncoated area
for lot number
and expiry date input
Read User Manual BEFORE Injecting
Preset dose: 20 mcg teriparatide once daily subcutaneously. Throw pen away 28 days after first use.
Do NOT transfer contents to a syringe. Each prefilled delivery device is filled with 2.7 mL to deliver 2.4 mL.
Keep in refrigerator at 2°C to 8°C (36°F to 46°F).
Do NOT freeze.
Each mL contains 250 mcg teriparatide, 0.41 mg glacial acetic acid, 0.10 mg sodium acetate (anhydrous), 45.4 mg mannitol, 3 mg metacresol, and water for injection. Hydrochloric acid solution and/or sodium hydroxide solution may have been added to adjust pH.
Sterile.
NOT a child-resistant container.
Toll free: 1-866-706-5575
Marketed by:
Apotex Corp.
Weston, FL 33326
Product of Canada
3 60505 61880 4
APOTEX CORP.
NDC 60505-6188-0
Teriparatide Injection, USP
For Single-Patient-Use Only
20 mcg per dose (given once daily subcutaneously)
600 mcg/2.4 mL (250 mcg/mL)
APOTEX CORP.
Do NOT transfer contents to a syringe.
ATTENTION PHARMACIST: Medication Guide and device User Manual for patient inside carton
NDC 60505-6188-0
Teriparatide Injection, USP
For Single-Patient-Use Only
20 mcg per dose (given once daily subcutaneously)
NDC 60505 6188 0
Teriparatide Injection, USP
20 mcg per dose (given once daily subcutaneously)
Do NOT transfer contents to a syringe. Read User Manual BEFORE Injecting
Each single-patient-use prefilled pen will deliver 28 subcutaneous doses.
600 mcg/2.4 mL (250 mcg/mL)
REFRIGERATE / DO NOT FREEZE
For subcutaneous use / ℞ Only
Needles not included
Becton, Dickinson and Company pen needles are recommended for use with this device
APOTEX CORP.
NDC 60505-6188-0
Teriparatide Injection, USP
For Single-Patient-Use Only
20 mcg per dose (given once daily subcutaneously)
600 mcg/2.4 mL (250 mcg/mL)
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Teriparatide Injection, USP
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 211097

LABELING REVIEW(s)

***** This document contains proprietary information that cannot be released to the public. Addendum Template for TL during Endorsement Process.*****

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	11/3/2023
ANDA Number(s)	211097
Review Number	Addendum #2 to Review # 6
Applicant Name	Apotex Inc.
Established Name & Strength(s)	Teriparatide Injection USP, 600 mcg/2.4 mL (250 mcg/mL) Single-Patient-Use Prefilled Pens
Proposed Proprietary Name	None
Submission Received Date	October 16, 2023 (Patent amendment)
Primary Labeling Reviewer	Danielle Russell
Secondary Labeling Reviewer	Refer to signature page

Review Conclusion

☒ ACCEPTABLE – No Comments.

☐ ACCEPTABLE – Include Post Approval Comments

☐ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the Letter to Applicant.

☐ Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Applicant

†Theme - Choose an item.

Justification for Major Deficiency - Choose an item.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List ☒ Yes ☐ No

Combined Insert/Outsert ☐ Yes ☒ No (If yes, indicate ANDA number)

1. **CHANGES FROM THE LAST REVIEW**

List the change(s) from the last review and this addendum review. Provide an explanation that the change(s) does NOT affect labeling.

After completion of the last labeling review, a new exclusivity (M-302) expiring on 11/16/2023 was added to the Orange Book. The applicant stated they are seeking final approval after expiration of the M-302 exclusivity, therefore, there is no labeling impact.

From the Orange Book (accessed 11/3/2023):

Patent and Exclusivity for: N021318

Product 002
TERIPARATIDE (FORTEO) SOLUTION 0.6MG/2.4ML (0.25MG/ML)

Patent Data

Product No	Patent No	Patent Expiration	Drug Substance	Drug Product	Patent Use Code
002	7517334	03/25/2025		DP	

Exclusivity Data

Product No	Exclusivity Code	Exclusivity Expiration
002	M-302	11/16/2023

INFORMATION ADDED TO LABELING REGARDING OSTEOSARCOMA

From the 10/16/2023 exclusivity statement:

Exclusivity Statement

According to information published in the Electronic Orange Book, Approved Drug Products with Therapeutic Equivalence Evaluations, current through October 2023, FORTEO (teriparatide injection), 0.6MG/2.4ML (0.25MG/ML) is entitled to a period of marketing exclusivity as below.

Name	Exclusivity Code	Exclusivity Expires
FORTEO (teriparatide injection), 0.6MG/2.4ML (0.25MG/ML)	M-302	November 16, 2023

Apotex Inc. certifies that sale of Teriparatide Injection USP, 20 mcg per dose (600 mcg/2.4 mL) will not begin until after expiry of the above exclusivity. Apotex seeks final approval of this product immediately upon expiration of M-302 exclusivity.

Ellen Koo

Digitally signed by Ellen Koo
Date: 11/03/2023 09:05:16AM
GUID: 508da73d0002b687dfbf9b3859d80789

Labeling Review

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	04/03/2023, 04/10/2023
ANDA Number(s)	211097
Review Number	6 Addendum (To correct the expression of strength on the cover letter from 250 mg/mL to 250 mcg/mL.)
Applicant Name	Apotex Inc.
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Teriparatide Injection USP, 600 mcg/2.4 mL (250 mcg/mL) Single-Patient-Use Prefilled Pens
Proposed Proprietary Name	None
Submission Received Date	February 17, 2023
Primary Labeling Reviewer	Danielle Russell
Secondary Labeling Reviewer	Ellen Koo

Review Conclusion

☒ Acceptable - No Comments
☐ Acceptable - Include Post Approval Comments
☐ Minor Deficiency* - Refer to Labeling Deficiencies and Comments for Letter to Applicant
☐ Major Deficiency** - Refer to Labeling Deficiencies and Comments for Letter to Applicant

On Policy Alert List	☒ Yes	☐ No
Acceptable For Filing	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No

TABLE OF CONTENTS

Appears this way on original

1 LABELING COMMENTS (C6 ADDENDUM)

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT (C6 ADDENDUM)

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE (C6 ADDENDUM)

The Division of Labeling has no further questions/comments at this time based on your labeling submission received February 17, 2023.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 POST-APPROVAL REVISIONS (C6 ADDENDUM)

These comments will be addressed post approval (in the first labeling supplement review).

2 INSTRUCTIONS FOR ASSESSMENT (C6 ADDENDUM)

General Comments:

Select the "no deficiency" or "deficiency" radio button as appropriate for each row. If a "Deficiency Comments" appears, ensure it is appropriate for your situation, edit, or enter "Reviewer Comments" if necessary.

If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has **expired** and the applicant needs to revise labeling.

Reviewer Comments:
Enter free text in this section as necessary.

Deficiency Comments:

- Standardized comments/deficiencies are available for certain questions. For a complete list of standardized comments, reference the DLR Standardized Comments SharePoint.
- Reviewers can modify standardized comments/deficiencies for their situation.
- Deficiencies will have a review number, deficiency number, and roman numeral in the user interface. For first original reviews the review number and iteration numeral will align; however, older reviews may have review numbers and iteration numerals that differ due to some reviews being completed under past practices.
- Deficiency comments will populate by default to the Labeling Comments deficiency section unless you select the Post-Approval checkbox. Assessors also have the option to move all comments to the Post-Approval Revisions section or vice versa from the Labeling Comments tab.

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED (C6 ADDENDUM)

Table 1: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Final	1 pen	05/12/2022	Satisfactory
Blister	N/A	N/A		
Carton	Final	Carton of 1 pen	05/12/2022	Satisfactory

Table 2: Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	Revised: 01/2023	02/17/2023	Satisfactory
Medication Guide	Draft	Medication Guide revised: January 2023	02/17/2023	Satisfactory
Patient Information	N/A	N/A		
Instructions for Use	N/A	N/A		
SPL Data Elements				
User Manual	Draft	March, 2018	03/20/2018	Satisfactory

4 LABELING REVIEW INFORMATION(C6 ADDENDUM)

4.1 REGULATORY INFORMATION (C6 ADDENDUM)

Yes	No	
☒	☐	Are there any applicable issues in DLR's SharePoint Drug Facts ?

1 Pages has been withheld in full as b4 (CCI/TS) immediately following this page

Yes	No	
		teriparatide subcutaneous solution *3-year exclusivity decision pending with CDER Exclusivity Board.* *021318/S-054* *No Final Approval Actions can be issued while Exclusivity is being determined* *Application Communications can continue; Labeling affected if exclusivity is granted* *Supplements that do not require updated labeling or labeling review are not affected.*

4.2 MODEL PRESCRIBING INFORMATION (C6 ADDENDUM)

Table 3: Review Model Labeling for Prescribing Inf (Check the box used as the Model
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING** *(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the* **NDA#/Supplement# (S-000 if original):** NDA021318 / S-056 **Supplement Approval Date:** 09/07/2021 **Proprietary Name:** Forteo **Established Name:** Teriparatide Injection **Description of Supplement:** This "Changes Being Effected" supplemental new drug application provides for updates to the strength expression in the Prescribing Information and on the Carton and Container labeling **Link:** https://analytics.fda.gov/workspace/hubble/external/object/v0/panorama-document?pk_panorama_document=55bc30a000aa5195a3720943b426ce70_60ad200a007e4e1833bff6ed67cf25a4_60ad200c007e516
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**
☐ **OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):**

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	ANDA is **up-to-date** with the RLD/Model labeling.
Reviewer Comments: **Deficiency Comments:**		

4.3 PATENTS AND EXCLUSIVITIES (C6 ADDENDUM)

The Orange Book was searched on 04/10/2023

Table 4 provides Orange Book patents for the Model Labeling (NDA021318) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 4: Impact of Model Labeling Patents on ANDA Labeling							
Strengths	**Patent Number**	**Patent Expiration**	**Patent Use Code**	**Patent Use Code Definition**	**Patent Certification**	**Date of Patent Cert Submission**	**Labeling Impact**
0.6 mg/2.4 mL (0.25 mg/mL), 0.75 mg/3 mL (0.25 mg/mL)	7517334	03/25/2025			IV	12/29/2017	None

Table 5 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling						
Strengths	**Exclusivity Code**	**Exclusivity Expiration**	**Exclusivity Code Definition**	**Exclusivity Statement**	**Date of Exclusivity Submission**	**Labeling Impact**
	N/A					

Reviewer Assessment:

Deficiency	**No Deficiency**	
☐	☒	There is information in the Orange Book that the applicant needs to address.
☐	☒	Information in the Orange Book has **expired** and the applicant needs to revise labeling.
Reviewer Comments: **Deficiency Comments:**		

4.4 UNITED STATES PHARMACOPEIA (USP) (C6 ADDENDUM)

The USP was searched on 04/03/2023

Table 6: USP				
	YES or NO	**Date**	**Monograph Title (N/A if no monograph)**	**Packaging and Storage/Labeling Statements (N/A if no monograph)**
Currently Official	Yes		Teriparatide Injection	•Packaging and Storage: (b) (4) [redacted] protected from light, at a temperature of 2°–8°. The Injection is not to be frozen.

Table 6: USP				
	YES or NO	Date	Monograph Title (N/A if no monograph)	Packaging and Storage/Labeling Statements (N/A if no monograph)
				•Labeling: Label it to indicate that the material has been produced by methods based on recombinant DNA technology.
Not Yet Official	No		N/A	N/A

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	**Established name** is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary **name is different from USP** established name.
☐	☒	**USP descriptor** is correctly used in the appropriate sections of the prescribing information.
USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):		
☐	☒	**DISSOLUTION**: The applicant's dissolution statement is appropriate.
☐	☒	**ORGANIC IMPURITIES**: Drug product meets USP acceptance criteria for organic impurities.
☐	☒	**ASSAY**: Drug product meets USP acceptance criteria for assay.

Reviewer Comments:

The applicant did not label to indicate that the material has been produced by methods based on recombinant DNA technology as the applicant's product is chemically synthesized.

The applicant has petitioned USP to update the monograph for Teriparatide Injection.

From the C2 review:

iii) You are requested to petition the United States Pharmacopeia (USP) to update the monograph for Teriparatide to either remove reference to the recombinant source of Teriparatide or add chemical synthesis as a second source.

Response:

A pending monograph petition, dated July 7, 2019, was submitted to the United States Pharmacopeia (USP) to update the monograph for Teriparatide to remove reference to the recombinant source of Teriparatide. A copy of the cover letter that was submnitted to the USP is included in section 3.2.S.4.1.

Deficiency Comments:

4.5 MODEL CONTAINER LABELS (C6 ADDENDUM)

Model container/carton/blister labels (Source: NDA 021318 AR-21 dated 11/10/2021 **)**

5 ASSESSMENT OF ANDA LABELING AND LABELS (C6 ADDENDUM)

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS) (C6 ADDENDUM)

5.1.1 DRUG PRODUCT REVIEW (C6 ADDENDUM)

Insert screenshot of Labeling portion from drug product review if completed:
Drug Product Review pending

Received email communication from DP reviewer on 12/16/2022:

Hi Danielle,

Just to let you know that DP is sending following labeling deficiency to the firm:

Please add the sentence "*The molecular formula of teriparatide is $C_{181}H_{291}N_{55}O_{51}S_2$.*" to the Description of your product labeling to be in line with the most recent RLD labeling.

DLR will review once the applicant re-submits.

From the DP review dated 12/22/2022:

Labeling & Package Insert

DESCRIPTION section

Is the information accurate? ☐ Yes ☒ No
If "No," explain.

Is the drug product subject of a USP monograph? ☒ Yes ☐ No
If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

(b) (4)

The firm will be asked to petition the USP requesting that the monograph for this drug substance be updated similarly to remove reference to the Teriparatide source or add chemical synthesis as a second source.

Labeling Reviewer (Katherine Won) comments dated 2/26/2018:

we are issuing the following deficiency comments

(b) (4)

b. DESCRIPTION
i. 1st sentence: Revise to read "Teriparatide in jection, USP contains chemically synthesized human parathyroid hormone (1-34), and is also called hPTH (1-34).
ii. Include the statement "Teriperitide is manufactured chemical synthesis." prior to the sentenance "Teriparatide injection, USP is supplied as a sterile, colorless, clear..."
iii. You are requested to petition the United States Pharmacopeia (USP) to update the monograph for Teriparatide to either remove reference to the recombinant source of Teriparatide or add chemical synthesis as a second source.

Reviewer's Assessment (Review #3): Inadequate

(b) (4)

C6 assessment:

The applicant submitted revised labeling on 2/17/2023 in response to the Quality IR.

Re: **INFORMATION REQUEST**
QUALITY
Teriparatide Injection USP, 20 mcg per dose (600 mcg/2.4 mL)
ANDA No. 211097

Apotex Inc. is hereby submitting a response to the Information Request – Quality Letter dated January 20, 2023, regarding Abbreviated New Drug Application No. 211097 for Teriparatide Injection USP, 20 mcg per dose (600 mcg/2.4 mL). The response is presented in a question-and-answer format and is appended to this cover letter.

C. **Labeling Deficiency**

Question 1:
Please add the sentence "The molecular formula of teriparatide is $C_{181}H_{291}N_{55}O_{51}S_2$" to the Description of your product labeling to be in line with the most recent RLD labeling.

Response:
We acknowledge your comment. As requested we have revised the Description section of our labeling to include "The molecular formula of teriparatide is $C_{181}H_{291}N_{55}O_{51}S_2$" to be in line with the most recent RLD labeling.

Revised Prescribing Information is provided in section 1.14.2.3

A word and pdf copy of the prescribing information is provided in section 1.14.2.3

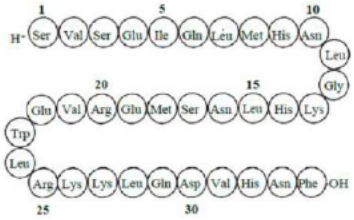
The DPQ review for this submission is still pending.

Previous labeling:

11 **DESCRIPTION**

Teriparatide injection, USP contains chemically synthesized human parathyroid hormone (1-34), and is also called hPTH (1-34). It has an identical sequence to the 34 N-terminal amino acids (the biologically active region) of the 84-amino acid human parathyroid hormone.

Teriparatide has a molecular weight of 4117.8 daltons and its amino acid sequence is shown below:

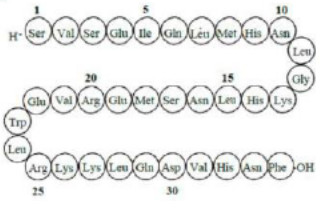


Current labeling:

11 **DESCRIPTION**

Teriparatide injection, USP contains chemically synthesized human parathyroid hormone (1-34), and is also called hPTH (1-34). It has an identical sequence to the 34 N-terminal amino acids (the biologically active region) of the 84-amino acid human parathyroid hormone.

The molecular formula of teriparatide is $C_{181}H_{291}N_{55}O_{51}S_2$ and a molecular weight of 4117.8 daltons and its amino acid sequence is shown below:



5.1.2 DESCRIPTION (C6 ADDENDUM)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling	Each mL contains 250 mcg of teriparatide (as a free base), 0.41 mg of glacial acetic acid, 0.1 mg of sodium acetate (anhydrous), 45.4 mg of mannitol, 3 mg of Metacresol, and Water for Injection. In addition, hydrochloric acid solution 10% and/or sodium hydroxide solution 10% may have been added to adjust the pH to 4.
Previous ANDA Labeling	Each mL contains 250 mcg teriparatide (corrected for acetate, chloride, and water content), 0.41 mg glacial acetic acid, 0.1 mg sodium acetate (anhydrous), 45.4 mg mannitol, 3 mg Metacresol, and Water for Injection. In addition, hydrochloric acid

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
	solution 10% and/or sodium hydroxide solution 10% may have been added to adjust the product to pH 4.
Current ANDA Labeling	Each mL contains 250 mcg teriparatide (corrected for acetate, chloride, and water content), 0.41 mg glacial acetic acid, 0.1 mg sodium acetate (anhydrous), 45.4 mg mannitol, 3 mg Metacresol, and Water for Injection. In addition, hydrochloric acid solution 10% and/or sodium hydroxide solution 10% may have been added to adjust the product to pH 4.

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C6 ADDENDUM)

Table 8: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	**16 HOW SUPPLIED/STORAGE AND HANDLING** **16.1 How Supplied** FORTEO (teriparatide injection) is a clear and colorless solution, available as single-patient-use prefilled delivery device (pen) in the following package size: • 600 mcg/2.4 mL (250 mcg/mL) [containing 28 daily doses of 20 mcg] NDC 0002-8400-01 (MS8400). **16.2 Storage and Handling** • Store FORTEO under refrigeration at 2° to 8°C (36° to 46°F) at all times except when administering the product. • Recap the delivery device (pen) when not in use to protect the cartridge from physical damage and light. • When using FORTEO, minimize the time out of the refrigerator; deliver the dose immediately following removal from the refrigerator. • Do not freeze. Do not use FORTEO if it has been frozen. **17 PATIENT COUNSELING INFORMATION** Advise the patient to read the FDA-approved patient labeling (Medication Guide and the User Manual) before starting FORTEO and each time the prescription is renewed. Failure to follow the instructions may result in inaccurate dosing.
Previous ANDA Labeling	16.1 How Supplied Teriparatide Injection is a clear and colorless solution, available as single-patient-use prefilled delivery device (pen) in the following package size: • 600 mcg/2.4 mL (250 mcg/mL) [containing 28 daily doses of 20 mcg] NDC 60505-6188-0. 16.2 Storage and Handling • Store teriparatide injection, USP under refrigeration at 2°C to 8°C (36°F to 46°F) at all times except when administering the product. • Recap the delivery device (pen) when not in use to protect the cartridge from physical damage and light. • When using teriparatide injection, minimize the time out of the refrigerator; deliver the dose immediately following removal from the refrigerator. • Do not freeze. Do not use teriparatide injection, USP if it has been frozen.
Current ANDA Labeling	**16 HOW SUPPLIED/STORAGE AND HANDLING** **16.1 How Supplied** Teriparatide Injection is a clear and colorless solution, available as single-patient-use prefilled delivery device (pen) in the following package size: • 600 mcg/2.4 mL (250 mcg/mL) [containing 28 daily doses of 20 mcg] NDC 60505-6188-0. **16.2 Storage and Handling** • Store teriparatide injection, USP under refrigeration at 2°C to 8°C (36°F to 46°F) at all times except when administering the product. • Recap the delivery device (pen) when not in use to protect the cartridge from physical damage and light. • When using teriparatide injection, minimize the time out of the refrigerator; deliver the dose immediately following removal from the refrigerator. • Do not freeze. Do not use teriparatide injection, USP if it has been frozen. No changes. Acceptable.

5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER (C6 ADDENDUM)

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
Previous ANDA Labeling	
Name and Address on ANDA Prescribing Information	Marketed by: Apotex Corp. 2400 N. Commerce Parkway, Weston, FL 33326 U.S.A.

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
Current ANDA Labeling	
Name and Address on ANDA Prescribing Information	Marketed by: Apotex Corp. 2400 N. Commerce Parkway, Weston, FL 33326 U.S.A.

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements			
Manufactured by	**Manufactured for**	**Distributed by**	**Distributed for**

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS) (C6 ADDENDUM)

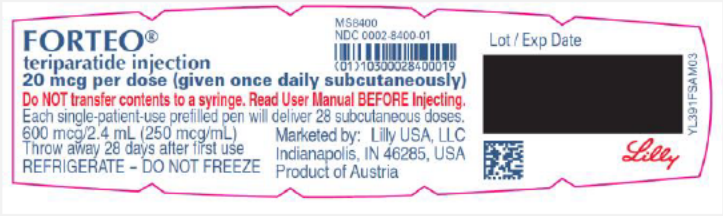
Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Container meets the **too small exemption** [21 CFR 201.10(i)]. Please enter Reviewer/Deficiency Comments if you select Deficiency.
		ESTABLISHED/PROPRIETARY NAME and STRENGTH:
☐	☒	**Tall Man** lettering complies with recommendations found on FDA webpage.
☐	☒	Established/proprietary **name and strength are the most prominent** information on the Principal Display Panel.
☐	☒	No **intervening text**(written, printed, or graphic matter) between established name and strength.
		THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:
☐	☒	**Net quantity** statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Dosage** statement.
☐	☒	**NDC number**: prominence, linear bar code, and its orientation.
☐	☒	**Expiration date and lot number** (or placeholder).
☐	☒	**Equivalency statement** (product strength).
☐	☒	**Medication Guide** Pharmacist instructions [21 CFR 208.24(d)].
☐	☒	Controlled Substance Symbol.
☐	☒	**Image of drug product** represents the true size, color, and imprint.
☐	☒	**Yellow #5** (tartrazine) warning statement is properly displayed.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Latex** warning statement is properly displayed [21 CFR 801.437.].
		PRODUCT DIFFERENTIATION:
☐	☒	ANDA is the **same color** as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Multiple **strengths are differentiated** by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from **related products**.
		STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:
☐	☒	**Storage/dispensing** statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe **container closure**, cite source, and any issues in Reviewer Comments below. Please enter Reviewer/Deficiency Comments if you select Deficiency.
		OVERALL ASSESSMENT:
☐	☒	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100). Please enter Reviewer/Deficiency Comments if you select Deficiency.

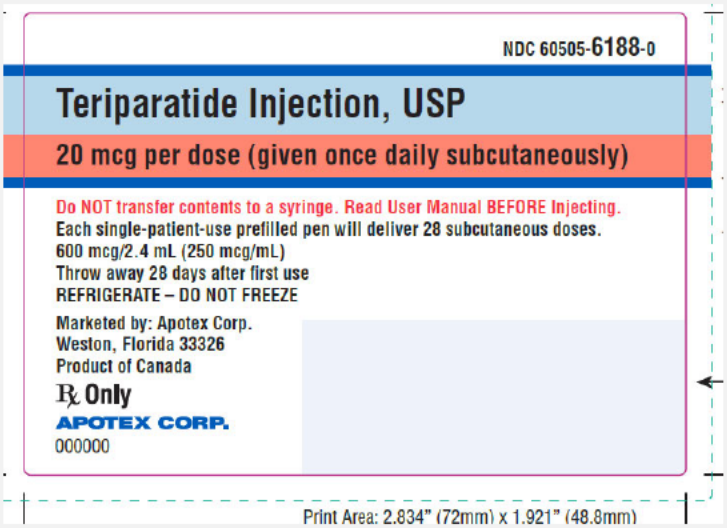
Reviewer Comments:
From the C3 review:
Labeling deficiencies based on your submissions received October 15, 2020 and December 16, 2020:

1. CARTON/CONTAINER LABEL
Revise your labels to be in accordance with the labeling for the reference listed drug (RLD), Forteo® (NDA 021318/S-054) approved on November 16, 2020 found on the Drugs@FDA website.

RLD:



C4 submission:



Medication Guide Pharmacist instructions are not present on the container label. The product is dispensed inside of a carton with the MG and device user manual enclosed with the drug product. This is acceptable and in line with the RLD.

The submitted container label is in line with the most recent RLD.

C5 assessment:
Adequate C4. No new submission. Acceptable.

C6 assessment:
Adequate C4. No new submission. Acceptable.

Deficiency Comments:

5.2.1 INJECTABLE PRODUCTS (C6 ADDENDUM)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Appropriate **package type term** was used (e.g. multiple-dose, single-dose, single-patient-use).

Deficiency	No Deficiency	
☐	☒	IV, IM, or SC was spelled out.
☐	☒	There is **text on the cap/ferrule** overseal of this injectable product. If "Yes", does the text comply with the recommendations in USP General Chapter <7> Labeling.
☐	☒	The **cap color** is N/A. ***NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate.***

Reviewer Comments:
Prefilled pen, thus no cap/ferrule.

Deficiency Comments:

5.3 CARTON (OUTER OR SECONDARY PACKAGING) LABELING (C6 ADDENDUM)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	The answers to the Container Label questions are the same for the Carton Labeling. Please enter Reviewer/Deficiency Comments if you select Deficiency.

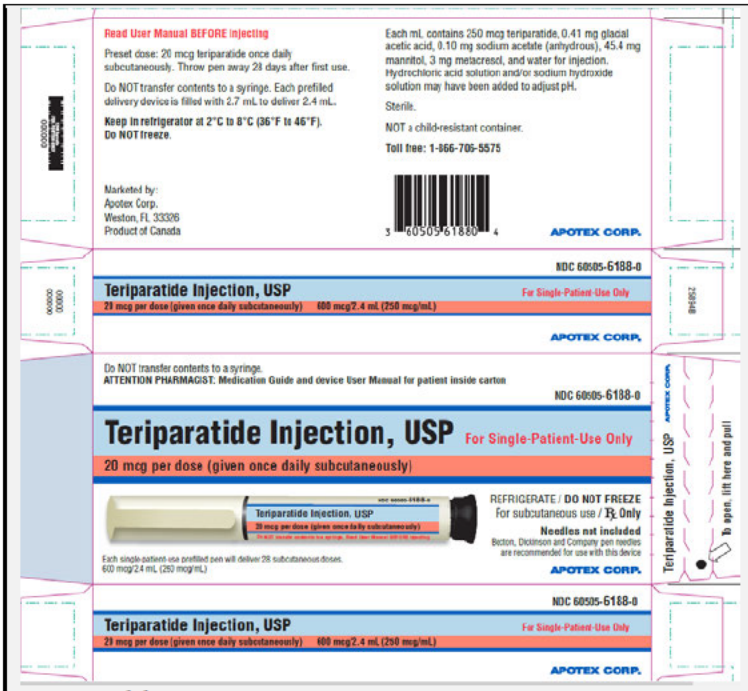
Reviewer Comments:
From the C3 review:
Labeling deficiencies based on your submissions received October 15, 2020 and December 16, 2020:

1. CARTON/CONTAINER LABEL

Revise your labels to be in accordance with the labeling for the reference listed drug (RLD), Forteo® (NDA 021318/S-054) approved on November 16, 2020 found on the Drugs@FDA website.

RLD:

C4 submission:



Acceptable. No comments.

C5 assessment:
Adequate C4. No new submission. Acceptable.

C6 assessment:
Adequate C4. No new submission. Acceptable.

Deficiency Comments:

5.4 PRESCRIBING INFORMATION (C6 ADDENDUM)

Reviewer Assessment:

Deficiency	No Deficiency	
	HIGHLIGHTS:	
☐	☒	**Contact information** for applicant and FDA are listed correctly.
☐	☒	**Revision date** appears at end of HIGHLIGHTS section.
	DESCRIPTION/INACTIVE INGREDIENTS:	
☐	☒	Appropriate **warning/precaution** statements for inactive ingredients are present (21 CFR 201) Check only if applicable: ☐ Sulfite (21 CFR 201.22) ☐ Yellow #5 (Tartrazine) (21 CFR 201.20) ☐ Phenylalanine/aspartame (21 CFR 201.21) ☐ Latex (21 CFR 801.437). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Gluten** statement is appropriately stated. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Sterile** product statement [21 CFR 201.57(c)(12)(D)].
☐	☒	**Dosage form and route** of administration properly listed [21 CFR 201.57(c)(12)(B)].
	HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:	
☐	☒	All **submitted labels** and labeling are consistent with the HOW SUPPLIED section.

Deficiency	No Deficiency	
☐	☒	**Physical description** (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☐	☒	**NDC** numbers are present.
☐	☒	Drug product is the **same color** as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin).
☐	☒	**Storage or dispensing** statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**"Discard unused portion"** for single-dose products.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(j)].
HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:		
☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the **Antiretroviral Pregnancy Registry** (APR) upon full approval.
☐	☒	**Pregnancy registry** information is appropriately included/excluded as required for the RLD. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Patent/exclusivity** carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

Comments from previous cycle review:

Labeling deficiencies based on your submissions received October 15, 2020 and December 16, 2020:

1. CARTON/CONTAINER LABEL
   Revise your labels to be in accordance with the labeling for the reference listed drug (RLD), Forteo® (NDA 021318/S-054) approved on November 16, 2020 found on the Drugs@FDA website.
2. HIGHLIGHTS OF PRESCRIBING INFORMATION
   DOSAGE FORMS AND STRENGTHS: Revise to read, "Injection: 620 mcg/2.48 mL (250 mcg/mL) in a single-patient-use prefilled delivery device (pen) containing 28 daily doses of 20 mcg (3)"
3. PRESCRIBING INFORMATION
   a. 3 DOSAGE FORMS AND STRENGTHS: Revise to read, "Injection: 620 mcg/2.48 mL (250 mcg/mL) clear, colorless solution in a single-patient-use prefilled delivery device (pen) containing 28 daily doses of 20 mcg."
   b. 11 DESCRIPTION: Revise the last sentence of the section to read, "Each prefilled delivery device (pen) delivers 20 mcg of teriparatide per dose for up to 28 days."
4. MEDICATION GUIDE
   Add "for subcutaneous use" under the established name and pronunciation in the title to be in line with the RLD.

For comments 2, 3a and 3b, the RLD labeling has since been updated and the current submission is in line with the most recently approved RLD.

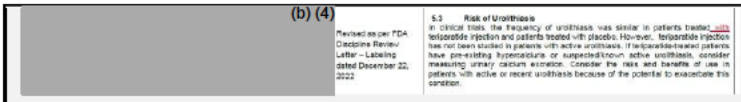
The initial US Approval date on the RLD is 1987. This was revised in the 021318/S-052 labeling at the request of the FDA.

Lilly asked for additional clarification regarding the request to revise the approval date. The FDA explained that 2002 was an error as the date should reflect the date of initial approval of the teriparatide, which was in 1987. The 1987-approved product has since been discontinued.

Based on an email and the DP review. The DESCRIPTION section requires revision. DP will issue the deficiency comment. See section 5.1.1.

C5 assessment:

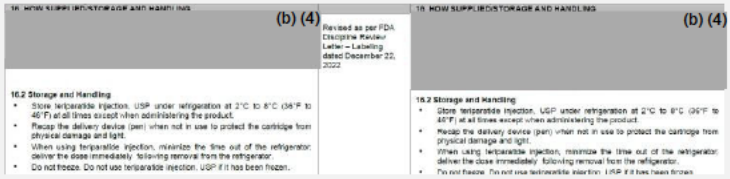
Apotex Inc's Last Submitted Prescribing Information November 2021	Reason for Change	Apotex Inc's Proposed Prescribing Information December 2022
HIGHLIGHTS OF PRESCRIBING INFORMATION		HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TERIPARATIDE INJECTION safely and effectively. See full prescribing information for TERIPARATIDE INJECTION. TERIPARATIDE injection for subcutaneous use Initial U.S. Approval: 2002	Revised as per FDA Discipline Review Letter – Labeling dated December 22, 2022	These highlights do not include all the information needed to use TERIPARATIDE INJECTION safely and effectively. See full prescribing information for TERIPARATIDE INJECTION. TERIPARATIDE injection for subcutaneous use Initial U.S. Approval: 1987~~2002~~


(b) (4)

Revised as per FDA Discipline Review Letter – Labeling dated December 22, 2022

5.3 Risk of Urolithiasis

In clinical trials, the frequency of urolithiasis was similar in patients treated with teriparatide injection and patients treated with placebo. However, teriparatide injection has not been studied in patients with active urolithiasis. If teriparatide-treated patients have pre-existing hypercalciuria or suspected/known active urolithiasis, consider measuring urinary calcium excretion. Consider the risks and benefits of use in patients with active or recent urolithiasis because of the potential to exacerbate this condition.


(b) (4)

Revised as per FDA Discipline Review Letter – Labeling dated December 22, 2022

(b) (4)

16.2 Storage and Handling

- Store teriparatide injection, USP under refrigeration at 2°C to 8°C (36°F to 46°F) at all times except when administering the product.
- Recap the delivery device (pen) when not in use to protect the cartridge from physical damage and light.
- When using teriparatide injection, minimize the time out of the refrigerator; deliver the dose immediately following removal from the refrigerator.
- Do not freeze. Do not use teriparatide injection, USP if it has been frozen.

16.2 Storage and Handling

- Store teriparatide injection, USP under refrigeration at 2°C to 8°C (36°F to 46°F) at all times except when administering the product.
- Recap the delivery device (pen) when not in use to protect the cartridge from physical damage and light.
- When using teriparatide injection, minimize the time out of the refrigerator; deliver the dose immediately following removal from the refrigerator.
- Do not freeze. Do not use teriparatide injection, USP if it has been frozen.

Additionally, the applicant revised the RECENT MAJOR CHANGES, revision date for PI, revision date for MG.

Acceptable.

C6 assessment:

The applicant submitted revised labeling on 2/17/2023 in response to the Quality IR.

Re: INFORMATION REQUEST
QUALITY
Teriparatide Injection USP, 20 mcg per dose (600 mcg/2.4 mL)
ANDA No. 211097

Apotex Inc. is hereby submitting a response to the Information Request – Quality Letter dated January 20, 2023, regarding Abbreviated New Drug Application No. 211097 for Teriparatide Injection USP, 20 mcg per dose (600 mcg/2.4 mL). The response is presented in a question-and-answer format and is appended to this cover letter.

C. Labeling Deficiency

Question 1:
Please add the sentence "The molecular formula of teriparatide is $C_{181}H_{291}N_{55}O_{51}S_2$" to the Description of your product labeling to be in line with the most recent RLD labeling.

Response:
We acknowledge your comment. As requested we have revised the Description section of our labeling to include "The molecular formula of teriparatide is $C_{181}H_{291}N_{55}O_{51}S_2$" to be in line with the most recent RLD labeling.

Revised Prescribing Information is provided in section 1.14.2.3

A word and pdf copy of the prescribing information is provided in section 1.14.2.3

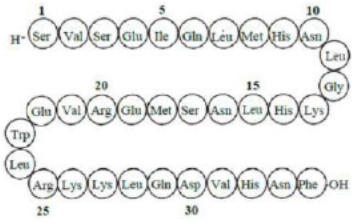
The DPQ review for this submission is still pending.

Previous labeling:

11 **DESCRIPTION**

Teriparatide injection, USP contains chemically synthesized human parathyroid hormone (1-34), and is also called hPTH (1-34). It has an identical sequence to the 34 N-terminal amino acids (the biologically active region) of the 84-amino acid human parathyroid hormone.

Teriparatide has a molecular weight of 4117.8 daltons and its amino acid sequence is shown below:

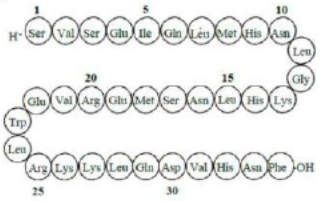


Current labeling:

11 DESCRIPTION

Teriparatide injection, USP contains chemically synthesized human parathyroid hormone (1-34), and is also called hPTH (1-34). It has an identical sequence to the 34 N-terminal amino acids (the biologically active region) of the 84-amino acid human parathyroid hormone.

The molecular formula of teriparatide is $C_{181}H_{291}N_{55}O_{51}S_2$ and a molecular weight of 4117.8 daltons and its amino acid sequence is shown below:



A SBS of the previously submitted labeling and currently submitted labeling shows the revision dates and the above change as the only differences. Acceptable.

Deficiency Comments:

5.5 MEDICATION GUIDE (C6 ADDENDUM)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Medication Guide is **up-to-date** with model labeling.
☐	☒	Medication Guide meets **content, format, and font size**.
☐	☒	**Phonetic spelling** of the established/proprietary name is present and correct.
☐	☒	Description of **child-resistant feature**(if also present in HOW SUPPLIED/STORAGE AND HANDLING).
☐	☒	**Revision date and approval statement** appear at the end of the Medication Guide correctly.
☐	☒	Applicant committed to provide a **sufficient number** of Medication Guides.
☐	☒	Applicant included the **1-800-FDA-1088** phone number.
☐	☒	Medication Guide is the same as the model labeling, except for allowable differences. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

NDA 021318/S-056 was not approved with a MG. The MG labeling used for the SBS is 021318/S-054.

No changes. Acceptable.

Deficiency Comments:

5.6 OTHER PATIENT LABELING (C6 ADDENDUM)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Other patient labeling is the same as the model labeling except for allowable differences. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

The User Manual submitted 3/20/2018 was deemed adequate the previous cycle review.

Deficiency Comments:

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES (C6 ADDENDUM)

A labeling statement required verification from another division discipline. Check only if applicable.

Reviewer Assessment:

☐	Rubber
☐	Latex
☐	Gluten
☐	Alcohol (ethanol)
☐	Aluminum (small/large volume parenteral and pharmacy bulk package)
☐	Sulfite
☐	Phenylalanine (aspartame) - content calculation
☐	Yellow #5 (tartrazine)
☐	Ghost tablet/capsule (i.e. solid or semi-solid mass in stool)
☒	Other

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB): (For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)

Reviewer Comments:

Received email communication from DP reviewer on 12/16/2022:


Hi Danielle,

Just to let you know that DP is sending following labeling deficiency to the firm:

Please add the sentence "*The molecular formula of teriparatide is $C_{181}H_{291}N_{55}O_{51}S_2$.*" to the Description of your product labeling to be in line with the most recent RLD labeling.

DLR will review once the applicant re-submits.

Deficiency Comments:

Danielle Russell

Digitally signed by Danielle Russell
Date: 4/10/2023 09:21:42AM
GUID: 52e7d22a0000efc87d53ad9352d2d4f5

Ellen Koo

Digitally signed by Ellen Koo
Date: 4/10/2023 11:58:30AM
GUID: 508da73d0002b687dfbf9b3859d80789

Labeling Review

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	04/03/2023
ANDA Number(s)	211097
Review Number	6
Applicant Name	Apotex Inc.
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Teriparatide Injection USP, 600 mcg/2.4 mL (250 mg/mL) Single-Patient-Use Prefilled Pens
Proposed Proprietary Name	None
Submission Received Date	February 17, 2023
Primary Labeling Reviewer	Danielle Russell
Secondary Labeling Reviewer	Ellen Koo

Review Conclusion

☒ Acceptable - No Comments
☐ Acceptable - Include Post Approval Comments
☐ Minor Deficiency* - Refer to Labeling Deficiencies and Comments for Letter to Applicant
☐ Major Deficiency** - Refer to Labeling Deficiencies and Comments for Letter to Applicant

On Policy Alert List	☒ Yes	☐ No
Acceptable For Filing	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No

TABLE OF CONTENTS

Appears this way on original

1 LABELING COMMENTS (C6)

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT (C6)

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE (C6)

The Division of Labeling has no further questions/comments at this time based on your labeling submission received February 17, 2023.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 POST-APPROVAL REVISIONS (C6)

These comments will be addressed post approval (in the first labeling supplement review).

2 INSTRUCTIONS FOR ASSESSMENT (C6)

General Comments:

Select the "no deficiency" or "deficiency" radio button as appropriate for each row. If a "Deficiency Comments" appears, ensure it is appropriate for your situation, edit, or enter "Reviewer Comments" if necessary.

If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has **expired** and the applicant needs to revise labeling.

Reviewer Comments:
Enter free text in this section as necessary.

Deficiency Comments:

- Standardized comments/deficiencies are available for certain questions. For a complete list of standardized comments, reference the DLR Standardized Comments SharePoint.
- Reviewers can modify standardized comments/deficiencies for their situation.
- Deficiencies will have a review number, deficiency number, and roman numeral in the user interface. For first original reviews the review number and iteration numeral will align; however, older reviews may have review numbers and iteration numerals that differ due to some reviews being completed under past practices.
- Deficiency comments will populate by default to the Labeling Comments deficiency section unless you select the Post-Approval checkbox. Assessors also have the option to move all comments to the Post-Approval Revisions section or vice versa from the Labeling Comments tab.

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED (C6)

Table 1: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Final	1 pen	05/12/2022	Satisfactory
Blister	N/A	N/A		
Carton	Final	Carton of 1 pen	05/12/2022	Satisfactory

Table 2: Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	Revised: 01/2023	02/17/2023	Satisfactory
Medication Guide	Draft	Medication Guide revised: January 2023	02/17/2023	Satisfactory
Patient Information	N/A	N/A		
Instructions for Use	N/A	N/A		
SPL Data Elements				
User Manual	Draft	March, 2018	03/20/2018	Satisfactory

4 LABELING REVIEW INFORMATION(C6)

4.1 REGULATORY INFORMATION (C6)

Yes	No	
☒	☐	Are there any applicable issues in DLR's SharePoint Drug Facts ?

1 Page has been withheld in full as b4 draft labeling

Yes	No	
		teriparatide subcutaneous solution *3-year exclusivity decision pending with CDER Exclusivity Board.* *021318/S-054* *No Final Approval Actions can be issued while Exclusivity is being determined* *Application Communications can continue; Labeling affected if exclusivity is granted* *Supplements that do not require updated labeling or labeling review are not affected.*

4.2 MODEL PRESCRIBING INFORMATION (C6)

Table 3: Review Model Labeling for Prescribing Inf (Check the box used as the Model
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING** *(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the* **NDA#/Supplement# (S-000 if original):** NDA021318 / S-056 **Supplement Approval Date:** 09/07/2021 **Proprietary Name:** Forteo **Established Name:** Teriparatide Injection **Description of Supplement:** This "Changes Being Effected" supplemental new drug application provides for updates to the strength expression in the Prescribing Information and on the Carton and Container labeling **Link:** https://analytics.fda.gov/workspace/hubble/external/object/v0/panorama-document?pk_panorama_document=55bc30a000aa5195a3720943b426ce70_60ad200a007e4e1833bff6ed67cf25a4_60ad200c007e516
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**
☐ **OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):**

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	ANDA is **up-to-date** with the RLD/Model labeling.
Reviewer Comments: **Deficiency Comments:**		

4.3 PATENTS AND EXCLUSIVITIES (C6)

The Orange Book was searched on 04/03/2023

Table 4 provides Orange Book patents for the Model Labeling (NDA021318) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 4: Impact of Model Labeling Patents on ANDA Labeling							
Strengths	**Patent Number**	**Patent Expiration**	**Patent Use Code**	**Patent Use Code Definition**	**Patent Certification**	**Date of Patent Cert Submission**	**Labeling Impact**
0.6 mg/2.4 mL (0.25 mg/mL), 0.75 mg/3 mL (0.25 mg/mL)	7517334	03/25/2025			IV	12/29/2017	None

Table 5 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling						
Strengths	**Exclusivity Code**	**Exclusivity Expiration**	**Exclusivity Code Definition**	**Exclusivity Statement**	**Date of Exclusivity Submission**	**Labeling Impact**
	N/A					

Reviewer Assessment:

Deficiency	**No Deficiency**	
☐	☒	There is information in the Orange Book that the applicant needs to address.
☐	☒	Information in the Orange Book has **expired** and the applicant needs to revise labeling.
Reviewer Comments: **Deficiency Comments:**		

4.4 UNITED STATES PHARMACOPEIA (USP) (C6)

The USP was searched on 04/03/2023

Table 6: USP				
	YES or NO	**Date**	**Monograph Title (N/A if no monograph)**	**Packaging and Storage/Labeling Statements (N/A if no monograph)**
Currently Official	Yes		Teriparatide Injection	•Packaging and Storage: (b) (4) [redacted] protected from light, at a temperature of 2°–8°. The Injection is not to be frozen.

Table 6: USP				
	YES or NO	Date	Monograph Title (N/A if no monograph)	Packaging and Storage/Labeling Statements (N/A if no monograph)
				•Labeling: Label it to indicate that the material has been produced by methods based on recombinant DNA technology.
Not Yet Official	No		N/A	N/A

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	**Established name** is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary **name is different from USP** established name.
☐	☒	**USP descriptor** is correctly used in the appropriate sections of the prescribing information.
USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):		
☐	☒	**DISSOLUTION**: The applicant's dissolution statement is appropriate.
☐	☒	**ORGANIC IMPURITIES**: Drug product meets USP acceptance criteria for organic impurities.
☐	☒	**ASSAY**: Drug product meets USP acceptance criteria for assay.

Reviewer Comments:

The applicant did not label to indicate that the material has been produced by methods based on recombinant DNA technology as the applicant's product is chemically synthesized.

The applicant has petitioned USP to update the monograph for Teriparatide Injection.

From the C2 review:

iii) You are requested to petition the United States Pharmacopeia (USP) to update the monograph for Teriparatide to either remove reference to the recombinant source of Teriparatide or add chemical synthesis as a second source.

Response:

A pending monograph petition, dated July 7, 2019, was submitted to the United States Pharmacopeia (USP) to update the monograph for Teriparatide to remove reference to the recombinant source of Teriparatide. A copy of the cover letter that was submnitted to the USP is included in section 3.2.S.4.1.

Deficiency Comments:

4.5 MODEL CONTAINER LABELS (C6)

Model container/carton/blister labels (Source: NDA 021318 AR-21 dated 11/10/2021 **)**

5 ASSESSMENT OF ANDA LABELING AND LABELS (C6)

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS) (C6)

5.1.1 DRUG PRODUCT REVIEW (C6)

Insert screenshot of Labeling portion from drug product review if completed:
Drug Product Review pending

Received email communication from DP reviewer on 12/16/2022:

Hi Danielle,

Just to let you know that DP is sending following labeling deficiency to the firm:

Please add the sentence "*The molecular formula of teriparatide is $C_{181}H_{291}N_{55}O_{51}S_2$.*" to the Description of your product labeling to be in line with the most recent RLD labeling.

DLR will review once the applicant re-submits.

From the DP review dated 12/22/2022:

Labeling & Package Insert

DESCRIPTION section

Is the information accurate? ☐ Yes ☒ No
If "No," explain.

Is the drug product subject of a USP monograph? ☒ Yes ☐ No
If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

(b) (4)

The firm will be asked to petition the USP requesting that the monograph for this drug substance be updated similarly to remove reference to the Teriparatide source or add chemical synthesis as a second source.

Labeling Reviewer (Katherine Won) comments dated 2/26/2018:

we are issuing the following deficiency comments

(b) (4)

b. DESCRIPTION
i. 1st sentence: Revise to read "Teriparatide in jection, USP contains chemically synthesized human parathyroid hormone (1-34), and is also called hPTH (1-34).
ii. Include the statement "Teriperitide is manufactured chemical synthesis." prior to the sentenance "Teriparatide injection, USP is supplied as a sterile, colorless, clear..."
iii. You are requested to petition the United States Pharmacopeia (USP) to update the monograph for Teriparatide to either remove reference to the recombinant source of Teriparatide or add chemical synthesis as a second source.

Reviewer's Assessment (Review #3): Inadequate

(b) (4)

C6 assessment:

The applicant submitted revised labeling on 2/17/2023 in response to the Quality IR.

Re: **INFORMATION REQUEST**
QUALITY
Teriparatide Injection USP, 20 mcg per dose (600 mcg/2.4 mL)
ANDA No. 211097

Apotex Inc. is hereby submitting a response to the Information Request – Quality Letter dated January 20, 2023, regarding Abbreviated New Drug Application No. 211097 for Teriparatide Injection USP, 20 mcg per dose (600 mcg/2.4 mL). The response is presented in a question-and-answer format and is appended to this cover letter.

C. **Labeling Deficiency**

Question 1:
Please add the sentence "The molecular formula of teriparatide is $C_{181}H_{291}N_{55}O_{51}S_2$" to the Description of your product labeling to be in line with the most recent RLD labeling.

Response:
We acknowledge your comment. As requested we have revised the Description section of our labeling to include "The molecular formula of teriparatide is $C_{181}H_{291}N_{55}O_{51}S_2$" to be in line with the most recent RLD labeling.

Revised Prescribing Information is provided in section 1.14.2.3

A word and pdf copy of the prescribing information is provided in section 1.14.2.3

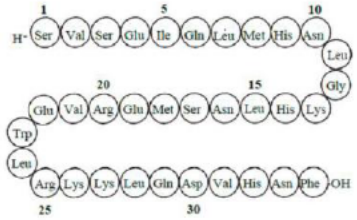
The DPQ review for this submission is still pending.

Previous labeling:

11 **DESCRIPTION**

Teriparatide injection, USP contains chemically synthesized human parathyroid hormone (1-34), and is also called hPTH (1-34). It has an identical sequence to the 34 N-terminal amino acids (the biologically active region) of the 84-amino acid human parathyroid hormone.

Teriparatide has a molecular weight of 4117.8 daltons and its amino acid sequence is shown below:

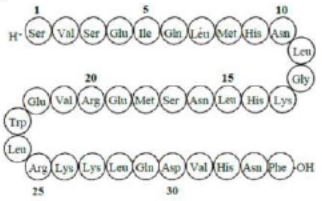


Current labeling:

11 **DESCRIPTION**

Teriparatide injection, USP contains chemically synthesized human parathyroid hormone (1-34), and is also called hPTH (1-34). It has an identical sequence to the 34 N-terminal amino acids (the biologically active region) of the 84-amino acid human parathyroid hormone.

The molecular formula of teriparatide is $C_{181}H_{291}N_{55}O_{51}S_2$ and a molecular weight of 4117.8 daltons and its amino acid sequence is shown below:



5.1.2 DESCRIPTION (C6)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling	Each mL contains 250 mcg of teriparatide (as a free base), 0.41 mg of glacial acetic acid, 0.1 mg of sodium acetate (anhydrous), 45.4 mg of mannitol, 3 mg of Metacresol, and Water for Injection. In addition, hydrochloric acid solution 10% and/or sodium hydroxide solution 10% may have been added to adjust the pH to 4.
Previous ANDA Labeling	Each mL contains 250 mcg teriparatide (corrected for acetate, chloride, and water content), 0.41 mg glacial acetic acid, 0.1 mg sodium acetate (anhydrous), 45.4 mg mannitol, 3 mg Metacresol, and Water for Injection. In addition, hydrochloric acid

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
	solution 10% and/or sodium hydroxide solution 10% may have been added to adjust the product to pH 4.
Current ANDA Labeling	Each mL contains 250 mcg teriparatide (corrected for acetate, chloride, and water content), 0.41 mg glacial acetic acid, 0.1 mg sodium acetate (anhydrous), 45.4 mg mannitol, 3 mg Metacresol, and Water for Injection. In addition, hydrochloric acid solution 10% and/or sodium hydroxide solution 10% may have been added to adjust the product to pH 4.

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C6)

Table 8: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	**16 HOW SUPPLIED/STORAGE AND HANDLING** **16.1 How Supplied** FORTEO (teriparatide injection) is a clear and colorless solution, available as single-patient-use prefilled delivery device (pen) in the following package size: • 600 mcg/2.4 mL (250 mcg/mL) [containing 28 daily doses of 20 mcg] NDC 0002-8400-01 (MS8400). **16.2 Storage and Handling** • Store FORTEO under refrigeration at 2° to 8°C (36° to 46°F) at all times except when administering the product. • Recap the delivery device (pen) when not in use to protect the cartridge from physical damage and light. • When using FORTEO, minimize the time out of the refrigerator; deliver the dose immediately following removal from the refrigerator. • Do not freeze. Do not use FORTEO if it has been frozen. **17 PATIENT COUNSELING INFORMATION** Advise the patient to read the FDA-approved patient labeling (Medication Guide and the User Manual) before starting FORTEO and each time the prescription is renewed. Failure to follow the instructions may result in inaccurate dosing.
Previous ANDA Labeling	16.1 How Supplied Teriparatide Injection is a clear and colorless solution, available as single-patient-use prefilled delivery device (pen) in the following package size: • 600 mcg/2.4 mL (250 mcg/mL) [containing 28 daily doses of 20 mcg] NDC 60505-6188-0. 16.2 Storage and Handling • Store teriparatide injection, USP under refrigeration at 2°C to 8°C (36°F to 46°F) at all times except when administering the product. • Recap the delivery device (pen) when not in use to protect the cartridge from physical damage and light. • When using teriparatide injection, minimize the time out of the refrigerator; deliver the dose immediately following removal from the refrigerator. • Do not freeze. Do not use teriparatide injection, USP if it has been frozen.
Current ANDA Labeling	**16 HOW SUPPLIED/STORAGE AND HANDLING** **16.1 How Supplied** Teriparatide Injection is a clear and colorless solution, available as single-patient-use prefilled delivery device (pen) in the following package size: • 600 mcg/2.4 mL (250 mcg/mL) [containing 28 daily doses of 20 mcg] NDC 60505-6188-0. **16.2 Storage and Handling** • Store teriparatide injection, USP under refrigeration at 2°C to 8°C (36°F to 46°F) at all times except when administering the product. • Recap the delivery device (pen) when not in use to protect the cartridge from physical damage and light. • When using teriparatide injection, minimize the time out of the refrigerator; deliver the dose immediately following removal from the refrigerator. • Do not freeze. Do not use teriparatide injection, USP if it has been frozen. No changes. Acceptable.

5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER (C6)

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
Previous ANDA Labeling	
Name and Address on ANDA Prescribing Information	Marketed by: Apotex Corp. 2400 N. Commerce Parkway, Weston, FL 33326 U.S.A.

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
Current ANDA Labeling	
Name and Address on ANDA Prescribing Information	Marketed by: Apotex Corp. 2400 N. Commerce Parkway, Weston, FL 33326 U.S.A.

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements			
Manufactured by	**Manufactured for**	**Distributed by**	**Distributed for**

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS) (C6)

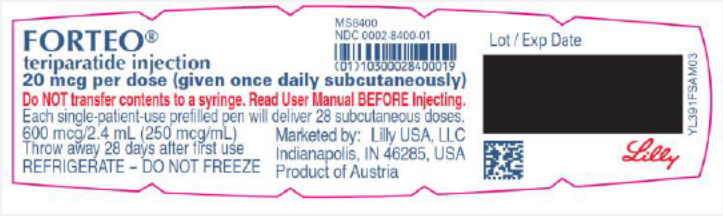
Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Container meets the **too small exemption** [21 CFR 201.10(i)]. Please enter Reviewer/Deficiency Comments if you select Deficiency.
		ESTABLISHED/PROPRIETARY NAME and STRENGTH:
☐	☒	**Tall Man** lettering complies with recommendations found on FDA webpage.
☐	☒	Established/proprietary **name and strength are the most prominent** information on the Principal Display Panel.
☐	☒	No **intervening text**(written, printed, or graphic matter) between established name and strength.
		THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:
☐	☒	**Net quantity** statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Dosage** statement.
☐	☒	**NDC number**: prominence, linear bar code, and its orientation.
☐	☒	**Expiration date and lot number** (or placeholder).
☐	☒	**Equivalency statement** (product strength).
☐	☒	**Medication Guide** Pharmacist instructions [21 CFR 208.24(d)].
☐	☒	Controlled Substance Symbol.
☐	☒	**Image of drug product** represents the true size, color, and imprint.
☐	☒	**Yellow #5** (tartrazine) warning statement is properly displayed.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Latex** warning statement is properly displayed [21 CFR 801.437.].
		PRODUCT DIFFERENTIATION:
☐	☒	ANDA is the **same color** as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Multiple **strengths are differentiated** by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from **related products**.
		STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:
☐	☒	**Storage/dispensing** statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe **container closure**, cite source, and any issues in Reviewer Comments below. Please enter Reviewer/Deficiency Comments if you select Deficiency.
		OVERALL ASSESSMENT:
☐	☒	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100). Please enter Reviewer/Deficiency Comments if you select Deficiency.

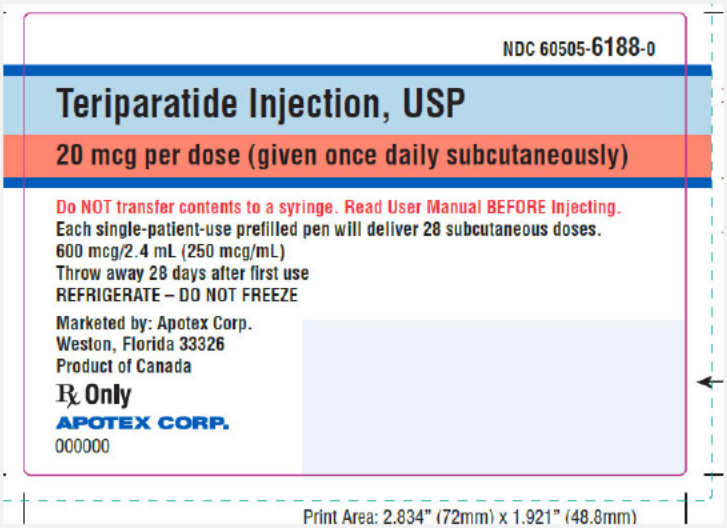
Reviewer Comments:
From the C3 review:
Labeling deficiencies based on your submissions received October 15, 2020 and December 16, 2020:

1. CARTON/CONTAINER LABEL
Revise your labels to be in accordance with the labeling for the reference listed drug (RLD), Forteo® (NDA 021318/S-054) approved on November 16, 2020 found on the Drugs@FDA website.

RLD:



C4 submission:



Medication Guide Pharmacist instructions are not present on the container label. The product is dispensed inside of a carton with the MG and device user manual enclosed with the drug product. This is acceptable and in line with the RLD.

The submitted container label is in line with the most recent RLD.

C5 assessment:
Adequate C4. No new submission. Acceptable.

C6 assessment:
Adequate C4. No new submission. Acceptable.

Deficiency Comments:

5.2.1 INJECTABLE PRODUCTS (C6)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Appropriate **package type term** was used (e.g. multiple-dose, single-dose, single-patient-use).

Deficiency	No Deficiency	
☐	☒	IV, IM, or SC was spelled out.
☐	☒	There is **text on the cap/ferrule** overseal of this injectable product. If "Yes", does the text comply with the recommendations in USP General Chapter <7> Labeling.
☐	☒	The **cap color** is N/A. ***NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate.***

Reviewer Comments:
Prefilled pen, thus no cap/ferrule.

Deficiency Comments:

5.3 CARTON (OUTER OR SECONDARY PACKAGING) LABELING (C6)

Reviewer Assessment:

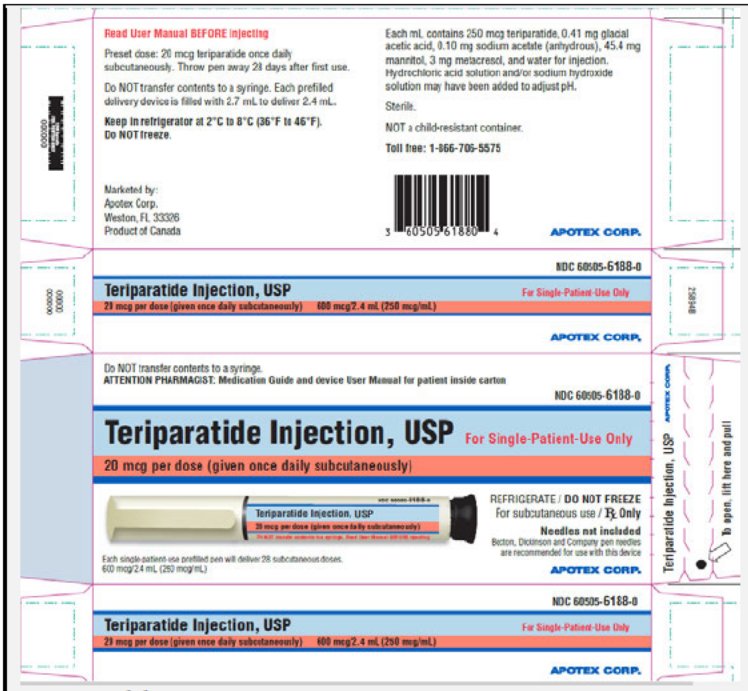
Deficiency	No Deficiency	
☐	☒	The answers to the Container Label questions are the same for the Carton Labeling. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:
From the C3 review:
Labeling deficiencies based on your submissions received October 15, 2020 and December 16, 2020:

1. CARTON/CONTAINER LABEL
Revise your labels to be in accordance with the labeling for the reference listed drug (RLD), Forteo® (NDA 021318/S-054) approved on November 16, 2020 found on the Drugs@FDA website.

RLD:

C4 submission:



Acceptable. No comments.

C5 assessment:
Adequate C4. No new submission. Acceptable.

C6 assessment:
Adequate C4. No new submission. Acceptable.

Deficiency Comments:

5.4 PRESCRIBING INFORMATION (C6)

Reviewer Assessment:

Deficiency	No Deficiency	
	HIGHLIGHTS:	
☐	☒	**Contact information** for applicant and FDA are listed correctly.
☐	☒	**Revision date** appears at end of HIGHLIGHTS section.
	DESCRIPTION/INACTIVE INGREDIENTS:	
☐	☒	Appropriate **warning/precaution** statements for inactive ingredients are present (21 CFR 201) Check only if applicable: ☐Sulfite (21 CFR 201.22) ☐Yellow #5 (Tartrazine) (21 CFR 201.20) ☐Phenylalanine/aspartame (21 CFR 201.21) ☐Latex (21 CFR 801.437). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Gluten** statement is appropriately stated. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Sterile** product statement [21 CFR 201.57(c)(12)(D)].
☐	☒	**Dosage form and route** of administration properly listed [21 CFR 201.57(c)(12)(B)].
	HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:	
☐	☒	All **submitted labels** and labeling are consistent with the HOW SUPPLIED section.

Deficiency	No Deficiency	
☐	☒	**Physical description** (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☐	☒	**NDC** numbers are present.
☐	☒	Drug product is the **same color** as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin).
☐	☒	**Storage or dispensing** statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**"Discard unused portion"** for single-dose products.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:		
☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the **Antiretroviral Pregnancy Registry** (APR) upon full approval.
☐	☒	**Pregnancy registry** information is appropriately included/excluded as required for the RLD. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Patent/exclusivity** carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

Comments from previous cycle review:

Labeling deficiencies based on your submissions received October 15, 2020 and December 16, 2020:

1. CARTON/CONTAINER LABEL
   Revise your labels to be in accordance with the labeling for the reference listed drug (RLD), Forteo® (NDA 021318/S-054) approved on November 16, 2020 found on the Drugs@FDA website.
2. HIGHLIGHTS OF PRESCRIBING INFORMATION
   DOSAGE FORMS AND STRENGTHS: Revise to read, "Injection: 620 mcg/2.48 mL (250 mcg/mL) in a single-patient-use prefilled delivery device (pen) containing 28 daily doses of 20 mcg (3)"
3. PRESCRIBING INFORMATION
   a. 3 DOSAGE FORMS AND STRENGTHS: Revise to read, "Injection: 620 mcg/2.48 mL (250 mcg/mL) clear, colorless solution in a single-patient-use prefilled delivery device (pen) containing 28 daily doses of 20 mcg."
   b. 11 DESCRIPTION: Revise the last sentence of the section to read, "Each prefilled delivery device (pen) delivers 20 mcg of teriparatide per dose for up to 28 days."
4. MEDICATION GUIDE
   Add "for subcutaneous use" under the established name and pronunciation in the title to be in line with the RLD.

For comments 2, 3a and 3b, the RLD labeling has since been updated and the current submission is in line with the most recently approved RLD.

The initial US Approval date on the RLD is 1987. This was revised in the 021318/S-052 labeling at the request of the FDA.

Lilly asked for additional clarification regarding the request to revise the approval date. The FDA explained that 2002 was an error as the date should reflect the date of initial approval of the teriparatide, which was in 1987. The 1987-approved product has since been discontinued.

Based on an email and the DP review. The DESCRIPTION section requires revision. DP will issue the deficiency comment. See section 5.1.1.

C5 assessment:

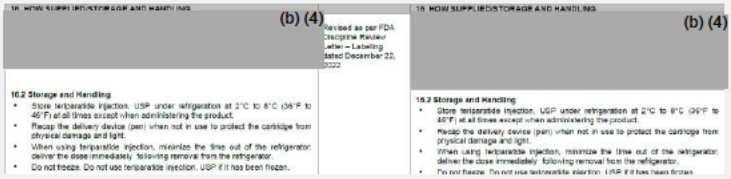
Apotex Inc's Last Submitted Prescribing Information November 2021	Reason for Change	Apotex Inc's Proposed Prescribing Information December 2022
HIGHLIGHTS OF PRESCRIBING INFORMATION		HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TERIPARATIDE INJECTION safely and effectively. See full prescribing information for TERIPARATIDE INJECTION. TERIPARATIDE injection for subcutaneous use Initial U.S. Approval: 2002	Revised as per FDA Discipline Review Letter – Labeling dated December 22, 2022	These highlights do not include all the information needed to use TERIPARATIDE INJECTION safely and effectively. See full prescribing information for TERIPARATIDE INJECTION. TERIPARATIDE injection for subcutaneous use Initial U.S. Approval: 1987~~2002~~


(b) (4)

Revised as per FDA Discipline Review Letter – Labeling dated December 22, 2022

5.3 Risk of Urolithiasis

In clinical trials the frequency of urolithiasis was similar in patients treated with teriparatide injection and patients treated with placebo. However, teriparatide injection has not been studied in patients with active urolithiasis. If teriparatide-treated patients have pre-existing hypercalciuria or suspected/known active urolithiasis, consider measuring urinary calcium excretion. Consider the risks and benefits of use in patients with active or recent urolithiasis because of the potential to exacerbate this condition.


(b) (4)

Revised as per FDA Discipline Review Letter – Labeling dated December 22, 2022

16.2 Storage and Handling

- Store teriparatide injection, USP under refrigeration at 2°C to 8°C (36°F to 46°F) at all times except when administering the product.
- Recap the delivery device (pen) when not in use to protect the cartridge from physical damage and light.
- When using teriparatide injection, minimize the time out of the refrigerator; deliver the dose immediately following removal from the refrigerator.
- Do not freeze. Do not use teriparatide injection, USP if it has been frozen.

16 HOW SUPPLIED/STORAGE AND HANDLING

(b) (4)

16.2 Storage and Handling

- Store teriparatide injection, USP under refrigeration at 2°C to 8°C (36°F to 46°F) at all times except when administering the product.
- Recap the delivery device (pen) when not in use to protect the cartridge from physical damage and light.
- When using teriparatide injection, minimize the time out of the refrigerator; deliver the dose immediately following removal from the refrigerator.
- Do not freeze. Do not use teriparatide injection, USP if it has been frozen.

Additionally, the applicant revised the RECENT MAJOR CHANGES, revision date for PI, revision date for MG.

Acceptable.

C6 assessment:

The applicant submitted revised labeling on 2/17/2023 in response to the Quality IR.

Re: INFORMATION REQUEST
QUALITY
Teriparatide Injection USP, 20 mcg per dose (600 mcg/2.4 mL)
ANDA No. 211097

Apotex Inc. is hereby submitting a response to the Information Request – Quality Letter dated January 20, 2023, regarding Abbreviated New Drug Application No. 211097 for Teriparatide Injection USP, 20 mcg per dose (600 mcg/2.4 mL). The response is presented in a question-and-answer format and is appended to this cover letter.

C. Labeling Deficiency

Question 1:
Please add the sentence "The molecular formula of teriparatide is $C_{181}H_{291}N_{55}O_{51}S_2$" to the Description of your product labeling to be in line with the most recent RLD labeling.

Response:
We acknowledge your comment. As requested we have revised the Description section of our labeling to include "The molecular formula of teriparatide is $C_{181}H_{291}N_{55}O_{51}S_2$" to be in line with the most recent RLD labeling.

Revised Prescribing Information is provided in section 1.14.2.3

A word and pdf copy of the prescribing information is provided in section 1.14.2.3

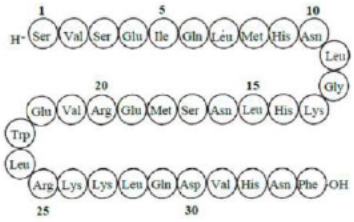
The DPQ review for this submission is still pending.

Previous labeling:

11 **DESCRIPTION**

Teriparatide injection, USP contains chemically synthesized human parathyroid hormone (1-34), and is also called hPTH (1-34). It has an identical sequence to the 34 N-terminal amino acids (the biologically active region) of the 84-amino acid human parathyroid hormone.

Teriparatide has a molecular weight of 4117.8 daltons and its amino acid sequence is shown below:

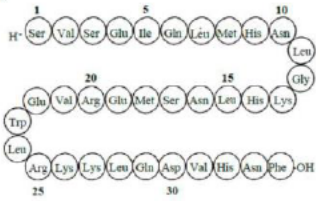


Current labeling:

11 DESCRIPTION

Teriparatide injection, USP contains chemically synthesized human parathyroid hormone (1-34), and is also called hPTH (1-34). It has an identical sequence to the 34 N-terminal amino acids (the biologically active region) of the 84-amino acid human parathyroid hormone.

The molecular formula of teriparatide is $C_{181}H_{291}N_{55}O_{51}S_2$ and a molecular weight of 4117.8 daltons and its amino acid sequence is shown below:



A SBS of the previously submitted labeling and currently submitted labeling shows the revision dates and the above change as the only differences. Acceptable.

Deficiency Comments:

5.5 MEDICATION GUIDE (C6)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Medication Guide is **up-to-date** with model labeling.
☐	☒	Medication Guide meets **content, format, and font size**.
☐	☒	**Phonetic spelling** of the established/proprietary name is present and correct.
☐	☒	Description of **child-resistant feature**(if also present in HOW SUPPLIED/STORAGE AND HANDLING).
☐	☒	**Revision date and approval statement** appear at the end of the Medication Guide correctly.
☐	☒	Applicant committed to provide a **sufficient number** of Medication Guides.
☐	☒	Applicant included the **1-800-FDA-1088** phone number.
☐	☒	Medication Guide is the same as the model labeling, except for allowable differences. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

NDA 021318/S-056 was not approved with a MG. The MG labeling used for the SBS is 021318/S-054.

No changes. Acceptable.

Deficiency Comments:

5.6 OTHER PATIENT LABELING (C6)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Other patient labeling is the same as the model labeling except for allowable differences. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:
The User Manual submitted 3/20/2018 was deemed adequate the previous cycle review.

Deficiency Comments:

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES (C6)

A labeling statement required verification from another division discipline. Check only if applicable.

Reviewer Assessment:

☐	Rubber
☐	Latex
☐	Gluten
☐	Alcohol (ethanol)
☐	Aluminum (small/large volume parenteral and pharmacy bulk package)
☐	Sulfite
☐	Phenylalanine (aspartame) - content calculation
☐	Yellow #5 (tartrazine)
☐	Ghost tablet/capsule (i.e. solid or semi-solid mass in stool)
☒	Other

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB): (For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)

Reviewer Comments:

Received email communication from DP reviewer on 12/16/2022:


Hi Danielle,

Just to let you know that DP is sending following labeling deficiency to the firm:

Please add the sentence "*The molecular formula of teriparatide is $C_{181}H_{301}N_{55}O_{51}S_2$.*" to the Description of your product labeling to be in line with the most recent RLD labeling.

DLR will review once the applicant re-submits.

Deficiency Comments:

Ellen Koo

Digitally signed by Ellen Koo
Date: 4/03/2023 01:19:10PM
GUID: 508da73d0002b687dfbf9b3859d80789

Danielle Russell

Digitally signed by Danielle Russell
Date: 4/03/2023 11:59:02AM
GUID: 52e7d22a0000efc87d53ad9352d2d4f5

Labeling Review

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	01/11/2023
ANDA Number(s)	211097
Review Number	5
Applicant Name	Apotex Inc.
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Teriparatide Injection USP, 600 mcg/2.4 mL (250 mg/mL) Single-Patient-Use Prefilled Pens
Proposed Proprietary Name	None
Submission Received Date	December 27, 2022
Primary Labeling Reviewer	Danielle Russell
Secondary Labeling Reviewer	Ellen Koo

Review Conclusion

☒ Acceptable - No Comments
☐ Acceptable - Include Post Approval Comments
☐ Minor Deficiency* - Refer to Labeling Deficiencies and Comments for Letter to Applicant
☐ Major Deficiency** - Refer to Labeling Deficiencies and Comments for Letter to Applicant

On Policy Alert List	☒ Yes	☐ No
Acceptable For Filing	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No

TABLE OF CONTENTS

Appears this way on original

1 LABELING COMMENTS (C5)

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT (C5)

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE (C5)

The Division of Labeling has no further questions/comments at this time based on your labeling submission received December 27, 2022.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 POST-APPROVAL REVISIONS (C5)

These comments will be addressed post approval (in the first labeling supplement review).

2 INSTRUCTIONS FOR ASSESSMENT (C5)

General Comments:

Select the "no deficiency" or "deficiency" radio button as appropriate for each row. If a "Deficiency Comments" appears, ensure it is appropriate for your situation, edit, or enter "Reviewer Comments" if necessary.

If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has **expired** and the applicant needs to revise labeling.

Reviewer Comments:
Enter free text in this section as necessary.

Deficiency Comments:

- Standardized comments/deficiencies are available for certain questions. For a complete list of standardized comments, reference the DLR Standardized Comments SharePoint.
- Reviewers can modify standardized comments/deficiencies for their situation.
- Deficiencies will have a review number, deficiency number, and roman numeral in the user interface. For first original reviews the review number and iteration numeral will align; however, older reviews may have review numbers and iteration numerals that differ due to some reviews being completed under past practices.
- Deficiency comments will populate by default to the Labeling Comments deficiency section unless you select the Post-Approval checkbox. Assessors also have the option to move all comments to the Post-Approval Revisions section or vice versa from the Labeling Comments tab.

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED (C5)

Table 1: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Final	1 pen	05/12/2022	Satisfactory
Blister	N/A	N/A		
Carton	Final	Carton of 1 pen	05/12/2022	Satisfactory

Table 2: Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	Revised: 12/2022	12/27/2022	Satisfactory
Medication Guide	Draft	Medication Guide revised: December 2022	12/27/2022	Satisfactory
Patient Information	N/A	N/A		
Instructions for Use	N/A	N/A		
SPL Data Elements				
User Manual	Draft	March, 2018	3/20/2018	Satisfactory

4 LABELING REVIEW INFORMATION(C5)

4.1 REGULATORY INFORMATION (C5)

Yes	No	
☒	☐	Are there any applicable issues in DLR's SharePoint Drug Facts ?

1 Page has been withheld in full as b4 draft labeling

Yes	No	
		teriparatide subcutaneous solution *3-year exclusivity decision pending with CDER Exclusivity Board.* *021318/S-054* *No Final Approval Actions can be issued while Exclusivity is being determined* *Application Communications can continue; Labeling affected if exclusivity is granted* *Supplements that do not require updated labeling or labeling review are not affected.*

4.2 MODEL PRESCRIBING INFORMATION (C5)

Table 3: Review Model Labeling for Prescribing Inf (Check the box used as the Model
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING** *(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the* **NDA#/Supplement# (S-000 if original):** NDA021318 / S-056 **Supplement Approval Date:** 09/07/2021 **Proprietary Name:** Forteo **Established Name:** Teriparatide Injection **Description of Supplement:** This "Changes Being Effected" supplemental new drug application provides for updates to the strength expression in the Prescribing Information and on the Carton and Container labeling **Link:** https://analytics.fda.gov/workspace/hubble/external/object/v0/panorama-document?pk_panorama_document=55bc30a000aa5195a3720943b426ce70_60ad200a007e4e1833bff6ed67cf25a4_60ad200c007e516
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**
☐ **OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):**

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	ANDA is **up-to-date** with the RLD/Model labeling.
Reviewer Comments: **Deficiency Comments:**		

4.3 PATENTS AND EXCLUSIVITIES (C5)

The Orange Book was searched on 01/11/2023

Table 4 provides Orange Book patents for the Model Labeling (NDA 021318) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 4: Impact of Model Labeling Patents on ANDA Labeling							
Strengths	**Patent Number**	**Patent Expiration**	**Patent Use Code**	**Patent Use Code Definition**	**Patent Certification**	**Date of Patent Cert Submission**	**Labeling Impact**
0.6 mg/2.4 mL (0.25 mg/mL), 0.75 mg/3 mL (0.25 mg/mL)	7517334	03/25/2025			IV	12/29/2017	None

Table 5 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling						
Strengths	**Exclusivity Code**	**Exclusivity Expiration**	**Exclusivity Code Definition**	**Exclusivity Statement**	**Date of Exclusivity Submission**	**Labeling Impact**
	N/A					

Reviewer Assessment:

Deficiency	**No Deficiency**	
☐	☒	There is information in the Orange Book that the applicant needs to address.
☐	☒	Information in the Orange Book has **expired** and the applicant needs to revise labeling.
Reviewer Comments: **Deficiency Comments:**		

4.4 UNITED STATES PHARMACOPEIA (USP) (C5)

The USP was searched on 01/11/2023

Table 6: USP				
	YES or NO	**Date**	**Monograph Title (N/A if no monograph)**	**Packaging and Storage/Labeling Statements (N/A if no monograph)**
Currently Official	Yes		Teriparatide Injection	•Packaging and Storage: (b) (4) [redacted] protected from light, at a temperature of 2°–8°. The Injection is not to be frozen.

Table 6: USP				
	YES or NO	Date	Monograph Title (N/A if no monograph)	Packaging and Storage/Labeling Statements (N/A if no monograph)
				•Labeling: Label it to indicate that the material has been produced by methods based on recombinant DNA technology.
Not Yet Official	No		N/A	N/A

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	**Established name** is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary **name is different from USP** established name.
☐	☒	**USP descriptor** is correctly used in the appropriate sections of the prescribing information.
USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):		
☐	☒	**DISSOLUTION**: The applicant's dissolution statement is appropriate.
☐	☒	**ORGANIC IMPURITIES**: Drug product meets USP acceptance criteria for organic impurities.
☐	☒	**ASSAY**: Drug product meets USP acceptance criteria for assay.

Reviewer Comments:

The applicant did not label to indicate that the material has been produced by methods based on recombinant DNA technology as the applicant's product is chemically synthesized.

The applicant has petitioned USP to update the monograph for Teriparatide Injection.

From the C2 review:

iii) You are requested to petition the United States Pharmacopeia (USP) to update the monograph for Teriparatide to either remove reference to the recombinant source of Teriparatide or add chemical synthesis as a second source.

Response:

A pending monograph petition, dated July 7, 2019, was submitted to the United States Pharmacopeia (USP) to update the monograph for Teriparatide to remove reference to the recombinant source of Teriparatide. A copy of the cover letter that was submnitted to the USP is included in section 3.2.S.4.1.

Deficiency Comments:

4.5 MODEL CONTAINER LABELS (C5)

Model container/carton/blister labels (Source: NDA 021318 AR-21 dated 11/10/2021 **)**

5 ASSESSMENT OF ANDA LABELING AND LABELS (C5)

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS) (C5)

5.1.1 DRUG PRODUCT REVIEW (C5)

Insert screenshot of Labeling portion from drug product review if completed:
Drug Product Review pending

Received email communication from DP reviewer on 12/16/2022:

Hi Danielle,

Just to let you know that DP is sending following labeling deficiency to the firm:

Please add the sentence "*The molecular formula of teriparatide is $C_{181}H_{291}N_{55}O_{51}S_2$.*" to the Description of your product labeling to be in line with the most recent RLD labeling.

DLR will review once the applicant re-submits.

From the DP review dated 12/22/2022:

Labeling & Package Insert

DESCRIPTION section

Is the information accurate? ☐ Yes ☒ No
If "No," explain.

Is the drug product subject of a USP monograph? ☒ Yes ☐ No
If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

[redacted] **The firm will be asked to petition the USP requesting that the monograph for this drug substance be updated similarly to remove reference to the Teriparatide source or add chemical synthesis as a second source.**

Labeling Reviewer (Katherine Won) comments dated 2/26/2018:

we are issuing the following deficiency comments

(b) (4)

[redacted]

b. DESCRIPTION
i. 1st sentence: Revise to read "Teriparatide in jection, USP contains chemically synthesized human parathyroid hormone (1-34), and is also called hPTH (1-34).
ii. Include the statement "Teriperitide is manufactured chemical synthesis." prior to the sentenance "Teriparatide injection, USP is supplied as a sterile, colorless, clear..."
iii. You are requested to petition the United States Pharmacopeia (USP) to update the monograph for Teriparatide to either remove reference to the recombinant source of Teriparatide or add chemical synthesis as a second source.

Reviewer's Assessment (Review #3): Inadequate

(b) (4)

[redacted]

5.1.2 DESCRIPTION (C5)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling	Each mL contains 250 mcg of teriparatide (as a free base), 0.41 mg of glacial acetic acid, 0.1 mg of sodium acetate (anhydrous), 45.4 mg of mannitol, 3 mg of Metacresol, and Water for Injection. In addition, hydrochloric acid solution 10%

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
	and/or sodium hydroxide solution 10% may have been added to adjust the pH to 4.
Previous ANDA Labeling	Each mL contains 250 mcg teriparatide (corrected for acetate, chloride, and water content), 0.41 mg glacial acetic acid, 0.1 mg sodium acetate (anhydrous), 45.4 mg mannitol, 3 mg Metacresol, and Water for Injection. In addition, hydrochloric acid solution 10% and/or sodium hydroxide solution 10% may have been added to adjust the product to pH 4.
Current ANDA Labeling	Each mL contains 250 mcg teriparatide (corrected for acetate, chloride, and water content), 0.41 mg glacial acetic acid, 0.1 mg sodium acetate (anhydrous), 45.4 mg mannitol, 3 mg Metacresol, and Water for Injection. In addition, hydrochloric acid solution 10% and/or sodium hydroxide solution 10% may have been added to adjust the product to pH 4.

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C5)

Table 8: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	**16 HOW SUPPLIED/STORAGE AND HANDLING** **16.1 How Supplied** FORTEO (teriparatide injection) is a clear and colorless solution, available as single-patient-use prefilled delivery device (pen) in the following package size: • 600 mcg/2.4 mL (250 mcg/mL) [containing 28 daily doses of 20 mcg] NDC 0002-8400-01 (MS8400). **16.2 Storage and Handling** • Store FORTEO under refrigeration at 2° to 8°C (36° to 46°F) at all times except when administering the product. • Recap the delivery device (pen) when not in use to protect the cartridge from physical damage and light. • When using FORTEO, minimize the time out of the refrigerator; deliver the dose immediately following removal from the refrigerator. • Do not freeze. Do not use FORTEO if it has been frozen. **17 PATIENT COUNSELING INFORMATION** Advise the patient to read the FDA-approved patient labeling (Medication Guide and the User Manual) before starting FORTEO and each time the prescription is renewed. Failure to follow the instructions may result in inaccurate dosing.
Previous ANDA Labeling	16.1 How Supplied The teriparatide injection, USP delivery device (pen) is available in the following package size: • 2.4 mL single-patient-use prefilled delivery device NDC 60505-6188-0. 16.2 Storage and Handling • Store teriparatide injection, USP under refrigeration at 2°C to 8°C (36°F to 46°F) at all times except when administering the product. • Recap the delivery device (pen) when not in use to protect the cartridge from physical damage and light. • When using teriparatide injection, minimize the time out of the refrigerator; deliver the dose immediately following removal from the refrigerator. • Do not freeze. Do not use teriparatide injection, USP if it has been frozen. Package Type Term revised. Acceptable per FDA guidance.
Current ANDA Labeling	16.1 How Supplied Teriparatide Injection is a clear and colorless solution, available as single-patient-use prefilled delivery device (pen) in the following package size: • 600 mcg/2.4 mL (250 mcg/mL) [containing 28 daily doses of 20 mcg] NDC 60505-6188-0. 16.2 Storage and Handling • Store teriparatide injection, USP under refrigeration at 2°C to 8°C (36°F to 46°F) at all times except when administering the product. • Recap the delivery device (pen) when not in use to protect the cartridge from physical damage and light.

Table 8: Comparison of Model Labeling to ANDA Labeling	
	• When using teriparatide injection, minimize the time out of the refrigerator; deliver the dose immediately following removal from the refrigerator. • Do not freeze. Do not use teriparatide injection, USP if it has been frozen. Revised per our comments. Acceptable.

5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER (C5)

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
Previous ANDA Labeling	
Name and Address on ANDA Prescribing Information	Marketed by: Apotex Corp. 2400 N. Commerce Parkway, Weston, FL 33326 U.S.A.
Current ANDA Labeling	
Name and Address on ANDA Prescribing Information	Marketed by: Apotex Corp. 2400 N. Commerce Parkway, Weston, FL 33326 U.S.A.

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements			
Manufactured by	**Manufactured for**	**Distributed by**	**Distributed for**

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS) (C5)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Container meets the **too small exemption** [21 CFR 201.10(i)]. Please enter Reviewer/Deficiency Comments if you select Deficiency.
		ESTABLISHED/PROPRIETARY NAME and STRENGTH:
☐	☒	**Tall Man** lettering complies with recommendations found on FDA webpage.
☐	☒	Established/proprietary **name and strength are the most prominent** information on the Principal Display Panel.
☐	☒	No **intervening text**(written, printed, or graphic matter) between established name and strength.
		THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:
☐	☒	**Net quantity** statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Dosage** statement.
☐	☒	**NDC number**: prominence, linear bar code, and its orientation.
☐	☒	**Expiration date and lot number** (or placeholder).
☐	☒	**Equivalency statement** (product strength).
☐	☒	**Medication Guide** Pharmacist instructions [21 CFR 208.24(d)].
☐	☒	Controlled Substance Symbol.
☐	☒	**Image of drug product** represents the true size, color, and imprint.
☐	☒	**Yellow #5** (tartrazine) warning statement is properly displayed.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Latex** warning statement is properly displayed [21 CFR 801.437.].
		PRODUCT DIFFERENTIATION:
☐	☒	ANDA is the **same color** as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Deficiency	No Deficiency	
☐	☒	Multiple **strengths are differentiated** by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from **related products**.
	STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:	
☐	☒	**Storage/dispensing** statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe **container closure**, cite source, and any issues in Reviewer Comments below. Please enter Reviewer/Deficiency Comments if you select Deficiency.
	OVERALL ASSESSMENT:	
☐	☒	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

From the C3 review:

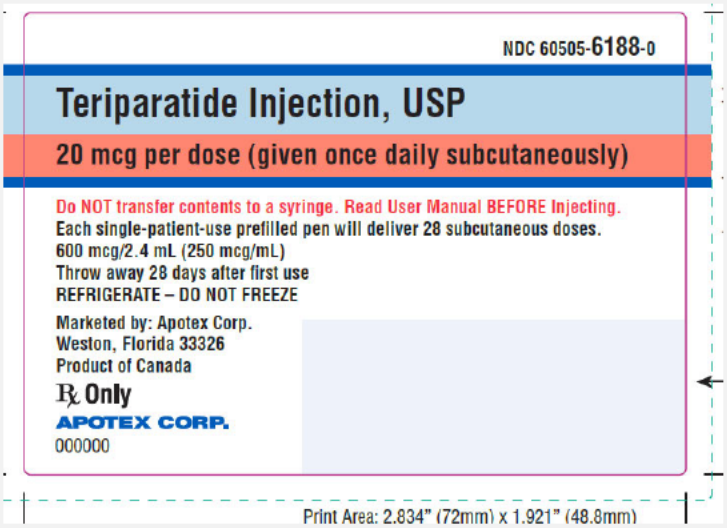
Labeling deficiencies based on your submissions received October 15, 2020 and December 16, 2020:

1. CARTON/CONTAINER LABEL

Revise your labels to be in accordance with the labeling for the reference listed drug (RLD), Forteo® (NDA 021318/S-054) approved on November 16, 2020 found on the Drugs@FDA website.

RLD:

C4 submission:



Medication Guide Pharmacist instructions are not present on the container label. The product is dispensed inside of a carton with the MG and device user manual enclosed with the drug product. This is acceptable and in line with the RLD.

The submitted container label is in line with the most recent RLD.

C5 ASSESSMENT:

ADEQUATE C4. NO NEW SUBMISSION. ACCEPTABLE.

Deficiency Comments:

5.2.1 INJECTABLE PRODUCTS (C5)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Appropriate **package type term** was used (e.g. multiple-dose, single-dose, single-patient-use).
☐	☒	IV, IM, or SC was spelled out.
☐	☒	There is **text on the cap/ferrule** overseal of this injectable product. If "Yes", does the text comply with the recommendations in USP General Chapter <7> Labeling.
☐	☒	The **cap color** is N/A. ***NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate.***

Reviewer Comments:
Prefilled pen, thus no cap/ferrule.

Deficiency Comments:

5.3 CARTON (OUTER OR SECONDARY PACKAGING) LABELING (C5)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	The answers to the Container Label questions are the same for the Carton Labeling. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:
From the C3 review:
Labeling deficiencies based on your submissions received October 15, 2020 and December 16, 2020:

1. CARTON/CONTAINER LABEL
Revise your labels to be in accordance with the labeling for the reference listed drug (RLD), Forteo® (NDA 021318/S-054) approved on November 16, 2020 found on the Drugs@FDA website.

RLD:

C4 submission:

Acceptable. No comments.

C5 ASSESSMENT:

ADEQUATE C4. NO NEW SUBMISSION. ACCEPTABLE.

Deficiency Comments:

5.4 PRESCRIBING INFORMATION (C5)

Reviewer Assessment:

Deficiency	No Deficiency	
	HIGHLIGHTS:	
☐	☒	**Contact information** for applicant and FDA are listed correctly.
☐	☒	**Revision date** appears at end of HIGHLIGHTS section.
	DESCRIPTION/INACTIVE INGREDIENTS:	
☐	☒	Appropriate **warning/precaution** statements for inactive ingredients are present (21 CFR 201) Check only if applicable: ☐Sulfite (21 CFR 201.22) ☐Yellow #5 (Tartrazine) (21 CFR 201.20) ☐Phenylalanine/aspartame (21 CFR 201.21) ☐Latex (21 CFR 801.437). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Gluten** statement is appropriately stated. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Sterile** product statement [21 CFR 201.57(c)(12)(D)].
☐	☒	**Dosage form and route** of administration properly listed [21 CFR 201.57(c)(12)(B)].
	HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:	
☐	☒	All **submitted labels** and labeling are consistent with the HOW SUPPLIED section.
☐	☒	**Physical description** (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☐	☒	**NDC** numbers are present.
☐	☒	Drug product is the **same color** as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin).
☐	☒	**Storage or dispensing** statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**"Discard unused portion"** for single-dose products.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
	HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:	
☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the **Antiretroviral Pregnancy Registry** (APR) upon full approval.
☐	☒	**Pregnancy registry** information is appropriately included/excluded as required for the RLD. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Patent/exclusivity** carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

Comments from previous cycle review:

Labeling deficiencies based on your submissions received October 15, 2020 and December 16, 2020:

1. CARTON/CONTAINER LABEL
   Revise your labels to be in accordance with the labeling for the reference listed drug (RLD), Forteo® (NDA 021318/S-054) approved on November 16, 2020 found on the Drugs@FDA website.
2. HIGHLIGHTS OF PRESCRIBING INFORMATION
   DOSAGE FORMS AND STRENGTHS: Revise to read, "Injection: 620 mcg/2.48 mL (250 mcg/mL) in a single-patient-use prefilled delivery device (pen) containing 28 daily doses of 20 mcg (3)"
3. PRESCRIBING INFORMATION
   a. 3 DOSAGE FORMS AND STRENGTHS: Revise to read, "Injection: 620 mcg/2.48 mL (250 mcg/mL) clear, colorless solution in a single-patient-use prefilled delivery device (pen) containing 28 daily doses of 20 mcg."
   b. 11 DESCRIPTION: Revise the last sentence of the section to read, "Each prefilled delivery device (pen) delivers 20 mcg of teriparatide per dose for up to 28 days."
4. MEDICATION GUIDE
   Add "for subcutaneous use" under the established name and pronunciation in the title to be in line with the RLD.

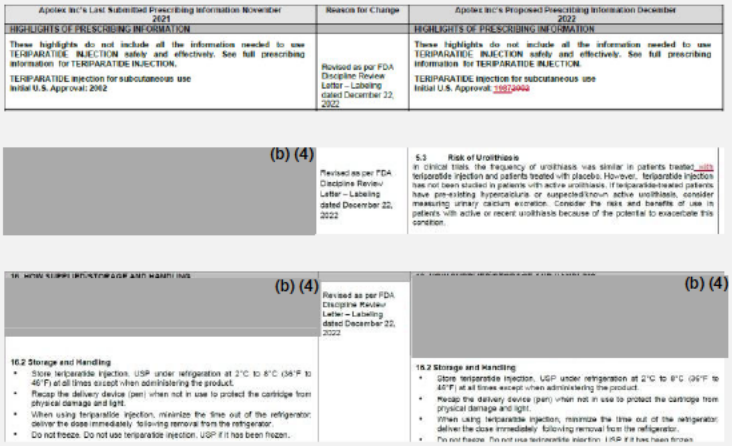
For comments 2, 3a and 3b, the RLD labeling has since been updated and the current submission is in line with the most recently approved RLD.

The initial US Approval date on the RLD is 1987. This was revised in the 021318/S-052 labeling at the request of the FDA.

> Lilly asked for additional clarification regarding the request to revise the approval date. The FDA explained that 2002 was an error as the date should reflect the date of initial approval of the teriparatide, which was in 1987. The 1987-approved product has since been discontinued.

Based on an email and the DP review. The DESCRIPTION section requires revision. DP will issue the deficiency comment. See section 5.1.1.

C5 assessment:



Apotex Inc's Last Submitted Prescribing Information November 2021	Reason for Change	Apotex Inc's Proposed Prescribing Information December 2022
HIGHLIGHTS OF PRESCRIBING INFORMATION		HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TERIPARATIDE INJECTION safely and effectively. See full prescribing information for TERIPARATIDE INJECTION. TERIPARATIDE injection for subcutaneous use Initial U.S. Approval: 2002	Revised as per FDA Discipline Review Letter – Labeling dated December 22, 2022	These highlights do not include all the information needed to use TERIPARATIDE INJECTION safely and effectively. See full prescribing information for TERIPARATIDE INJECTION. TERIPARATIDE injection for subcutaneous use Initial U.S. Approval: 1987 2002
(b) (4)	Revised as per FDA Discipline Review Letter – Labeling dated December 22, 2022	5.3 Risk of Urolithiasis In clinical trials, the frequency of urolithiasis was similar in patients treated with teriparatide injection and patients treated with placebo. However, teriparatide injection has not been studied in patients with active urolithiasis. If teriparatide-treated patients have pre-existing hypercalciuria or suspected/known active urolithiasis, consider measuring urinary calcium excretion. Consider the risks and benefits of use in patients with active or recent urolithiasis because of the potential to exacerbate this condition.
(b) (4) 16.2 Storage and Handling • Store teriparatide injection, USP under refrigeration at 2°C to 8°C (36°F to 46°F) at all times except when administering the product. • Recap the delivery device (pen) when not in use to protect the cartridge from physical damage and light. • When using teriparatide injection, minimize the time out of the refrigerator; deliver the dose immediately following removal from the refrigerator. • Do not freeze. Do not use teriparatide injection, USP if it has been frozen.	Revised as per FDA Discipline Review Letter – Labeling dated December 22, 2022	(b) (4) 16.2 Storage and Handling • Store teriparatide injection, USP under refrigeration at 2°C to 8°C (36°F to 46°F) at all times except when administering the product. • Recap the delivery device (pen) when not in use to protect the cartridge from physical damage and light. • When using teriparatide injection, minimize the time out of the refrigerator; deliver the dose immediately following removal from the refrigerator. • Do not freeze. Do not use teriparatide injection, USP if it has been frozen.

Additionally, the applicant revised the RECENT MAJOR CHANGES, revision date for PI, revision date for MG.

Acceptable.

Deficiency Comments:

Deficiency # 1 Created in C4 Prescribing Information	HIGHLIGHTS OF PRESCRIBING INFORMATION: Revise Initial U.S. Approval to read, "Initial U.S. Approval: 1987" to be in line with the RLD.
Response / Assessment:	Revised.
Deficiency # 2 Created in C4 Prescribing Information	Section 16.1 How Supplied: To be in line with the RLD, revise to read: Teriparatide Injection is a clear and colorless solution, available as single-patient-use prefilled delivery device (pen) in the following package size: • 600 mcg/2.4 mL (250 mcg/mL) [containing 28 daily doses of 20 mcg] NDC 60505-6188-0
Response / Assessment:	Revised.
Deficiency # 3 Created in C4	5.3 Risk of Urolithiasis: Revise the first sentence (b) (4) to read "…patients treated with teriparatide injection…"

Prescribing Information Response / Assessment: Revised.

5.5 MEDICATION GUIDE (C5)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Medication Guide is **up-to-date** with model labeling.
☐	☒	Medication Guide meets **content, format, and font size**.
☐	☒	**Phonetic spelling** of the established/proprietary name is present and correct.
☐	☒	Description of **child-resistant feature**(if also present in HOW SUPPLIED/STORAGE AND HANDLING).
☐	☒	**Revision date and approval statement** appear at the end of the Medication Guide correctly.
☐	☒	Applicant committed to provide a **sufficient number** of Medication Guides.
☐	☒	Applicant included the **1-800-FDA-1088** phone number.
☐	☒	Medication Guide is the same as the model labeling, except for allowable differences. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

NDA 021318/S-056 was not approved with a MG. The MG labeling used for the SBS is 021318/S-054.

Acceptable.

Deficiency Comments:

5.6 OTHER PATIENT LABELING (C5)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Other patient labeling is the same as the model labeling except for allowable differences. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:
The User Manual submitted 3/20/2018 was deemed adequate the previous cycle review.

Deficiency Comments:

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES (C5)

A labeling statement required verification from another division discipline. Check only if applicable.

Reviewer Assessment:

☐	Rubber
☐	Latex
☐	Gluten
☐	Alcohol (ethanol)
☐	Aluminum (small/large volume parenteral and pharmacy bulk package)

☐	Sulfite
☐	Phenylalanine (aspartame) - content calculation
☐	Yellow #5 (tartrazine)
☐	Ghost tablet/capsule (i.e. solid or semi-solid mass in stool)
☒	Other

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB): (For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)

Reviewer Comments:

Received email communication from DP reviewer on 12/16/2022:


Hi Danielle,

Just to let you know that DP is sending following labeling deficiency to the firm:

Please add the sentence "*The molecular formula of teriparatide is $C_{181}H_{291}N_{55}O_{51}S_2$.*" to the Description of your product labeling to be in line with the most recent RLD labeling.

DLR will review once the applicant re-submits.

Deficiency Comments:

Danielle Russell

Digitally signed by Danielle Russell
Date: 1/13/2023 09:28:28AM
GUID: 52e7d22a0000efc87d53ad9352d2d4f5

Ellen Koo

Digitally signed by Ellen Koo
Date: 1/13/2023 09:58:43AM
GUID: 508da73d0002b687dfbf9b3859d80789

Labeling Review

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	12/15/2022
ANDA Number(s)	211097
Review Number	4
Applicant Name	Apotex Inc.
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Teriparatide Injection USP, 600 mcg/2.4 mL (250 mg/mL) Single-Patient-Use Prefilled Pens
Proposed Proprietary Name	None
Submission Received Date	May 12, 2022
Primary Labeling Reviewer	Danielle Russell
Secondary Labeling Reviewer	Ellen Koo

Review Conclusion

☐ Acceptable - No Comments
☐ Acceptable - Include Post Approval Comments
☒ Minor Deficiency* - Refer to Labeling Deficiencies and Comments for Letter to Applicant
☐ Major Deficiency** - Refer to Labeling Deficiencies and Comments for Letter to Applicant

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List	☒ Yes	☐ No
Acceptable For Filing	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No

TABLE OF CONTENTS

Appears this way on original

1 LABELING COMMENTS (C4)

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT (C4)

The following comments have been identified by the Division of Labeling Review (DLR) based on your submission(s) on May 12, 2022. Prior to final approval, the proposed labeling should be clear and precise (grammar, spelling, and formatting) for end users, and accurately reflect the Reference Listed Drug (RLD) information to comply with FDA policies, laws, regulations (i.e., 21 CFR 314.94(a)(8)), official compendia, and relevant guidance.

1. PRESCRIBING INFORMATION
    a. HIGHLIGHTS OF PRESCRIBING INFORMATION: Revise Initial U.S. Approval to read, "Initial U.S. Approval: 1987" to be in line with the RLD.
    b. Section 16.1 How Supplied: To be in line with the RLD, revise to read:

        Teriparatide Injection is a clear and colorless solution, available as single-patient-use prefilled delivery device (pen) in the following package size:
        • 600 mcg/2.4 mL (250 mcg/mL) [containing 28 daily doses of 20 mcg] NDC 60505-6188-0
    c. 5.3 Risk of Urolithiasis: Revise the first sentence (b) (4) to read "…patients treated with teriparatide injection…"

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE (C4)

1.3 POST-APPROVAL REVISIONS (C4)

These comments will be addressed post approval (in the first labeling supplement review).

2 INSTRUCTIONS FOR ASSESSMENT (C4)

General Comments:

Select the "no deficiency" or "deficiency" radio button as appropriate for each row. If a "Deficiency Comments" appears, ensure it is appropriate for your situation, edit, or enter "Reviewer Comments" if necessary.

If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has **expired** and the applicant needs to revise labeling.

Reviewer Comments:
Enter free text in this section as necessary.

Deficiency Comments:

- Standardized comments/deficiencies are available for certain questions. For a complete list of standardized comments, reference the DLR Standardized Comments SharePoint.
- Reviewers can modify standardized comments/deficiencies for their situation.
- Deficiencies will have a review number, deficiency number, and roman numeral in the user interface. For first original reviews the review number and iteration numeral will align; however, older reviews may have review numbers and iteration numerals that differ due to some reviews being completed under past practices.
- Deficiency comments will populate by default to the Labeling Comments deficiency section unless you select the Post-Approval checkbox. Assessors also have the option to move all comments to the Post-Approval Revisions section or vice versa from the Labeling Comments tab.

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED (C4)

Table 1: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Final	1 pen	05/12/2022	Satisfactory
Blister	N/A	N/A		
Carton	Final	Carton of 1 pen	05/12/2022	Satisfactory

Table 2: Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	Revised: November 2021	05/12/2022	Revise
Medication Guide	Draft	Medication Guide revised: November 2021	05/12/2022	Satisfactory
Patient Information	N/A	N/A		
Instructions for Use	N/A	N/A		
SPL Data Elements				
User Manual	Draft	March, 2018	03/20/2018	Satisfactory

4 LABELING REVIEW INFORMATION(C4)

4.1 REGULATORY INFORMATION (C4)

1 page has been withheld in full as b4 draft labeling

Yes	No	
		Forteo *teriparatide subcutaneous solution* *3-year exclusivity decision pending with CDER Exclusivity Board.* *021318/S-054* *No Final Approval Actions can be issued while Exclusivity is being determined* *Application Communications can continue; Labeling affected if exclusivity is granted* *Supplements that do not require updated labeling or labeling review are not affected.*

4.2 MODEL PRESCRIBING INFORMATION (C4)

Table 3: Review Model Labeling for Prescribing Inf (Check the box used as the Model
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING** *(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the* **NDA#/Supplement# (S-000 if original)**: NDA 021318 / S-056 **Supplement Approval Date**: 09/07/2021 **Proprietary Name**: Forteo **Established Name**: Teriparatide Injection **Description of Supplement**: This "Changes Being Effected" supplemental new drug application provides for updates to the strength expression in the Prescribing Information and on the Carton and Container labeling **Link**: https://analytics.fda.gov/workspace/hubble/external/object/v0/panorama-document?pk_panorama_document=55bc30a000aa5195a3720943b426ce70_60ad200a007e4e1833bff6ed67cf25a4_60ad200c007e516
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**
☐ **OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):**

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	ANDA is **up-to-date** with the RLD/Model labeling.
Reviewer Comments: **Deficiency Comments:**		

4.3 PATENTS AND EXCLUSIVITIES (C4)

The Orange Book was searched on 12/15/2022

Table 4 provides Orange Book patents for the Model Labeling (NDA 021318) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 4: Impact of Model Labeling Patents on ANDA Labeling							
Strengths	**Patent Number**	**Patent Expiration**	**Patent Use Code**	**Patent Use Code Definition**	**Patent Certification**	**Date of Patent Cert Submission**	**Labeling Impact**
0.6 mg/2.4 mL (0.25 mg/mL), 0.75 mg/3 mL (0.25 mg/mL)	7517334	03/25/2025			IV	12/29/2017	None

Table 5 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling						
Strengths	**Exclusivity Code**	**Exclusivity Expiration**	**Exclusivity Code Definition**	**Exclusivity Statement**	**Date of Exclusivity Submission**	**Labeling Impact**
	N/A					

Reviewer Assessment:

Deficiency	**No Deficiency**	
☐	☒	There is information in the Orange Book that the applicant needs to address.
☐	☒	Information in the Orange Book has **expired** and the applicant needs to revise labeling.
Reviewer Comments: **Deficiency Comments:**		

4.4 UNITED STATES PHARMACOPEIA (USP) (C4)

The USP was searched on 12/15/2022

Table 6: USP				
	YES or NO	**Date**	**Monograph Title (N/A if no monograph)**	**Packaging and Storage/Labeling Statements (N/A if no monograph)**
Currently Official	Yes		Teriparatide Injection	•Packaging and Storage: (b) (4) [redacted] protected from light, at a temperature of 2°–8°. The Injection is not to be frozen.

Table 6: USP				
	YES or NO	Date	Monograph Title (N/A if no monograph)	Packaging and Storage/Labeling Statements (N/A if no monograph)
				•Labeling: Label it to indicate that the material has been produced by methods based on recombinant DNA technology.
Not Yet Official	No		N/A	N/A

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	**Established name** is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary **name is different from USP** established name.
☐	☒	**USP descriptor** is correctly used in the appropriate sections of the prescribing information.
USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):		
☐	☒	**DISSOLUTION**: The applicant's dissolution statement is appropriate.
☐	☒	**ORGANIC IMPURITIES**: Drug product meets USP acceptance criteria for organic impurities.
☐	☒	**ASSAY**: Drug product meets USP acceptance criteria for assay.

Reviewer Comments:

The applicant did not label to indicate that the material has been produced by methods based on recombinant DNA technology as the applicant's product is chemically synthesized.

The applicant has petitioned USP to update the monograph for Teriparatide Injection.

From the C2 review:

iii) You are requested to petition the United States Pharmacopeia (USP) to update the monograph for Teriparatide to either remove reference to the recombinant source of Teriparatide or add chemical synthesis as a second source.

Response:

A pending monograph petition, dated July 7, 2019, was submitted to the United States Pharmacopeia (USP) to update the monograph for Teriparatide to remove reference to the recombinant source of Teriparatide. A copy of the cover letter that was submnitted to the USP is included in section 3.2.S.4.1.

Deficiency Comments:

4.5 MODEL CONTAINER LABELS (C4)

Model container/carton/blister labels (Source: NDA 021318 AR-21 dated 11/10/2021 **)**

5 ASSESSMENT OF ANDA LABELING AND LABELS (C4)

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS) (C4)

5.1.1 DRUG PRODUCT REVIEW (C4)

Insert screenshot of Labeling portion from drug product review if completed:
Drug Product Review pending

Received email communication from DP reviewer on 12/16/2022:

Hi Danielle,

Just to let you know that DP is sending following labeling deficiency to the firm:

Please add the sentence "*The molecular formula of teriparatide is $C_{181}H_{291}N_{55}O_{51}S_2$.*" to the Description of your product labeling to be in line with the most recent RLD labeling.

DLR will review once the applicant re-submits.

Labeling & Package Insert

DESCRIPTION section

Is the information accurate? ☐ Yes ☒ No
If "No," explain.

Is the drug product subject of a USP monograph? ☒ Yes ☐ No
If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

(b) (4)

The firm will be asked to petition the USP requesting that the monograph for this drug substance be updated similarly to remove reference to the Teriparatide source or add chemical synthesis as a second source.

Labeling Reviewer (Katherine Won) comments dated 2/26/2018:

we are issuing the following deficiency comments

(b) (4)

b. DESCRIPTION
i. 1st sentence: Revise to read "Teriparatide in jection, USP contains chemically synthesized human parathyroid hormone (1-34), and is also called hPTH (1-34).
ii. Include the statement "Teriperitide is manufactured chemical synthesis." prior to the sentenance "Teriparatide injection, USP is supplied as a sterile, colorless, clear..."
iii. You are requested to petition the United States Pharmacopeia (USP) to update the monograph for Teriparatide to either remove reference to the recombinant source of Teriparatide or add chemical synthesis as a second source.

Reviewer's Assessment (Review #3): Inadequate

(b) (4)

5.1.2 DESCRIPTION (C4)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling	Each mL contains 250 mcg of teriparatide (as a free base), 0.41 mg of glacial acetic acid, 0.1 mg of sodium acetate (anhydrous), 45.4 mg of mannitol, 3 mg of Metacresol, and Water for Injection. In addition, hydrochloric acid solution 10% and/or sodium hydroxide solution 10% may have been added to adjust the pH to 4.
Previous ANDA Labeling	Each mL contains 250 mcg teriparatide (corrected for acetate, chloride, and water content), 0.41 mg glacial acetic acid, 0.1 mg sodium acetate (anhydrous), 45.4 mg

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
	mannitol, 3 mg Metacresol, and Water for Injection. In addition, hydrochloric acid solution 10% and/or sodium hydroxide solution 10% may have been added to adjust the product to pH 4.
Current ANDA Labeling	Each mL contains 250 mcg teriparatide (corrected for acetate, chloride, and water content), 0.41 mg glacial acetic acid, 0.1 mg sodium acetate (anhydrous), 45.4 mg mannitol, 3 mg Metacresol, and Water for Injection. In addition, hydrochloric acid solution 10% and/or sodium hydroxide solution 10% may have been added to adjust the product to pH 4. No changes.

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C4)

Table 8: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	**16 HOW SUPPLIED/STORAGE AND HANDLING** **16.1 How Supplied** FORTEO (teriparatide injection) is a clear and colorless solution, available as single-patient-use prefilled delivery device (pen) in the following package size: • 600 mcg/2.4 mL (250 mcg/mL) [containing 28 daily doses of 20 mcg] NDC 0002-8400-01 (MS8400). **16.2 Storage and Handling** • Store FORTEO under refrigeration at 2° to 8°C (36° to 46°F) at all times except when administering the product. • Recap the delivery device (pen) when not in use to protect the cartridge from physical damage and light. • When using FORTEO, minimize the time out of the refrigerator; deliver the dose immediately following removal from the refrigerator. • Do not freeze. Do not use FORTEO if it has been frozen. **17 PATIENT COUNSELING INFORMATION** Advise the patient to read the FDA-approved patient labeling (Medication Guide and the User Manual) before starting FORTEO and each time the prescription is renewed. Failure to follow the instructions may result in inaccurate dosing.
Previous ANDA Labeling	16.1 How Supplied The teriparatide injection, USP delivery device (pen) is available in the following package size: • 2.4 mL prefilled delivery device NDC 60505-6188-0. 16.2 Storage and Handling • Store teriparatide injection, USP under refrigeration at 2°C to 8°C (36°F to 46°F) at all times except when administering the product. • Recap the delivery device (pen) when not in use to protect the cartridge from physical damage and light. • When using teriparatide injection, minimize the time out of the refrigerator; deliver the dose immediately following removal from the refrigerator. • Do not freeze. Do not use teriparatide injection, USP if it has been frozen.
Current ANDA Labeling	16.1 How Supplied The teriparatide injection, USP delivery device (pen) is available in the following package size: • 2.4 mL single-patient-use prefilled delivery device NDC 60505-6188-0. 16.2 Storage and Handling • Store teriparatide injection, USP under refrigeration at 2°C to 8°C (36°F to 46°F) at all times except when administering the product. • Recap the delivery device (pen) when not in use to protect the cartridge from physical damage and light. • When using teriparatide injection, minimize the time out of the refrigerator; deliver the dose immediately following removal from the refrigerator. • Do not freeze. Do not use teriparatide injection, USP if it has been frozen. Package Type Term revised. Acceptable per FDA guidance.

5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER (C4)

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
Previous ANDA Labeling	
Name and Address on ANDA Prescribing Information	Marketed by: Apotex Corp. 2400 N. Commerce Parkway, Weston, FL 33326 U.S.A.
Current ANDA Labeling	
Name and Address on ANDA Prescribing Information	Marketed by: Apotex Corp. 2400 N. Commerce Parkway, Weston, FL 33326 U.S.A.

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements			
Manufactured by	**Manufactured for**	**Distributed by**	**Distributed for**

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS) (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Container meets the **too small exemption** [21 CFR 201.10(i)]. Please enter Reviewer/Deficiency Comments if you select Deficiency.
		ESTABLISHED/PROPRIETARY NAME and STRENGTH:
☐	☒	**Tall Man** lettering complies with recommendations found on FDA webpage.
☐	☒	Established/proprietary **name and strength are the most prominent** information on the Principal Display Panel.
☐	☒	No **intervening text**(written, printed, or graphic matter) between established name and strength.
		THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:
☐	☒	**Net quantity** statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Dosage** statement.
☐	☒	**NDC number**: prominence, linear bar code, and its orientation.
☐	☒	**Expiration date and lot number** (or placeholder).
☐	☒	**Equivalency statement** (product strength).
☐	☒	**Medication Guide** Pharmacist instructions [21 CFR 208.24(d)].
☐	☒	Controlled Substance Symbol.
☐	☒	**Image of drug product** represents the true size, color, and imprint.
☐	☒	**Yellow #5** (tartrazine) warning statement is properly displayed.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Latex** warning statement is properly displayed [21 CFR 801.437.].
		PRODUCT DIFFERENTIATION:
☐	☒	ANDA is the **same color** as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Multiple **strengths are differentiated** by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from **related products**.
		STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:
☐	☒	**Storage/dispensing** statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].

Deficiency	No Deficiency	
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe **container closure**, cite source, and any issues in Reviewer Comments below. Please enter Reviewer/Deficiency Comments if you select Deficiency.
OVERALL ASSESSMENT:		
☐	☒	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

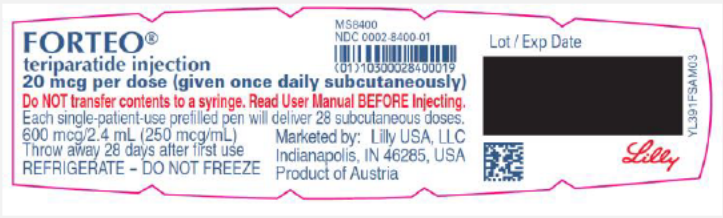
From the C3 review:

Labeling deficiencies based on your submissions received October 15, 2020 and December 16, 2020:

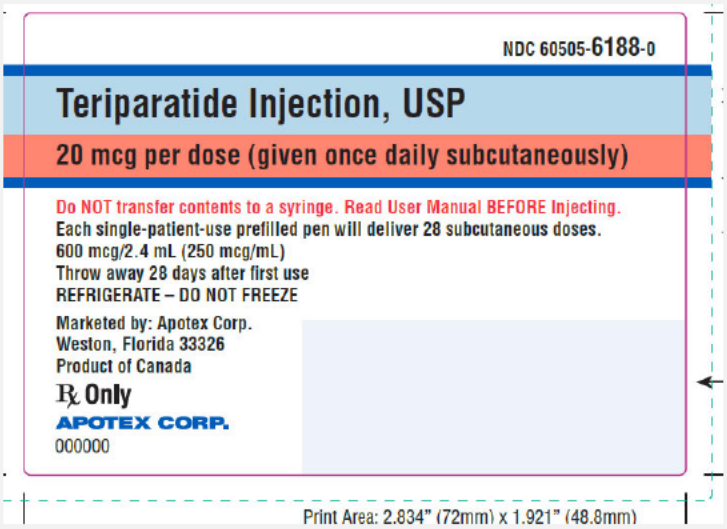
1. CARTON/CONTAINER LABEL

Revise your labels to be in accordance with the labeling for the reference listed drug (RLD), Forteo® (NDA 021318/S-054) approved on November 16, 2020 found on the Drugs@FDA website.

RLD:



C4 submission:



Medication Guide Pharmacist instructions are not present on the container label. The product is dispensed inside of a carton with the MG and device user manual enclosed with the drug product. This is acceptable and in line with the RLD.

The submitted container label is in line with the most recent RLD.

Deficiency Comments:

5.2.1 INJECTABLE PRODUCTS (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Appropriate **package type term** was used (e.g. multiple-dose, single-dose, single-patient-use).
☐	☒	IV, IM, or SC was spelled out.
☐	☒	There is **text on the cap/ferrule** overseal of this injectable product. If "Yes", does the text comply with the recommendations in USP General Chapter <7> Labeling.
☐	☒	The **cap color** is N/A. ***NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate.***

Reviewer Comments:
Prefilled pen, thus no cap/ferrule.

Deficiency Comments:

5.3 CARTON (OUTER OR SECONDARY PACKAGING) LABELING (C4)

Reviewer Assessment:

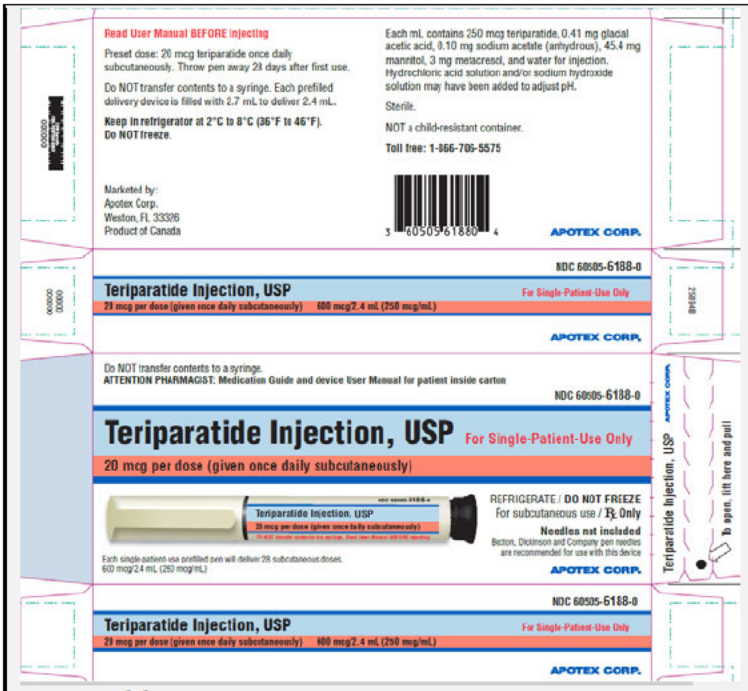
Deficiency	No Deficiency	
☐	☒	The answers to the Container Label questions are the same for the Carton Labeling. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:
From the C3 review:
Labeling deficiencies based on your submissions received October 15, 2020 and December 16, 2020:

1. CARTON/CONTAINER LABEL
Revise your labels to be in accordance with the labeling for the reference listed drug (RLD), Forteo® (NDA 021318/S-054) approved on November 16, 2020 found on the Drugs@FDA website.

RLD:

C4 submission:



Acceptable. No comments.

Deficiency Comments:

5.4 PRESCRIBING INFORMATION (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
	HIGHLIGHTS:	
☐	☒	**Contact information** for applicant and FDA are listed correctly.
☐	☒	**Revision date** appears at end of HIGHLIGHTS section.
	DESCRIPTION/INACTIVE INGREDIENTS:	
☐	☒	Appropriate **warning/precaution** statements for inactive ingredients are present (21 CFR 201) Check only if applicable: ☐Sulfite (21 CFR 201.22) ☐Yellow #5 (Tartrazine) (21 CFR 201.20) ☐Phenylalanine/aspartame (21 CFR 201.21) ☐latex (21 CFR 801.437). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Gluten** statement is appropriately stated. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Sterile** product statement [21 CFR 201.57(c)(12)(D)].
☐	☒	**Dosage form and route** of administration properly listed [21 CFR 201.57(c)(12)(B)].
	HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:	
☐	☒	All **submitted labels** and labeling are consistent with the HOW SUPPLIED section.
☐	☒	**Physical description** (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☐	☒	**NDC** numbers are present.
☐	☒	Drug product is the **same color** as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin).
☐	☒	**Storage or dispensing** statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Deficiency	No Deficiency	
☐	☒	**"Discard unused portion"** for single-dose products.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:		
☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the **Antiretroviral Pregnancy Registry** (APR) upon full approval.
☐	☒	**Pregnancy registry** information is appropriately included/excluded as required for the RLD. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Patent/exclusivity** carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☒	☐	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

Comments from previous cycle review:

Labeling deficiencies based on your submissions received October 15, 2020 and December 16, 2020:

1. CARTON/CONTAINER LABEL
   Revise your labels to be in accordance with the labeling for the reference listed drug (RLD), Forteo® (NDA 021318/S-054) approved on November 16, 2020 found on the Drugs@FDA website.
2. HIGHLIGHTS OF PRESCRIBING INFORMATION
   DOSAGE FORMS AND STRENGTHS: Revise to read, "Injection: 620 mcg/2.48 mL (250 mcg/mL) in a single-patient-use prefilled delivery device (pen) containing 28 daily doses of 20 mcg (3)"
3. PRESCRIBING INFORMATION
   a. 3 DOSAGE FORMS AND STRENGTHS: Revise to read, "Injection: 620 mcg/2.48 mL (250 mcg/mL) clear, colorless solution in a single-patient-use prefilled delivery device (pen) containing 28 daily doses of 20 mcg."
   b. 11 DESCRIPTION: Revise the last sentence of the section to read, "Each prefilled delivery device (pen) delivers 20 mcg of teriparatide per dose for up to 28 days."
4. MEDICATION GUIDE
   Add "for subcutaneous use" under the established name and pronunciation in the title to be in line with the RLD.

For comments 2, 3a and 3b, the RLD labeling has since been updated and the current submission is in line with the most recently approved RLD.

The initial US Approval date on the RLD is 1987. This was revised in the 021318/S-052 labeling at the request of the FDA.

Lilly asked for additional clarification regarding the request to revise the approval date. The FDA explained that 2002 was an error as the date should reflect the date of initial approval of the teriparatide, which was in 1987. The 1987-approved product has since been discontinued.

Based on an email and the DP review. The DESCRIPTION section requires revision. DP will issue the deficiency comment. See section 5.1.1.

Deficiency Comments:

Deficiency # 1 Created in C4 Prescribing Information Response / Assessment:	HIGHLIGHTS OF PRESCRIBING INFORMATION: Revise Initial U.S. Approval to read, "Initial U.S. Approval: 1987" to be in line with the RLD.
Deficiency # 2 Created in C4 Prescribing Information	Section 16.1 How Supplied: To be in line with the RLD, revise to read: Teriparatide Injection is a clear and colorless solution, available as single-patient-use prefilled delivery device (pen) in the following package size:

Response / Assessment:	• 600 mcg/2.4 mL (250 mcg/mL) [containing 28 daily doses of 20 mcg] NDC 60505-6188-0
Deficiency # 3 Created in C4 Prescribing Information Response / Assessment:	5.3 Risk of Urolithiasis: Revise the first sentence [redacted] (b) (4) to read "…patients treated with teriparatide injection…"

5.5 MEDICATION GUIDE (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Medication Guide is **up-to-date** with model labeling.
☐	☒	Medication Guide meets **content, format, and font size**.
☐	☒	**Phonetic spelling** of the established/proprietary name is present and correct.
☐	☒	Description of **child-resistant feature**(if also present in HOW SUPPLIED/STORAGE AND HANDLING).
☐	☒	**Revision date and approval statement** appear at the end of the Medication Guide correctly.
☐	☒	Applicant committed to provide a **sufficient number** of Medication Guides.
☐	☒	Applicant included the **1-800-FDA-1088** phone number.
☐	☒	Medication Guide is the same as the model labeling, except for allowable differences. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

Comments from previous cycle review:

Labeling deficiencies based on your submissions received October 15, 2020 and December 16, 2020:

1. CARTON/CONTAINER LABEL
   Revise your labels to be in accordance with the labeling for the reference listed drug (RLD), Forteo® (NDA 021318/S-054) approved on November 16, 2020 found on the Drugs@FDA website.
2. HIGHLIGHTS OF PRESCRIBING INFORMATION
   DOSAGE FORMS AND STRENGTHS: Revise to read, "Injection: 620 mcg/2.48 mL (250 mcg/mL) in a single-patient-use prefilled delivery device (pen) containing 28 daily doses of 20 mcg (3)"
3. PRESCRIBING INFORMATION
   a. 3 DOSAGE FORMS AND STRENGTHS: Revise to read, "Injection: 620 mcg/2.48 mL (250 mcg/mL) clear, colorless solution in a single-patient-use prefilled delivery device (pen) containing 28 daily doses of 20 mcg."
   b. 11 DESCRIPTION: Revise the last sentence of the section to read, "Each prefilled delivery device (pen) delivers 20 mcg of teriparatide per dose for up to 28 days."
4. MEDICATION GUIDE
   Add "for subcutaneous use" under the established name and pronunciation in the title to be in line with the RLD.

NDA 021318/S-056 was not approved with a MG. The MG labeling used for the SBS is 021318/S-054.

The applicant revised the MG per our comments. Acceptable.

Deficiency Comments:

5.6 OTHER PATIENT LABELING (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Other patient labeling is the same as the model labeling except for allowable differences. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:
The User Manual submitted 3/20/2018 was deemed adequate the previous cycle review.

Deficiency Comments:

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES (C4)

A labeling statement required verification from another division discipline. Check only if applicable.

Reviewer Assessment:

☐	Rubber
☐	Latex
☐	Gluten
☐	Alcohol (ethanol)
☐	Aluminum (small/large volume parenteral and pharmacy bulk package)
☐	Sulfite
☐	Phenylalanine (aspartame) - content calculation
☐	Yellow #5 (tartrazine)
☐	Ghost tablet/capsule (i.e. solid or semi-solid mass in stool)
☒	Other

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB): (For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)

Reviewer Comments:
Received email communication from DP reviewer on 12/16/2022:

Hi Danielle,

Just to let you know that DP is sending following labeling deficiency to the firm:

Please add the sentence "*The molecular formula of teriparatide is $C_{181}H_{291}N_{55}O_{51}S_2$.*" to the Description of your product labeling to be in line with the most recent RLD labeling.

DLR will review once the applicant re-submits.

Deficiency Comments:

Danielle Russell

Digitally signed by Danielle Russell
Date: 12/20/2022 10:23:54AM
GUID: 52e7d22a0000efc87d53ad9352d2d4f5

Ellen Koo

Digitally signed by Ellen Koo
Date: 12/20/2022 01:12:34PM
GUID: 508da73d0002b687dfbf9b3859d80789

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	2/11/2021
ANDA Number(s)	211097
Review Number	3
Applicant Name	Apotex Inc.
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Teriparatide Injection, 600 mcg/2.4 mL (250 mg/mL) in prefilled delivery device (pen)
Proposed Proprietary Name	NA
Submission Received Date	October 15, 2020 and December 16, 2020
Primary Labeling Reviewer	Danielle Russell
Secondary Labeling Reviewer	Refer to signature page

Review Conclusion

☐ ACCEPTABLE – No Comments

☐ ACCEPTABLE – Include Post Approval Comments

☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant

☐ Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Applicant

†Theme - Choose an item.

Justification for Major Deficiency - Choose an item.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List ☒ Yes ☐ No

Combined Insert/Outsert ☐ Yes ☒ No (If yes, indicate ANDA number)

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling deficiencies based on your submissions received October 15, 2020 and December 16, 2020:

1. CARTON/CONTAINER LABEL
   Revise your labels to be in accordance with the labeling for the reference listed drug (RLD), Forteo® (NDA 021318/S-054) approved on November 16, 2020 found on the Drugs@FDA website.
2. HIGHLIGHTS OF PRESCRIBING INFORMATION
   DOSAGE FORMS AND STRENGTHS: Revise to read, “Injection: 620 mcg/2.48 mL (250 mcg/mL) in a single-patient-use prefilled delivery device (pen) containing 28 daily doses of 20 mcg (3)”
3. PRESCRIBING INFORMATION
   a. 3 DOSAGE FORMS AND STRENGTHS: Revise to read, “Injection: 620 mcg/2.48 mL (250 mcg/mL) clear, colorless solution in a single-patient-use prefilled delivery device (pen) containing 28 daily doses of 20 mcg.”
   b. 11 DESCRIPTION: Revise the last sentence of the section to read, “Each prefilled delivery device (pen) delivers 20 mcg of teriparatide per dose for up to 28 days.”
4. MEDICATION GUIDE
   Add “for subcutaneous use" under the established name and pronunciation in the title to be in line with the RLD.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission (s) received (add date)

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia

– National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 POST APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).
NA

Appears this way on original

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].

Reviewer Comments: Deficiency comments from C2 review:

Labeling Deficiencies determined on June 26, 2018 based on your submission dated March 20, 2018:

- PRESCRIBING INFORMATION
  - a. (b) (4)
  - b.
  - c. Add the following subsection:
    (b) (4) Osteosarcoma
    Patients should be made aware that in rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration.
  - d. DESCRIPTION
    - i. 1st sentence: Revise to read "Teriparatide injection, USP contains chemically synthesized human parathyroid hormone (1-34), and is also called hPTH (1-34).
    - ii. Include the statement "Teriperitide is manufactured chemical synthesis." prior to the sentenance "Teriparatide injection, USP is supplied as a sterile, colorless, clear…"
    - iii. You are requested to petition the United States Pharmacopeia (USP) to update the monograph for Teriparatide to either remove reference to the recombinant source of Teriparatide or add chemical synthesis as a second source.

The RLD has since been updated since these comments were made. The applicant is in line with RLD Forteo® (NDA 021318/S-054) approved on November 16, 2020. The applicant addressed the above comments in their CR response dated 10/15/2020, howver, there has been an RLD update which supersedes these comments and therefore have been addressed with the 12/16/2020 submission. RLD container and carton labeling were updated with NDA 021318/S-054. The applicant will be requested to revise their container and carton labeling to be in accordance with the RLD. The applicant responded to deficiency comment d.iii. See response in section 3.4.

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments: Container and carton labeling were updated with NDA 021318/S-054 with the following changes: Addition of "For single-patient use only" and the addition of "given once daily subcutaneously" after the strength statement.

Applicant needs to submit new carton and container labels to be in line with RLD update Forteo® (NDA 021318/S-054) approved on November 16, 2020.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments:

10/15/2020 submission: Response to CR that addressed the C2 deficiency comments

12/16/2020 submission: Submitted to address an RLD update, Forteo® (NDA 021318/S-054) approved on November 16, 2020.

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? YES If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review

1 Pages has been withheld in full as b4 draft labeling

(b) (4)

Is the drug product listed on the Susceptibility Test Interpretive Criteria web page**?** NO

3.2 MODEL LABELING

Table 1: Review Model Labeling
(Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so enter the most recently approved ANDA labeling information as applicable.)

NDA#/Supplement# (S-000 if original): 021318/S-054

Supplement Approval Date: 11/16/2020

Proprietary Name: Forteo

Established Name: Teriparatide (rDNA origin) Injection

Description of Supplement:

This Prior Approval supplemental new drug application provides for:

a. Removal of the Boxed Warning regarding osteosarcoma.
b. Modification of Section 2.3 (Dosage and Administration, Recommended Treatment Duration) to allow for longer duration of treatment in patients who remain at or return to having a high risk for fracture.
c. Addition of the risk of cutaneous calcification including calciphylaxis to the existing warning regarding hypercalcemia and hypercalcemic disorders
d. Revision of Section 6.3 (Adverse Reactions, Postmarketing Experience) to reflect the findings from the long-term osteosarcoma surveillance studies.
e. Revisions to the carton and container labeling.

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

ANDA#/Supplement# (S-000 if original): Click here to enter text.

Supplement Approval Date: Click here to enter text.

Proprietary Name: Click here to enter text.

Established Name: Click here to enter text.

Description of Supplement:

☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** Click here to enter text.

☐ **OTHER (Describe):** Click here to enter text.

Reviewer Assessment:

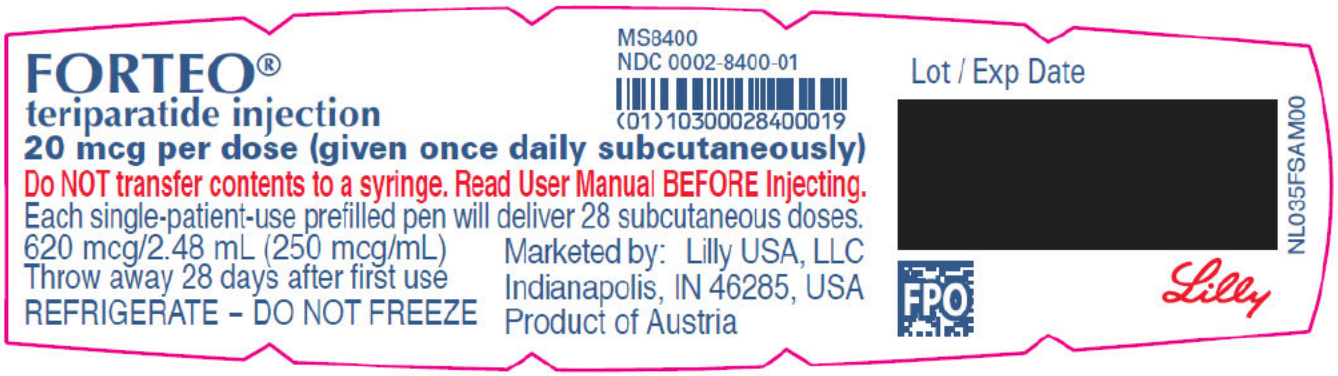
Is the Prescribing Information or Drug Facts Labeling (OTC) same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **NO**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old), or 201.66 (OTC)? **YES**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments:

Click here to enter text.

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: 021318/S-054 approved 11/16/2020]



3.4 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 2/11/2021.

Table 2: United States Pharmacopeia (USP)				
	YES or NO	**Date**	**Monograph Title (NA if no monograph)**	**Packaging and Storage/Labeling Statements (NA if no monograph)**
Currently Official	Yes	[redacted]	Teriparatide Injection	•Packaging and Storage: [redacted (b) (4)] protected from light, at a temperature of 2°–8°. The Injection is not to be frozen. •Labeling: Label it to indicate that the material has been produced by methods based on recombinant DNA technology.
Not Yet Official	No			

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling and labels? **YES**

Reviewer Comments: The applicant does not have to label to indicate that the material has been produced by methods based on recombinant DNA technology as the applicant's product is chemically synthesized. From the chemistry review in C2 review:

[redacted (b) (4)] **The firm will be asked to petition the USP requesting that the monograph for this drug substance be updated similarly to remove reference to the Teriparatide source or add chemical synthesis as a second source.**

Deficiency comment from C2 review:

iii) You are requested to petition the United States Pharmacopeia (USP) to update the monograph for Teriparatide to either remove reference to the recombinant source of Teriparatide or add chemical synthesis as a second source.

Response:

A pending monograph petition, dated July 7, 2019, was submitted to the United States Pharmacopeia (USP) to update the monograph for Teriparatide to remove reference to the recombinant source of Teriparatide. A copy of the cover letter that was submnitted to the USP is included in section 3.2.S.4.1.

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 2/11/2021.

Table 3 provides Orange Book patents for the Model Labeling NDA 021318 and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	**Patent Expiration**	**Patent Use Code**	**Patent Use Code Definition**	**Patent Certification**	**Date of Patent Cert Submission**	**Labeling Impact (enter Carve-out or None)**
7517334	3/25/2025			IV	12/29/2017	None

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments:

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	**Exclusivity Expiration**	**Exclusivity Code Definition**	**Exclusivity Statement**	**Date of Exclusivity Submission**	**Labeling Impact (enter Carve-out or None)**
NA					

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments:

Click here to enter text.

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**
Are there changes to the manufacturer/distributor/packer statements? **NO**
If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)

Previous Labeling Review	Currently Proposed	Assessment
Each mL contains 250 mcg teriparatide (corrected for acetate, chloride, and water content), 0.41 mg glacial acetic acid, 0.1 mg sodium acetate (anhydrous), 45.4 mg mannitol, 3 mg Metacresol, and Water for Injection. In addition, hydrochloric acid solution 10% and/or sodium hydroxide solution 10% may have been added to adjust the product to pH 4.	Each mL contains 250 mcg teriparatide (corrected for acetate, chloride, and water content), 0.41 mg glacial acetic acid, 0.1 mg sodium acetate (anhydrous), 45.4 mg mannitol, 3 mg Metacresol, and Water for Injection. In addition, hydrochloric acid solution 10% and/or sodium hydroxide solution 10% may have been added to adjust the product to pH 4.	**Acceptable**

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products

Previous Labeling Review	Currently Proposed	Assessment
16.1 HOW SUPPLIED The teriparatide injection, USP delivery device (pen) is available in the following package size: • 2.4 mL prefilled delivery device NDC 60505-6188-0. (b) (4)	16.1 How Supplied The teriparatide injection, USP delivery device (pen) is available in the following package size: • 2.4 mL prefilled delivery device NDC 60505-6188-0. 16.2 Storage and Handling • Store teriparatide injection, USP under refrigeration at 2°C to 8°C (36°F to 46°F) at all times except when administering the product. • Recap the delivery device (pen) when not in use to protect the cartridge from physical damage and light. • When using teriparatide injection, minimize the time out of the refrigerator; deliver the dose mmediately following removal from the refrigerator. • Do not freeze. Do not use teriparatide injection, USP if it has been frozen.	**Acceptable.**

Table 7: Manufacturer/Distributor/Packer Statements

Previous Labeling Review	Currently Proposed	Assessment

Table 7: Manufacturer/Distributor/Packer Statements		
Marketed by: Apotex Corp. 2400 N. Commerce Parkway, Weston, FL 33326 U.S.A.	Marketed by: Apotex Corp. 2400 N. Commerce Parkway, Weston, FL 33326 U.S.A.	**Acceptable**

5. COMMENTS/CONSULTS FOR OTHER DISCIPLINES

Describe questions, issues and consults sent to and/or received from other discipline(s) (e.g., OPQ, OB, DCR):

Refer to the Consult Screening flow chart to determine any necessary consults.

(For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue). Reminder: Refer to chemistry review to verify labeling section (per Chemistry-Labeling MOU) is complete. Refer to DCR review for combination product to verify if labeling comments were communicated to applicant.

Reviewer Comments:

Click here to enter text.

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item "Final, Draft, or "NA". If you enter "NA" under the second column, you do NOT need to enter "NA" for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Draft	1 pen	3/20/18	Revise
Blister	NA			
Carton	Draft	1 pen/carton	3/20/18	Revise
(Other – specify)	NA			
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	Revised: December 2020	12/16/2020	Revise
Medication Guide	Draft	Medication Guide revised: December 2020	12/16/2020	Revise
User Manual	Draft	March, 2018	3/20/18	Satisfactory

Ellen Koo

Digitally signed by Ellen Koo
Date: 2/23/2021 12:48:07PM
GUID: 508da73d0002b687dfbf9b3859d80789

Danielle Russell

Digitally signed by Danielle Russell
Date: 2/23/2021 10:36:11AM
GUID: 52e7d22a0000efc87d53ad9352d2d4f5

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	6/26/18
ANDA Number(s)	211097
Review Number	2
Applicant Name	Apotex Inc.
Established Name & Strength(s)	Teriparatide Injection, 600 mcg/2.4 mL (250 mg/mL) in prefilled delivery device (pen)
Proposed Proprietary Name	NA
Submission Received Date	4/5/18 (Patent and Exclusivities Information) 3/20/18 (Labeling amendment)
Primary Labeling Reviewer	Katherine Won
Secondary Labeling Reviewer	Lisa Kwok

Review Conclusion

☐ ACCEPTABLE – No Comments.

☐ ACCEPTABLE – Include Post Approval Comments

☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the Letter to Applicant.

☐ Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Applicant

†Theme - Choose an item.

Justification for Major Deficiency - Choose an item.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List ☐YES ☒NO

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on June 26, 2018 based on your submission dated March 20, 2018:

- PRESCRIBING INFORMATION
  a. (b) (4)
  b.
  c. Add the following subsection:
  (b) (4) Osteosarcoma
  Patients should be made aware that in rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration.
  d. DESCRIPTION
    i. 1st sentence: Revise to read "Teriparatide injection, USP contains chemically synthesized human parathyroid hormone (1-34), and is also called hPTH (1-34).
    ii. Include the statement "Teriperitide is manufactured chemical synthesis." prior to the sentenance "Teriparatide injection, USP is supplied as a sterile, colorless, clear…"
    iii. You are requested to petition the United States Pharmacopeia (USP) to update the monograph for Teriparatide to either remove reference to the recombinant source of Teriparatide or add chemical synthesis as a second source.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

NA

1.3 POST APPROVAL REVISIONS

These comments will NOT be sent to the applicants at this time.
These comments will be addressed post approval (in the first labeling supplement review).

NA

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].

LABELING HISTORY:

The last labeling review, 1st cycle, based on the 12/29/17 submission issued the following comments:

1. CONTAINER LABEL
   [redacted] (b) (4) We refer you to the reference listed drug (RLD).

2. CARTON LABELING
   a. [redacted] (b) (4) Refer to the RLD.
   b. Please confirm that the lot number and expiration date will appear on the carton labeling.

3. MEDICATION GUIDE
   Add the phonetic spelling of the established name in the Title in accordance with 21 CFR 208.20(b)(1).

4. USER MANUAL
   a. Throughout the User Manual labeling, please revise to use red text to increase prominence of the important information (e.g., paragraph beginning with "The teriparatide injection delivery device contains…", "Do not transfer teriparatide injection…", "Wash your hands…" among other things) in accordance with the RLD.
   b. We recommend that you include the title of each step (e.g., 1 Pull off pen cap, 2 Attach new needle, etc.) to be inside the box to clearly delineate each step. We refer you to the RLD.
   c. Troubleshooting section: Please add a blue colored boxing around the paragraph beginning with "You can prevent this problem by always using a NEW needle…" to increase prominence of the important information and to be in accordance with the RLD.
   d. Include the revision date.

Applicant has addressed the comments satisfactorily.

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

2 Pages have been withheld in full as b4 draft labeling

Reviewer Comments:

The following entry is listed on DLR's Sharepoint Drug Facts:

Entry title and description: Forteo/Forteo NDA 21318 has patient registry in the labeling which is NOT part of the REMS and is not required for approval for ANDAs.

An email was added on 3/3/16 regarding the Patient Registry for the innovator NDA 021318 which confirmed that the Patient Registry was created as part of a PMR for the RLD and not a part of REMS. Thus, the registry may be omitted from ANDA labeling.

Of note, for ANDA 208569, which was the first generic product submitted for Forteo, OGD Policy determined that the patient registry was created as part of a PMR for the RLD. Since DRISK has confirmed the registry is NOT part of the REMS, and it is part of the RLD's PMR, Policy is okay with ANDAs omitting reference to the registry.

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? YES If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? NO If Yes, please explain.
Is the drug product listed in the Susceptibility Test Interpretive Criteria web page? NO

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING** *(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA model labeling information.)* **NDA#/Supplement# (S-000 if original):** 021318/S-036* **Supplement Approval Date:** 8/30/2013 **Proprietary Name:** Forteo **Established Name:** Teriparatide (rDNA origin) Injection **Description of Supplement:** This supplemental new drug application provides for revisions to your Medication Guide for FORTEO, consistent with our February 14, 2013, REMS modification notification letter. The purpose of the revisions is to more effectively communicate the risk of osteosarcoma. Note that only the package insert is posted on the Drugs@FDA website. The MG is attached to this supplement in DARRTS. ***The last approved User Manual labeling is from NDA 021318/S-026, approved 08/10/2011.**
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING** **ANDA#/Supplement# (S-000 if original):** Click here to enter text. **Supplement Approval Date:** Click here to enter text. **Proprietary Name:** Click here to enter text. **Established Name:** Click here to enter text. **Description of Supplement:**

☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** Click here to enter text.

☒ **OTHER (Describe):**

- An SLC notification letter was issued on 1/25/18. The applicant submitted a rebuttal to the SLC request. The SLC is still in the discuission period as of 6/5/18.

  Since FORTEO was approved on November 26, 2002, we have become aware of new safety information about the serious risk of osteosarcoma with the drug class of which FORTEO is a member. This information was obtained from the data of a recently approved product, Tymlos (abaloparatide). Teriparatide is a parathyroid hormone (PTH) analog which acts through the PTH1 receptor. Abaloparatide is a parathyroid hormone related protein (PTHrP) analog that acts through the same PTH1 receptor. The data indicated that osteosarcoma develops in rats with abaloparatide use, in the same manner as the osteosarcoma seen with teriparatide. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.
- The REMS supplement S-051, approved on 4/27/17, provides to eliminate the requirement for the approved REMS for Forteo. The approval eliminates the communication plan and the medication guide from the REMS requirement. Medication guide is maintained as part of approved labeling.
- The chemistry supplements S-037, S-038, S-039, S-040, S-041, S-042, S-043, S-044, and S-050 do NOT affect labeling.

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **YES**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **YES**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments:

The following deficiency comments will be issued

a. (b) (4)

b.

c. Add the following subsection:

(b) (4) Osteosarcoma

Patients should be made aware that in rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bones tumor) that was dependent on dose and treatment duration.

d. DESCRIPTION

iv. 1st sentence: Revise to read "Teriparatide injection, USP contains chemically synthesized human parathyroid hormone (1-34), and is also called hPTH (1-34).

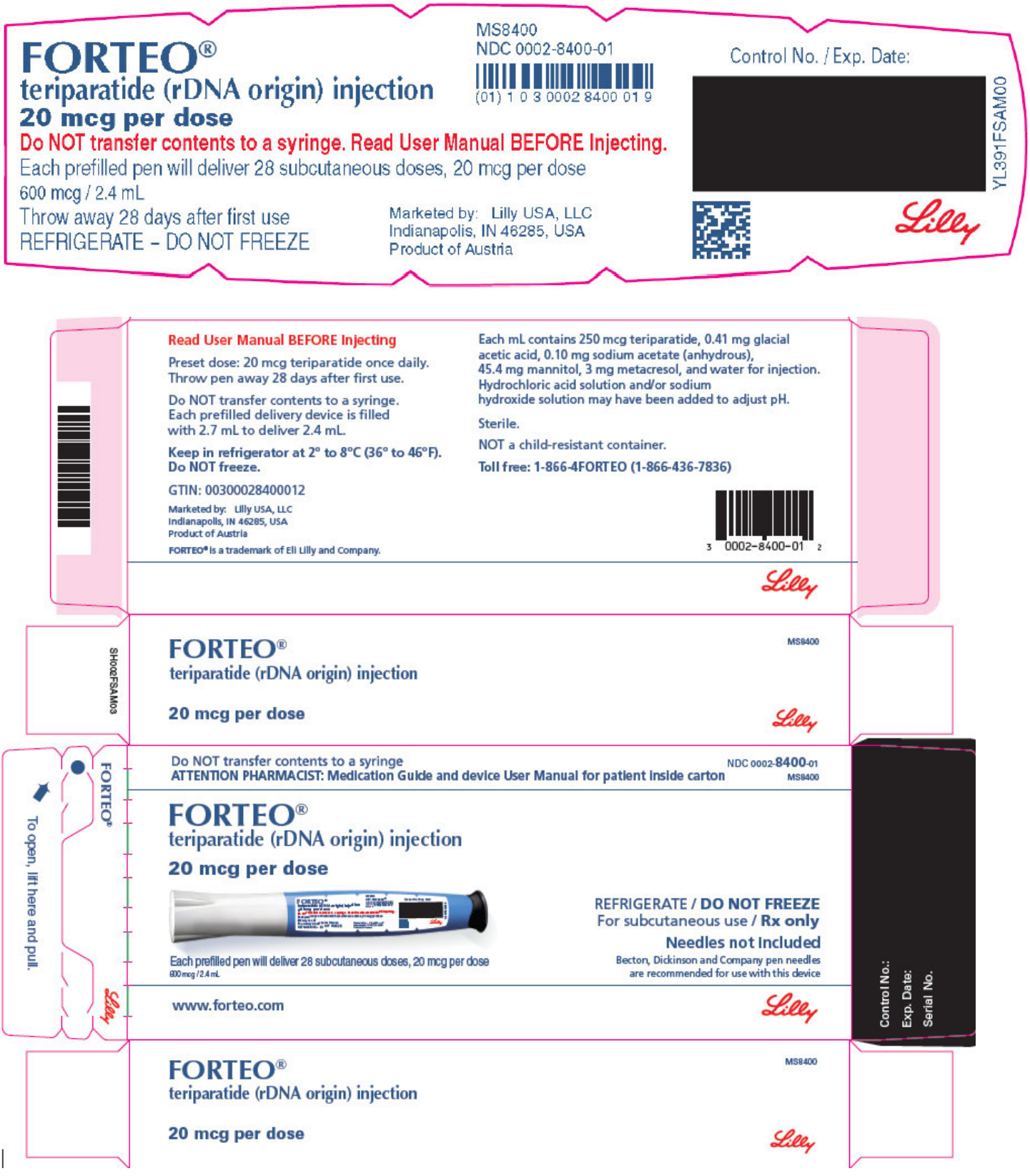
v. Include the statement "Teriperitide is manufactured chemical synthesis." prior to the sentenance "Teriparatide injection, USP is supplied as a sterile, colorless, clear…"

vi. You are requested to petition the United States Pharmacopeia (USP) to update the monograph for Teriparatide to either remove reference to the recombinant source of Teriparatide or add chemical synthesis as a second source.

Refer to section 3.4 United States Pharmacopeia and Pharmacopeia Forum (PF) for additional information regarding the DESCRIPTION section.

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: DARRTS NDA 021318 AR-12 submitted 11/6/13 for container label and AR-17 submitted 11/8/17 for carton labeling]



3.4 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

The USP was searched on 6/26/2018.

Table 2: USP				
	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Official Monograph	YES	[redacted]	Teriparatide Injection	**Packaging and Storage**: (b) (4) [redacted] protected from light, at a temperature of 2°–8°. The Injection is not to be frozen. **Labeling**: Label it to indicate that the material has been produced by methods based on recombinant DNA technology.
Pending Monograph Proposed	YES	8/1/2018	Teriparatide Injection	No updates from above.

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling and labels? **YES**

Reviewer Comments:

- The NDA is manufactured using a strain of E. coli modified by recombinant DNA technology. Apotex's drug product seems to be manufactured by chemical synthesis. The NDA had a descriptor "rDNA origin" in the established name to designate that the drug product is manufactured by recombinant DNA technology. The established name is teriparatide injection per Chemistry Review #1 found under the NDA in Drugs@FDA dated 11/26/2002.
- We note the NDA product already includes "rDNA origin" in the labeling as shown below: However, this subject ANDA would not contain a similar labeling statement as the applicant's product is chemically synthesized. The following is a comparison of the information under the DESCRIPTION section of the PI:
  NDA RLD: FORTEO (teriparatide [rDNA origin] injection) contains recombinant human parathyroid hormone (1-34), and is also called rhPTH (1-34). It has an identical sequence to the 34 N-terminal amino acids (the biologically active region) of the 84-amino acid human parathyroid hormone.
  Subject ANDA: Teriparatide injection, USP contains a human parathyroid hormone (1-34), and is also called rhPTH (1-34). It has an identical sequence to the 34 N-terminal amino acids (the biologically active region) of the 84-amino acid human parathyroid hormone.

The completed chemistry review states the following:

DESCRIPTION section

Is the information accurate? ☒ Yes ☐ No
If "No," explain.

Is the drug product subject of a USP monograph? ☒ Yes ☐ No
If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

(b) (4) [redacted] **The firm will be asked to petition the USP requesting that the monograph for this drug substance be updated similarly to remove reference to the Teriparatide source or add chemical synthesis as a second source.**

List of Deficiencies:

1. You are requested to petition the United States Pharmacopeia (USP) to update the monograph for Teriparatide to either remove reference to the recombinant source of Teriparatide or add chemical synthesis as a second source.

FYI, the following is stated in the ANDA 208569 chemistry review:

DESCRIPTION section

Is the information accurate? ☐ Yes ☒ No

If "No," explain.

The firm included the statement (b) (4) (b) (4) (b) (4) **"Teriparatide is manufactured by chemical synthesis." This is acceptable and the annotated comparison document is assumed to be in error.** (b) (4)

Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

Although there is no official USP DP monograph, there is one in draft form in the USP-PF. However, an official USP DS monograph is current.

The firm modified the text of the Description section to (b) (4) **state that the Teriparatide is synthesized by a synthetic process. The firm will be asked to petition the USP requesting that the monograph for this drug substance be updated similarly to remove reference to the Teriparatide source or add chemical synthesis as a second source.**

Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer.

The subject ANDA does not have the statement "Teriperitide is manufactured chemical synthesis." under the DESCRIPTION section. We will request that they add it.

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 6/26/2018.

Table 3 provides Orange Book patents for the Model Labeling NDA 021318 and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling

Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
6770623	Dec 8, 2018	U-982	A method of treating osteoporosis	III	12/29/17	None

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
6977077	Aug 19, 2019	U-982 U-994	A method of treating osteoporosis Method of treatment of osteoporis wherein the osteoporosis is steroid-induced	III		None
7144861	Dec 8, 2018			III		None
7163684	Aug 19, 2019	U-983 U-994	Method of treating osteoporosis in a post-menopausal woman at risk for fracture Method of treatment of osteoporis wherein the osteoporosis is steroid-induced	III		None
7351414	Aug 19, 2019	U-984 U-994	Method for the treatment of a woman with osteoporis and at risk for bone fracture Method of treatment of osteoporis wherein the osteoporosis is steroid-induced	III		None
7517334	Mar 25, 2025			IV		None
7550434	Dec 8, 2018	U-982	A method of treating osteoporosis	III		None

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments:

Applicant notifed the Agency on 4/5/18 about the following litigation notice:

Re: PATENT AMENDMENT — Notice of Litigation for U.S. Patent Number No. 7,517,334
ANDA No. 211097: Teriparatide Injection, USP, 20 mcg/dose (600 mcg/2.4 ml)

Dear Sir or Madam:

Apotex is hereby providing notice of litigation for US Patent Number 7,517,334 (Civil Action No. 1:18-cv-1037; United States District Court, Southern District of Indiana, Indianapolis Division) brought prior to the expiry of the 45 day period commencing on the patent holder's receipt date of Apotex's notice of patent certification. A copy of the pertinent information surrounding the notice of litigation is provided in Section 1.3.5.2.

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter "Carve-out" or "None")
NA					

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments:

NA

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**
Are there changes to the manufacturer/distributor/packer statements? **NO**
If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Each mL contains 250 mcg teriparatide (corrected for acetate, chloride, and water content), 0.41 mg glacial acetic acid, 0.1 mg sodium acetate (anhydrous), 45.4 mg mannitol, 3 mg Metacresol, and Water for Injection. In addition, hydrochloric acid solution 10% and/or sodium hydroxide solution 10% mayhave been added to adjust the product to pH 4.	Each mL contains 250 mcg teriparatide (corrected for acetate, chloride, and water content), 0.41 mg glacial acetic acid, 0.1 mg sodium acetate (anhydrous), 45.4 mg mannitol, 3 mg Metacresol, and Water for Injection. In addition, hydrochloric acid solution 10% and/or sodium hydroxide solution 10% mayhave been added to adjust the product to pH 4.	**No changes**

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	**Currently Proposed**	**Assessment**

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
16.1 HOW SUPPLIED The teriparatide injection, USP delivery device (pen) is available in the following package size: • 2.4 mL prefilled delivery device NDC 60505-6188-0. **16.2 STORAGE AND HANDLING** • The teriparatide injection, USP delivery device should be stored under refrigeration at 2° to 8°C (36° to 46°F) at all times. • Recap the delivery device when not in use to protect the cartridge from physical damage and light. • During the use period, time out of the refrigerator should be minimized; the dose may be delivered immediately following removal from the refrigerator. • Do not freeze. Do not use teriparatide injection, USP if it has been frozen.	**16.1 HOW SUPPLIED** The teriparatide injection, USP delivery device (pen) is available in the following package size: • 2.4 mL prefilled delivery device NDC 60505-6188-0. **16.2 STORAGE AND HANDLING** • The teriparatide injection, USP delivery device should be stored under refrigeration at 2° to 8°C (36° to 46°F) at all times. • Recap the delivery device when not in use to protect the cartridge from physical damage and light. • During the use period, time out of the refrigerator should be minimized; the dose may be delivered immediately following removal from the refrigerator. • Do not freeze. Do not use teriparatide injection, USP if it has been frozen.	**No changes**
(b) (4)		

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Container/Carton: Marketed by: Apotex Corp. Weston, Florida 33326 Product of Canada **Insert labeling:** Marketed by: Apotex Corp. 2400 N. Commerce Parkway, Weston, FL 33326 U.S.A.	**Container/Carton:** Marketed by: Apotex Corp. Weston, Florida 33326 Product of Canada **Insert labeling:** Marketed by: Apotex Corp. 2400 N. Commerce Parkway, Weston, FL 33326 U.S.A.	**No changes**

5. COMMENTS FOR OTHER REVIEW DISCIPLINES

DESCRIBE QUESTIONS/ISSUE(S) SENT TO AND/OR RECEIVED FROM OTHER DISCIPLINE (E.G., OPQ, OB) REVIEWER(S):

Reviewer Comments:

The following information is from the completed chemistry review:

Labeling & Package Insert

DESCRIPTION section

Is the information accurate? ☒ Yes ☐ No
If "No," explain.

Is the drug product subject of a USP monograph? ☒ Yes ☐ No
If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

(b) (4)

The firm will be asked to petition the USP requesting that the monograph for this drug substance be updated similarly to remove reference to the Teriparatide source or add chemical synthesis as a second source.

HOW SUPPLIED section

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☒ Yes ☐ No ☐ N/A

If "No," explain.

For OTC Drugs and Controlled Substances: N/A

For solid oral drug products, only: drug product length(s) of commercial batch(es): N/A

Describe issue(s) sent to and/or received from the OGD Labeling Reviewer: None

List of Deficiencies:

1. You are requested to petition the United States Pharmacopeia (USP) to update the monograph for Teriparatide to either remove reference to the recombinant source of Teriparatide or add chemical synthesis as a second source.

The following issue was created for the chemist on 6/26/18:

We would like to let you know that we are issuing the following comments, which also include your comment about petitioning the USP that was noted in your review. Please let me know if you have any questions or concerns.

- PRESCRIBING INFORMATION
  a. (b) (4)
  b. DESCRIPTION
     i. 1st sentence: Revise to read "Teriparatide in jection, USP contains chemically synthesized human parathyroid hormone (1-34), and is also called hPTH (1-34).
     ii. Include the statement "Teriperitide is manufactured chemical synthesis." prior to the sentenance "Teriparatide injection, USP is supplied as a sterile, colorless, clear…"
     iii. You are requested to petition the United States Pharmacopeia (USP) to update the monograph for Teriparatide to either remove reference to the recombinant source of Teriparatide or add chemical synthesis as a second source.

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item "Final, Draft, or "NA". If you enter "NA" under the second column, you do NOT need to enter "NA" for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Draft	1 pen	3/20/18	Satisfactory
Blister	NA	Click here to enter text.	Click here to enter text.	Click here to enter text.
Carton	Draft	1 pen/carton	3/20/18	Satisfactory
(Other – specify)	NA	Click here to enter text.	Click here to enter text.	Click here to enter text.
Table 9: Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	03/2018	3/20/18	Revise
Medication Guide	Draft	March 2018	3/20/18	Satisfactory
User Manual	Draft	March, 2018	3/20/18	Satisfactory
SPL Data Elements	NA	9/2017	3/20/18	Satisfactory

Katherine Won

Digitally signed by Katherine Won
Date: 6/27/2018 03:20:26PM
GUID: 508da6ea00027496d7a9d068086637ee

Lisa Kwok

Digitally signed by Lisa Kwok
Date: 6/27/2018 03:23:20PM
GUID: 508da70800028c5cddf24c815a550d26

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	2/9/18
ANDA Number(s)	211097
Review Number	1
Applicant Name	Apotex Inc.
Established Name & Strength(s)	Teriparatide Injection, 600 mcg/2.4 mL (250 mg/mL) in prefilled delivery device (pen)
Proposed Proprietary Name	None
Submission Received Date	12/29/17 (Original)
Labeling Reviewer	Katherine Won
Labeling Team Leader	Lisa Kwok

Review Conclusion

☐ ACCEPTABLE – No Comments

☐ ACCEPTABLE – Include Post Approval Comments

☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant

☐ Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Applicant

†Theme - Choose an item.

Justification for Major Deficiency - Choose an item.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List ☐ Yes ☒ No

Acceptable for Filing ☐ Yes ☒ No (Filing review on hold as of 2/9/18)

TABLE OF CONTENTS

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on February 9, 2018 based on your submissions dated December 29, 2017:

1. CONTAINER LABEL

   [redacted] (b) (4) We refer you to the reference listed drug (RLD).

2. CARTON LABELING
   a. [redacted] (b) (4) Refer to the RLD.
   b. Please confirm that the lot number and expiration date will appear on the carton labeling.

3. MEDICATION GUIDE
   Add the phonetic spelling of the established name in the Title in accordance with 21 CFR 208.20(b)(1).

4. USER MANUAL
   a. Throughout the User Manual labeling, please revise to use red text to increase prominence of the important information (e.g., paragraph beginning with "The teriparatide injection delivery device contains…", "Do not transfer teriparatide injection…", "Wash your hands…" among other things) in accordance with the RLD.
   b. We recommend that you include the title of each step (e.g., 1 Pull off pen cap, 2 Attach new needle, etc.) to be inside the box to clearly delineate each step. We refer you to the RLD.
   c. Troubleshooting section: Please add a blue colored boxing around the paragraph beginning with "You can prevent this problem by always using a NEW needle…" to increase prominence of the important information and to be in accordance with the RLD.
   d. Include the revision date.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

NA

1.3 POST APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).
NA

2. LABELING REVIEW INFORMATION

2.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? YES

If Yes, please explain.

Entry title and description: Forteo/Forteo NDA 21318 has patient registry in the labeling which is NOT part of the REMS and is not required for approval for ANDAs.

An email was added on 3/3/16 regarding the Patient Registry for the innovator NDA 021318 which confirmed that the Patient Registry was created as part of a PMR for the RLD and not a part of REMS. Thus, the registry may be omitted from ANDA labeling.

Of note, for ANDA 208569, which was the first generic product submitted for Forteo, OGD Policy determined that the patient registry was created as part of a PMR for the RLD. Since DRISK has confirmed the registry is NOT part of the REMS, and it is part of the RLD's PMR, Policy is okay with ANDAs omitting reference to the registry.

Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? NO

If Yes, please explain.

Is the drug product listed in the Susceptibility Test Interpretive Criteria web page? NO

Is there a mid-review cycle meeting (MRCM) task in Platform? Or, if filing review is not complete, was there a Product Development or Pre-ANDA Submission Project under the ANDA Program? NO

If **YES** is answered, there is a potential for holding MRCM. What is the proposed agenda from DLR for MRCM?

2.2 MODEL LABELING

2.2.1 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING** *(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA RLD information.)* **NDA#/Supplement# (S-000 if original):** 021318/S-036* **Supplement Approval Date:** 8/30/2013 **Proprietary Name:** Forteo **Established Name:** Teriparatide (rDNA origin) Injection **Description of Supplement:** This supplemental new drug application provides for revisions to your Medication Guide for FORTEO, consistent with our February 14, 2013, REMS modification notification letter. The purpose of the revisions is to more effectively communicate the risk of osteosarcoma. Note that only the package insert is posted on the Drugs@FDA website. The MG is attached to this supplement in DARRTS. ***The last approved User Manual labeling is from NDA 021318/S-026, approved 08/10/2011.**
☐ **MOST RECENTLY APPROVED ANDA RLD LABELING** **ANDA#/Supplement# (S-000 if original):** Click here to enter text. **Supplement Approval Date:** Click here to enter text. **Proprietary Name:** Click here to enter text. **Established Name:** Click here to enter text. **Description of Supplement:** Click here to enter text.
☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** Click here to enter text.
☒ OTHER (Describe): • The REMS supplement S-051, approved on 4/27/17, provides to eliminate the requirement for the approved REMS for Forteo. The approval eliminates the communication plan and the medication guide from the REMS requirement. Medication guide is maintained as part of approved labeling. • The chemistry supplements S-037, S-038, S-039, S-040, S-041, S-042, S-043, and S-044 do NOT affect labeling.

2.2.2 MODEL CONTAINER LABELS

Model container/carton/blister labels (Source: DARRTS NDA 021318 AR-12 submitted 11/6/13 for container label and AR-17 submitted 11/8/17 for carton labeling)

2.3 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

The USP was searched on 1/18/2018.

Table 2: USP

	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Official Monograph	YES	[redacted]	Teriparatide Injection	**Packaging and** [redacted] (b) (4) . protected from light. at a temperature of 2°–8°. The Injection is not to be frozen. **Labeling**: Label it to indicate that the material has been produced by methods based on recombinant DNA technology.

Pending Monograph Proposed	YES	5/1/2018	Click here to enter text.	No updates from above.

- The NDA is manufactured using a strain of E. coli modified by recombinant DNA technology. Apotex's drug product seems to be manufactured by chemical synthesis. The NDA had a descriptor "rDNA origin" in the established name to designate that the drug product is manufactured by recombinant DNA technology. The established name is teriparatide injection per Chemistry Review #1 found under the NDA in Drugs@FDA dated 11/26/2002.
- We note the NDA product already includes "rDNA origin" in the labeling as shown below: However, this subject ANDA would not contain a similar labeling statement as the applicant's product is chemically synthesized. The following is a comparison of the information under the DESCRIPTION section of the PI:
  NDA RLD: FORTEO (teriparatide [rDNA origin] injection) contains recombinant human parathyroid hormone (1-34), and is also called rhPTH (1-34). It has an identical sequence to the 34 N-terminal amino acids (the biologically active region) of the 84-amino acid human parathyroid hormone.
  Subject ANDA: Teriparatide injection, USP contains a human parathyroid hormone (1-34), and is also called rhPTH (1-34). It has an identical sequence to the 34 N-terminal amino acids (the biologically active region) of the 84-amino acid human parathyroid hormone.
- As of the date of this review, the chemistry review is pending.

2.4 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 1/18/2018.

Table 3 provides Orange Book patents for the Model Labeling NDA 021318 and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 3: Impact of Model Labeling Patents on ANDA Labeling

Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
6770623	Dec 8, 2018	U-982	A method of treating osteoporosis	III	12/29/17	None
6977077	Aug 19, 2019	U-982 U-994	A method of treating osteoporosis Method of treatment of osteoporis wherein the osteoporosis is steroid-induced	III		None
7144861	Dec 8, 2018			III		None
7163684	Aug 19, 2019	U-983 U-994	Method of treating osteoporosis in a post-menopausal woman at risk for fracture Method of treatment of osteoporis wherein the osteoporosis is steroid-induced	III		None
7351414	Aug 19, 2019	U-984 U-994	Method for the treatment of a woman with osteoporis and at risk for bone fracture Method of treatment of osteoporis wherein the osteoporosis is steroid-induced	III		None
7517334	Mar 25, 2025			IV		None
7550434	Dec 8, 2018	U-982	A method of treating osteoporosis	III		None

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling

Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
NA					

2.5 MANUFACTURING FACILITY

Table 5 provides a description of the drug product manufacturing facility.

Table 5: Comparison of Manufacturer/Distributor/Packer Labeling Statements		
Name and Address of Facility ANDA Manufacturer/Distributor/Packer	Name and Address on ANDA Container/Carton	Name and Address on ANDA Prescribing Information
(b) (4)	**Container/Carton:** Marketed by: Apotex Corp. Weston, Florida 33326 Product of Canada	**Insert labeling:** Marketed by: Apotex Corp. 2400 N. Commerce Parkway, Weston, FL 33326 U.S.A.

3. ASSESSMENT OF ANDA LABELING AND LABELS

The results for each material reviewed in this section provide the basis for the labeling comments to the applicant.

Is this product Rx or OTC? Please check one.

☒ Rx Product (If Rx, skip 3.2 OTC DRUG PRODUCT and go to 3.3 CONTAINER/CLOSURE.)
☐ OTC Product (If OTC, skip 3.1 RX DRUG PRODUCT and go to 3.3 CONTAINER/CLOSURE)

3.1 RX (PRESCRIPTION) DRUG PRODUCT

3.1.1 RX: PRESCRIBING INFORMATION

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **YES**
Is the established name the same as the USP monograph title appearing in section 2.3? **YES**
Is the established name the same as the RLD's nonproprietary name? **NO but see information below.**
If YES is answered to both questions, then continue with review.
If NO is answered to EITHER questions, then advise firm to revise to the USP name (if applicable) and include justification language under Reviewer Comments.
Does the Model Labeling have combined insert labeling for multiple NDAs or dosage forms? **NO**
Is the applicant's "patent carve out" acceptable? **NA**
Is the applicant's "exclusivity carve out" acceptable? **NA**
Is the Manufacturer statement acceptable? **YES**

Reviewer Comments:

- The NDA is manufactured using a strain of E. coli modified by recombinant DNA technology. Apotex's drug product seems to be manufactured by chemical synthesis. The NDA had a descriptor "rDNA origin" in the established name to designate that the drug product is manufactured by recombinant DNA technology. The established name is teriparatide injection per Chemistry Review #1 found under the NDA in Drugs@FDA dated 11/26/2002.
- Patient Registry: DRISK confirmed the registry is NOT part of the REMS, and it is part of the RLD's PMR. Policy is okay with ANDAs omitting reference to the registry. The subject NDA has deleted the information regarding the registry from subsections 5.1 (b) (4) Potential Risk of Osteosarcoma (b) (4) from their PI.

Prescribing Information is found satisfactory.

3.1.1.1 RX: DESCRIPTION

We reviewed the DESCRIPTION section for accuracy (with input from the chemistry review, if appropriate) and acceptability from a Labeling perspective. We compared the list of inactive ingredients contained in this product to those contained in the Model Labeling.

Table 6: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling Inactive Ingredients	**ANDA Labeling Inactive Ingredients**
0.41 mg glacial acetic acid, 0.1 mg sodium acetate (anhydrous), 45.4 mg mannitol, 3 mg Metacresol, and Water for Injection. In addition, hydrochloric acid solution 10% and/or sodium hydroxide solution 10% may have been added to adjust the product to pH 4	0.41 mg glacial acetic acid, 0.1 mg sodium acetate (anhydrous), 45.4 mg mannitol, 3 mg Metacresol, and Water for Injection. In addition, hydrochloric acid solution 10% and/or sodium hydroxide solution 10% may have been added to adjust the product to pH 4

Reviewer Assessment:

Are the inactive ingredients accurate? **PENDING CHEMISTRY REVIEW**
For products required to be qualitatively and quantitatively the same in regards to active and inactive ingredients (Q1/Q2), are the ANDA ingredients consistent with the Model Labeling? **YES**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **NO**
Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling? **NA**
If the labeling includes a "Does not contain…" statement, is it acceptable/allowed? **NA** Has the statement been verified by chemistry? **NA**

Reviewer Comments:
From 12/29/17 submission 3.2.P.1 QOS:

Strength (Label Claim):		250 mcg/mL (600 mcg/2.4mL)				
Component Grade	**Quality Standard**	**Function**	**Quantity per mL**	**RLD FORTEO™ (each mL contains)[1]**	**Quantity per vial (mg)**	**% w/v total unit dose**
Teriparatide	In-House	Active	0.250 mg	(b) (4)		
Glacial Acetic Acid	USP	(b) (4)	0.41 mg			
Sodium Acetate (Anhydrous)	USP		0.1 mg			
Mannitol	USP		45.4 mg			
Metacresol	USP		3 mg			
Water for Injection	USP-NF		q.s.			
Sodium Hydroxide	NF	pH Adjuster	q.s. to pH			
Hydrochloric Acid	NF	pH Adjuster	q.s. to pH			
(b) (4)						
TOTAL:						**100.00%**

[1] Composition information is taken from the RLD labeling, FORTEO™ (teriparatide [rDNA origin]) Injection, provided in section 1.14.3. and is considered to be Q1/Q2 with the RLD, FORTEO™ (teriparatide [rDNA origin]) Injection, 600mcg/2.4mL – NDA number 021318.

The inactive ingredients appear to be accurate based on the information submitted by the applicant. We will verify this information once the chemistry review is complete.

3.1.1.2 RX: HOW SUPPLIED/STORAGE AND HANDLING

We compared the descriptions of the model product to the ANDA finished product. Product differences, such as scoring configuration and storage conditions, are highlighted in Table 7 and will be referred to the appropriate review discipline for evaluation.

Table 7: Comparison of Model Labeling to ANDA Labeling

Model Labeling	PI: **16.1 How Supplied** The FORTEO delivery device (pen) is available in the following package size: • 2.4 mL prefilled delivery device NDC 0002-8400-01 (MS8400). **16.2 Storage and Handling** • The FORTEO delivery device should be stored under refrigeration at 2° to 8°C (36° to 46°F) at all times. • Recap the delivery device when not in use to protect the cartridge from physical damage and light. • During the use period, time out of the refrigerator should be minimized; the dose may be delivered immediately following removal from the refrigerator. • Do not freeze. Do not use FORTEO if it has been frozen. MG: Keep your FORTEO delivery device in the refrigerator between 36° to 46°F (2° to 8°C). • Do not freeze the FORTEO delivery device. Do not use FORTEO if it has been frozen.
ANDA Labeling	PI: **16.1 HOW SUPPLIED** The teriparatide injection, USP delivery device (pen) is available in the following package size: • 2.4 mL prefilled delivery device NDC 60505-6188-0. **16.2 STORAGE AND HANDLING** • The teriparatide injection, USP delivery device should be stored under refrigeration at 2° to 8°C (36° to 46°F) at all times. • Recap the delivery device when not in use to protect the cartridge from physical damage and light. • During the use period, time out of the refrigerator should be minimized; the dose may be delivered immediately following removal from the refrigerator. • Do not freeze. Do not use teriparatide injection, USP if it has been frozen. (b) (4)

Reviewer Assessment:

Are all of the submitted labels and labeling reflected in the How Supplied section? **YES**
Is the description (e.g., scoring, color, imprint) of the finished product in the HOW SUPPLIED section consistent with the information in Module 3.2.P.5.1 for Drug Product Specification? **NA**
Does the ANDA require the same color coding as the Model Labeling? **NO**
Is there any difference in scoring configuration between the ANDA and the Model Labeling? **NA**
Are the packaging sizes and configurations acceptable as compared to the Model Labeling? **YES**
If the packaging configuration is different than the Model Labeling, does it require addition or deletion of labeling statements? **NA**

Is the storage or dispensing statement acceptable as compared to the Model Labeling? **YES**
Is the storage or dispensing statement acceptable as compared to the USP? **YES**

Reviewer Comments:
No further comments.

3.1.2 RX: MEDICATION GUIDE

Is Medication Guide required? **YES**
If YES go to Reviewer Assessment below, if NO go to section 3.1.3.

Reviewer Assessment:

Was Medication Guide submitted? **YES**
Is the Medication Guide same as the model labeling, except for allowable differences? **YES**
Does the Medication Guide meet the requirements of 21 CFR 208.20? **YES**
Has the Applicant committed to provide a sufficient number of medication guides? **YES**
Is the phonetic spelling of the proprietary or established name present? **NO**
Is FDA 1-800-FDA-1088 phone number included? **YES**

Reviewer Comments:
The following information was provided in the 12/29/17 labeling QbR:

2. **How will the Medication Guide be provided with the product and how many will accompany each package size?**

   - The medication guide will be provided in each carton of product as part of the product insert.

3. **Are the conditions of 21 CFR 208.20 met with regard to proper Medication Guide formatting?**

   - The content and format of the final printed mediation guide meet all the applicable conditions specified under 21 CFR 208.20.

Patient Registry: DRISK confirmed the registry is NOT part of the REMS, and it is part of the RLD's PMR. Policy is okay with ANDAs omitting reference to the registry. The subject NDA has deleted the information regarding the registry from the MG.

We will issue the following comment:

- Add the phonetic spelling of the established name in the Title in accordance with 21 CFR 208.20(b)(1).

3.1.3 RX: OTHER PATIENT LABELING

Are other patient labeling required? **YES**
If YES go to Reviewer Assessment below, if NO go to section 3.1.4.

Reviewer Assessment:

Was other patient labeling submitted? **YES**
Is the patient labeling the same as the model labeling, except for allowable differences? **NO**

Reviewer Comments:
We will issue the following comments:

a. Throughout the User Manual labeling, please revise to use red text to increase prominence of the important information (e.g., paragraph beginning with "The teriparatide injection delivery device contains…", "Do not transfer teriparatide injection…", "Wash your hands…" among other things) in accordance with the RLD.
b. We recommend that you include the title of each step (e.g., 1 Pull off pen cap, 2 Attach new needle, etc.) to be inside the box to clearly delineate each step. We refer you to the RLD.
c. Troubleshooting section: Please add a blue colored boxing around the paragraph beginning with "You can prevent this problem by always using a NEW needle…" to increase prominence of the important information and to be in accordance with the RLD.
d. Include the revision date.

3.1.4 RX: CONTAINER LABEL

Was container label (other than Blisters) submitted? **YES**
(For BLISTER labels, go to section 3.1.5.)

We evaluated the container labels for the inclusion of all required statements and safety considerations.

Reviewer Assessment:

Is the established name acceptable? **YES**
Is title case used in expressing the established name? **YES**
Does labeling comply with Tall Man lettering recommendations found on FDA webpage? **NA**
Is container label too small to contain all required information? **YES** If yes, does the container meet the "too small" exemption found in 21 CFR 201.10(j)? **YES**

Are established name (proprietary name, if applicable) and strength the most prominent information on the Principal Display Panel? **YES**

Is the following information properly displayed?

Net quantity statement: **YES**
Route(s) of administration (other than oral): **NO but stated on the carton**
Warnings (if any) or cautionary statements (if any): **NO**
Medication Guide Pharmacist instructions per 21 CFR 208.24(d): **NO but stated on the carton labeling**
Controlled substance symbol: **NA**
Usual Dosage statement: **NO but stated on the carton labeling**
Product strength equivalency statement: **NA**
NDC: **YES**
Bar code per 21 CFR 201.25(c)(2): **See comment from applicant.**

Is the Manufacturer/Distributor/Packager statement acceptable? **YES**
For foreign manufacturers, does the labeling have the country of origin? **YES**
Are the required USP recommendations reflected on the label(s)? **YES**
Are the USP recommendations and/or differences in test methods (e.g., organic impurities, assay) reflected on the label(s)? **NA**
Is the storage or dispensing statement consistent with the How Supplied section of the insert? **YES**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **NO**
Are multiple strengths differentiated by use of different color or other acceptable means? **NA**
Are the labels of related products differentiated to avoid selection errors? **NA**
Does the ANDA require the same color coding as the Model Labeling? **NO**
Are requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100)? **YES**

Reviewer Comments:
The prefilled pen label could be considered a small label and a lot of the information such as inactive ingredients, and route of administration are displayed on the carton label.

(b) (4)

[redacted]

3.1.4.1 RX: CONTAINER LABEL FOR PARENTERAL SOLUTIONS

Is container for parenteral solution? **YES**
If YES go to Reviewer Assessment below, if NO go to section 3.1.4.2.

Reviewer Assessment:

Is the product strength expressed as total quantity per total volume followed by the concentration per milliliter (mL), as described in the USP, General Chapter <1> Injection? **NA**
If volume is less than 1 mL, is strength per fraction of a milliliter the only expression of strength? **NA**
Is the quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)? **No but stated on the carton labeling**

Reviewer Comments:

The product strength is expressed as "20 mcg per dose" which is the same as the RLD. USP Chapter 1 does NOT pertain to the strength and total volume for prefilled delivery device.

3.1.4.2 RX: CONTAINER LABEL FOR SOLID INJECTABLE

Is container for solid injectable? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.4.3.

Reviewer Assessment:

Is the strength in terms of the total amount of drug per vial? **CLICK HERE**
Are instructions for reconstitution and resultant concentration provided, if space permits? **CLICK HERE**
Is the quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)? **CLICK HERE**

Reviewer Comments:
None

3.1.4.3 RX: CONTAINER LABEL FOR PHARMACY BULK PACKAGE

Is container a Pharmacy Bulk Package (parenteral preparations for admixtures)? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.5.

Reviewer Assessment:

Is there a prominent, boxed declaration reading "Pharmacy Bulk Package – Not for Direct Infusion" on the principal display panel following the expression of strength? **CLICK HERE**
Does the container label include graduation marks? **CLICK HERE**
Does label contain the required information on proper aseptic technique including time frame in which the container may be used once it has been entered? **CLICK HERE**
Is the quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)? **CLICK HERE**

Reviewer Comments:
None

3.1.5 RX: UNIT DOSE BLISTER LABEL

Is container a Unit Dose Blister Pack? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.6.

Reviewer Assessment:

Does each blister include only one dosage unit (e.g., one tablet, one capsule)? **CLICK HERE**
Do proprietary name, established name, strength, bar code, and manufacturer appear accurately on each blister cell? **CLICK HERE**

Reviewer Comments:
None

3.1.6 RX: CARTON (OUTER OR SECONDARY PACKAGING) LABELING

Was carton labeling submitted? **YES**
If YES go to Reviewer Assessment below, if NO go to section 3.3.

Reviewer Assessment:

Are the answers to the Container Label questions the same for the Carton Labeling? **YES** If no, please explain the differences in the Reviewer Comments section.
If container is too small or otherwise unable to accommodate a label with enough space to include all required information, is all required information present on the carton labeling? **YES**

If country of origin is not on Container, does it appear on outer packaging labeling? **NA**

Reviewer Comments:

The barcode exists on the carton labeling.

We will issue the following comments:

a. [redacted] (b) (4)

b. Please confirm that the lot number and expiration date will appear on the carton labeling.

3.2 OTC (OVER THE COUNTER) DRUG PRODUCT

3.2.1 OTC: LABELING THAT INCLUDES DRUGS FACTS INFORMATION

Reviewer Assessment:

Is the patient labeling the same as the model labeling, except for allowable differences? **CLICK HERE**
Is Drug Facts Labeling format acceptable per 21 CFR 201.66? **CLICK HERE**
Does "Questions?" have a toll-free number no less than 6 pt. font size per 21 CFR 201.66(c)(9) or "1-800-FDA-1088" per 21 CFR 201.66 (c)(5)(vii)? **CLICK HERE**
Did firm submit a Labeling Format Information Table to evaluate the font size? **CLICK HERE**
Is the applicant's "patent carve out" acceptable? **CLICK HERE**
Is the applicant's "exclusivity carve out" acceptable? **CLICK HERE**
Is the established name for this ANDA acceptable? **CLICK HERE**
Is title case used in expressing the established name? **CLICK HERE**
Are established name (proprietary name, if applicable) and strength the most prominent information on the Principal Display Panel? **CLICK HERE**
Is the following information properly displayed?
- Pharmacological category: **CLICK HERE**
- Net quantity statement: **CLICK HERE**
- Route(s) of administration (other than oral): **CLICK HERE**
- Warnings (if any) or cautionary statements (if any): **CLICK HERE**
- NDC: **CLICK HERE**
- Bar code per 21 CFR 201.25(c)(2): **CLICK HERE**

Is the Manufacturer/Distributor/Packager statement acceptable? **CLICK HERE**
For foreign manufacturers, does the labeling have the country of origin? **CLICK HERE**
Are the required USP recommendations reflected in the labeling? **CLICK HERE**
Is the storage statement acceptable? **CLICK HERE**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **CLICK HERE**
Are multiple strengths differentiated by use of different color or other acceptable means? **CLICK HERE**
Are the labels of related products differentiated to avoid selection errors? **CLICK HERE**

Reviewer Comments:

Click here to enter text.

3.2.1.1 OTC: INACTIVE INGREDIENTS COMPARISON

We compared the list of inactive ingredients contained in this product to those contained in the Model Labeling.

Table 8: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling Inactive Ingredients	ANDA Inactive Ingredients

Table 8: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Click here to enter text.	Click here to enter text.

Reviewer Assessment:

Are the inactive ingredients information consistent with "Components and Composition" information as provided in Module 3.2.P.1? **CLICK HERE**
Are the inactive ingredients listed in alphabetical order? **CLICK HERE**
For products required/recommended to be qualitatively and quantitatively the same in regards to active and inactive ingredients (Q1/Q2), are the ANDA ingredients consistent with the Model Labeling? **CLICK HERE**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **CLICK HERE**
If the labeling includes a "Does not contain…" statement, is it acceptable/allowed? **CLICK HERE** Has the statement been verified by chemistry? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.2.1.2 OTC: HOW SUPPLIED AND STORAGE INFORMATION

We compared the descriptions of the model product to the ANDA finished product. Product differences, such as scoring configuration and storage conditions, are highlighted in Table 9 and will be referred to the appropriate review discipline for evaluation.

Table 9: Comparison of Model Labeling to ANDA finished product	
Model Labeling	Click here to enter text.
ANDA (enter source of information of product description on the right hand column; e.g., chemistry Review & date, Module 3.2.P.5.1)	Click here to enter text.

Reviewer Assessment:

Is the description (scoring, color and imprint) of the finished product consistent with the Drug Product Quality submission? **CLICK HERE**
Is there any difference in scoring configuration between the ANDA and the Model Labeling? **CLICK HERE**
Are the packaging sizes and configurations acceptable as compared to the Model Labeling? **CLICK HERE**
If the packaging configuration is different than the Model Labeling, does it require addition or deletion of labeling statements? **CLICK HERE**
Is the storage or dispensing statement acceptable as compared to the Model Labeling? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.2.2 OTC: OTHER PATIENT LABELING

Are other patient labeling required? **CLICK HERE**
If YES go to Reviewer Assessment below, if NO go to section 3.3.

Reviewer Assessment:

Was other patient labeling submitted? **CLICK HERE**
Is the patient labeling the same as the model labeling, except for allowable differences? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.3 CONTAINER/CLOSURE

Reviewer Assessment:

Describe container closure (e.g., 30s CRC, 100s non-CRC) and cite source of information in **Reviewer Comments** text box.

Does the container require a child-resistant closure (CRC) as described in the Poison Prevention Act and regulations? **NO**

Are the tamper evident requirements met for OTC and Controlled Substances? **NA**

For ophthalmic products:

Does this ophthalmic product cap color match the American Academy of Ophthalmology (AAO) packaging color-coding scheme? **NA**

For parenteral products:

Is there text on the cap/ferrule overseal of this injectable product? **NA**

If YES, does text comply with the recommendations in USP General Chapter <7> Labeling? **NA**

What is the cap and ferrule color? **NA**

NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate.

Reviewer Comments:

Per 12/27/17 submission 3.2.P.7 QOS:

(b) (4)

[redacted]

1 Page has been withheld in full as b4 (CCI/TS) immediately following this page

3.4 CALCULATIONS FOR CONTENTS IN LABELING

Is calculation of ingredient(s) required? **NO**
If YES, go to Table 10 and Reviewer Assessment below, if NO go to section 3.5.

We verified the calculation on the following content.

Table 10: Ingredients		
Ingredient	**Stated Content**	**Location of the Information**
Click here to enter text.	Click here to enter text.	Click here to enter text.

(Note: For Rx products, if chemistry review follows the MOU, chemistry reviewer will verify the accuracy of the active and inactive ingredient amount(s) if information is in the DESCRIPTION and HOW SUPPLIED sections for all products, and additionally, DOSAGE AND ADMINISTRATION section for parenteral products. See Chemistry-Labeling MOU, Appendix A, Miscellaneous section for discussion on calculations.)

Reviewer Assessment:

Does the chemistry review follow the Chemistry/Labeling MOU? **CLICK HERE**
Are the stated contents in the table above acceptable? **CLICK HERE**
Aluminum content in small volume parenterals, large volume parenterals, and pharmacy bulk packages, which are used in TPNs, need to be in the labeling per 21 CFR 201.323.
Did the chemistry reviewer verify the aluminum content? **CLICK HERE**
Are the labeling requirements met per 21 CFR 201.323? **CLICK HERE**

Reviewer Comments:
None

3.5 STRUCTURED PRODUCT LABELING (SPL) DATA ELEMENTS

Was SPL submitted? **YES**

Table 11: ANDA Tablet/Capsule Size and Imprint		
Tablet/Capsule Strength	**ANDA Tablet/Capsule Size (mm) and imprint code from SPL**	**ANDA Tablet/Capsule Size (mm) and imprint code (Cite source of information such as the chemistry review that follows the MOU, Product Specification in 3.2.P.5.1, Commercial Batch Record in 3.2.P.3.3. etc.)**
NA		

Reviewer Assessment:

For solid oral dosage forms: Do size and imprint code from the SPL data elements match the information provided in the quality submission? **NA**
Are all the other data elements (strength, inactive ingredients, product characteristics, packaging etc.) consistent with the information submitted in the ANDA labeling? **YES**

Reviewer Comments:
SPL data elements are found satisfactory.

4. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

Reviewer Comments:
None

5. SPECIAL CONSIDERATIONS

None

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 12 and 13 provide a summary of recommendations for each labeling piece analyzed in this review.

Table 12: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Draft	1 pen	12/29/17	Revise
Blister	NA	Click here to enter text.	Click here to enter text.	Click here to enter text.
Carton	Draft	1 pen/carton	12/29/17	Revise
(Other – specify)	NA	Click here to enter text.	Click here to enter text.	Click here to enter text.
Table 13 Review Summary of Prescribing Information and Patient Labeling				

	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Draft	09/2017	12/29/17	Satisfactory
Medication Guide	Draft	September 06, 2017	12/29/17	Revise
User Manual	Draft	Literature revised XXX xx, 20xx	12/29/17	Revise
SPL Data Elements	NA	9/2017	12/29/17	Satisfactory

Katherine Won

Digitally signed by Katherine Won
Date: 2/09/2018 04:33:39PM
GUID: 508da6ea00027496d7a9d068086637ee

Lisa Kwok

Digitally signed by Lisa Kwok
Date: 2/10/2018 09:22:14PM
GUID: 508da70800028c5cddf24c815a550d26

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 211097

MEDICAL REVIEW(s)

CLINICAL CONSULTATION REVIEW
Division of Clinical Review (DCR)
Office of Safety and Clinical Review (OSCE), Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)
Teriparatide Injection, USP, 600 mcg/2.4 mL

Drug Product	Teriparatide injection, synthetic, 600 mcg/2.4 mL (250 mcg/mL)
ANDA#/Applicant	211097, Apotex, Inc./ (b) (4)
RLD# **Approval Date** **Sponsor**	Forteo (teriparatide [rDNA origin] injection) Subcutaneous Injection, 600 mcg/2.4 mL (250 mcg/mL) NDA 021318 Approved 11/26/2002 Eli Lilly and Company
Clinical Primary Reviewer	Tracy Franzos, MD, MS Medical Officer
Clinical Secondary Reviewer	Raquel Tapia, MD Medical Officer
Tertiary Reviewer	William Chong, MD Associate Director for Clinical Affairs (OGD)
Subject	Review of Applicant Response to Clinical Deficiencies conveyed in Complete Response (CR) Letter dated 10/26/2018
Date of Submission(s)	12/29/2017 – Original ANDA submission 10/15/2020 – CR Response 3/9/2021 – Clinical Information Request (IR) Response 4/15/2021 – Clinical IR Response
Date of Completion	6/10/2021
Conclusion	DCR concludes that the design difference between the proposed generic drug product and the RLD are acceptable.

1 Introduction and Background

This review evaluates Apotex's (Applicant) response to clinical deficiencies conveyed in Complete Response Letter (CRL) dated 10/26/2018,[1] related to the delivery device constituent part/user interface of the proposed drug-device combination product teriparatide injection, ANDA 211097. This review also includes the Division of Medical Errors and Prevention's (DMEPA) review of the comparative use human factor (HF) study submitted with the Applicant's response.

The reference listed drug (RLD) is Forteo (teriparatide, rDNA origin), Subcutaneous Injection, 600 mcg/2.4 mL (250 mcg/mL), NDA 021318, by Eli Lilly and Company, approved 11/26/2002,

[1] A211097, teriparatide injection, A211097N000DPM-Complete-Response-01, uploaded by Aaron Sigler on 10/26/2018 http://panorama.fda.gov/document/view?versionID=5bd37b8d01110e09b9e20967ff6ae700

for the treatment of osteoporosis in postmenopausal women, men with primary or hypogonadal osteoporosis, and men and women with sustained systemic glucocorticoid therapy at high risk of fracture.[2] The original Forteo (b) (4) (IndePEN), a slim cylindrical pen, was redesigned in 2008 after difficulties with its use were reported by female patients (70+ years of age). The redesigned (second generation) (b) (4) simplified operating steps and visual cues to make the device easier to operate; it was approved on 6/25/2008, under NDA 021318/S-016.[3] See Appendix Figure A with pictures of the original Forteo device (IndePEN) and the current Forteo device.

The proposed teriparatide (b) (4) is a slim cylindrical (b) (4) pen, similar in external design to the original RLD device. See Appendix Figure B. Prior to ANDA submission, on 7/12/2017, the Applicant submitted Controlled Correspondence (CC) #16343726, requesting evaluation of the (b) (4) for substitutability with the RLD.[4] The CC included a threshold analysis (TA) and the results of a formative human factors (HF) study comparing the proposed (b) (4) and the RLD Forteo (second generation). CC #16343726 was reviewed by the Division of Therapeutic Performance (DTP) in the Office of Research and Standards (ORS) who raised concerns that identified differences in some external critical design attributes, i.e., (b) (4) may generate usability issues when substituted for the RLD and recommended the Applicant submit a pre-ANDA meeting request for discussion of the human factors study.[5] Following this CC, the (b) (4) was redesigned to incorporate some changes, (b) (4) (b) (4). The Applicant did not request a pre-ANDA meeting prior to submission of the ANDA.

ANDA 211097 was submitted on 12/29/2017.[6] The submission included the same TA and formative (non-comparative) HF study submitted under CC #16343726, which used the Applicant's original device design, not the redesigned device. (b) (4) .

1.1 Additional Regulatory History and DCR/DMEPA Reviews of ANDA 211097

DCR, jointly with DMEPA, has reviewed ANDA 211097 and communicated with the Applicant on multiple occasions following its original submission in 2017, as detailed below:

- 9/11/2018 – DCR conducted Comparative Analysis (CA) review of the proposed device compared to the RLD, including labeling comparison, task analysis, and physical comparison of the devices (b) (4) We also consulted DMEPA (on 8/20/2018) to review the validation HF studies provided by the Applicant and for opinion

[2] NDA 021318/SUPPL-54, Forteo (teriparatide injection) label from 11/16/2020 https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021318Orig1s054lbl.pdf

[3] NDA 021318/SUPPL-16 Forteo (teriparatide injection) approval letter uploaded in DARRTS by Oluchi Elekwachi on 6/25/2008 https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af801393c4&showAsPdf=true

[4] CC #16343726 submitted 07/12/2017 (b) (4)

[5] ORS/DTP review by Bryan Newman entered in GDRP by Wendy Good on 09/11/2017 (b) (4)

[6] A211097, teriparatide injection, original submission by Applicant \\CDSESUB1\evsprod\anda211097\0000\m1\us\12-cover-letters\cover-letter-anda-2017-12-08.pdf

on the difference in shape.[7] We identified no significant difference in the labeling or task analysis but differences in external design attributes (overall body shape, size, and tactile features) that we found unacceptable because the lack of data the proposed different shape [redacted] (b) (4) would not impact users' ability to safely and effectively operate the device.[8,9] For the full CA review, see links below.

https://panorama.fda.gov/internal/document/preview?versionID=5b9861c10036439a207566024606b25b&ID=5b9806330024329298a1bf6193d7c563

https://panorama.fda.gov/internal/document/preview?versionID=5bcddd690088d4c6b38df9327f02074d&ID=5bca5c0a0008ce1220b537484ea28110 (Addendum clarifying language to be conveyed to Applicant)

On their end, DMEPA concluded that, in verbatim,[10]

> "We have determined that the proposed device's slimmer body, shape and tactile/texture differences may have the potential to impact the intended users' ability to safely and effectively operate the device [redacted] (b) (4) [redacted] (b) (4) and thus, may affect how the user performs the critical task of dose injection. We request that you provide additional information and/or data, such as data from a comparative use human factors study, to further assess whether the identified differences in the user interface for your proposed product impacts the clinical effect or safety profile when compared to its RLD.
>
> If you choose to conduct a Comparative Use Human Factors Study, you may consider submitting your study protocol for feedback before commencing your study via a General Correspondence to your application."

Joint DCR/DMEPA deficiency comments were conveyed to the Applicant in Complete Response (CR) Letter dated 10/26/2018 under CLINICAL.[11]

- 12/19/2018 – Post-CR Teleconference Meeting for clarification on the formative HF study.[12] Upon review, OGD/DMEPA elected against answering the question (and the associated sub-questions) because the submitted questions were not clarification

[7] A211097, teriparatide injection, DCR human factors consult to DMEPA, uploaded by Nitin K Patel on 8/28/2018 https://panorama.fda.gov/internal/document/preview?versionID=5b854dca004566cfe5725242a4e0621b&ID=5b854dca004566ce9860e3f9f3f0044a

[8] A211097, teriparatide injection, DCR Review-Comparative Analysis uploaded by Nitin K Patel on 9/11/2018 https://panorama.fda.gov/internal/document/preview?versionID=5b9861c10036439a207566024606b25b&ID=5b9806330024329298a1bf6193d7c563 ; and

[9] A211097, teriparatide injection, DCR CA Review Addendum uploaded by Nitin K Patel on 10/22/2018 https://panorama.fda.gov/internal/document/preview?versionID=5bcddd690088d4c6b38df9327f02074d&ID=5bca5c0a0008ce1220b537484ea28110

[10] A211097, teriparatide injection, Human Factors Review, uploaded in DARRTS by Denise Baugh on 9/11/2018 https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af804b508c

[11] A211097, teriparatide injection, A211097N000DPM-Complete-Response-01, uploaded by Aaron Sigler on 10/26/2018 http://panorama.fda.gov/document/view?versionID=5bd37b8d01110e09b9e20967ff6ae700

[12] A211097, teriparatide injection, Post-CR Meeting via Teleconference on 11/9/2018, Applicant submission \\cdsesub1\evsprod\anda211097\0012\m1\us\12-cover-letters\addendum-1-post-cr-letter-meeting-request-20181109.pdf

questions, but rather, they appeared to be questions that requested the Agency's input on study design and/or would require additional FDA assessment of information (e.g., data) to develop a response.[13]

- 2/1/2019 - Applicant submitted a General Correspondence (GC) for Agency's feedback on a proposed study protocol for a comparative use HF (CUHF) study between the RLD, Forteo, and the proposed generic teriparatide pen injector, A211097.[14] DCR consulted DMEPA for feedback on the study protocol,[15] who found the protocol unacceptable and made recommendations on the critical tasks used in the study and recommended including open-ended follow-up questions for all instances of use errors.[16] During this GC review, DMEPA consulted Biometrics, who identified multiple additional protocol issues regarding study design.[17] A full list of recommendations from DMEPA and Biometrics can be found in the links below.

  DMEPA: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80527498
  Biometrics: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80526c36

  The Applicant subsequently submitted clarifying questions regarding study inclusion criteria.[18,19] DMEPA responded by reiterating that inclusion of surrogates (in lieu of RLD users) and inclusion of caregivers is unacceptable.[20] Questions and responses can be found below:

  https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80537571

- 7/29/2020 – The Applicant submitted a second GC with modification to the CUHF study protocol, from lab-based testing to in-home testing, citing COVID-19 restrictions.[21] DCR

[13] A211097, teriparatide injection, Clinical Response to Post-CR meeting, uploaded by Raquel Tapia on 12/20/2018 https://panorama.fda.gov/internal/document/preview?versionID=5c1bd72e0000ca9e7978cba04634833d&ID=5c1bd72e0000ca9dfec72dd50bf14edc

[14] A211097 teriparatide injection, Gen Correspondence submitted by Applicant, dated 2/1/2019, Sequence 0015, Module 1.2 \\CDSESUB1\evsprod\anda211097\0015\m1\us\12-cover-letters\cover-letter-general-correspondence-20190201.pdf

[15] A211097 DCR Consult to DMEPA on 2/11/2019- GC/CUHF study protocol review https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af804db287

[16] DARRTS - A211097 CONSULT REV-SAFETY-18 (Comparative Use Human Factors Protocol), uploaded by Millie Shah on11/12/2019 https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80527498

[17] DARRTS - A211097 CONSULT REV-BIOMETRICS-01 (General Consult Review) uploaded 11/11/2019 by Yifan Wang https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80526c36

[18] DARRTS – A211097 COR-ANDAIR-OR 9 (Advice/Information Request) uploaded 11/25/2019 by Kimberly A Moore-McCullough https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8052acb6

[19] DARRTS – A211097 FRM-ADMIN-01 (Memorandum to File) uploaded 12/5/2019 by Kimberly A Moore-McCullough https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8052d4e6

[20] DARRTS – A211097 CONSULT REV-SAFETY-18 (Review of Comparative Human Factors Protocol Clarifying Question) uploaded 1/13/2020 by Millie B Shah https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80537571

[21] A211097 teriparatide injection Gen Correspondence dated 7/29/2020 \\CDSESUB1\evsprod\anda211097\0021\m1\us\12-cover-letters\cover-letter-general-correspondence-20200729.pdf

again consulted DMEPA (8/28/2020),[22] who identified concerning issues regarding the Applicant's approach to remote testing, including: possible participant early familiarization with study materials; variation in study environment and equipment; limited viewing ability by moderators; issues related to computer setup by study participants; and ability to recruit participants representative of intended drug user groups.[23] A detailed explanation of DMEPA's concerns can be found in the link below.

https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8059ec2f

Note that the Applicant submitted the current post CR Response, including the results of their CUHF study, before this GC was completed. This GC was subsequently closed and no feedback on their study question was conveyed to the Applicant.[24]

- 10/15/2020 – Post CR Response Submission, currently under review, including a CUHF study report for Study APO-TCU2-VT-503.[25,26] The submission does not include a new comparative (threshold) analysis report.

1.2 Additional Background Information

1.2.1 Orange Book

As of 5/18/2021, there are no marketed generic teriparatide injection products listed in Orange Book.[27] NDA 211939, Bonsity (teriparatide injection), 0.62 mg/2.48 mL (0.25 mg/mL), a 505(b)(2) to Forteo, uses (b) (4) cylindrical (b) (4) approved 10/4/2019.[28,29] Bonsity does not have therapeutic equivalence (TE) designation. A CU study was recently completed for this product and a review by DMEPA is pending.[30]

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[22] DARRTS – A211097 FRM-CONSULT-06 (OSE Consult), uploaded by Nitin K Patel on 8/28/2020 https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8058fd09

[23] DARRTS – A211097 CONSULT REV-SAFETY-18 (Comparative Human Factors Protocol) uploaded by James H Schlick on 10/7/2020 https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8059ec2f

[24] A211097 teriparatide injection, GC Review 01, uploaded by Nitin K Patel on 12/16/2020 https://panorama.fda.gov/internal/document/preview?versionID=5fda2ac6005a5af9f742eafa02507a77&ID=5fc80589000cf49a1ce9d2dff51a1b0c

[25] ANDA 211097, Teriparatide injection, Response to Complete Response Dated October 26, 2018, submitted by Applicant 10/15/2020 Sequence 0020, Module 1.2 Cover Letters \\CDSESUB1\evsprod\anda211097\0020\m1\us\12-cover-letters\response-to-complete-response-letter-pdf-20201015.pdf

[26] ANDA 211097, Teriparatide injection, Comparative Use – Human Factors Study submitted by Applicant 10/15/2020 Sequence 0020, Module 5.3.5.4 \\CDSESUB1\evsprod\anda211097\0020\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5354-other-stud-rep\apo-tcu2-vt-503\comparative-use-human-factors-study-apo-tcu2-vt-503.pdf

[27] Orange Book, search term "teriparatide" on 5/18/2021 https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm

[28] Orange Book search term "teriparatide" on 5/24/2021 https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm

[29] N211939, Bonsity (teriparatide injection), (b) (4) Applicant submission on 8/23/2019 (b) (4)

[30] N211939, Bonsity (teriparatide injection), Human Factor study acknowledgement, uploaded to DARRTS by Deveonne Hamilton-Stokes on 3/9/2021 https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af805db681

[redacted] (b) (4)

1.2.3 Controlled Correspondence

A search on Panorama's Controlled Correspondence Dashboard retrieved two control correspondences by this Applicant, related to ANDA 211097, neither of which is relevant to this review.[33]

2 Discussion

On 10/15/2020, OGD received the current post-CR Response to clinical deficiencies outlined in a 10/26/2018 CR Letter.[34] Based on review of submitted information, the Applicant has made no modifications to the [redacted] (b) (4) device since we last evaluated it in 2018, and the submission does not include a new CA report for DCR to review. The Applicant's response to clinical deficiencies only contains results of Study APO-TCU2-VT-503, a CUHF study addressing the design differences related to shape, size, and tactile/texture differences.[35] The Applicant's response states (excerpted below):[36]

> "Apotex acknowledges the Agency's request for additional data, to the already submitted threshold analyses, to demonstrate that the differences in body size/shape and tactile/texture characteristics between the proposed product and Reference Listed Drug (RLD) are minor and will not impact the clinical effect or safety profile of the proposed product when compared to the RLD.
>
> To address this request, and having modified the study protocol as per FDA responses and recommendations received on November 13, 2019 and January 30, 2020, to our general correspondence letter dated February 1, 2019, and additional questions submitted for clarification on November 20, 2019, Apotex have now performed a comparative Use Human Factors Study in order to further assess whether the identified minor differences in the user interface for our proposed product could impact the clinical effect or safety profile when compared to the RLD.

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[31] Submission search in DARRTS, search term "teriparatide" on 5/24/2021 https://darrts.fda.gov/darrts/faces/SubmissionSearchResultTF/SubmissionSearchResults?_afrRedirect=2037780472114249&_afrPage=10

[32] [redacted] (b) (4)

[33] Panorama Control Correspondence Dashboard, search term "teriparatide" on 5/18/2021 https://panorama.fda.gov/dashboard/view?ID=55cb223000052e2c687712de73fd40a1

[34] A211097, teriparatide injection, A211097N000DPM-Complete-Response-01, uploaded by Aaron Sigler on 10/26/2018 http://panorama.fda.gov/document/view?versionID=5bd37b8d01110e09b9e20967ff6ae700

[35] ANDA 211097, Teriparatide injection, Comparative Use – Human Factors Study submitted by Applicant 10/15/2020 Sequence 0020, Module 5.3.5.4 \\CDSESUB1\evsprod\anda211097\0020\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5354-other-stud-rep\apo-tcu2-vt-503\comparative-use-human-factors-study-apo-tcu2-vt-503.pdf

[36] ANDA 211097, Teriparatide injection, Response to Complete Response Dated October 26, 2018, submitted by Applicant 10/15/2020 Sequence 0020, Module 1.2 Cover Letters \\CDSESUB1\evsprod\anda211097\0020\m1\us\12-cover-letters\response-to-complete-response-letter-pdf-20201015.pdf

[…]

The results of the Comparative Use Human Factors Study provides [sic] definitive conclusion that the differences in device between the Teriparatide PFP device and the Forteo® device are acceptable and that the Teriparatide PFP device and the Forteo® device can be substituted with the full expectation that the Teriparatide PFP device will produce the same clinical effect and safety profile as the Forteo® device under the conditions specified in the labeling."

2.1 Overview of Comparative Use Human Factor (CUHF) Study, APO-TCU2-VT-503

Study APO-TCU2-VT-503 is a randomized, crossover study; forty-nine subjects participated in the study. Participants self-injected Forteo, followed by teriparatide, or vice-versa, into an injection pad strapped to the body. Each participant was given the choice of participating in-person or remotely via web conference, and each participant was asked to choose their own administration site (thigh or abdomen). For in-person testing, the moderator was present in the room with the participant during execution of the session. For remote testing, a web conference was set up with the participant in their own home and the moderator in another location.

Participants were asked to open Box A (needles, alcohol swabs, sharps bin, injection pad) and, as per moderator instructions, start with (depending on the randomization scheme) either Box B (teriparatide prefilled pen and Instructions for Use [IFU]) or Box C (Forteo pen and IFU), followed by the other box. Participants were allowed to reference the IFU while a moderator observed participant performance for evidence of critical task use errors. Afterward, participants were given a Post-Test Interview that included a review of any issues encountered and questions aimed at assessing the participant's understanding of critical knowledge tasks relating to safe use of the product.

Primary endpoint for each injection was a success/failure score, where "success" was defined as the participant completed each critical task without a use error, and "failure" defined as the participant made a use error on one or more critical tasks. Overall success rate for each device was the proportion of participants who had a successful injection with the device. Primary analysis was to determine the difference between the proportion of successful usage of the generic teriparatide device and the proportion of successful usage of the Forteo device.

Since this study is beyond the scope of DCR's CA review, we consulted DMEPA for evaluation of the CUHF study. [37] See Section 2.3 with DMEPA's evaluation.

2.2 DMEPA Consult

On 10/17/2020 DCR sent a consult to DMEPA for feedback on the Applicant's CUHF study report.[38] The consult stated (in part):

[37] A211097 teriparatide injection, DCR consult to DMEPA, uploaded by Nitin K Patel on 1/5/2021 https://panorama.fda.gov/document/preview?versionID=5ff4964a0048fa44e59cda7dd59beb52&ID=5ff4964a0048fa436d3202c9ff739503

[38] A211097 teriparatide injection, DCR consult to DMEPA, uploaded by Nitin K Patel on 1/5/2021 https://panorama.fda.gov/document/preview?versionID=5ff4964a0048fa44e59cda7dd59beb52&ID=5ff4964a0048fa436d3202c9ff739503

> DCR requests DMEPA to review the results of the submitted comparative use HF study APO-TCU2-VT-503 report (attached below) and comment whether the submitted human factors study can adequately address our clinical concern that the proposed pen device's slimmer body, shape and tactile/texture differences may have the potential to impact the intended users' ability to safely and effectively operate the device, particularly in elderly patients.

On 6/9/2021, DMEPA provided the following feedback to DCR, which includes input from Division of Biometrics VIII (DBVIII):[39]

> According to the DBVIII review,[40] the CUHF study results demonstrated that in terms of use success, the proposed product Teriparatide PFP met the non-inferiority margin and is non-inferior to the RLD Forteo.
>
> The review results identified 22 use errors with the proposed ANDA product and 23 use errors with the RLD. The primary use error observed during the study occurred with Critical Task 4: Hold the injection button down while delivering the medication. Seventeen participants failed to hold the injection button down while simulating medication delivery with the Forteo device and 17 participants failed to hold the injection button down with the Teriparatide pen. Of the aforementioned failures, 15 participants committed the same error with both devices.
>
> The second use error, observed during the study occurred with for Critical Task 5: Hold in place to deliver the medication. Six participants did not hold the Forteo device in place for a count of 5 to deliver the medication and 5 participants did not hold the Teriparatide PFP device in place for a count of 5 to deliver the medication. Of the aforementioned failures, 5 participants committed the same use error with both devices.
>
> We also note that in the root cause analysis of the identified use errors, study participants did not attribute the differences in design of the device as being a cause of the use errors. Based on the totality of evidence and the assessment by DBVIII, we determine that the CUHF study results supports non-inferiority of the proposed Teriparatide PFP when substituted for the RLD. No further information or data is needed from DMEPA at this time.
>
> […]
>
> We reviewed the CUHF study results and determined that the CUHF study results demonstrate that the proposed Teriparatide PFP is non-inferior to the RLD Forteo when used by patients in representative use scenarios and use environments consistent with the labeled conditions of use. As such, we conclude that, from a usability perspective, the proposed Teriparatide product can be substituted with the full expectation that it will produce the same clinical effect and safety profile as the RLD under the conditions specified in the labeling.

Reviewer Comment:

- *The review included two Clinical IR requests from DMEPA for clarification of study design and analysis. Questions and Clinical IR Responses can be found here:*

[39] A211097 teriparatide injection, DMEPA response to DCR consult (Teriparatide CUHF Study Result Review ANDA 211097), uploaded in DARRTS by Avani Bhalodia on 6/9/2021
https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af805f8152
[40] A211097 teriparatide injection, DBVIII Stat review,
https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af805f7425

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\\CDSESUB1\evsprod\anda211097\0026\m1\us\12-cover-letters\cover-letter-response-to-information-request-20210415.pdf (4/15/2021)

- *DMEPA's consult to DBVIII and DBVIII's response can be found here: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af805f7425*
- *DMEPA finds the CUHF study supports non-inferiority of the proposed teriparatide product when compared to the RLD with respect to use success.*

3 Conclusion

Based on DMEPA's consult review, the design differences between the proposed Teriparatide PFP drug product and the current Forteo Pen Injector will not impact the safe and effective use of the proposed generic drug product when substituted for the RLD. No additional data are needed to support that the proposed design for the applicant's Teriparatide PFP is acceptable.

4 Comments to Convey to the Applicant by RPM

N/A. There are no deficiencies or comments to convey to the applicant with respect to device usability and design differences compared to the RLD.

5 Appendix

Figure A. Comparison Original Forteo Pen (IndePEN) with Current Forteo Pen

Comparison of Forteo IndePEN and Current Forteo Pen

Feature	Forteo IndePEN	Current Forteo Pen
Priming required prior to first use of pen	No	Yes
Priming required before each dose	No	Yes
Number of operation steps for each dose delivery	2	8
Visual clues for patients	Easy to see colors	Arrows and numbers in small dose window
Injection force	Approximately 3 times less than current Forteo pen	
User manual	One page – front and back; color illustrations, bigger font	Single page black and white leaflet in 8 point font.

Forteo Pen (pen injector device approved on 11/26/2002 when NDA was originally approved

Forteo IndePEN (pen injector device approved on 06/25/2008 via Supplement- 16

Source (original device): https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/21318slr002_forteo_lbl.pdf accessed 5/27/2021; p. 4 of 4

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Tracy Franzos

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William Chong

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CLINICAL CONSULTATION REVIEW
Division of Clinical Review (DCR)
Office of Bioequivalence (OB), Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)
Teriparatide Injection, USP, 600 mcg/2.4 mL

Drug Product	Teriparatide Injection, USP, 600 mcg/2.4 mL (250 mcg/mL)
ANDA# **Applicant**	211097 Apotex, Inc./ (b) (4)
RLD# **Approval Date** **Sponsor**	Forteo® (teriparatide [rDNA origin] injection) Subcutaneous Injection, 600 mcg/2.4 mL (250 mcg/mL) NDA 021318, approved 11/26/2002 Eli Lilly and Company
Clinical **Primary Reviewer**	Tracy Franzos, MD, MS Medical Officer
Clinical **Secondary Reviewer**	Raquel Tapia, MD Medical Officer, Acting Team Lead (Clinical Team 1)
Tertiary Reviewer	Lolita Lopez, MD Acting Deputy Division Director
Subject	Review of General Correspondence (GC) requesting to modify previously submitted Comparative Use Human Factor (CUHF) study protocol for their proposed generic teriparatide (b) (4) and the RLD. Due to the current COVID-19 pandemic restrictions, the Applicant proposes utilizing remote moderator led CUHF testing, with some participants remaining in their homes.
Date of Submission(s)	Original ANDA submission: 12/29/2017 General Correspondence (GC) submission: 7/29/2020
Date of Completion	12/2/2020
Conclusion	DCR completed this GC review but the Applicant submitted their ANDA Complete Response prior to sending our recommendations/comments. See Section 4 for Comments to be conveyed to the Applicant by the RPM.

1 Introduction and Background

This is a review of Apotex, Inc's (Applicant) General Correspondence (GC) dated 7/29/2020 in which the Applicant seeks feedback on modifications to their previously submitted Comparative Use Human Factor (CUHF) study protocol for their proposed generic teriparatide injection, USP, 600 mcg/2.4 mL, submitted under ANDA 211097. The Applicant proposes utilizing remote moderator led CUHF testing, with participants remaining in their homes due to the current COVID-19 pandemic restrictions. The RLD for this ANDA is Forteo® (teriparatide [rDNA origin] injection), Subcutaneous Injection, 600 mcg/2.4 mL (250 mcg/mL) (b) (4) NDA 021318, by Eli Lilly and Company, approved 11/26/2002 for the treatment osteoporosis in

postmenopausal women, in men with primary or hypogonadal osteoporosis, and in men and women with sustained systemic glucocorticoid therapy at high risk of fracture.[1] The proposed (b) (4) pen device has slimmer body shape compared to the RLD.

ANDA 211097 was initially submitted on 12/29/2017.[2] Both DCR and DMEPA reviewed this application for issues related to the pen device and on 10/26/2018 provided the following Complete Response to the Applicant, in part:[3,4]

> We reviewed your threshold analyses and your conclusion that the differences between your proposed device and the RLD are minor. However, you have not provided sufficient information and/or data to support your conclusion. We have determined that the (b) (4) may have the potential to impact the intended users' ability to safely and effectively operate the device (b) (4), and thus, may affect how the user performs the critical task of daily dose injection, particularly in postmenopausal women with osteoporosis and elderly patients. We request that you provide additional information and/or data, such as data from a Comparative Use Human Factors Study, to further assess whether the identified differences in the user interface for your proposed product impact the clinical effect or safety profile when compared to its RLD.
>
> If you choose to conduct a Comparative Use Human Factors Study, you may consider submitting your study protocol for feedback before commencing your study via a General Correspondence to your application.

On 2/1/2019, the Applicant submitted a CUHF study protocol of Forteo® and teriparatide prefilled pen,[5] for which FDA provided feedback.[6,7,8]

On 7/29/2020, the Applicant submitted a General Correspondence (GC) (current submission) and seeks to modify their protocol due to the current COVID-19 pandemic restrictions. The Applicant is requesting FDA feedback on these modifications (in verbatim), the Applicant states:[9]

> Apotex Inc. is seeking the FDA's feedback on modifications to the currently agreed upon protocol, regarding acceptability on whether remote execution of a Comparative Use Human

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[1] NDA 021318/SUPPL-53, Forteo (teriparatide injection) label from 4/6/2020 https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process
[2] A211097 Teriparatide injection, original submission by Applicant \\CDSESUB1\evsprod\anda211097\0000\m1\us\12-cover-letters\cover-letter-anda-2017-12-08.pdf
[3] A211097 Teriparatide Injection Complete Response Letter dated 10/26/2018 -PANORAMA http://panorama.fda.gov/document/view?versionID=5bd37b8d01110e09b9e20967ff6ae700
[4] DARRTS - A211097 DMEPA response to DCR consult, uploaded by Denise Baugh, PharmD on 9/11/2018 https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af804b508c
[5] A211097 Teriparatide injection, Applicant submission, Sequence 0015, Module 5.3.5.4 dated 2/1/2019 \\cdsesub1\evsprod\ANDA211097\0015\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5354-other-stud-rep\apo2016teriparatidef1503\apo2016teriparatidef1503-report-body.pdf
[6] DARRTS - A211097 CONSULT REV-SAFETY-18 (Comparative Use Human Factors Protocol), uploaded by Millie Shah on 11/12/2019 https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80527498
[7] DARRTS - A211097 CONSULT REV-BIOMETRICS-01 (General Consult Review) uploaded 11/11/2019 by Yifan Wang https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80527498
[8] DARRTS - A211097 CONSULT REV-SAFETY-18 (Comparative Use Human Factors Protocol), uploaded by Millie Shah on 1/13/2020 https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80537571
[9] A211097 Teriparatide injection Gen Correspondence dated 7/29/2020 \\CDSESUB1\evsprod\anda211097\0021\m1\us\12-cover-letters\general-correspondence-20200729.pdf

Factors study, for a Drug-Device Combination Injectable Product, for some of the participants would be acceptable. The study is designed to assess the difference in use error rate associated with a change in an external critical design attribute for the proposed user interface between the test and reference products. The assessment is based on a simulated-use test. Each participant is to complete two injections, one for each product, into an injection pad worn on the participant's own body. For each simulated injection, the moderator is to observe the participant's performance and record whether use errors were made. Should use errors be observed with either injection, the moderator will interview the participant after both injections are completed.

Under this proposed modification, the test environments would be inclusive of:

- **The agreed upon In-Person Execution**: For study sessions conducted at the research facility, the test room will be configured as a typical home environment (with normal lighting, temperature, and humidity). The room will include two chairs, a table, injection pad and injection supplies. The moderator will be present, in the room, with the participant during the execution of the session.

- **Alternatively, the proposed modification includes Remote Execution**: Some study sessions will be conducted via web conference with the participant in their own home and the moderator in another location as participants in this study are considered a vulnerable population and are more susceptible to COVID-19. Thus, participants will be given the choice of participating in-person or remotely. Test stimuli will be the same between in-person and remote test sessions with the same test procedure followed.

Under this remote testing modification, neither participants nor staff would have to travel and come in close proximity with each other. Rather than coming to a central facility testing room for the study, which is itself already configured as a typical home environment, the entire package, inclusive of all that is required to execute the Comparative Use Study, will be sent to the participant's home, and the moderator would lead the study remotely with the participants, via video conference. Under the current COVID-19 pandemic, execution of such a study where a high-risk elderly population is expected to travel and sit in a room with a moderator is very difficult to execute. Discussions and feedback from viable participants, who were ready to engage prior to the pandemic, is that they don't feel comfortable doing this currently. This makes an already difficult to recruit study extremely difficult to conclude based on current design. Thus, the rationale for this proposal is based on the current social distancing requirements during COVID-19, particularly for a study, which for the most part, requires a high-risk elderly patient population.

To ensure there is no bias introduced with this approach, the package and its components will be tamper-sealed and participants will be required to follow detailed instructions and not open certain elements until they have established the remote video connection with their moderator. Once video connection is established, the moderator will follow the script as they would have if this study was being executed in person and walk the participant through the next steps. Additionally, by nature of how these types of studies are executed, participants will be audio and video recorded in order to better evaluate the use of this product, therefore assuring no outside interference during the execution of the testing.

It is noteworthy that as each participant serves as his/her own control in the comparison of the test and reference products, very little bias on the comparison should be introduced due to the proposed changes. Apotex Inc. would like to receive confirmation whether this approach of utilizing remote moderator led Comparative Use Human Factors testing, with participants

> remaining in their homes, is an appropriate modification to operations during the time when COVID-19 restrictions are in place.

On 8/28/2020 DCR consulted DMEPA to review the Applicant's proposed CUHF study modifications proposed by the Applicant (details below).[10]

1.1 Additional Background Information

1.1.1 Orange book

There are no marketed generic teriparatide injection products listed in Orange Book.[11]

1.1.2 Controlled Correspondence

A search on Panorama's Controlled Correspondence Dashboard retrieved two control correspondences by this Applicant, related to ANDA 211097. Neither is relevant to the issue in this GC. [12]

2 Discussion

2.1 DMEPA Consult

On 8/28/2020, DCR send a consult to DMEPA for comments regarding the Applicant's proposal to modify the conduct of the CUHF due to challenges with enrolling study participants related to ongoing COVID-19 pandemic. On 10/7/2020, DMEPA provided the following recommendations:[13]

> We reference your submission on July 29, 2020 notifying us of your intent to conduct your comparative use human factors (CUHF) study remotely due to restrictions associated with the COVID-19. FDA recognizes that the COVID-19 public health emergency may impact your ability to conduct in person human factors (HF) testing of medical products. Please note there are currently no data that the Agency is aware of that support remote HF testing nor are we aware of any consensus scientific guidelines or standards that can inform an acceptable virtual/remote HF testing approach. As such, the Agency would need to carefully consider each individual protocol in its entirety in order to provide more informed feedback on a remote testing approach. While the decision to proceed with a remotely conducted CUHF study is a business decision for your company, this decision carries some risk. We strongly urge you to submit your CUHF study protocol, taking into account the preliminary concerns we have identified that are detailed below, and await agency review before commencing your study. This will allow us to provide a detailed and comprehensive review, and ensure that the HF study maintains compliance with

[10] DARRTS - A211097, FRM-CONSULT-06 (OSE Consult) uploaded by Nitin Patel on 8/28/2020 https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af8058fd09&_afrRedirect=2290535244257891

[11] Orange Book, search term "teriparatide" on 10/29/2020 https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm

[12] Panorama Control Correspondence Dashboard, search term "teriparatide" on 10/29/2020 https://panorama.fda.gov/dashboard/view?ID=55cb223000052e2c687712de73fd40a1

[13] DARRTS - A211097, CONSULT REV-SAFETY-18 (Comparative Human Factors Protocol) uploaded by James H Schlick on 10/7/2020 https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af8059ec2f&_afrRedirect=22906632667489 84

best practices, minimizes risks to study integrity, and supports public health priorities.

We have particular concerns about your proposed approach to remote testing, some of which include:

1. Participants may open and familiarize themselves with the study materials prior to conducting the study despite instruction not to. Clarify how you intend to handle such scenarios (e.g., will participants who open and familiarize themselves with study materials be disqualified?) and the impact to your collected data.
2. Variations in the conditions of a remote study use environment may be more representative of actual use for the individual participant in the study but may also make both collection and interpretation of study data more difficult. Clarify how you will address the lack of control over the environment, which may also introduce test artifacts.
3. Study moderators may have difficulty seeing all of the interactions that a participant has with the user interface, which may limit their ability to conduct a robust root cause analysis. There are many different types of video cameras that can be used to conduct virtual testing (e.g. smart phone video cameras, Webcams, built-in laptop cameras, digital video cameras). Each of these camera types have different features that may or may not be necessary for your virtual testing. For example, certain Webcams have pan/tilt/zoom features that would enable a more detailed observation of participants. Some camera types may come with a stand or can easily be placed on a tabletop for ideal positioning while others may require a stand. Provide a brief description of the technical specifications of the video device (e.g. frame rate, resolution, lens type, autofocus features) used for each participant's session and justification for the adequacy of these specifications in capturing non-verbal behavior.
4. To minimize disruptions to the natural use of the product, participants should not be expected to adjust the camera position in the middle of testing. Provide the instructions you intend to provide to participants on where to set up the camera relative to the workspace.
5. We note that you intend to have a setup period. Clarify what criteria you will use to determine whether the setup is sufficient to collect meaningful data from the test participants, and what conditions may be used to determine that the study session cannot continue (for example, if you are unable to achieve an acceptable setup)
6. Difficulty during setup may increase participant frustration, and inadvertently bias their responses. Clarify how you intend to address these situations should they arise.
7. Recruitment of participants willing and able to participate in a remote study may not be adequately representative of the intended user groups. Clarify how you intend to recruit representative participants.

Please note that these are examples of some areas of concern and are not inclusive of all potential concerns with your proposal to conduct a remote CUHF study.

Reviewer Comment: *DCR concurs with DMEPA's recommendations and we intended to convey the recommendations to the Applicant.*

2.2 Applicant's Complete Response Submission

On 10/15/2020, the Applicant submitted a document titled, "Response to COMPLETE RESPONSE LETTER dated October 26, 2018," before DCR could convey

recommendations/comments to the Applicant in response to the GC. The Applicant explains, (excerpt):[14]

> Apotex acknowledges the Agency's request for additional data, to the already submitted threshold analyses, to demonstrate that the differences in body size/shape and tactile/texture characteristics between the proposed product and Reference Listed Drug (RLD) are minor and will not impact the clinical effect or safety profile of the proposed product when compared to the RLD.
>
> To address this request, and having modified the study protocol as per FDA responses and recommendations received on November 13, 2019 and January 30, 2020, to our general correspondence letter dated February 1, 2019, and additional questions submitted for clarification on November 20, 2019, Apotex have now performed a comparative Use Human Factors Study in order to further assess whether the identified minor differences in the user interface for our proposed product could impact the clinical effect or safety profile when compared to the RLD.
>
> …the protocol was amended to allow for remote participation, in line with FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency (issued March 2020, Updated Sept 2020), which allows for changes to be made to the investigational plan or protocol without prior FDA review or approval, if the change is intended to eliminate an apparent immediate hazard or to protect the life and well-being of trial participants. Therefore, the changes set forth in the protocol (to allow for remote participation, rather than in person) were necessary to immediately assure participant safety and avoid travel and close contact during COVID-19, for such a high-risk elderly population.

Reviewer Comment:

- *The document includes a copy of their Comparative Use Human Factors Study (No. APO-TCU2-VT-503) report, which will be reviewed as part of the 10/15/2020 post CR submission.*[15]
- *Since this post CR response was received before formal completion of the GC, it closes out the current GC request.*

3 Conclusion

We concur with DMEPA's comments/recommendations listed in section 2.1 of this review. Note that DCR completed the GC review but the Applicant submitted Response to Complete Response on 10/15/2020, before recommendations/comments, including recommendations from Division of Medication Errors and Analysis (DMEPA), could be conveyed to the Applicant.

Since post CR response was received prior to formal completion of the GC, it closes out the current GC request.

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[14] ANDA 211097, Teriparatide injection, Response to COMPLETE RESPONSE LETTER dated October 26, 2018, submitted by Applicant 10/15/2020 Sequence 0020, Module 1.2 Cover Letters \\CDSESUB1\evsprod\anda211097\0020\m1\us\12-cover-letters\response-to-complete-response-letter-pdf-20201015.pdf

[15] ANDA 211097, Teriparatide injection, Comparative Use – Human Factors Study submitted by Applicant 10/15/2020 Sequence 0020, Module 5.3.5.4 \\CDSESUB1\evsprod\anda211097\0020\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5354-other-stud-rep\apo-tcu2-vt-503\comparative-use-human-factors-study-apo-tcu2-vt-503.pdf

4 Comments to Convey to the Applicant by RPM

The Division of Clinical Review has reviewed your General Correspondence (GC) dated 7/29/2020, regarding proposed modifications to your Comparative Use Human Factors (CUHF) study protocol.

DCR provides the following comments on your proposed modifications to your CUHF study protocol for your proposed generic teriparatide injection, USP, 600 mcg/2.4 mL:

- Since you have already submitted your CUHF study results on 10/15/2020 in a response titled, "Response to COMPLETE RESPONSE (CR) LETTER dated October 26, 2018," your submission closes out this GC request.

Tracy Franzos

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Raquel Tapia

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Lolita Lopez

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Date: 12/10/2020 08:11:45AM
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Clinical Review of Comparative (Threshold) Analyses for Drug-Device Combination Products

Division of Clinical Review (DCR)
Office of Bioequivalence (OB), Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

ANDA	211097
Drug Product/Strength(s)	Teriparatide Injection, USP, 600 mcg/2.4 mL (250 mcg/mL)
ANDA Applicant/DMF Holder	Apotex, Inc./ (b) (4)
RLD#/ Product Name	NDA 021318 Forteo® (teriparatide [rDNA origin] injection) Subcutaneous Injectable, 600 mcg/2.4 mL (250 mcg/mL) Approved 11/26/2002
RLD Sponsor	Eli Lilly and Company
Primary Reviewer	Raquel Tapia, MD Medical Officer
Secondary Reviewer	Lolita Lopez, MD Team Leader
Tertiary Reviewer	Daiva Shetty, MD Division Deputy Director
Submission Date	2/1/2019
Date of Review	11/15/2019
GDUFA Goal Date	N/A
Subject	Review of General Correspondence (GC) which includes a proposed study protocol for a Comparative Use Human Factors (CUHF) Study of Forteo (RLD) and generic Teriparatide Prefilled Pen.
Conclusion	The proposed CUHF study protocol is not acceptable. See DMEPA and Division of Biometrics VIII conclusion and recommendations to be conveyed to the Applicant in Section 4.

1 Background

This review addresses a General Correspondence (GC) sent by Apotex (Applicant) which included a study protocol for a Comparative Use Human Factors (CUHF) Study of Forteo (RLD) and proposed Teriparatide Prefilled Pen.

On 12/29/2017, Apotex, Inc. submitted ANDA 211097 for a generic teriparatide injection, 600 mcg/2.4 mL (250 mcg/mL) in reference to Forteo® (teriparatide recombinant human) 600 mcg/2.4 mL (NDA 021318) approved on 11/26/2002 (the RLD). Forteo is indicated for the treatment of osteoporosis, and is a drug-device combination product supplied in a glass cartridge pre-assembled into a disposable delivery device (pen) for subcutaneous injection.[1] Forteo was originally designed as a slim, cylindrical-shaped body (b) (4) pen. In 2007, under supplement 016, it was redesigned to (b) (4) design with a broader body, to address reports of difficulties with operating the device (largely by 70 years and older female patients).[2]

(b) (4) In support of the application, the Applicant submitted a Formative (noncomparative) Human Factors (HF) study which was reviewed by the Division of Medication Errors and Prevention (DMEPA) (see review entered in DARRTS dated 9/11/2018).[3] DCR performed comparative (threshold) analyses of the delivery device constituent part of the proposed teriparatide injection combination product and its related product labeling to the RLD (see DCR review dated 9/11/2018 and addendum dated 10/19/2018).[4,5] Both DCR and DMEPA concluded that additional information was necessary to evaluate whether the design differences (overall body shape, size, and tactile features) do not impact the intended users' ability to safely and effectively operate the device. FDA communicated this deficiency to the Applicant in the Complete Response Letter (CRL) dated 10/26/2018, under Clinical.[6]

> We reviewed your threshold analyses and your conclusion that the differences between your proposed device and the RLD are minor. However, you have not provided sufficient information and/or data to support your conclusion. We have determined that the proposed device's slimmer body, shape and tactile/texture differences may have the potential to impact the intended users' ability to safely and effectively operate the device (b) (4) and thus, may affect how the user performs the critical task of daily dose injection, particularly in postmenopausal women with osteoporosis and elderly patients. We request that you provide

[1] Drugs@FDA Drug Label for Forteo (Teriparatide) Recombinant Human Subcutaneous Injection. Accessed 07/18/2018 https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021318s036lbl.pdf.
[2] Note to the Reviewer NDA021318/S-016 New Supplement submitted 10/30/2007 - DARRTS
[3] A211097 Teriparatide injection DMEPA response to DCR consult, entered in DARRTS by Denise Baugh, PharmD on 9/11/2018
https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af804b508c&_afrRedirect=5669097170451369
[4] A211097_0_DCR Review_Teriparatide Injection_Comparative Analysis GDRP entry by Nitin Patel on 9/11/2018
http://panorama.fda.gov/document/view?versionID=5b9861c10036439a207566024606b25b
[5] A211097_0_ DCR Review-Addendum dated 10/19/2018
http://panorama.fda.gov/document/view?versionID=5bcddd690088d4c6b38df9327f02074d
[6] A211097N000DPM-Complete Response, GDRP entry 10/26/2018
http://panorama.fda.gov/document/view?ID=5bc3f14e0005847190604f6ef020de20

> additional information and/or data, such as data from a Comparative Use Human Factors Study, to further assess whether the identified differences in the user interface for your proposed product impact the clinical effect or safety profile when compared to its RLD.
> …If you choose to conduct a Comparative Use Human Factors Study, you may consider submitting your study protocol for feedback before commencing your study via a General Correspondence to your application.

On 11/9/2018, the Applicant submitted a Post-CRL Meeting Request seeking clarification on the CRL deficiencies. One of the questions requested clarification on the Agency's reference to "additional information" mentioned in the clinical deficiency, which upon further consideration, DCR denied answering because the question was not for clarification, but rather, appeared to request the Agency's input on a study design and/or would require additional FDA assessment of information (e.g., data) to develop a response.[7]

On 2/1/2019, the Applicant submitted a GC to address clinical deficiencies in the Post-CR Letter issued on 10/26/2018.

2 Discussion

In the current GC, the Applicant seeks Agency guidance on their proposed study protocol for a Comparative Use Human Factors (CUHF) Study of Forteo and Teriparatide Prefilled Pen.

2.1 Applicant's (Apotex) General Correspondence (verbatim) dated 2/1/2019: [8]

> Apotex acknowledges the Agency's request for additional data to demonstrate that the differences (b) (4) are minor and will not impact the clinical effect or safety profile of the proposed product when compared to its RLD. To address this request Apotex has already performed a formative study in addition to the threshold analysis (including addendum) to guide the development of this drug-device combination product, both of which were included in the original ANDA. The threshold analysis concluded that there were no non-minor differences between the proposed pen and the Forteo pen. To further support the threshold study conclusion, a formative study was also conducted in 18 individuals, which included women with osteoporosis and elderly patients, reflecting the user population referenced in the Agency's Clinical CR question. The formative study confirmed that current and past Forteo® users perceived the Apotex pen to be comparable to the Forteo® pen, no unanticipated use errors were found in this study, and no design changes were recommended for the Apotex pen. Therefore, the results of this study combined with the threshold analysis showed that the proposed device's slimmer body, shape and tactile/texture differences did not impact the intended users' ability to safely and effectively operate the device. This conclusion is further supported by a study sponsored by (b) (4) which also included women of post-menopausal age. Similar to the Apotex-sponsored study, there were no issues cited by the participants as a result of either device's body shape or ergonomics (Lange, J. and Nemeth, T (2018). Formative usability evaluation of a fixed-dose pen-injector platform device. Med Devices (Auckl). Vol. 11: 105-112) … Apotex believes that the studies, combined

[7] A211097_DCR-Clinical Response to Q1_Teriparatide Meeting Requested, dated 12/20/2018 http://panorama.fda.gov/document/download?ID=5c1bd72e0000ca9dfec72dd50bf14edc
[8] A211097 Teriparatide injection Gen Correspondence dated 2/1/2019 Application 211097 - Sequence 0015 - General correspondence - 20190201

with [redacted] (b) (4), provides sufficient evidence to address the Agency's concern.

However, if the Agency does not agree that this data/information would provide sufficient evidence to resolve the Agency's concern, enclosed is a protocol for the Agency's review for a 'Comparative Use Human Factors Study of Forteo and Teriparatide Prefilled Pen'.

Apotex has designed the protocol in accordance with FDA Guidance for Industry: Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA (January 2017) and would appreciate the Agency's feedback in order to address the Clinical CR question.

2.2 DCR Consult to DMEPA and Response

On 2/11/2019, DCR consulted DMEPA to evaluate the information submitted under the GC. Specifically, DCR requested DMEPA to:[9]

1. Evaluate if the information submitted in the GC dated 2/1/2019, which includes a literature article (Lange J. and Nemeth T 2018), would adequately address the Clinical deficiency in the CRL dated 10/26/2018.
2. Based on the information submitted in the GC, do you recommend that the Applicant conduct a Comparative Use Human Factors Study?
3. Please review the proposed **Comparative Use HF study protocol** [CUHF] and provide any comments or recommendations to be provided to the Applicant.

On 11/12/2019, DMEPA completed their review and concluded that the comparative use HF [CUHF] study protocol is not acceptable. DMEPA's review stated, "Our overall assessment of the comparative use HF protocol indicated that the testing conditions and user groups require revisions to ensure that adequate data are captured during the testing."[10]

DCR Reviewer Comments:
During review of the protocol, DMEPA:

- *Consulted the Division of Biostatistics VIII in the Office of Translational Sciences (DBVIII/OTS) on the statistical plan of the proposed CUHF study protocol.*
- *Discussed their concerns about the protocol during several meetings with the Office of Chief Compliance (OCC), DBVIII, and DCR.*

DMEPA did not provide responses to our questions 1 and 2.

DMEPA's Recommendations to the Applicant prior to commencing their CUHF study are listed in Table 1 below.

[9] A211097 OSE Consult GDRP entry 2/11/2019 by Nitin Patel
[10] DMEPA Consult Rev-Safety-18 Comparative Human Factor Protocol, uploaded in DARRTS 11/12/2019 by Millie B. Shah. https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80527498

Table 1. CUHF Study Protocol: Identified Issues and Recommendations by DMEPA

Identified Issues and Recommendations for Sponsor			
	Identified Issue	**Rationale for Concern**	**Recommendation**
Comparative Use HF Study Methodology			
1.	We note that you have identified all tasks as critical tasks for evaluation in this study; however, we believe only a subset of these tasks are critical tasks for your proposed product	A critical task is, for example, a task that if performed incorrectly or not performed at all, would or could cause harm.[5] For the purposes of a comparative-use HF study, FDA is focused on those critical tasks that may be impacted by a difference in an external critical design attribute between the RLD and the proposed product. In this instance, we determined that tasks 3, 4, 5, 6 and 7 are the critical tasks that may be impacted by a difference in an external critical design attribute and therefore these tasks should be the focus of the study. Tasks 1, 2, 8, and 9 are not likely to be affected by an identified difference in external critical design attribute between the RLD and your proposed product.	Revise your critical tasks that will be evaluated in the study to tasks 3, 4, 5, 6, and 7 and update your protocol accordingly.
2.	The protocol states that no follow-up questions will be asked if the participant did not have task failures on either pen or made the same errors with the Teriparatide PFP as with the Forteo pen (page 23).	Appropriate follow-up questions are necessary to learn the participant's perspective on all task failures to aid in the assessment of root causes. This information will help confirm whether differences in external critical design attributes contributed to use errors.	Revise the study protocol to ensure that open-ended follow-up questions are asked of study participants for all instances of use errors to inform your root cause analysis.
General Recommendations			
For additional information, please see draft guidance below: Comparative Analyses and Related Comparative Use Human Factors Studies for Drug-Device Combination Products Submitted in an ANDA and can be found online at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM536959.pdf			

Source: DMEPA Review dated 11/12/2019, pages 4-5/8

Division of Biostatistics Consult:
On 3/2/2019, DMEPA consulted the Division of Biometrics VIII (DBVIII) to comment on the appropriateness of the Applicant's proposed Statistical Plan for the CHUF protocol to establish the non-inferiority in use error rates of the proposed pen compared to the RLD.[11]

On 11/11/2019, DBVIII completed their consult review and provided comments related to endpoints, inferiority margins, sample size, and randomization procedures and provided the following recommendations to be conveyed to the Applicant, in verbatim:[12]

1. The use of surrogates for the primary analysis is not acceptable. The surrogates may not represent the patient population. You should recruit an adequate number of RLD users in the study.

2. The Agency will focus on the first injection in this study. A second and third injection is not necessary in this study, and we will not consider your proposed second and third Teriparatide PFP injections as they will be subject to learning and recency bias.

3. We note that you proposed to combine the critical tasks you identified by calculating the error rate using "the total number of errors divided by the total of nine critical tasks for each participant, for each individual injection". We suggest an endpoint that would be consistent with principles of the draft guidance, would encompass all of the critical tasks we believe a comparative human factors study should assess for your proposed product, and would also evaluate the final outcome of the injection. To do this, we propose an endpoint that would be defined as a binary yes/no, for which success would be recorded for a given subject only when that subject successfully completes all the critical tasks we recommend a comparative human factors study for the Teriparatide PFP evaluate. If one or more of the identified critical tasks are not successfully completed, an overall use failure would be recorded for that subject. Once all subjects complete the study using the two devices, the rates for overall use success and overall use failure for the set of patients could be calculated for both devices and then compared. Please also submit the data about success/failure for each participant for each individual critical task evaluated. Because each subject has an overall use success or an overall use failure, the success and failure rates convey the complementary information. For example, once we know the overall use success rate, the overall use failure rate is exactly known and equal to the number one (1) minus the success rate. Although mathematically equivalent because they are complementary, we suggest using "overall use success rate" rather than "overall use failure rate" or "error rate" to avoid potential confusion with other uses of the term error. Please propose and justify the non-inferiority margin based on the new primary endpoint recommended above.

4. Please provide justification for the sample size based on your targeted power.

5. Please provide more details about the randomization procedure in the protocol. Other than randomization, no efforts should be made to balance the proportion of subjects completing each sequence.

[11] DMEPA's Consult to Division of Biometrics VIII (DBVIII) (ANDA 211097) 3/2/2019
https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af804e1113&_afrRedirect=1788559238277146
[12] DARRTS Wang, Y. Statistical Review and Evaluation for Teriparatide injection (ANDA 211097) 11/11/2019
https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80526c36

3 Conclusion and Recommendations

DCR concludes that data from a Comparative Use Human Factor study protocol will further assess whether the identified differences in the user interface for the proposed product impact the clinical effect or safety profile when compared to its RLD. However, based on the review by DMEPA and DBVIII, the submitted comparative use human factors study protocol is not acceptable. The protocol requires revisions outlined in DMEPA and DBVIII reviews. The Applicant is advised to implement these recommendations prior to commencing their comparative use HF study.

4 Recommendations to be conveyed to the Applicant by the RPM

Comments to be sent to the Applicant

We completed a review of your proposed Comparative Use Human Factor (CUHF) study protocol submitted as a general correspondence on 2/1/2019. We have the following comments and recommendations for your proposed CUHF study protocol:

Recommendation from the Division of Medication Error Prevention and Analysis:

Our review of the comparative use human factors study protocol identified several areas of concern. Please see the **Identified Issues and Recommendations** table. We recommend that you implement all recommendations before commencing your comparative use human factors study. In addition, please see the recommendations from the Division of Biometrics on the statistical plan (below).

Identified Issues and Recommendations for Sponsor			
	Identified Issue	Rationale for Concern	Recommendation
Comparative Use HF Study Methodology			
1.	We note that you have identified all tasks as critical tasks for evaluation in this study; however, we believe only a subset of these tasks are critical tasks for your proposed product	A critical task is, for example, a task that if performed incorrectly or not performed at all, would or could cause harm.[9] For the purposes of a comparative-use HF study, FDA is focused on those critical tasks that may be impacted by a difference in an external critical design attribute between the RLD and the proposed product. In this instance, we determined that tasks 3, 4, 5, 6 and 7 are the critical tasks that may be impacted by a difference in an external critical design attribute and therefore these tasks should be the focus of the study. Tasks 1, 2, 8, and 9 are not likely to be affected by an identified difference in external critical design attribute between the RLD and your proposed product.	Revise your critical tasks that will be evaluated in the study to tasks 3, 4, 5, 6, and 7 and update your protocol accordingly.

2.	The protocol states that no follow-up questions will be asked if the participant did not have task failures on either pen or made the same errors with the Teriparatide PFP as with the Forteo pen (page 23).	Appropriate follow-up questions are necessary to learn the participant's perspective on all task failures to aid in the assessment of root causes. This information will help confirm whether differences in external critical design attributes contributed to use errors.	Revise the study protocol to ensure that open-ended follow-up questions are asked of study participants for all instances of use errors to inform your root cause analysis.
General Recommendations			
For additional information, please see draft guidance below: Comparative Analyses and Related Comparative Use Human Factors Studies for Drug-Device Combination Products Submitted in an ANDA and can be found online at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM536959.pdf			

Recommendations from Division of Biometrics on the Statistical Plan:

1. The use of surrogates for the primary analysis is not acceptable. The surrogates may not represent the patient population. You should recruit an adequate number of RLD users in the study.

2. The Agency will focus on the first injection in this study. A second and third injection is not necessary in this study, and we will not consider your proposed second and third Teriparatide PFP injections as they will be subject to learning and recency bias.

3. We note that you proposed to combine the critical tasks you identified by calculating the error rate using "the total number of errors divided by the total of nine critical tasks for each participant, for each individual injection". We suggest an endpoint that would be consistent with principles of the draft guidance, would encompass all of the critical tasks we believe a comparative human factors study should assess for your proposed product, and would also evaluate the final outcome of the injection. To do this, we propose an endpoint that would be defined as a binary yes/no, for which success would be recorded for a given subject only when that subject successfully completes all the critical tasks we recommend a comparative human factors study for the Teriparatide PFP evaluate. If one or more of the identified critical tasks are not successfully completed, an overall use failure would be recorded for that subject. Once all subjects complete the study using the two devices, the rates for overall use success and overall use failure for the set of patients could be calculated for both devices and then compared. Please also submit the data about success/failure for each participant for each individual critical task evaluated. Because each subject has an overall use success or an overall use failure, the success and failure rates convey the complementary information. For example, once we know the overall use success rate, the overall use failure rate is exactly known and equal to the number one (1) minus the success rate. Although mathematically equivalent because they are complementary, we suggest using "overall use success rate" rather than "overall use failure rate" or "error rate" to avoid potential confusion with other

uses of the term error. Please propose and justify the non-inferiority margin based on the new primary endpoint recommended above.

4. Please provide justification for the sample size based on your targeted power.

5. Please provide more details about the randomization procedure in the protocol. Other than randomization, no efforts should be made to balance the proportion of subjects completing each sequence.

Raquel Tapia

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Lolita Lopez

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Daiva Shetty

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Addendum

Clinical Review of Comparative (Threshold) Analyses

Division of Clinical Review (DCR)
Office of Bioequivalence (OB), Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

ANDA	211097
Drug Product/Strength	Teriparatide Injection, USP, 600 mcg/2.4 mL (250 mcg/mL)
ANDA Applicant	Apotex, Inc./ (b) (4)
RLD#/ Product Name	NDA 021318 Forteo® (teriparatide [rDNA origin] injection) Subcutaneous Injectable, 600 mcg/2.4 mL (250 mcg/mL) Approved 11/26/2002
RLD Sponsor	Eli Lilly and Company
Primary Reviewer	Raquel Tapia, MD Medical Officer
Secondary Reviewer	Lolita Lopez, MD Team Leader
Tertiary Reviewer	Daiva Shetty, MD Division Deputy Director
Submission Date	12/29/2017
Date of Addendum	10/19/2018
GDUFA Goal Date	10/28/2018
Conclusion	DCR concludes there are other than minor design differences in the external critical design attribute of the proposed generic combination product compared to the RLD that may impact the intended users' ability to safely and effectively operate the device to perform the critical task of dose injection.
Deficiency Classification	☒ Major ☐ Minor **(See section 5 for Comments to be conveyed to the Applicant by the RPM)** ☐ N/A (Review is Adequate) ☒ **Comments to the Applicant in CR Letter**
Justification of Major Designation	The Clinical deficiencies have been classified as MAJOR because the deficiencies pertain to device or container-closure design issues that may affect safety or efficacy as noted in Appendix A, Section B.4.g of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). The review of the response will require, in FDA's judgment, a substantial expenditure of FDA resources.

This Memorandum is an addendum to DCR original comparative (threshold) analysis review of ANDA 211097 teriparatide injection, 600 mcg/2.4 mL (250 mcg/mL), uploaded in Panorama on 9/11/2018. Refer to the original DCR comparative analysis review for full details.[1] This addendum provides clarification on the language to be conveyed to the Applicant. Below are DCR's revised comments/recommendations based on a meeting discussion on 10/19/2018 among review teams in OGDP, ORO, DCR and OSE/DMEPA.

Clinical Comments/Recommendations to be conveyed to the APPLICANT in Complete Response (CR) Letter.

To DPM Regulatory Project Manager: The following comments/deficiencies and/or recommendations should be conveyed to the ANDA applicant. DCR considers these deficiencies to be MAJOR deficiencies to be communicated under the 'Clinical' heading of the COMPLETE RESPONSE Letter. These should NOT be communicated to the Applicant in an Information Request.

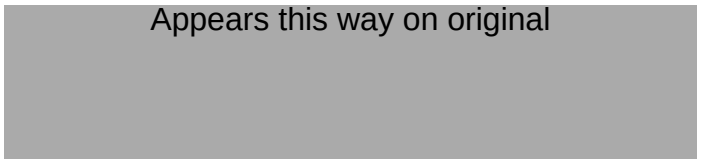
CLINICAL

The deficiencies pertain to device or container-closure design issues that may affect safety or efficacy as noted in Appendix A, Section B.4.g of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). The review of the response will require, in FDA's judgment, a substantial expenditure of FDA resources.

We reviewed your threshold analyses and your conclusion that the differences between your proposed device and the RLD are minor. However, you have not provided sufficient information and/or data to support your conclusion. We have determined that the proposed device's slimmer body, shape and tactile/texture differences may have the potential to impact the intended users' ability to safely and effectively operate the device (b) (4) and thus, may affect how the user performs the critical task of dose injection on a daily basis particularly in postmenopausal women with osteoporosis and elderly patients. We request that you provide additional information and/or data, such as data from a Comparative Use Human Factors Study, to further assess whether the identified differences in the user interface for your proposed product impact the clinical effect or safety profile when compared to its RLD.

We refer you to the draft guidance for Industry: Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA, published January 2017.
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM536959.pdf

If you choose to conduct a Comparative Use Human Factors Study, you may consider submitting your study protocol for feedback before commencing your study via a General Correspondence to your application.



Raquel Tapia

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Lolita Lopez

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Daiva Shetty

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Clinical Review of Comparative (Threshold) Analyses for Drug-Device Combination Products

Division of Clinical Review (DCR)
Office of Bioequivalence (OB), Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

ANDA	211097
Drug Product/Strength(s)	Teriparatide Injection, USP, 600 mcg/2.4 mL (250 mcg/mL)
ANDA Applicant/DMF Holder	Apotex, Inc./ (b) (4)
RLD#/ Product Name	NDA 021318 Forteo® (teriparatide [rDNA origin] injection) Subcutaneous Injectable, 600 mcg/2.4 mL (250 mcg/mL) Approved 11/26/2002
RLD Sponsor	Eli Lilly and Company
Primary Reviewer	Raquel Tapia, MD Medical Officer
Secondary Reviewer	Lolita Lopez, MD Team Leader
Tertiary Reviewer	Daiva Shetty, MD Division Deputy Director
Submission Date	12/29/2017
Date of Review	09/11/2018
GDUFA Goal Date	10/28/2018
Conclusion	DCR concludes there are other than minor design differences in the external critical design attribute of the proposed generic combination product compared to the RLD that may impact the intended users' ability to safely and effectively operate the device to perform the critical task of dose injection.
Deficiency Classification	☒ Major ☐ Minor **(See section 5 for Comments to be conveyed to the Applicant by the RPM)** ☐ N/A (Review is Adequate) ☒ **Comments to the Applicant in CR Letter** ☐ **Comments to the Division of Labeling Review**
Justification of Major Designation	The deficiency requires justification that will likely include data that supports the safety of the proposed drug product. Review of the submitted justification and data will require substantial expenditure of FDA resources.

1 INTRODUCTION AND BACKGROUND

1.1 Summary of Drug Product Information Pertinent to Review

This review is DCR's comparative (threshold) analysis to assess end-user interface of the drug device combination product, teriparatide injection, 600 mcg/2.4 mL (250 mcg/mL), submitted by Apotex, Inc., on 12/29/2017 under ANDA 211097.

The RLD, Forteo® (teriparatide recombinant human) 20 mcg per dose (600 mcg/2.4 mL), NDA 021318, was approved on 11/26/2002 (b) (4) Forteo is supplied in a glass cartridge pre-assembled into a disposable delivery device (pen) for subcutaneous injection prefilled with 2.7 mL of teriparatide, 250 mcg/mL. The pen delivers 20 mcg of teriparatide per dose each day for up to 28 days.[1] Forteo's labeling contains Prescribing Information, Medication Guide, Pen Label (affixed to the device), Pen Carton label, and User Manual.

The Applicant intents to market the proposed generic drug-device combination product (drug and a delivery device intended to administer a drug) in the same configuration as the RLD. In support of their application, the Applicant submitted comparative (threshold) analyses along with the results of a formative (noncomparative) human factors (HF) study and samples of the proposed (b) (4) and the RLD for evaluation. Currently, there are no generic versions of Forteo. Therefore, ANDA 211097 is a potential first generic.

DCR reviewed the following materials pertinent to this review:

- RLD Background Information: sNDA 021318/S-016, Chemistry (CMC) Review dated 02/25/2008, Office of Surveillance and Epidemiology (OSE) Review dated 04/15/2008; Product Information/Prescribing Information/ User Manual.
- A211097 Submission: Labeling/User Manual; Threshold Analysis; Formative Human Factors Study
- Product samples sent by the Applicant, RLD and proposed.
- Pre-ANDA: Control Correspondence #16343726 dated 07/12/2017; Division of Therapeutic Performance (DTP) Control Response dated 09/11/2017.
- Consult: Division of Medication Errors and Prevention (DMEPA) consult Response dated 08/20/2018.
- Published Medical Literature

In this review, DCR evaluates the delivery device constituent part of the proposed teriparatide injection combination product and related product labeling. This review focuses on the analysis of the user interface for the proposed device compared to the RLD. For the purposes of this review, (b) (4) pen, (b) (4) and device are used interchangeably.

[1] Drugs@FDA Drug Label for Forteo (Teriparatide) Recombinant Human Subcutaneous Injection. Accessed 07/18/2018 https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021318s036lbl.pdf.

1.2 Pertinent RLD History on (b) (4) Design: ForteoPen Vs. Forteo IndePEN

The RLD, Forteo® was approved 11/26/2002. The picture below shows the originally approved and marketed Forteo (b) (4) (Forteo Pen).

Figure 1: Original Forteo Pen Approved 11/26/2002

Source: https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/21318slr002_forteo_lbl.pdf , accessed 08/16/2018; p. 4 of 4

(b) (4)

Table 1 summarizes the changes to the operating principles, visual feedback mechanisms, and related User Manual of the original Forteo (b) (4)

Table 1: Comparison redesigned Forteo (b) (4) (IndePEN) and original (b) (4) (Forteo Pen)

Feature	Current Forteo Pen (IndePEN) Approved 06/25/2008 (sNDA 021318/S-016)	Original Forteo Pen Approved 11/26/2002 (NDA 021318)
Priming required prior to first use of pen	No	Yes
Priming required before each dose	No	Yes

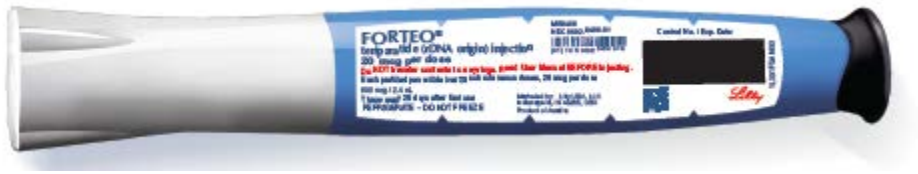
[2] Cover Letter NDA021318/S-016 New Supplement submitted 10/30/2007 - DARRTS
[3] Note to the Reviewer NDA021318/S-016 New Supplement submitted 10/30/2007 - DARRTS

Feature	Current Forteo Pen (IndePEN) Approved 06/25/2008 (sNDA 021318/S-016)	Original Forteo Pen Approved 11/26/2002 (NDA 021318)
Number of operation steps for each dose delivery	2	8
Visual clues for patients	Easy to see colors	Arrows and numbers in small dose window
Injection force	Approximately 3 times less than current Forteo pen	
User manual	One page – front and back; color illustrations, bigger font	Single page black and white leaflet in 8 point font.

Reviewer Table. Source: Note to the Reviewer NDA021318/S-016 New Supplement submitted 10/30/2007, p. 2/56

The redesigned RLD Forteo (b) (4), as shown in Figure 2 below, was approved on 06/25/2008 under NDA 021318/S-016.

Figure 2: Redesigned Forteo IndePEN, Approved 06/26/2008, NDA 021318/S-016



Source: NDA 021318 Carton label. GS Module 1.14.2.1

Reviewer Comment: *According to Sponsor, the redesigned Forteo IndePen simplified the functionality and operating principles of the device through reducing the steps required to operate the pen, lowering the force required for injection, and improving patient feedback during the injection process. In addition, the body of the pen was redesigned from a cylindrical shape to a broader pen with an elliptical-shaped body,* (b) (4)

1.3 Pertinent Background (Pre-ANDA) History of Proposed Generic Teriparatide, ANDA 211097

On 07/12/2017, five months before the ANDA submission, Apotex, Inc., the Applicant, submitted control correspondence (CC) #16343726, for evaluation of their proposed (b) (4) for teriparatide in reference to the RLD Forteo IndePen.[4] The CC submission contains the results of their Comparative Threshold Analyses and a formative (noncomparative) HF study.

(b) (4)

[4] CC #16343726 submitted 07/12/2017
http://panorama.fda.gov/document/view?versionID=5968dffe001b6e8803efc9e74ded2ae5

On 09/11/2017, the Division of Therapeutic Performance (DTP) in the Office of Research and Standards (ORS) reviewed the control correspondence and provided the following comments *in verbatim:* [5]

1) Your proposed test device appears to be similar to the reference device with respect to external operating principles only.

2) We have identified differences between your test device and the reference device with respect to some external critical design attributes – (b) (4). We are concerned that these differences may generate usability issues and confusion to the intended patient population if your proposed product were to be substituted for the RLD product. Therefore, we strongly recommend that you consider modifying the design (b) (4) of your proposed test device, to minimize differences from the RLD product.

3) FDA acknowledges that, in addition to your threshold analyses, you also submitted a human factors study within this package. Evaluation of any human factors study data is beyond the scope of a Test device threshold analyses assessment submitted within a Controlled Correspondence.

4) If you wish to continue your development program with your as-proposed test device… we strongly encourage you submit a pre-ANDA meeting request to OGD. The package should contain sufficient detailed information in order to discuss your proposed development plans,

[5] ORS/DTP review by Bryan Newman entered in GDRP by Wendy Good on 09/11/2017
http://panorama.fda.gov/document/view?versionID=59b6e3b0001a819e4f6967494b9d05c1

including the need for additional information and/or data such as comparative human factors studies, prior to initiation of any data collection.

5) As a general matter, the labeling for a generic product should be the same as the RLD product, except for certain labeling changes permitted under 21 CFR 314.94(a)(8)(iv). We note several differences in labeling, specifically within the proposed Instructions For Use (IFU), when compared to the approved labeling for the RLD. We recommend you more closely align your proposed labeling to the approved labeling for the RLD. Please note that the permissibility of any labeling differences between test and reference products will be assessed during the ANDA review.

Reviewer Comments:

1. *Despite FDA's advice to submit a pre-ANDA meeting request to OGD to discuss their proposed development plans (see section 1.3, item #4), the Applicant did not request a pre-ANDA Meeting or any other pre-ANDA communications prior to the submission of the ANDA.*
2. (b) (4)
3. *The proposed pen design and shape has the same cylindrical-shaped* (b) (4) *as the originally approved RLD Forteo.*
4. *The submission also includes Addendum to the Threshold Analysis related* (b) (4) *the proposed redesigned pen.*
5. *The formative HF study submitted in the CC on 7/12/2017, which was performed with the previous* (b) (4) *was also submitted in the ANDA. The Applicant did not submit comparative HF study with the proposed redesigned device.*

2 COMPARATIVE (THRESHOLD) ANALYSES REVIEW AND DISCUSSION

DCR conducted a comparative analysis review of the user interface of the device component of proposed generic combination product and its RLD Forteo (teriparatide recombinant human) Injection, NDA 021318. The comparative analysis comprised labeling comparison, comparative task, and physical comparison of the delivery device constituent part.

2.1 Labeling comparison of the delivery device constituent part: RLD vs. Proposed

Labeling comparison was conducted using the most recent labeling version of the RLD, Forteo Injection, approved 08/30/2013,[6] User Manual revised in March 2018,[7] and the ANDA proposed Final Labeling submitted 03/20/2018.[8]

For purposes of this review, DCR only compared labeling materials pertinent to user interface, i.e., Delivery Device Description/Design, Administration, Illustrations, and Instructions for Use

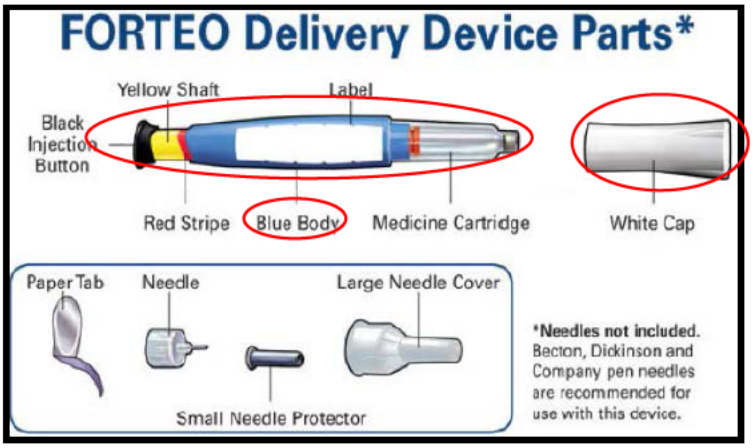
[6] Forteo Current Label, approved 08/20/2013 (SUPPL-36)
https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021318s036lbl.pdf
[7] Forteo User Manual – NDA 021318; revised March 2018
\\cdsesub1\evsprod\nda021318\0188\m1\us\usermanual.pdf
[8] A211097 Proposed Final Labeling submitted 03/20/2018, GS SEQ 0004 Module 1.14.2.3
\\cdsesub1\evsprod\anda211097\0004\m1\us\114-labeling\final-labeling\final-labeling-text\proposed-prescribing-information.pdf

for the RLD and the proposed device. Table 2 highlights the results of the labeling comparison of the Delivery Device Constituent Part: RLD vs. Proposed.

Table 2: Labeling Comparison of the Delivery Device Constituent Part: RLD vs. Proposed

Delivery device constituent part labeling: RLD vs. Proposed	Yes/No/NA
(1) Any difference in the **description/design**?	Yes (see comparison in Figure 3 below)
(2) Any difference in the **administration or directions for use**?	No
(3) Any difference in the **illustration(s)/figure(s)**?	No (except for those in the description/design, see (1))
(4) Any differences in the end-user **IFU**?	Yes (see Section 2.1.1)

Figure 3: Differences in Description/Design RLD Forteo (left) vs. ANDA (right)



(b) (4)

Reviewer Comments:

1. (b) (4)
2.

(b) (4)

1 Page has been withheld in full as b4 (CCI/TS) immediately following this page

Reviewer Table.

Reviewer Comments:

1. *The provided samples are accurately represented and described in the proposed teriparatide product's labeling.*
2. *In general, the proposed device's functionality is very similar to the RLD and feedback mechanisms (visual cues to indicate the status of the pen) are the same.*
3. (b) (4)
4. (b) (4)
5. *Comparing usability of the proposed* (b) (4) *versus the RLD (simulated repeat use of each device), DCR found both devices are easy to assemble, easy to learn to use, easy to use, and force needed for an injection is about the same.*

2.3 Applicant's Comparative Task Analysis[10]

The Applicant submitted three study reports: Threshold Analysis, Threshold Analysis Addendum, and Formative Human Factors (HF) Study. DCR reviewed both threshold analyses and consulted Division of Medication Errors and Prevention (DMEPA) for evaluation of the HF

[10]A211097 Comparative Task Analysis (Addendum), GS SEQ 0000 (undated) Module 5.3.5.4. Study Report-Addendum Threshold Analysis \\cdsesub1\evsprod\anda211097\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5354-other-stud-rep\apo2016teriparatidef1503\apo2016teriparatidef1503-report-body-3.pdf

study. The threshold analyses performed are consistent with draft guidance *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*, recommended in January 2017:[11]

Overall, the Applicant found no differences with task and labeling comparisons, but identified the following differences with the physical comparisons of the devices, which they classified as "minor":

(b) (4)

The Applicant concluded that "The analysis confirmed that users are required to perform the same tasks – the same sequence of actions in the same manner – when using the Forteo® and Teriparatide PFP devices. Based on a comparison of tasks alone, there is no reason to expect any differences in a user's ability to perform critical tasks when switching from Forteo® to the Teriparatide PFP product."

Reviewer Comments:

- *DCR agrees the tasks to operate the proposed* (b) (4) *are the same as the RLD, the devices are equally easy to use* (b) (4)*, and IFU are the same.*

- *However, there is no data to support that the different external design attributes between the RLD and the proposed device is a minor difference. The data the ANDA Applicant has provided to date do not address* (b) (4) (b) (4) *design impact ease of use or affect the user's ability to perform critical tasks (holding the pen, administering a dose) on a daily basis, particularly in postmenopausal women with osteoporosis and elderly patients (ages 70 and older) when the proposed device is used as a substitute for the RLD. Per RLD sponsor, the redesigned Forteo device incorporates* (b) (4) *design to increase control and stability during use.*

- *As noted in Section 1.2, The RLD device redesign, including its* (b) (4) *shape, was in part to address complaints in the elderly population to increase control and stability.* (b) (4)

[11] Draft Guidance Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA, released in January 2017
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM536959.pdf

2.4 Review of Published Medical Literature: Patient Experience with the redesigned Forteo (b) (4)

Dore RK, *et al.*, published study *Patient experience with a new teriparatide delivery device* in the Journal of Current Medical Research and Opinion in 2009,[12] where the authors evaluated acceptability and common complaints of the redesigned Forteo (b) (4) This was an eight week, single-arm, multicenter, open-label clinical trial. Patients received teriparatide 20 mcg/day by subcutaneous injection using a new delivery device. Men and postmenopausal women with osteoporosis at high risk for fracture were stratified to Current User (n = 92) or Not Current User (n = 107) groups. Current Users had used the original delivery device for > or =8 weeks, including uninterrupted use for four weeks before enrollment.

The primary objective was to detect common complaints (> or =3% for all patients) regarding the functionality and acceptability of the new device. Complaints were categorized as functional (e.g., malfunction), nonfunctional (e.g., size), or user manual. Secondary objectives included questionnaire assessment of preference of the new versus original device, features of the new delivery device, and analysis of adverse events. The authors found that 92% of patients who used the original (b) (4) preferred the new delivery device, but a common complaint was device size (4%). Overall, patients agreed that the new device was easy to use (99.5%), easy to learn to use (99%), easy to attach a needle (97%), easy to hold while injecting (95%), and that it reduced their reluctance to take injections (90%). Adverse events reported by > or =2% of patients were upper respiratory infection (3.5%), urinary tract infection (2%), influenza (2%), and headache (2%).

Reviewer Comment: *The authors found the new device was easy to use, easy to hold while injecting, and reduced their reluctance to take injections. Overall, 92 percent of patients who used the original (b) (4) preferred the new redesigned delivery device; only 4 percent complained of the of the new size.*

3 Formative Human Factors Study

In addition to the Threshold Analysis, the Applicant submitted the results of Formative Human Factors (HF) Study conducted by Human Factors MD to assess:

- Whether there are any unanticipated use errors related to the use of the Teriparatide Prefilled Pen and/or the supporting materials
- Whether any further changes to the pen design or supporting materials are needed as risk mitigations
- Whether the Teriparatide Prefilled Pen is comparable, in usage, to the on market RLD
- Suitability of the protocol for the final human factors validation test of the Teriparatide Prefilled Pen

The study was a simulated-use study in 6 previous/current RLD users, 6 patients being prescribed the proposed device for the first time, and 6 healthcare professionals (HCPs) (N=18 subjects). Each test lasted up 60 minutes, where each subject was given the commercial presentation of the drug product (commercial device design and draft labeling) and instructed to simulate use of the product by injecting into an injection pad or mannequin.

[12] Dore RK, Feldman RG, Taylor KA, See K, Daisky GP, Warmer MR (2009), Patient experience with a new teriparatide delivery device. Curr Med Res Opin. Oct;25(10):2413-22

Reviewer Comment: *Review of any HF studies is beyond the scope of DCR's threshold analysis. Thus, we consulted DMEPA for evaluation of the submitted formative HF study and opinion on the different external design attributes.*

3.1 DCR Consult to Division of Medication Errors and Prevention (DMEPA)

On 04/20/2018, DCR requested DMEPA to evaluate the submitted formative HF study data and answer the following questions:[13]

1. Is the Formative Human Factory study conducted with (b) (4) design different than the "to-be marketed" (b) (4) submitted under ANDA 211097 acceptable? See Figures A to D.
    a. If yes, does the HF study adequately demonstrate that the proposed (b) (4) does not pose any significant risks to patients switching between the RLD and the proposed (b) (4) (and vice-versa)?
    b. If no, do you recommend that the applicant conduct human factors studies comparing the proposed generic to-be marketed (b) (4) and the RLD Forteo? Please provide recommendations to convey to the applicant.
2. Do the differences in design between the proposed (b) (4) and the RLD pose any medication errors or usability concerns?
3. Does DMEPA have any further comments or recommendations?

3.2 DMEPA Responses to Consult Questions[14]

The following section presents DMEPA responses to DCR questions in a Questions/Response format. DCR questions are in **Bold** letter font; DMEPA's responses (*in verbatim*) are presented in 11-point font.

Question 1: Is the Formative Human Factor study conducted with (b) (4) design different from the 'to-be-marketed' (b) (4) submitted under ANDA 211097 acceptable?

DMEPA Response:
Yes, it is acceptable to use a device other than the 'to-be-marketed' version in a formative study. However, it is important to note that a formative study's objective generally differs from the objective for a comparative HF study. A formative study is typically conducted on a product prototype user interface at one or more stages during the iterative product development process to assess user interaction with the product and identify potential use errors. See our additional comments in question #1a.

[13] A211097 Teriparatide injection, DCR consult request to DMEPA, entered in DARRTS 04/20/2018 by Nitin Patel https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af804929 27&_afrRedirect=1620356714791602

[14] A211097 Teriparatide injection DMEPA response to DCR consult, entered in DARRTS by Denise Baugh, PharmD on 09/11/20118 https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af804b508c&_afrRedirect=320554892013083

a. If yes, does the HF study adequately demonstrate that the proposed (b) (4) does not pose any significant risks to patients switching between the reference listed drug (RLD) and the proposed (b) (4) (and vice versa)?

DMEPA Response:
No, the methodology used in the formative human factors (HF) study is not designed to generate data to answer this question. In circumstances where, based on the findings of threshold analyses, we find that additional data from a comparative use human factors study may be warranted to answer this question, then the design of the study would differ from that of the formative study that was submitted by Apotex under ANDA 211097.

b. "If no, do you recommend that the applicant conduct HF studies with the proposed 'to-be-marketed' pen and the RLD, Forteo? Please provide language to convey to the applicant."

DMEPA Response: N/A

Question 2: Do the differences in design between the proposed (b) (4) and the RLD pose any medication errors or usability concerns?

DMEPA Response:
See our response to question 3 below.

Question 3: Does DMEPA have any further comments or recommendations?

DMEPA Response:
Our review of the threshold analysis identified differences in external critical design attributes of the proposed combination product when compared to the RLD, Forteo (see Appendix G). Specifically, there are differences in the overall shape, size, and tactile features of the proposed combination product when compared to the RLD and these differences can impact the critical task of dose injection for this product.

We note that the generic applicant, Apotex, finds that the differences in the external critical design attributes of the proposed device in comparison to the RLD (Forteo) are minor. However [,] the applicant has not provided information and/or data to support that conclusion. We are concerned, given the labeled indication and intended user of this product, that the proposed device's slimmer body and shape and texture differences may impact the intended users' ability to safely and effectively operate the device (b) (4) and thus, may affect how the user performs the critical task of dose injection. As such, we find that additional information and/or data, such as data from a comparative use human factors study, may be warranted to further assess whether the design differences identified might impact the clinical effect or safety profile of the proposed product as compared to the RLD when the generic is substituted for the RLD.

DMEPA provide letter the following letter-ready comments for OGD to consider communicating to the Applicant.

We reviewed your threshold analyses and your conclusion that the differences between your proposed device and the RLD are minor. However, you have not provided sufficient information

> and/or data to support your conclusion. We have determined that the proposed device's slimmer body, shape and tactile/texture differences may have the potential to impact the intended users' ability to safely and effectively operate the device (b) (4) , and thus, may affect how the user performs the critical task of dose injection. We request that you provide additional information and/or data, such as data from a comparative use human factors study, to further assess whether the identified differences in the user interface for your proposed product impacts [impact] the clinical effect or safety profile when compared to its RLD.

Reviewer Comment: *DCR agrees with DMEPA's concerns about the proposed device external design differences compared to the RLD device and agrees that the Applicant should provide additional data, specifically a comparative human factors study, to address the concerns.*

4 CONCLUSION

Based on available information, DCR concludes there are other than minor design differences (overall body shape, size, and tactile features) in the external critical design attribute of the proposed generic combination product device compared to the RLD that may impact the intended users' ability to safely and effectively operate the device to perform the critical task of dose injection.

5 RECOMMENDATION

Clinical Comments/Recommendations to be conveyed to the APPLICANT in Complete Response (CR) Letter.

To DPM Regulatory Project Manager: The following comments/deficiencies and/or recommendations should be conveyed to the ANDA applicant. DCR considers these deficiencies to be MAJOR deficiencies to be communicated under the 'Clinical' heading of the COMPLETE RESPONSE Letter. These should NOT be communicated to the Applicant in an Information Request.

We reviewed your threshold analyses and your conclusion that the differences between your proposed device and the RLD are minor. However, you have not provided sufficient information and/or data to support your conclusion. We have determined that the proposed device's slimmer body, shape and tactile/texture differences may have the potential to impact the intended users' ability to safely and effectively operate the device (b) (4) and thus, may affect how the user performs the critical task of dose injection on a daily basis particularly in postmenopausal women with osteoporosis and elderly patients. We request that you provide additional information and/or data, such as data from a Comparative Use Human Factors Study, to further assess whether the identified differences in the user interface for your proposed product impact the clinical effect or safety profile when compared to its RLD.

We refer you to the draft guidance for Industry: Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA, published January 2017.

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM536959.pdf

We recommend that before you submit the results of your Comparative Use Human Factors Study, you consider providing us with your study protocol so that we can provide feedback on its potential applicability to your ANDA.

3 Pages have been withheld in full as b4 draft labeling

Raquel Tapia

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Date: 9/11/2018 02:20:03PM
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Lolita Lopez

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Date: 9/11/2018 02:30:33PM
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Daiva Shetty

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Date: 9/11/2018 03:01:59PM
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COMPARATIVE USE HUMAN FACTORS STUDY REPORT

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:	June 8, 2021
Requesting Office or Division:	Division of Clinical Review (DCR) Office of Bioequivalence (OB)/Office of Generic Drugs (OGD)
Application Type and Number:	ANDA 211097
Product Type: Drug Constituent Name and Strength Device Constituent:	Combination Product Teriparatide Injection, 600 mcg/2.4 mL (250 mcg/mL) prefilled pen delivery device
Rx or OTC:	Rx
Applicant/Sponsor Name:	Apotex Inc.
Submission Date:	October 15, 2020
OSE RCM #:	2018-836
DMEPA Safety Evaluator:	Avani Bhalodia, PharmD, BCPS
DMEPA Team Leader (Acting):	Ebony Whaley, PharmD, BCPPS
DMEPA Associate Director for Human Factors (Acting):	Lolita White, PharmD
DMEPA Deputy Director:	Irene Z. Chan, PharmD, BCPS

1 REASON FOR REVIEW

This review evaluates the comparative use human factors (CUHF) study report submitted under ANDA 211097 for teriparatide injection.

1.1 PRODUCT DESCRIPTION

This is a combination product with a proposed pre-filled pen (PFP) device constituent part that is intended to treat osteoporosis. The reference listed drug (RLD) is Forteo (NDA 021318). (b) (4)

(b) (4)

1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

On July 18, 2017, the Applicant submitted comparative analyses under ANDA 211097. Our review identified differences in external critical design attributes of the proposed combination product when compared to the RLD Forteo. As such, we requested that the Applicant provide additional information and/or data, such as data from a comparative use human factors study, to further assess whether the identified differences in the user interface for the proposed product impact the clinical effect or safety profile when compared to the RLD[1].

On February 1, 2019, the Applicant submitted their CUHF study protocol under ANDA 211097. Our review of the CUHF study protocol identified several areas of concern. We communicated our findings to the Division of Clinical Review (DCR)[2] and our recommendations were conveyed to the Applicant.

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[1] Baugh, D. Human Factors Study Review for Teriparatide (ANDA 211097). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 AUG 17. RCM No.: 2018-836.

[2] Shah M. Comparative Use Human Factors Protocol Review for Teriparatide (ANDA 211097). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 NOV 12. RCM No.: 2018-836.

On November 20, 2019 and December 5, 2019, Apotex submitted clarifying questions that were in response to our previous CUHF protocol recommendation regarding the patient user group[3]. DMEPA communicated our responses to OGD via e-mail on December 10, 2019[4].

On July 29, 2020, the Applicant submitted a clarifying question via a General Correspondence (GC) in response to recommendations that we made during a previous CUHF study protocol review and responses to subsequent clarifying questions[5,6]. The Applicant requested feedback on the viability of remote testing in the CUHF study, given the Covid-19 public health emergency. We developed general feedback related to areas of concern that may arise with remote testing and strongly encouraged the Applicant to submit the CUHF study protocol for remote testing for Agency review before commencing the study. We communicated our feedback to OGD via e-mail on October 1, 2020[7]. OGD concurred with our recommendations. However, the Applicant submitted their Response to Complete Response on October 15, 2020, before our recommendations could be conveyed to the Applicant. The Applicant conducted their CUHF study prior to receiving feedback from the agency on their remote testing approach. The CUHF study results report submitted on October 15, 2020 is the subject of the review.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide our findings and evaluation of each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B

[3] Shah M. Comparative Use Human Factors Protocol Review for Teriparatide (ANDA 211097). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 NOV 12. RCM No.: 2018-836.

[4] Shah M. Review of Comparative Use Human Factors Study Protocol Clarifying Question for Teriparatide (ANDA 211097). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JAN 10. RCM No.: 2018-836-1.

[5] Shah M. Comparative Use Human Factors Protocol Review for Teriparatide (ANDA 211097). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 NOV 12. RCM No.: 2018-836.

[6] Shah, M. Comparative Use Human Factors Study Protocol Clarifying Question for Teriparatide (ANDA 211097). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JAN 10. RCM No.: 2018-836-1.

[7] Schlick, J. Comparative Use Human Factors Study Protocol Clarifying Question for Teriparatide (ANDA 211097). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 07. RCM No.: 2018-836-2.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Human Factors CUHF Study Report	C
Information Requests Issued During the Review	D
Division of Biostatistics (DBVIII) Consult Review	E

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design, CUHF study results, and our analysis to determine if the results demonstrate that the proposed Teriparatide PFP is non-inferior to the RLD Forteo when used by patients in representative use scenarios and use environments consistent with the labeled conditions of use.

3.1 SUMMARY OF STUDY DESIGN

Table 2 presents a summary of the HF validation study design. We note that the CUHF study included an in-person as well as a remote methodology. In discussion with the Office of Generic Drugs and with the DBVIII team, we find the information Apotex, Inc. provided to support their remote testing methodology is acceptable in this particular case. See Appendix C and D for more details on the study design.

Table 2. Study Methodology for Comparative Use Human Factors (CUHF) Study	
Study Design Elements	Details
Primary endpoint	Proportion of subjects with successful usage of Teriparatide device and the RLD device, Forteo.
Participants	N = 49 • N = 28 current Forteo users • N = 21 past Forteo users
Training	Participants were not trained prior to their test sessions but had access to the Instructions for Use (IFU) for each device to reference it, if they chose to use it. However, the moderator did not compel them to review these materials.
Test Environment	• In-person - typical home environment (with normal lighting, temperature, and humidity). The room will include two chairs, a table, injection pad and injection supplies

	• Remote testing – executed via web conference with the participant in their own home and the moderator in another location. Test stimuli (i.e., devices, IFUs, supplies, etc.) were the same between in-person and remote test sessions with the same test procedure followed. See Appendix C and D for additional details regarding remote testing.
Sequence of Study	Simulated injection 1 → Break (5 min) → simulated injection 2 → Use error interview The order in which the participant demonstrates use of pens was randomized across participants with either the Forteo first followed by the Teriparatide, or vice versa.

4 DISCUSSION OF RESULTS AND ANALYSES

According to the DBVIII review, the CUHF study results demonstrated that in terms of use success, the proposed product Teriparatide PFP met the non-inferiority margin and is non-inferior to the RLD Forteo[8].

The review results identified 22 use errors with the proposed ANDA product and 23 use errors with the RLD. The primary use error observed during the study occurred with Critical Task 4: Hold the injection button down while delivering the medication. Seventeen participants failed to hold the injection button down while simulating medication delivery with the Forteo device and 17 participants failed to hold the injection button down with the Teriparatide pen. Of the aforementioned failures, 15 participants committed the same use error with both devices.

The second use error, observed during the study occurred with for Critical Task 5: Hold in place to deliver the medication. Six participants did not hold the Forteo device in place for a count of 5 to deliver the medication and 5 participants did not hold the Teriparatide PFP device in place for a count of 5 to deliver the medication. Of the aforementioned failures, 5 participants committed the same use error with both devices.

We also note that in the root cause analysis of the identified use errors, study participants did not attribute the differences in design of the device as being a cause of the use errors.

Based on the totality of evidence and the assessment by DBVIII, we determine that the CUHF study results supports non-inferiority of the proposed Teriparatide PFP when substituted for the RLD. No further information or data is needed from DMEPA at this time.

[8] Wang, Y. Statistical Review and Evaluation (Biometrics Consult). Silver Spring (MD): FDA, CDER, OTS, OB, DBVIII (US); 2021 JUN 7.

5 CONCLUSION

We reviewed the CUHF study results and determined that the CUHF study results demonstrate that the proposed Teriparatide PFP is non-inferior to the RLD Forteo when used by patients in representative use scenarios and use environments consistent with the labeled conditions of use. As such, we conclude that, from a usability perspective, the proposed Teriparatide product can be substituted with the full expectation that it will produce the same clinical effect and safety profile as the RLD under the conditions specified in the labeling.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Teriparatide Injection that Apotex Inc. submitted on October 15, 2020.

Table 3. Relevant Product Information	
Initial Approval Date	N/A
Therapeutic Drug Class or New Drug Class	Recombinant human parathyroid hormone analog
Active Ingredient (Drug or Biologic)	Teriparatide
Indication	• Treatment of postmenopausal women with osteoporosis at high risk for fracture • Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture • Treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture
Route of Administration	Subcutaneous
Dosage Form	Injection
Strength	600 mcg/2.4 mL (250 mcg/mL)
Dose and Frequency	Recommended dose is 20 mcg subcutaneously once a day
How Supplied	2.4 mL prefilled pen delivery device
Storage	• Refrigeration at 2°C to 8°C (36°F to 46°F) • Recap the delivery device when not in use to protect the cartridge from physical damage and light • During the use period, time out of the refrigerator should be minimized; the dose may be delivered immediately following removal from the refrigerator. • Do not freeze. Do not use teriparatide injection, USP if it has been frozen.
Container Closure/Device Constituent	Multi-dose prefilled delivery device (pen)
Intended Users	• Postmenopausal women with osteoporosis and • Elderly patients (including women and men 65 and older) with osteoporosis.
Intended Use Environment	Home settings

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On January 29, 2021, we searched the L:drive and AIMS using the terms, 211097 to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified four previous reviews[9,10,11,12], and we confirmed that our previous recommendations were implemented.

APPENDIX C. COMPARATIVE USE HUMAN FACTORS STUDY RESULTS REPORT

The HF study results report can be accessible in EDR via:
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APPENDIX D. INFORMATION REQUESTS ISSUED DURING THE REVIEW

- On March 2, 2021, we sent an IR to the Applicant to request comprehensive detail of their remote testing and obtain a specific duration of use including last use of Forteo for each previous Forteo user in their study. The Applicant's IR response on March 9, 2021 provided information of previous Forteo users and remote testing details which we found acceptable for this particular case.
    - \\CDSESUB1\evsprod\anda211097\0025\m1\us\12-cover-letters\response-to-information-request-pdf-20210309.pdf
- On April 13, 2021, we sent an IR to the Applicant to request their rationale for asking participants to take time to review the materials in the box for the Forteo injection scenario during remote testing and indicate which participants, if any, chose to familiarize themselves with the materials prior to simulated injection for both Forteo and their proposed product. The Applicant's IR response on April 15, 2021 clarified that the cue for the option to review was the prompt to start the testing and not a 'familiarization' step.
    - \\CDSESUB1\evsprod\anda211097\0026\m1\us\12-cover-letters\response-to-information-request-pdf-20210415.pdf

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[9] Baugh, D. Human Factors Study Review for Teriparatide (ANDA 211097). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 AUG 17. RCM No.: 2018-836.

[10] Shah M. Comparative Use Human Factors Protocol Review for Teriparatide (ANDA 211097). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 NOV 12. RCM No.: 2018-836.

[11] Shah, M. Comparative Use Human Factors Study Protocol Clarifying Question for Teriparatide (ANDA 211097). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JAN 10. RCM No.: 2018-836-1.

[12] Schlick, J. Comparative Use Human Factors Study Protocol Clarifying Question for Teriparatide (ANDA 211097). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 07. RCM No.: 2018-836-2.

APPENDIX E: DIVISION OF BIOSTATISTICS (DBVIII) CONSULT REVIEW

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DARRTS link:
https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af805f7425&_afrRedirect=912381564510130

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

AVANI BHALODIA
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EBONY A WHALEY
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EBONY A WHALEY on behalf of LOLITA G WHITE
06/08/2021 03:42:54 PM

IRENE Z CHAN
06/09/2021 07:44:11 AM

MEMORANDUM

REVIEW OF COMPARATIVE USE HUMAN FACTORS STUDY PROTOCOL CLARIFYING QUESTION

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:	January 10, 2020
Requesting Office or Division:	Division of Clinical Review (DCR)/Office of Bioequivalence (OB)/Office of Generic Drugs (OGD)
Application Type and Number:	ANDA 211097
Product Type:	Combination Product
Drug Constituent Name and Strength:	Teriparatide injection, 20 mcg
Device Constituent:	Pre-filled Pen
Rx or OTC:	Rx
Applicant/Sponsor Name:	Apotex, Inc.
FDA Received Date:	November 20, 2019 and December 5, 2019
OSE RCM #:	2018-836-1
DMEPA Safety Evaluator:	Millie Shah, PharmD, BCPS
DMEPA Team Leader:	Lolita White, PharmD
DMEPA Associate Director for Human Factors:	QuynhNhu Nguyen, MS

1 PURPOSE OF MEMORANDUM

On November 20, 2019 and December 5, 2019, Apotex submitted clarifying questions (see Appendix A) in response to recommendations that we made during a previous comparative use human factors study protocol review.[a] Apotex is developing a combination product with a proposed prefilled pen device constituent part that is intended to treat osteoporosis. The reference listed drug is Forteo (NDA 021318). This memorandum provides our response to Apotex's clarifying questions.

[a] Shah M. Comparative Use Human Factors Protocol Review for Teriparatide (ANDA 211097). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 NOV 12. RCM No.: 2018-836.

2 COMMUNICATION OF DMEPA'S RESPONSES TO OFFICE OF GENERIC DRUGS (OGD)

DMEPA communicated our findings to OGD via e-mail on December 10, 2019. At that time, we also requested concerns that could inform our review. Per e-mail correspondence from OGD on January 10, 2020, they stated no additional concerns and did not object to DMEPA's responses.

3 CONCLUSION

We provide our responses to Apotex's clarifying question in Section 4.

4 RECOMMENDATIONS FOR APOTEX, INC.

Please see our response to your clarifying questions related to your comparative use human factors study protocol.

Agency's Recommendation (dated November 12, 2019)	Apotex's Clarifying Question (submitted November 20, 2019)	Agency's Response to Clarifying Question
The use of surrogates for the primary analysis is not acceptable. The surrogates may not represent the patient population. You should recruit an adequate number of RLD users in the study.	The feedback we have received to date from the CRO's conducting the research, is that recruitment of such a patient population may be difficult as the prescribed usage of Forteo is only 2 years, which poses a significant limitation on availability of participants. As such, we would like to request, should recruitment of a sufficient number of patients currently on Forteo® prove difficult, would it be acceptable to allow for inclusion of previous Forteo® users in the study? A previous user would be defined as someone who has administered daily Forteo® injections for a minimum of three weeks within the past two years.	We understand you propose to include previous Forteo® users in the study should recruitment of a sufficient number of patients currently on Forteo® proves difficult. We are concerned that the inclusion of previous Forteo users does not allow assessment of current RLD users with your proposed product. As such, we recommend that you recruit as many current users of Forteo as possible. Should you encounter difficulty in recruiting current Forteo users, you may proceed as you propose. You should collect information on each participant's duration of use including last use of Forteo and report this information in your comparative use human factors study results.

Apotex's Clarifying Question (submitted December 5, 2019)	Agency's Response to Clarifying Question
Through discussion with the CRO in planning for the comparative study, a question has been raised on whether it would be acceptable to include participants who are caregivers who administer Forteo? From a comparative design perspective it is considered that this should be acceptable as caregivers are true representatives of the end users of Forteo, and thus can be included in the study to asses possible differences in user interface.	We acknowledge that caregivers who administer Forteo are intended users; however, in this instance we do not find it acceptable to include caregivers in your comparative use human factors study. Specifically, we are concerned that inclusion of caregivers will not provide data on the ability of the intended patients (e.g. elderly patients with osteoporosis) to grasp and control your proposed product and identify any usability concerns due to the slimmer body, shape and tactile/texture differences when compared to Forteo. Thus, we do not find it acceptable to recruit caregivers who administer Forteo.

APPENDIX A. COMPARATIVE USE HUMAN FACTORS STUDY PROTOCOL CLARIFYING QUESTIONS RECEIVED ON NOVEMBER 20, 2019 AND DECEMBER 5, 2019

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/s/

MILLIE B SHAH
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LOLITA G WHITE
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QUYNHNHU T NGUYEN
01/13/2020 11:10:29 AM

MEMORANDUM

REVIEW OF COMPARATIVE USE HUMAN FACTORS STUDY PROTOCOL CLARIFYING QUESTION

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 7, 2020
Requesting Office or Division:	Division of Clinical Review (DCR)/Office of Bioequivalence (OB)/Office of Generic Drugs (OGD)
Application Type and Number:	ANDA 211097
Product Type:	Combination Product
Drug Constituent Name and Strength:	Teriparatide injection, 20 mcg
Device Constituent:	Pre-filled Pen
Rx or OTC:	Rx
Applicant/Sponsor Name:	Apotex, Inc.
FDA Received Date:	July 29, 2020
OSE RCM #:	2018-836-2
DMEPA Safety Evaluator:	James Schlick, MBA, RPh
DMEPA Team Leader:	Millie Shah, PharmD, BCPS
DMEPA Associate Director for Human Factors (Acting):	Jason Flint, MBA, PMP
DMEPA Associate Director of Nomenclature & Labeling:	Mishale Mistry, PharmD, MPH

1 PURPOSE OF MEMORANDUM

On July 29, 2020, Apotex submitted a clarifying question via a General Correspondence (GC) (see Appendix A) in response to recommendations that we made during a previous comparative use human factors (CUHF) study protocol review and responses to subsequent clarifying

questions.[a,b] Apotex is seeking feedback on the viability of remote testing in the CUHF study, given the challenges of recruiting participants during the Covid-19 public health emergency. Apotex is developing a combination product with a proposed prefilled pen device constituent part that is intended to treat osteoporosis. The reference listed drug is Forteo (NDA 021318). This memorandum provides our response to Apotex's clarifying questions found in the GC.

2 COMMUNICATION OF DMEPA'S RESPONSES TO OFFICE OF GENERIC DRUGS (OGD)

DMEPA communicated our findings to OGD via e-mail on October 1, 2020. At that time, we also requested concerns that could inform our review. Per e-mail correspondence from OGD on October 7, 2020, they stated no additional concerns and did not object to DMEPA's responses.

3 CONCLUSION

We provide our responses to Apotex's clarifying question in Section 4.

4 RECOMMENDATIONS FOR APOTEX, INC.

We reference your submission on July 29, 2020 notifying us of your intent to conduct your comparative use human factors (CUHF) study remotely due to restrictions associated with the COVID-19. FDA recognizes that the COVID-19 public health emergency may impact your ability to conduct in person human factors (HF) testing of medical products. Please note there are currently no data that the Agency is aware of that support remote HF testing nor are we aware of any consensus scientific guidelines or standards that can inform an acceptable virtual/remote HF testing approach. As such, the Agency would need to carefully consider each individual protocol in its entirety in order to provide more informed feedback on a remote testing approach.

While the decision to proceed with a remotely conducted CUHF study is a business decision for your company, this decision carries some risk. We strongly urge you to submit your CUHF study protocol, taking into account the preliminary concerns we have identified that are detailed below, and await agency review before commencing your study. This will allow us to provide a detailed and comprehensive review, and ensure that the HF study maintains compliance with best practices, minimizes risks to study integrity, and supports public health priorities.

We have particular concerns about your proposed approach to remote testing, some of which include:

1. Participants may open and familiarize themselves with the study materials prior to conducting the study despite instruction not to. Clarify how you intend to handle such

[a] Shah M. Comparative Use Human Factors Protocol Review for Teriparatide (ANDA 211097). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 NOV 12. RCM No.: 2018-836.

[b] Shah, M. Comparative Use Human Factors Study Protocol Clarifying Question for Teriparatide (ANDA 211097). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JAN 10. RCM No.: 2018-836-1.

scenarios (e.g., will participants who open and familiarize themselves with study materials be disqualified?) and the impact to your collected data.

2. Variations in the conditions of a remote study use environment may be more representative of actual use for the individual participant in the study but may also make both collection and interpretation of study data more difficult. Clarify how you will address the lack of control over the environment, which may also introduce test artifacts.
3. Study moderators may have difficulty seeing all of the interactions that a participant has with the user interface, which may limit their ability to conduct a robust root cause analysis. There are many different types of video cameras that can be used to conduct virtual testing (e.g. smart phone video cameras, Webcams, built-in laptop cameras, digital video cameras). Each of these camera types have different features that may or may not be necessary for your virtual testing. For example, certain Webcams have pan/tilt/zoom features that would enable a more detailed observation of participants. Some camera types may come with a stand or can easily be placed on a tabletop for ideal positioning while others may require a stand. Provide a brief description of the technical specifications of the video device (e.g. frame rate, resolution, lens type, auto-focus features) used for each participant's session and justification for the adequacy of these specifications in capturing non-verbal behavior.
4. To minimize disruptions to the natural use of the product, participants should not be expected to adjust the camera position in the middle of testing. Provide the instructions you intend to provide to participants on where to set up the camera relative to the workspace.
5. We note that you intend to have a setup period. Clarify what criteria you will use to determine whether the setup is sufficient to collect meaningful data from the test participants, and what conditions may be used to determine that the study session cannot continue (for example, if you are unable to achieve an acceptable setup)
6. Difficulty during setup may increase participant frustration, and inadvertently bias their responses. Clarify how you intend to address these situations should they arise.
7. Recruitment of participants willing and able to participate in a remote study may not be adequately representative of the intended user groups. Clarify how you intend to recruit representative participants.

Please note that these are examples of some areas of concern and are not inclusive of all potential concerns with your proposal to conduct a remote CUHF study.

APPENDIX A. COMPARATIVE USE HUMAN FACTORS STUDY PROTOCOL CLARIFYING QUESTIONS RECEIVED VIA GENERAL CORRESPONDENCE ON JUY 29, 2020

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/s/

MILLIE B SHAH on behalf of JAMES H SCHLICK
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COMPARATIVE USE HUMAN FACTORS STUDY PROTOCOL 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:	November 12, 2019
Requesting Office or Division:	Division of Clinical Review (DCR)/Office of Bioequivalence (OB)/Office of Generic Drugs (OGD)
Application Type and Number:	ANDA 211097
Product Type:	Combination Product
Drug Constituent Name and Strength:	Teriparatide injection, 20 mcg
Device Constituent:	Pre-filled Pen
Rx or OTC:	Rx
Applicant/Sponsor Name:	Apotex, Inc.
FDA Received Date:	February 1, 2019
OSE RCM #:	2018-836
DMEPA Safety Evaluator:	Millie Shah, PharmD, BCPS
DMEPA Team Leader:	Lolita White, PharmD
DMEPA Associate Director for Human Factors:	QuynhNhu Nguyen, MS
DMEPA Deputy Director:	Irene Chan, PharmD, BCPS

1 REASON FOR REVIEW

This review evaluates a comparative use human factors (HF) study protocol submitted under ANDA 211097 for Teriparatide injection. This is a combination product with a proposed pre-filled pen (PFP) device constituent part that is intended to treat osteoporosis. The reference listed drug (RLD) is Forteo (NDA 021318).

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide our findings and evaluation of the material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH) and FDA/Sponsor Interactions	B
Human Factors Validation Study Protocol	C
Information Requests Issued During the Review	D-N/A
Product Sample, Label and Labeling, Packaging	E-N/A

3 REVIEW SUMMARY AND DISCUSSION

Our overall assessment of the comparative use HF study protocol indicated that the testing conditions and user groups require revisions to ensure that adequate data are captured during testing.

Please see the table below in section 5.1 for our evaluation and recommendations.

We also consulted the Division of Biometrics VIII (DBVIII) team to review the protocol's statistical plan. The DBVIII team identified additional deficiencies under a separate cover[a]. We agree with DBVIII's deficiencies and will convey the deficiencies to the sponsor.

4 COMMUNICATION OF DMEPA'S ANALYSIS TO OFFICE OF GENERIC DRUGS

DMEPA communicated our findings to the Division of Clinical Review during several meetings. We also requested concerns that could inform our review, which we considered and incorporated into our evaluation.

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[a] Wang, Y. Statistical Review and Evaluation for Teriparatide injection (ANDA 211097). Silver Spring (MD): FDA, CDER, OTS, OB, DB VIII (US); 2019 NOV 11.

5 CONCLUSION & RECOMMENDATIONS

We find that the comparative use HF study protocol is not acceptable. Please see section 5.1 for our recommendations. We advise that the Sponsor implement our recommendations prior to commencing their comparative use HF study.

5.1 RECOMMENDATIONS FOR APOTEX, INC.

Our review of the comparative use human factors study protocol identified several areas of concern. Please see the Identified Issues and Recommendations table. In addition, please see the recommendations from the Division of Biometrics on the statistical plan. We recommend that you implement all recommendations before commencing your comparative use human factors study.

Identified Issues and Recommendations for Sponsor			
	Identified Issue	Rationale for Concern	Recommendation
Comparative Use HF Study Methodology			
1.	We note that you have identified all tasks as critical tasks for evaluation in this study; however, we believe only a subset of these tasks are critical tasks for your proposed product	A critical task is, for example, a task that if performed incorrectly or not performed at all, would or could cause harm.[b] For the purposes of a comparative-use HF study, FDA is focused on those critical tasks that may be impacted by a difference in an external critical design attribute between the RLD and the proposed product. In this instance, we determined that tasks 3, 4, 5, 6 and 7 are the critical tasks that may be impacted by a difference in an external critical design attribute and therefore these tasks should be the focus of the study. Tasks 1, 2, 8, and 9 are not likely to be affected by an identified difference in external critical design attribute between the RLD and your proposed product.	Revise your critical tasks that will be evaluated in the study to tasks 3, 4, 5, 6, and 7 and update your protocol accordingly.

[b] Guidance for Industry: Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development. Food and Drug Administration. 2016. Available from https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm484345.pdf

2.	The protocol states that no follow-up questions will be asked if the participant did not have task failures on either pen or made the same errors with the Teriparatide PFP as with the Forteo pen (page 23).	Appropriate follow-up questions are necessary to learn the participant's perspective on all task failures to aid in the assessment of root causes. This information will help confirm whether differences in external critical design attributes contributed to use errors.	Revise the study protocol to ensure that open-ended follow-up questions are asked of study participants for all instances of use errors to inform your root cause analysis.
General Recommendations			
For additional information, please see draft guidance below: Comparative Analyses and Related Comparative Use Human Factors Studies for Drug-Device Combination Products Submitted in an ANDA and can be found online at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM536959.pdf			

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Teriparatide Injection received on February 1, 2019 from Apotex, Inc.

Table 3. Relevant Product Information	
Initial Approval Date	N/A
Therapeutic Drug Class or New Drug Class	Recombinant human parathyroid hormone analog
Active Ingredient (Drug)	teriparatide
Indication	Treatment of postmenopausal women with osteoporosis at high risk for fracture; increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture; treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture
Route of Administration	subcutaneous
Dosage Form	injection
Strength	20 mcg
Dose and Frequency	20 mcg subcutaneously once daily into the thigh or abdominal (b) (4)
How Supplied	Multi-dose, prefilled pen containing 28 daily doses of 20 mcg
Storage	Refrigeration at 2°C to 8°C (36°F to 46°F); (b) (4) Do not freeze. Do not use if (teriparatide) is frozen.
Container Closure/Device Constituent	Pre-filled pen
Intended Users	(b) (4) post-menopausal women with osteoporosis
Intended Use Environment	Home settings

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On March 29, 2019, we searched FDA previous reviews using the terms, 211097, to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified one previous review[c], and we confirmed that our previous recommendations were implemented or considered.

B.2 PREVIOUS FDA/SPONSOR INTERACTIONS PERTAINING TO HF

N/A

APPENDIX C. COMPARATIVE USE HUMAN FACTORS STUDY PROTOCOL

The HF study protocol can be accessible in EDR via:
\\cdsesub1\evsprod\anda211097\0015\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5354-other-stud-rep\apo2016teriparatidef1503\apo2016teriparatidef1503-report-body.pdf

APPENDIX D. N/A

APPENDIX E: N/A

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[c] Baugh, D. Human Factors Study Review for Teriparatide injection (ANDA 211097). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 AUG 17. RCM No.: 2018-836.

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HUMAN FACTORS STUDY 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:	August 17, 2018
Requesting Office or Division:	Division of Clnical Review (DCCR)/Office of Bioequivalence (OB)/Office of Generic Drugs (OGD)
Application Type and Number:	ANDA 211097
Product Type:	Combination Product
Drug Constituent Name and Strength:	Teriparatide Injection, 250 mcg/mL
Device Constituent:	Pre-filled Syringe
Rx or OTC:	Rx
Applicant/Sponsor Name:	Apotex
FDA Received Date:	July 18, 2017
OSE RCM #:	2018-836
DMEPA Safety Evaluator:	Denise V. Baugh, PharmD, BCPS
DMEPA Team Leader:	Lolita G. White, PharmD
DMEPA Associate Director for Human Factors:	QuynhNhu Nguyen, MS
DMEPA Deputy Director:	Danielle Harris, PharmD, BCPS
DMEPA Deputy Director:	Irene Z. Chan, PharmD, BCPS

1 REASON FOR REVIEW

The Division of Clinical Review (DCR)/ Office of Bioequivalence (OB)/Office of Generic Drugs (OGD) requested a Human Factors consultative review of a human factors study and a threshold analysis submitted under ANDA 211097 for Teriparatide Injection. This is a combination product with a proposed pre-filled syringe device constituent part that is intended to treat osteoporosis.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH) and FDA/Sponsor Interactions	B
Human Factors Formative Study and Threshold Analysis	C
Review of Product Sample	D
Information Requests Issued During the Review	E (N/A)
CDRH Human Factors Consult Review	F (N/A)

3 REVIEW SUMMARY AND DISCUSSION

The consult request from DCR/OB/OGD asks DMEPA the following questions:

1. Is the Formative Human Factor study conducted with [redacted] (b) (4) design different from the 'to-be-marketed' [redacted] (b) (4) submitted under ANDA 211097 acceptable?

    a. If yes, does the HF study adequately demonstrate that the proposed [redacted] (b) (4) does not pose any significant risks to patients switching between the reference listed drug (RLD) and the proposed [redacted] (b) (4) (and vice versa)?

    b. If no, do you recommend that the applicant conduct human factors studies comparing the proposed generic to-be-marketed [redacted] (b) (4) and the RLD Forteo? Please provide recommendations to convey to the applicant.

2. Do the differences in design between the proposed [redacted] (b) (4) and the RLD pose any medication errors or usability concerns?

3. Does DMEPA have any further comments or recommendations?

See Section 3.1 and 3.2 below for our detailed response to these questions.

3.1 RESPONSES TO CONSULT QUESTIONS

1. Is the Formative Human Factor study conducted with [redacted] (b) (4) design different from the 'to-be-marketed' [redacted] (b) (4) submitted under ANDA 211097 acceptable?

   DMEPA Response: Yes, it is acceptable to use a device other than the 'to-be-marketed' version in a formative study. However, it is important to note that a formative study's objective generally differs from the objective for a comparative HF study. A formative study is typically conducted on a product prototype user interface at one or more stages during the iterative product development process to assess user interaction with the product and identify potential use errors. See our additional comments in question #1a.

   a. If yes, does the HF study adequately demonstrate that the proposed [redacted] (b) (4) does not pose any significant risks to patients switching between the reference listed drug (RLD) and the proposed [redacted] (b) (4) (and vice versa)?

      DMEPA Response: No, the methodology used in the formative human factors (HF) study is not designed to generate data to answer this question. In circumstances where, based on the findings of threshold analyses, we find that additional data from a comparative use human factors study may be warranted to answer this question, then the design of the study would differ from that of the formative study that was submitted by Apotex under ANDA 211097.

   b. If no, do you recommend that the applicant conduct HF studies with the proposed 'to-be-marketed' pen and the RLD, Forteo? Please provide language to convey to the applicant.

      DMEPA Response: N/A

2. Do the differences in design between the proposed [redacted] (b) (4) and the RLD pose any medication errors or usability concerns?

   DMEPA Response: See our response to question 3 below.

3. Does DMEPA have any further comments or recommendations?

DMEPA Response: Our review of the threshold analysis identified differences in external critical design attributes of the proposed combination product when compared to the RLD, Forteo (b) (4)

We note that the generic applicant, Apotex, finds that the differences in the external critical design attributes of the proposed device in comparison to the RLD (Forteo) are minor. However the applicant has not provided information and/or data to support that conclusion. We are concerned, given the labeled indication and intended user of this product, that the proposed device's slimmer body and shape and texture differences may impact the intended users' ability to safely and effectively operate the device (b) (4) and thus, may affect how the user performs the critical task of dose injection. As such, we find that additional information and/or data, such as data from a comparative use human factors study, may be warranted to further assess whether the design differences identified might impact the clinical effect or safety profile of the proposed product as compared to the RLD when the generic is substituted for the RLD.

We provide letter ready comments in section 3.2 for OGD to consider communicating to the applicant.

3.2 LETTER READY COMMENTS TO APPLICANT

We reviewed your threshold analyses and your conclusion that the differences between your proposed device and the RLD are minor. However, you have not provided sufficient information and/or data to support your conclusion. We have determined that the proposed device's slimmer body, shape and tactile/texture differences may have the potential to impact the intended users' ability to safely and effectively operate the device (b) (4) and thus, may affect how the user performs the critical task of dose injection. We request that you provide additional information and/or data, such as data from a comparative use human factors study, to further assess whether the identified differences in the user interface for your proposed product impacts the clinical effect or safety profile when compared to its RLD.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Teriparatide Injection received on July 18, 2017 from Apotex.

Table 2. Relevant Product Information	
Initial Approval Date	Not applicable
Therapeutic Drug Class or New Drug Class	Recombinant human parathyroid hormone analog
Active Ingredient (Drug or Biologic)	teriparatide
Indication	Treatment of postmenopausal women with osteoporosis at high risk for fracture; increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture; treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture
Route of Administration	subcutaneous
Dosage Form	injection
Strength	20 mcg
Dose and Frequency	20 mcg subcutaneously once daily into the thigh or abdominal (b) (4)
How Supplied	Multi-dose, prefilled pen containing 28 daily doses of 20 mcg
Storage	Refrigeration at 2°C to 8°C (36°F to 46°F); (b) (4) Do not freeze. Do not use if (teriparatide) is frozen.
Container Closure/Device Constituent	
Intended Users	(b) (4) post-menopausal women with osteoporosis
Intended Use Environment	Home settings

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On July 13, 2018, we searched FDA previous reviews using the terms, 'ANDA 211097' to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified no previous reviews relevant to this review.

B.2 PREVIOUS FDA/SPONSOR INTERACTIONS

OGD provided the following information in their consult dated April 20, 2018:

Prior to the ANDA submission, the Applicant submitted control correspondence (CC) #16343726 on 07/12/2017, requesting evaluation of the [redacted] (b) (4) for substitutability with the RLD. In the CC, the applicant also submitted and requested the Agency to evaluate the TA and HF study results comparing their Test [redacted] (b) (4) (see Figures A and B below) and RLD Forteo (second generation) submitted. Note that the Applicant did not request FDA's advice prior to conducting HF studies prior to submission.

CC #16343726 was reviewed by Office of Research and Standards (ORS) in OGD and recommended redesigning the proposed [redacted] (b) (4). ORS also stated that evaluation of any human factors study data is beyond the scope of a proposed device TA assessment submitted within a Controlled Correspondence; ORS recommended submitting a pre-ANDA meeting request to OGD if the Applicant wished to continue the development of this generic drug product. The CC review can be accessed through the following link: http://panorama.fda.gov/project/view?ID=5968e12000060d97b5f595be9ee08760). There was no pre-ANDA meeting prior to the submission of this ANDA.

APPENDIX C. HUMAN FACTORS STUDY

The formative human factors study results and the threshold analysis conducted by the applicant were forwarded to DMEPA via e-mail from OGD on June 6, 2018 and June 22, 2018 respectively.

APPENDIX D. REVIEW OF PRODUCT SAMPLE

We received 1 product sample for evaluation. Additionally, OGD provided the following background information regarding the desing of the RLD, Forteo:

Background: After approval in 2002, the original (b) (4) for Forteo was redesigned in 2008 after some difficulties with its use were reported by old females (70 + years of age). The redesigned (second generation) prefilled (b) (4), Forteo IndePEN, approved under NDA 021318/S-016 on 06/25/2008, incorporates (b) (4) design to increase control and stability during use and colored visual cues to aid in device operation and troubleshooting. It also requires fewer steps to set and deliver a dose and less effort to push the injection button down as compared to the first generation Forteo (b) (4) [1] These modifications were intended to make the device easier for the target population to operate.

(b) (4)

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

None.

APPENDIX F: CDRH HUMAN FACTORS CONSULT REVIEW

None.

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/s/

DENISE V BAUGH
08/20/2018

LOLITA G WHITE
09/11/2018

QUYNHNHU T NGUYEN
09/11/2018

DANIELLE M HARRIS
09/11/2018

DANIELLE M HARRIS on behalf of IRENE Z CHAN
09/11/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 211097

CHEMISTRY REVIEW(s)

ANDA Executive Summary

1. Application/Product Information

ANDA Number.	211097
Review Cycle #	3
Applicant Name	Apotex Inc.
Drug Product Name	Teriparatide Injection, USP
Dosage Form. (click (+) for more than one)	Injection
Proposed Strength(s)	20 mcg per dose (600 mcg/2.4 mL)
Route of Administration (click (+) for more than one)	Subcutaneous
Maximum Daily Dose	20 mcg
Rx/OTC Dispensed	Rx
Proposed Indication	Teriparatide injection is indicated. • For the treatment of postmenopausal women with osteoporosis at high risk for fracture (defined herein as having a history of osteoporotic fracture or multiple risk factors for fracture) or who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, teriparatide injection reduces the risk of vertebral and nonvertebral fractures. • To increase bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture or who have failed or are intolerant to other available osteoporosis therapy. • For the treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy (daily dosage equivalent to 5 mg or greater of prednisone) at high risk for fracture or who have failed or are intolerant to other available osteoporosis therapy.
Drug Product Description	Teriparatide injection, USP contains chemically synthesized human parathyroid hormone (1-34), and is also called hPTH (1-34). It has an identical sequence to the 34 N-

<table>
<tr><td></td><td colspan="3">terminal amino acids (the biologically active region) of the 84-amino acid human parathyroid hormone. Teriparatide has a molecular weight of 4117.8 daltons. Teriparatide is manufactured by chemical synthesis. Teriparatide injection, USP is supplied as a sterile, colorless, clear, isotonic solution in a glass cartridge which is pre-assembled into a disposable delivery device (pen) for subcutaneous injection. Each prefilled delivery device is filled with 2.7 mL to deliver 2.4 mL. Each mL contains 250 mcg teriparatide (corrected for acetate, chloride, and water content), 0.41 mg glacial acetic acid, 0.1 mg sodium acetate (anhydrous), 45.4 mg mannitol, 3 mg Metacresol, and Water for Injection. In addition, hydrochloric acid solution 10% and/or sodium hydroxide solution 10% may have been added to adjust the product to pH 4. Each prefilled delivery device (pen) delivers 20 mcg of teriparatide per dose for up to 28 days.</td></tr>
<tr><td>Co-packaged product information</td><td colspan="3">N/A</td></tr>
<tr><td>Device information, if any:</td><td colspan="3">(b) (4)</td></tr>
<tr><td>Storage Temperature/ Conditions</td><td colspan="3">• Store teriparatide injection, USP under refrigeration at 2°C to 8°C (36°F to 46°F) at all times except when administering the product.
• Recap the delivery device (pen) when not in use to protect the cartridge from physical damage and light.
• When using teriparatide injection, minimize the time out of the refrigerator; deliver the dose immediately following removal from the refrigerator.
• Do not freeze. Do not use teriparatide injection, USP if it has been frozen.</td></tr>
<tr><td rowspan="6">Review Team</td><td>Discipline</td><td>Primary</td><td>Secondary</td></tr>
<tr><td>Drug Substance</td><td>Yili Li</td><td>Cameron Smith</td></tr>
<tr><td>Drug Product/ Labeling</td><td>Yili Li</td><td>Cameron Smith</td></tr>
<tr><td>Manufacturing</td><td>Allison Aldridge</td><td>Rose Xu</td></tr>
<tr><td>Biopharmaceutics</td><td>N/A</td><td>N/A</td></tr>
<tr><td>Microbiology</td><td>Andrew P Brown (OPQ)</td><td>Denise Miller</td></tr>
</table>

	Other (specify):	N/A	N/A
	RBPM	Erin Andrews	
	ATL	Cameron Smith	

	Discipline Consulted	Recommendation	Date
Consults	CDRH/OPEQ/OHT3	Adequate	04/18/2023
	OTR (NMR)	Adequate	08/28/2022
	OTR (Method Verification)	Inadequate – Deficiencies were found adequate by drug product assessor in drug product quality review of SD-36 (Review Cycle #3a), no consult review needed	09/29/2022
	OBP (Immunogenicity)	Adequate	09/13/2022

2. Submission Document(s) Reviewed

Submission(s) Assessed	Documents Date	Disciplines Affected
Quality/Response to Information Request (SD-36)	02/17/2023	Drug Product
Method Verification Materials Shipment (SD-34)	09/14/2022	Drug Product
Method Verification Materials Shipment (SD-33)	08/26/2022	Drug Product
Quality/Response To Information Request (SD-32)	08/18/2022	Drug Product
Resubmission/After Action- Complete; Quality/Facility Information; Quality/Quality Information (SD-31)	05/12/2022	Drug Product, Manufacturing

Post CRL Meeting Request (SD-30)	08/12/2021	Drug Product
Post CRL Meeting Request (SD-29)	07/02/2021	Drug Product, Manufacturing
Post CRL Meeting Request (SD-28)	06/24/2021	Drug Product, Manufacturing
Previous Submission(s) Reviewed	Document Date	Discipline(s) Affected
Quality/Response To Information Request (SD-25)	02/10/2021	Drug Product
Quality/Response To Information Request (SD-24)	02/01/2021	Drug Product
Resubmission/After Action- Complete; Quality/Quality Information; Quality/Microbiology Information (SD-22)	10/15/2020	Drug Product, Manufacturing, Microbiology
Quality/Presubmission Facility Correspondence (SD-19)	06/27/2019	Manufacturing
Quality/Response To Information Request (SD-17)	02/14/2019	Drug Product
Post CRL Meeting Request (SD-15)	01/09/2019	Drug Product
Quality/Quality Information (SD-14)	12/11/2018	Drug Product
Post CRL Meeting Request (SD-13)	11/09/2018	Drug Product
Quality/Quality Information (SD-12)	08/21/2018	Drug Product
Quality/Quality Information (SD-11)	08/21/2018	Drug Product
Quality/Response to Discipline Review Letter (SD-10)	07/27/2018	Drug Product, Manufacturing, Microbiology
Method Verification Materials Shipment (SD-9)	06/29/2018	Drug Product
Quality/Response to Information Request (SD-8)	04/16/2018	Drug Product
Quality/Response to Information Request (SD-6)	04/02/2018	Drug Product
Labeling/Response to Discipline Review Letter (SD-5)	03/20/2018	Drug Product
Clinical/Response to Information Request (SD-4)	03/19/2018	Drug Product
Filing/Response to Information Request (SD-2)	02/09/2018	Drug Product
New/ANDA (SD-1)	12/29/2017	All

3. Related/Supporting Documents

a. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Assessor/ Comments
(b) (4)	II	(b) (4)	Teriparatide Acetate	Adequate	02/09/2023	Review #4 by Manivannan Ethirajan
	III		(b) (4)	N/A		
	III			N/A		
	III			N/A		
	III			N/A		
	III			N/A		
	V			Adequate	11/04/2020	D23840M02R01 by Yuansha Chen

b. Other Documents: *IND, RLD, RS, Approved ANDA*

Document	Application Number	Description
RLD	N21318	Forteo, Teriparatide Injection, 0.6mg/2.4mL by Eli Lilly and Co.

4. Final Overall recommendation – Approval

<u>Deficiencies</u> (if applicable):

Overall Quality Deficiencies

None.

Drug Substance Deficiencies

None.

Drug Product Deficiencies

None.

Labeling Deficiencies

None.

Manufacturing Deficiencies

None.

Biopharmaceutics Deficiencies

N/A

Microbiology Deficiencies

None.

Other Deficiencies

None.

Additional Comments:

In addition to responding to the deficiencies presented above, please note and acknowledge the following comment(s) in your response:

None.

5. Basis for Recommendation

a. Summary of Rationale for Recommendation:

This ANDA is approvable from OPQ perspective based on the following:

- Satisfactory responses to all deficiencies pertaining to the drug substance, drug product, manufacturing process and microbiology
- All drug substance and drug product-related facilities are acceptable
- Low risk of product properties/CQAs based on risk analysis and upon risk-mitigation and the implementation of the control strategies

b. Recommendation by Subdiscipline:

Drug Substance: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

N/A

Drug Product: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

N/A

Quality Labeling: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

N/A

Manufacturing: ADEQUATE

Process: Adequate
Facilities: Adequate

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

N/A

Biopharmaceutics: N/A

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

N/A

Microbiology: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

N/A

Environmental: N/A

Provide justification(s) (for major deficiencies only):
(Click link to view Justification Statements)

N/A

6. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments: N/A

Comparability Protocols (PACMP): No
Comments: N/A

Additional Comments: N/A

Cameron Smith

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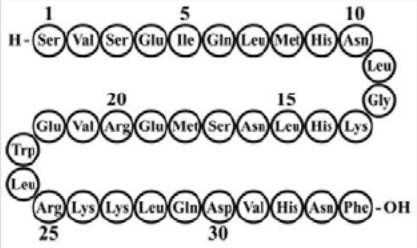
DRUG SUBSTANCE

IQA Review Guide Reference

Product Background: Teriparatide Injection

NDA/ANDA (review cycle number): A211097 (Review#3a)

Chemical Name and Structure: Teriparatide



DMF # (if applicable): (b) (4)

Applicant Name/DMF Holder: Apotex Inc. / (b) (4)

Review Recommendation: **Adequate**

Theme (ANDA only): **N/A**

Justification (ANDA only): N/A

(b) (4)

➢ *Document(s) Reviewed in Review #3 and 3a*	➢ *Date Received*
Meeting/Meeting Request (SD-28), eCTD#27	06/24/2021
Meeting/Meeting Request (SD-29), eCTD#28	07/02/2021
Meeting/Other (SD-30), eCTD#29	08/12/2021
Quality/Quality Information (SD-31), eCTD#30	05/12/2022
Quality/Response to Information Request (SD-32), eCTD#31	08/18/2022
Correspondence/Method Verification (SD-33), eCTD#32	08/26/2022
Correspondence/Method Verification (SD-34), eCTD#33	09/14/2022
Quality/Response to Information Request (SD-36), eCTD#35	02/17/2023

➢ *Document(s) Reviewed in Review #1*	➢ *Date Received*
New/ANDA (SD-1)	12/29/2017
Filing/Response to Information Request (SD-2)	02/09/2018
Clinical/Response to Information Request (SD-4)	03/19/2018
Labeling/Response to Discipline Review Letter (SD-5)	03/20/2018
Quality/Response to Information Request (SD-6)	04/02/2018
Quality/Response to Information Request (SD-8)	04/16/2018
Quality/Response to Discipline Review Letter (SD-10)	07/27/2018
Document(s) Reviewed in Review #2	***Date Received***
Quality/Quality Information (SD-22), eCTD#20	10/15/2020
Quality/Quality Information (SD-24), eCTD#23	02/01/2021
Quality/Quality Information (SD-25), eCTD#24	02/10/2021

Highlight Key Outstanding Issues from Last Cycle: Inadequate DMF.

Concise Description Outstanding Issues Remaining: None.

List Number of Comparability Protocols (ANDA only): None

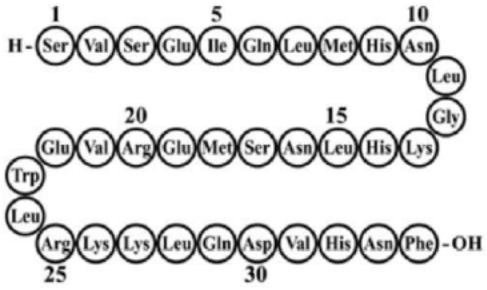
S.1 General Information

Summary of the info provided. Information from Application

Recommended International Non-proprietary Name (INN):	Teriparatide
Compendial name, if relevant:	Teriparatide
Chemical name(s):	(1) L-Phenylalanine, L-seryl-L-valyl-L-seryl-L-a-glutamyl-L-isoleucyl-L-glutaminyl-L-leucyl-L-methionyl-L-histidyl-L-asparaginyl-L-leucylglycyl-L-lysyl-L-histidyl-L-leucyl-L-asparaginyl-L-seryl-L-methionyl-L-a-glutamyl-L-arginyl-L-valyl-L-a-glutamyl-L-triptophyl-L-leucyl-L-arginyl-L-lysyl-L-lysyl-L-leucyl-L-glutaminyl-L-a-aspartyl-L-valyl-L-histidyl-L-asparaginyl-, acetate salt; (2) L-Seryl-L-valyl-L-seryl-L-a-glutamyl-L-isoleucyl-L-glutaminyl-L-leucyl-L-methionyl-L-histidyl-L-asparaginyl-L-leucylglycyl-L-lysyl-L-histidyl-L-leucyl-L-asparaginyl-L-seryl-L-methionyl-L-a-glutamyl-L-arginyl-L-valyl-L-a-glutamyl-L-tryptophyl-L-leucyl-L-arginyl-L-lysyl-L-lysyl-L-leucyl-L-glutaminyl-L-a-aspartyl-L-valyl-L-histidyl-L-asparaginyl-L-phenylalanine, acetate salt.
Other non-proprietary name(s) (e.g., national name, USAN):	Teriparatide Acetate, also called rhPTH 1-34 [redacted] (b) (4) is a single-chain peptide containing 34 amino acids identical to the 34 N-terminal amino acids of human parathyroid hormone.
Chemical Abstracts Service (CAS) registry number:	52232-67-4 (Teriparatide) 99294-94-7 (Teriparatide Acetate)

Structural formula (including relative and absolute stereochemistry):

The amino acid sequence of Teriparatide is shown below:



The structure of Teriparatide Acetate can therefore be depicted as follows:

Molecular formula:	$C_{181}H_{291}N_{55}O_{51}S_2$ [redacted] (b) (4)
Molecular mass:	4117.7 Daltons [redacted] (b) (4)

LABELING

IQA Review Guide Reference

{For ANDA only}

R Regional Information

1.14 Labeling

Labeling & Package Insert

DESCRIPTION section

Is the information accurate? ☐ Yes ☒ No
If "No," explain.

Is the drug product subject of a USP monograph? ☒ Yes ☐ No
If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

The firm has modified all the RLD labeling by removing "rDNA origin" and the text of "Teriparatide is manufactured using a strain of *Escherichia coli* modified by chemical synthesis DNA technology" in the Description section. The firm will be asked to petition the USP requesting that the monograph for this drug substance be updated similarly to remove reference to the Teriparatide source or add chemical synthesis as a second source.

Labeling Reviewer (Katherine Won) comments dated 2/26/2018:

we are issuing the following deficiency comments

(b) (4)

b. DESCRIPTION
i. 1st sentence: Revise to read "Teriparatide in jection, USP contains chemically synthesized human parathyroid hormone (1-34), and is also called hPTH (1-34).
ii. Include the statement "Teriperitide is manufactured chemical synthesis." prior to the sentenance "Teriparatide injection, USP is supplied as a sterile, colorless, clear..."
iii. You are requested to petition the United States Pharmacopeia (USP) to update the monograph for Teriparatide to either remove reference to the recombinant source of Teriparatide or add chemical synthesis as a second source.

Reviewer's Assessment (Review #3): Inadequate

In the Description, the sentence (b) (4) is changed to "*Each prefilled delivery device (pen) delivers 20 mcg of teriparatide per dose for up to 28 days*" in order to be in line with reference listed drug (RLD), Forteo® (NDA 021318/S-056) labeling updated on April 29, 2021.

In the Description, the sentence "*The molecular formula of teriparatide is $C_{181}H_{291}N_{55}O_{51}S_2$*" is missing. A deficiency is issued, and the labeling reviewer, Danielle Russell, is notified by email.

Deficiencies (Review #3):

Please add the sentence "*The molecular formula of teriparatide is $C_{181}H_{291}N_{55}O_{51}S_2$*" to the Description of your product labeling to be in line with the most recent RLD labeling.

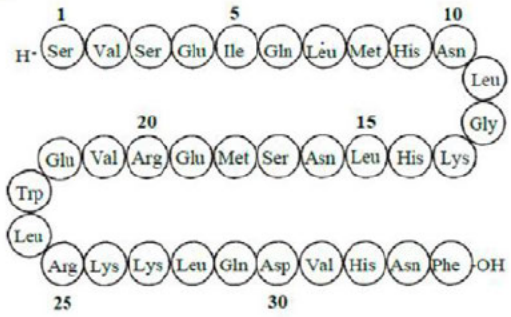
IRL Response on 02/17/2023:

As requested, we have revised the Description section of our labeling to include "The molecular formula of teriparatide is $C_{181}H_{291}N_{55}O_{51}S_2$" to be in line with the most recent RLD labeling.

Reviewer's Assessment (Review #3a): Adequate

The revised labeling is acceptable.

The molecular formula of teriparatide is $C_{181}H_{291}N_{55}O_{51}S_2$ and a molecular weight of 4117.8 daltons and its amino acid sequence is shown below:



HOW SUPPLIED section

i) Is the information accurate? ☒ Yes ☐ No

Reviewer's Assessment (Review #3): Adequate

There are differences between the RLD labeling and the firm's labeling. From the quality perspective, the differences are insignificant.

RLD labeling:

16.1 How Supplied

FORTEO (teriparatide injection) is a clear and colorless solution, available as single-patient-use prefilled delivery device (pen) in the following package size:

- 600 mcg/2.4 mL (250 mcg/mL) [containing 28 daily doses of 20 mcg] NDC 0002-8400-01 (MS8400).

The ANDA labeling:

How Supplied

The teriparatide injection, USP delivery device (pen) is available in the following package size:

- 2.4 mL single-patient-use prefilled delivery device NDC 60505-6188-0.

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☒ Yes ☐ No ☐ N/A

If "No," explain.

For OTC Drugs and Controlled Substances: N/A

For solid oral drug products, only: drug product length(s) of commercial batch(es): N/A

Describe issue(s) sent to and/or received from the OGD Labeling Reviewer: None

List of Deficiencies:

None

Primary Drug Product Reviewer Name and Date: Yili Li, Ph.D., Review#1, 5/24/2018, 09/06/2018; Review #2, 4/7/2021; Review #3, 11/23/2022; Review #3a, 4/4/2023

Secondary Drug Product Reviewer Name and Date: Cameron J. Smith, Ph.D., Review#1, 06/13/2018, 09/06/2018; Review #3, Cameron Smith, 11/29/2022; Review #3a, 04/18/2023

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PROCESS

Product Background:

Teriparatide Injection, USP 600 mcg/ 2.4 mL is indicated for treatment of postmenopausal women with osteoporosis at high risk for fracture and for increase of bone mass in men with primary or hypogonadal osteoporosis at high risk of fracture. The API is a chemically synthesized PTH hormone analogue. (b) (4)

ANDA:	211097
RLD:	021318 (Forteo® by Eli Lilly)
Drug Product:	Teriparatide Injection, USP; 600 mcg/ 2.4 mL (20 mcg per dose) Pen-injector Device
Route of Administration:	Subcutaneous Injection
Applicant Name:	Apotex Inc.

Process Review Recommendation (R1): **Adequate**

Theme (ANDA only): **N/A**

Justification (ANDA only): N/A

(b) (4)

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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VII: MICROBIOLOGY

IQA ANDA Assessment Guide Reference

Product Information	Sterile solution for multidose injection
ANDA Number	211097
Assessment Cycle Number	2
Drug Product Name / Strength	Teriparatide Injection USP, 20 µg per dose (600 µg/2.4 mL)
Route of Administration	Subcutaneous
Applicant Name	Apotex Inc.
Manufacturing Site	(b) (4)
Method of Sterilization	

Assessment Recommendation: **Adequate**

Theme:

☒ N/A	☐ Depyrogenation Validation Data
☐ Product Sterility Assurance	☐ Product Release and/or Stability Specifications
☐ Media Fill Data	☐ Validation for Product Release and/or Stability Test Method
☐ Validation of Product Test	☐ Other (Requires Division Director Approval)
☐ Due to Consult	

Justification: *view justification statements found at:* **Justification Statements**

N/A
Other (Requires Division Director Approval) – *Assessor writes-in justification here if "other" selected as theme.*

Assessment Summary: The applicant has submitted a response to a Complete Response Letter dated October 26th, 2018. This review covers remaining issues from the previous cycle.

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received

eCTD 0022	10/15/2020

Highlight Key Issues from Last Cycle and Their Resolution: The description of the container closure system was clarified, (b) (4) [redacted]. DMF (b) (4) [redacted] was inadequate previously and has since been reviewed and found adequate.

Remarks: A Complete Response Letter (CRL) was issued to the applicant by the Agency on October 26th, 2018. Microbiology deficiencies were items # 19 – 29 in the CRL. The applicant's responses received October 15th, 2020 are included and addressed in the appropriate sections of this review.

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): N/A

Supporting Documents: A211097MR01.pdf, dated August 30th, 2018 (Inadequate).
DMF (b) (4) [redacted], Updated qualification data was reviewed for (b) (4) [redacted] (Adequate). LOA dated September 28th, 2017.

Select Number of Approved Comparability Protocols: 0

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Assessment: *Adequate*

MICROBIOLOGY LIST OF DEFICIENCIES

N/A

Primary Microbiology Assessor Name and Date:
Andrew Brown, Ph.D.
Microbiologist
CDER/OPQ/OPMA/DMAII/B5
May 29, 2021

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Denise Miller
Senior Product Quality Assessor
CDER/OPQ/OPMA/DMAII/B5
May 29, 2021

Andrew P Brown (OPQ)

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Denise Miller

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MICROBIOLOGY

Product Background:

ANDA: 211097

Drug Product Name / Strength: Teriparatide Injection

Route of Administration: subcutaneously

Applicant Name: Apotex Inc.

(b) (4)

[redacted]

Review Recommendation: **Inadequate - Minor**

Theme (ANDA only): **N/A**

Justification (ANDA only): N/A

(b) (4)

[redacted]

List Submissions Being Reviewed:

Submit	Received	Review Request	Assigned to Reviewer
12/29/2017	12/29/2017	N/A	01/30/2018
07/27/2018*	07/27/2018	N/A	07/31/2018

*IR amendment

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: This is an eCTD submission.

On 08/24/2018, the Project Manager for the ANDA informed the review team that the applicant provided partial responses to the DP deficiencies issued in the DRL, and that the Agency would be rolling all the outstanding deficiencies from all quality disciplines into a CR letter.

Concise Description Outstanding Issues Remaining: Questions remain regarding: (b) (4) (b) (4) DMF (b) (4) is inadequate.

Supporting Documents:

- Microbiology review (b) (4) (dated 04/17/2018) is referenced for relevant sterility assurance information of the manufacturing facility.
- (b) (4)
-

List Number of Comparability Protocols (ANDA only): N/A

P.1 Description of the Composition of the Drug Product

- **Description of drug product –**

The drug product is supplied as a sterile, colorless, clear, solution for injection (b) (4) glass cartridge which is pre-assembled into a disposable delivery device (b) (4) for subcutaneous injection.

- **Drug product composition –**

Strength (Label Claim):		250 mcg/mL (600 mcg/2.4mL)			
Component Grade	Quality Standard	Function	Quantity per mL	Quantity per vial (mg)	% w/v total unit dose
Teriparatide	In-House	Active	0.250 mg	(b) (4)	
Glacial Acetic Acid	USP	(b) (4)	0.41 mg		
Sodium Acetate (Anhydrous)	USP		0.1 mg		
Mannitol	USP		45.4 mg		
Metacresol	USP		3 mg		
Water for Injection	USP-NF		q.s.		
Sodium Hydroxide	NF	pH Adjuster	q.s. to pH		
Hydrochloric Acid	NF	pH Adjuster	q.s. to pH		

- **Description of container closure system –**

(Section P.7)

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Jesse Wells

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Cameron Smith

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Cameron Smith

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Erin Andrews

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PROCESS

Product Background:

Teriparatide Injection, USP 600 mcg/ 2.4 mL is indicated for treatment of postmenopausal women with osteoporosis at high risk for fracture and for increase of bone mass in men with primary or hypogonadal osteoporosis at high risk of fracture. The API is a chemically synthesized PTH hormone analogue. (b) (4) .

ANDA:	211097
RLD:	021318 (Forteo® by Eli Lilly)
Drug Product:	Teriparatide Injection, USP; 600 mcg/ 2.4 mL (20 mcg per dose) Pen-injector Device
Route of Administration:	Subcutaneous Injection
Applicant Name:	Apotex Inc.

Process Review Recommendation (R1): **Adequate**

Theme (ANDA only): **N/A**

Justification (ANDA only): N/A

(b) (4)

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Allison Aldridge

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GUID: 508da7170002981da764ca33dfb39a19

Rose Xu

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Date: 12/19/2022 11:31:43AM
GUID: 5277e72900088dc65127c01f0d78be60

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☐ Approval
☐ Complete Response-Minor
☒ Complete Response-Major
☐ Complete Response-Major-Facilities Only

U.S. FOOD & DRUG ADMINISTRATION

ANDA 211097
Assessment #2

Drug Product Name	Teriparatide Injection, USP
Dosage Form	Injection
Strength	20 mcg per dose (600 mcg/2.4 mL)
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Apotex Inc.
US agent, if applicable	Apotex Corp.

Submission(s) Assessed	Document Date	Discipline(s) Affected
SD- 22	10/15/2020	DP, Process, Micro
SD-24	02/01/2021	BioTech (DP)
SD-25	02/10/2021	BioTech (DP)
Previously Submission(s) Reviewed	Document Date	Discipline(s) Affected
SD-11	08/21/2018	Drug Product
SD-10	07/27/2018	Drug Product, Process, Microbiology
SD-8	04/16/2018	Drug Product
SD-6	04/02/2018	Drug Product
SD-5	03/20/2018	Drug Product
SD-4	03/19/2018	Drug Product
SD-2	02/09/2018	Drug Product
SD-1	12/29/2017	All

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	DMF Team	DMF Team
Drug Product	Yili Li	Shin Chou
Manufacturing	Allison Aldridge	Rose Xu
Microbiology	Andrew P. Brown	Denise Miller
Biopharmaceutics		
Regulatory Business Process Manager	Erin Andrews	
Application Technical Lead	Shin Chou	
ORA Lead		
Laboratory (OTR)		
Environmental		

U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESMENT DATA SHEET

IQA ANDA Assessment Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	(b) (4)	Teriparatide, DS	Adequate	5/5/2021	R02, by Manivannan Ethirajan
	III		(b) (4)	N/A*		
	III			N/A*		
	III			N/A*		

* There is enough data in the application; therefore, the DMF did not need to be assessed.

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved ANDA*

Document	Application Number	Description
RLD	N21318	Forteo, Teriparatide Injection, 0.6mg/2.4mL by Eli Lilly and Co.

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH-ODE	Complete	Inadequate	04/30/2021	Shawn Shermer
CDRH-OC	Complete	Inadequate	04/30/2021	Shawn Shermer
Clinical	Complete	Adequate	06/10/2021	Tracy Franzos
OTR	Complete	Inadequate	11/23/2020	Kang Chen
OBP	Complete	Inadequate	03/12/2021	Seth Thacker

ABBREVIATED EXECUTIVE SUMMARY (CR ONLY)

IQA ANDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Major

The application is not recommended for approval due to quality related deficiencies summarized in Section II. OPQ recommends issuing a Complete Response Letter – Major

The drug product deficiencies have been classified as MAJOR because of insufficient data to demonstrate drug substance sameness as noted in Appendix A, Section A(2)(l) of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). Upon Submission, in FDA's judgement, the review of this information will result in substantial expenditure of FDA resources.

The drug product deficiencies have been classified as MAJOR because of insufficient data to support drug/device compatibility and sustainability for the proposed product as noted in Appendix A, Section A(2)(n) of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). This information is required to ensure proper patient in-use of the product. Upon receipt, in FDA's judgement, the review of this information will require thorough evaluation and potentially affects other aspects of the application and the related conclusions.

The drug product deficiencies have been classified as MAJOR because of the failure of accelerated stability data (for device) as noted in Appendix A, Section A(2)(g) of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018) which prevents FDA from confidently granting an extended expiration date for the product, and requires the firm to submit real time data for approval.

II. QUALITY ASSESSMENT OVERVIEW

A. Drug Substance: Inadequate-Minor

Teriparatide Acetate, also called rhPTH 1-34 (acetate salt), is a single-chain peptide containing 34 amino acids identical to the 34 N-terminal

amino acids of human parathyroid hormone. The RLD peptide is produced by a method based on recombinant DNA (rNDA) technology. [redacted] *It has a molecular weight of 4117.7 Daltons and molecular formula of* $C_{181}H_{291}N_{55}O_{51}S_2$ [redacted]

Teriparatide is the subject of a USP monograph. The firm referred to DMF [redacted] *for information regarding the chemistry, manufacturing and controls of its production. DMF* [redacted] *was reviewed by Manivannan Ethirajan on 5/5/2021 and deemed adequate.*

Minor deficiencies were identified, and they are included in the next section of the summary.

Drug Product: Inadequate-Major

1. Primary Justification:

The drug product deficiencies have been classified as MAJOR because of insufficient data to demonstrate drug substance sameness as noted in Appendix A, Section A(2)(l) of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). Upon Submission, in FDA's judgement, the review of this information will result in substantial expenditure of FDA resources.

2. Secondary Justification (if necessary):

The drug product deficiencies have been classified as MAJOR because of insufficient data to support drug/device compatibility and sustainability for the proposed product as noted in Appendix A, Section A(2)(n) of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). This information is required to ensure proper patient in-use of the product. Upon receipt, in FDA's judgement, the review of this information will require thorough evaluation and potentially affects other aspects of the application and the related conclusions.

3.Tertiary Justification (if necessary):

The drug product deficiencies have been classified as MAJOR because of the failure of accelerated stability data (for device) as noted in Appendix A, Section A(2)(g) of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018) which prevents FDA from confidently granting an extended expiration date for the product, and requires the firm to submit real time data for approval.

Teriparatide Injection is supplied as a sterile solution intended for subcutaneous injection in a glass cartridge pre-assembled in a pen-

injector device. Each mL contains 250µg of teriparatide, 0.41 mg glacial acetic acid, 0.10 mg sodium acetate, 45.4 mg mannitol, 3.0 mg metacresol, hydrochloride acid and sodium hydroxide to adjust to pH 4 and q.s. water for injection. The proposed formulation is qualitatively (Q1) and quantitatively (Q2) the same as that of the RLD.

(b) (4)

Label indicated that the PD should be stored under refrigeration at 2° to 8°C (36° to 46°F) at all times. Do not freeze and do not use if it has been frozen.

(b) (4)

Additional deficiencies were identified in other areas, and they are included in the next section of the summary.

Labeling: Inadequate-Minor

Minor issues are identified in this review cycle, and the deficiencies are communicated separately from OGD.

B. Manufacturing: Inadequate-Minor

(b) (4)

Process - inadequate with minor deficiencies
Facilities - inadequate with CDRH minor deficiencies

C. Microbiology: Adequate

D. List of Deficiencies for Complete Response

1. Drug Substance Deficiencies

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Shin Chou

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Date: 6/14/2021 02:44:45PM
GUID: 51defe4b00010821ff38f29e384b0ab5

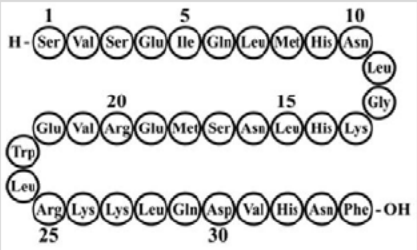
DRUG SUBSTANCE

IQA Review Guide Reference

Product Background: Teriparatide Injection

NDA/ANDA (review cycle number): A211097 (Review#2)

Chemical Name and Structure: Teriparatide



DMF # (if applicable): (b) (4)

Applicant Name/DMF Holder: Apotex Inc. / (b) (4)

Review Recommendation: **Inadequate - Minor**

Theme (ANDA only): **N/A**

Justification (ANDA only): N/A

(b) (4)

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LABELING

IQA Review Guide Reference

{For ANDA only}

R Regional Information

1.14 Labeling

Labeling & Package Insert

DESCRIPTION section

Is the information accurate? ☒ Yes ☐ No
If "No," explain.

Is the drug product subject of a USP monograph? ☒ Yes ☐ No
If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

(b) (4)

The firm will be asked to petition the USP requesting that the monograph for this drug substance be updated similarly to remove reference to the Teriparatide source or add chemical synthesis as a second source.

Labeling Reviewer (Katherine Won) comments dated 2/26/2018:

we are issuing the following deficiency comments

(b) (4)

b. DESCRIPTION
i. 1st sentence: Revise to read "Teriparatide in jection, USP contains chemically synthesized human parathyroid hormone (1-34), and is also called hPTH (1-34).
ii. Include the statement "Teriperitide is manufactured chemical synthesis." prior to the sentenance "Teriparatide injection, USP is supplied as a sterile, colorless, clear..."
iii. You are requested to petition the United States Pharmacopeia (USP) to update the monograph for Teriparatide to either remove reference to the recombinant source of Teriparatide or add chemical synthesis as a second source.

HOW SUPPLIED section

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☒ Yes ☐ No ☐ N/A

If "No," explain.

For OTC Drugs and Controlled Substances: N/A

For solid oral drug products, only: drug product length(s) of commercial batch(es): N/A

Describe issue(s) sent to and/or received from the OGD Labeling Reviewer: None

List of Deficiencies:

None

Primary Drug Product Reviewer Name and Date: Yili Li, Ph.D., Review#1, 5/24/2018, 09/06/2018; Review #2, 4/7/2021

Secondary Drug Product Reviewer Name and Date: Cameron J. Smith, Ph.D., 06/13/2018, 09/06/2018

Yili Li

Digitally signed by Yili Li
Date: 5/27/2021 12:15:50PM
GUID: 57573c63003677e420bfae1fb7770d72

Cameron Smith

Digitally signed by Cameron Smith
Date: 5/27/2021 03:09:12PM
GUID: 544e4d7a0002b355935ebaf76373f79e

Shin Chou

Digitally signed by Shin Chou
Date: 5/27/2021 12:28:29PM
GUID: 51defe4b00010821ff38f29e384b0ab5

PROCESS

Product Background:

Teriparatide Injection, USP 600 mcg/ 2.4 mL is indicated for treatment of postmenopausal women with osteoporosis at high risk for fracture and for increase of bone mass in men with primary or hypogonadal osteoporosis at high risk of fracture. The API is a chemically synthesized PTH hormone analogue. (b) (4)

ANDA:	211097
RLD:	021318 (Forteo® by Eli Lilly)
Drug Product:	Teriparatide Injection, USP; 600 mcg/ 2.4 mL (20 mcg per dose) Pen-injector Device
Route of Administration:	Subcutaneous Injection
Applicant Name:	Apotex Inc.

Process Review Recommendation (R1): **Inadequate - Minor**

Theme (ANDA only): **Inadequate supporting data/information**

Justification (ANDA only): N/A

(b) (4)

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Allison Aldridge

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Date: 5/10/2021 03:32:23PM
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Rose Xu

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Date: 5/10/2021 03:28:51PM
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Recommendation: Complete Response - Major

ANDA 211097
Review 1

Drug Name/Dosage Form	Teriparatide Injection, USP
Strength	20 mcg per dose (600 mcg/2.4 mL)
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Apotex Inc.
US agent, if applicable	Apotex Corp.

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
SD-11	*08/21/2018*	*Drug Product*
SD-10	*07/27/2018*	*Drug Product, Process, Microbiology*
SD-8	*04/16/2018*	*Drug Product*
SD-6	*04/02/2018*	*Drug Product*
SD-5	*03/20/2018*	*Drug Product*
SD-4	*03/19/2018*	*Drug Product*
SD-2	*02/09/2018*	*Drug Product*
SD-1	*12/29/2017*	*All*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Delaram Moshkelani Manivannan Ethirajan	Kshitij Patkar Jane Chang
Drug Product	Yili Li	Cameron Smith
Process	Delaram Moshkelani	Kshitij Patkar
Microbiology	Yarery Smith	Jesse Wells
Facility	Ruth Moore	
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Tristen Cook	N/A
Application Technical Lead	Cameron Smith	N/A

Laboratory (OTR)	N/A
ORA Lead	
Environmental	

Appears this way on original

Quality Review Data Sheet

IQA Review Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II	(b) (4)	Teriparatide Acetate	Inadequate	06/14/2018	Manivannan Ethirajan Delaram Moshkelani
	V		(b) (4)	Inadequate	04/17/2018	Yarery Smith
	III			N/A		
	V			Adequate	03/26/2018	Jennifer Patro
	V			Adequate	06/26/2018	Yarery Smith
	III			N/A		

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	021318	RLD

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Pharmacology/ Toxicology	Complete	Inadequate	06/11/2018	Melanie Mueller
CDRH/ODE	Complete	Inadequate	08/07/2018	Peter Petrochenko
CDRH/OC	Complete	Delay	07/02/2018	Philip Lafleur
OPQ/OBP	Complete	Inadequate	05/18/2018	Daniela Verthelyi

Abbreviated Executive Summary

IQA Review Guide Reference

I. Recommendations and Conclusion on Approvability

The application is not recommended for approval due to quality related deficiencies summarized in Section II. OPQ recommends issuing a Complete Response Letter – **Major**.

II. Quality Assessment Overview

A. Drug Substance, Drug Product, and Labeling: Inadequate-Major

DMF (b) (4), for drug substance Teriparatide manufactured by (b) (4) is inadequate with major deficiencies. (b) (4) Major deficiencies were identified regarding the DMF (Justification: Submission of additional information is needed. Upon receipt, this information will require thorough evaluation and will potentially affects other aspects of the application and the related conclusions). Minor deficiencies were identified regarding the drug substance specification and analytical methods.

The drug product is a sterile solution of Teriparatide in a multi-dose prefilled delivery device (pen) for subcutaneous injection, (b) (4) Major deficiencies were (b) (4)

Minor deficiencies were also identified regarding the drug product specifications, analytical methods container closure system and stability data.

No labeling issue was found.

B. Process: Inadequate-Minor

(b) (4)

[redacted]

C. Facility: Adequate

The manufacturing facilities were found to be acceptable.

D. Biopharmaceutics: N/A

E. Microbiology: Inadequate-Minor

(b) (4)

[redacted]

Questions remain regarding:

The description of the container closure system; the CCIT; the antimicrobial effectiveness testing; the contract facilities for stability testing; the building and facilities; the production filters; the holding period; and the stability program. DMF (b) (4) is inadequate.

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Cameron Smith

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PROCESS

Product Background:

Teriparatide Injection, USP 600 mcg/ 2.4 mL is indicated for treatment of postmenopausal women with osteoporosis at high risk for fracture and for increase of bone mass in men with primary or hypogonadal osteoporosis at high risk of fracture. The API is a chemically synthesized PTH hormone analogue. (b) (4)

ANDA:	211097
RLD:	021318 (Forteo® by Eli Lilly)
Drug Product:	Teriparatide Injection, USP; 600 mcg/ 2.4 mL (20 mcg per dose) Pen-injector Device
Route of Administration:	Subcutaneous Injection
Applicant Name:	Apotex Inc.

Process Review Recommendation (R1): **Inadequate - Minor**

Theme (ANDA only): **Inadequate supporting data/information**

Justification (ANDA only): N/A

(b) (4)

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Delaram Moshkelani

Digitally signed by Delaram Moshkelani
Date: 10/04/2018 11:59:43AM
GUID: 5461144a00034e88cd04be3bcc25f606

Kshitij Patkar

Digitally signed by Kshitij Patkar
Date: 10/15/2018 11:26:32AM
GUID: 51269608000063f3a8e5c1ed3ccea237

FACILITIES

IQA Review Guide Reference

Product Background: Treatment of postmenopausal women with osteoporosis at high risk for fracture.

NDA/ANDA:ANDA 211097

Drug Product Name / Strength: Teriparatide Injection, 250 mcg (600mcg/2.4mL), 20 mcg per dose (Pen Injector Device)

Route of Administration: Injection (Pen Injector Device)

Applicant Name: Apotex Inc.

Review Recommendation: **Adequate**

Theme (ANDA only): **N/A**

Justification (ANDA only): N/A

Review Summary:

All facilities are acceptable for the functions listed in ANDA 211097.

List Submissions being reviewed (table):

Sequence #	*Date Received*	*Comment*
0001	12/29/2017	Original Submission

Highlight Key Outstanding Issues from Last Cycle: NA

Concise Description Outstanding Issues Remaining: None

List Number of Comparability Protocols (ANDA only): NA

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Ruth Moore

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Date: 9/28/2018 11:06:50AM
GUID: 530ccf7a000e6e04759cc41593877e4d

Zhihao Peter Qiu

Digitally signed by Zhihao Peter Qiu
Date: 9/28/2018 11:54:07AM
GUID: 508da7480002bfb5825e149b2b4eb91d

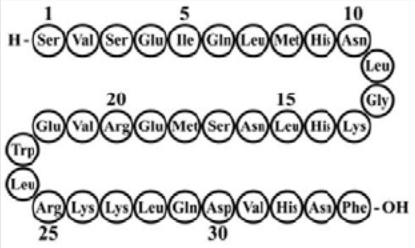
DRUG SUBSTANCE

IQA Review Guide Reference

Product Background: Teriparatide Injection

NDA/ANDA (review cycle number): A211097 (Review#1)

Chemical Name and Structure: Teriparatide



DMF # (if applicable): (b) (4)

Applicant Name/DMF Holder: Apotex Inc. / (b) (4)

Review Recommendation: **Inadequate - Major**

Theme (ANDA only): **DMF**

Justification (ANDA only): N/A

(b) (4)

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LABELING

IQA Review Guide Reference

{For ANDA only}

R Regional Information

1.14 Labeling

Labeling & Package Insert

DESCRIPTION section

Is the information accurate? ☒ Yes ☐ No
If "No," explain.

Is the drug product subject of a USP monograph? ☒ Yes ☐ No
If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

(b) (4)

The firm will be asked to petition the USP requesting that the monograph for this drug substance be updated similarly to remove reference to the Teriparatide source or add chemical synthesis as a second source.

Labeling Reviewer (Katherine Won) comments dated 2/26/2018:

we are issuing the following deficiency comments

(b) (4)

b. DESCRIPTION
i. 1st sentence: Revise to read "Teriparatide in jection, USP contains chemically synthesized human parathyroid hormone (1-34), and is also called hPTH (1-34).
ii. Include the statement "Teriperitide is manufactured chemical synthesis." prior to the sentenance "Teriparatide injection, USP is supplied as a sterile, colorless, clear..."
iii. You are requested to petition the United States Pharmacopeia (USP) to update the monograph for Teriparatide to either remove reference to the recombinant source of Teriparatide or add chemical synthesis as a second source.

HOW SUPPLIED section

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☒ Yes ☐ No ☐ N/A

If "No," explain.

For OTC Drugs and Controlled Substances: N/A

For solid oral drug products, only: drug product length(s) of commercial batch(es): N/A

Describe issue(s) sent to and/or received from the OGD Labeling Reviewer: None

List of Deficiencies:

None

Primary Drug Product Reviewer Name and Date: Yili Li, Ph.D., Review#1, 5/24/2018, 09/06/2018;

Secondary Drug Product Reviewer Name and Date: Cameron J. Smith, Ph.D., 06/13/2018, 09/06/2018

Cameron Smith

Digitally signed by Cameron Smith
Date: 9/07/2018 09:16:40AM
GUID: 544e4d7a0002b355935ebaf76373f79e

Yili Li

Digitally signed by Yili Li
Date: 9/07/2018 09:18:42AM
GUID: 57573c63003677e420bfae1fb7770d72

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 211097

BIO PHARM /TOX REVIEW(s)

FDA/CDER/OPQ/OTR
Division of Pharmaceutical Analysis
645 S. Newstead Ave.
St. Louis MO 63110
P: 314.539.2135

METHOD VERIFICATION REPORT SUMMARY

Date: September 27, 2022

To: Yili Li, Senior Pharmaceutical Quality Assessor OPQ/OLDP/DLBPI
Cameron Smith, Supervisory Chemist
OPQ/OLDP/DLBPI

Through: Sommers, Cynthia, Lab Chief, OPQ/OTR/DCDA

Cynthia D. Sommers -S
Digitally signed by Cynthia D. Sommers -S
Date: 2022.09.27 16:55:24 -05'00'

From: Josh Shipman, Chemist, OPQ/OTR/DCDA

Alicia Hoover., Method Verification Coordinator, OPQ/OTR/DPA

Subject: Method Verification for ANDA 211097: Teriparatide for injection, 250 µg/mL

The following methods were evaluated and are <u>acceptable</u> for quality control and regulatory purposes:

(b) (4)

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PHARMACOLOGY-TOXICOLOGY CONSULTATION REVIEW
Division of Clinical Review (DCR)
Office of Bioequivalence (OB), Office of Generic Drugs (OGD)
Center for Drug Evaluation & Research (CDER)
Teriparatide Injection

Drug Product:	Teriparatide Injection, 0.6 mg/2.4 mL
ANDA#: **Applicant:**	ANDA 211097 Apotex, Inc.
RLD#/Approval Date: **Sponsor:**	NDA 021318 Forteo® (teriparatide) for subcutaneous injection; November 26, 2002; Lilly
Pharmacology-Toxicology Primary Reviewer:	Melanie Mueller, PhD Toxicologist
Pharmacology-Toxicology Secondary Reviewer:	Irene Inok Surh, PhD Acting Lead Toxicologist
Tertiary Reviewer:	Robert Dorsam, PhD Associate Director of Pharmacology/Toxicology, DCR
To:	Cameron Smith Division of Liquid Based Products (DLBP), Office of Pharmaceutical Quality (OPQ)
Reason for Consult:	To evaluate the adequacy of the applicant's data and conclusion on the safety of extractables identified from the container closure system (CCS) and the manufacturing equipment.
Date of Submission:	December 29, 2017
Date Consult Received:	February 21, 2018
Date of Completion:	May 30, 2018
Conclusion:	After internal discussion with chemists from OLDP and OPF, OGD Pharmacology/Toxicology defers the safety review of extractables from the CCS and manufacturing equipment. Both OLDP and OPF identified deficiencies in the extraction reports provided by the applicant. OLDP and/or OPF will consult Pharmacology/Toxicology on the safety of leachables/extractables, if deemed necessary, after the applicant responds to the identified deficiencies. **See Section 2 for Internal Recommendations.**
Deficiency Classification:	☐ Major ☐ Minor ☒ N/A

1 Memorandum:

This Memorandum responds to a consult issued by the Office of Lifecycle Drug Products (OLDP) requesting a safety assessment on extractables identified in the container closure system (CCS) and manufacturing equipment of a generic teriparatide injection under ANDA 211097.

On December 29, 2017 Apotex submitted ANDA 211097 for generic teriparatide injection USP 600 µg/2.4 mL.[1] The reference listed drug (RLD) Forteo® (teriparatide) 600 µg/2.4 mL (NDA 021318) was approved on November 26, 2002, and is sponsored by Lilly. Teriparatide, a recombinant human parathyroid hormone (PTH) analogue, is indicated for the treatment of postmenopausal, primary or hypogonadal, or glucocorticoid-induced osteoporosis.[2]

The applicant conducted extractable studies on the container closure system (CCS) and manufacturing equipment.[3, 4] To justify the safety of the proposed drug product, the applicant submitted a risk assessment on extractables from the CCS and manufacturing equipment.[5, 6]

On February 22, 2018, OLDP in the Office of Pharmaceutical Quality (OPQ) consulted DCR regarding the adequacy of the applicant's data and conclusion on the safety of extractables in the generic teriparatide injection under ANDA 211097.[7]

DCR Pharmacology/Toxicology requested an interdisciplinary meeting with the drug product review team from OLDP and the process review team from the Office of Process and Facilities (OPF) to discuss adequacy of the two extraction reports provided by the applicant. During this interdisciplinary meeting on June 5th, deficiencies with both extraction reports identified by OLDP and OPF chemists were discussed. Due to the nature of the chemistry deficiencies, OLDP and OPF both intended to request leachable studies for the generic teriparatide injection in the Discipline Review Letter (DRL) to be sent to the applicant on or about June 28, 2018. Therefore, at this time, a safety assessment of extractables identified in the CCS and manufacturing equipment used for the generic teriparatide injection is not warranted. Hence, Pharmacology/Toxicology defers the safety review of extractables from the CCS and manufacturing equipment. OLDP and/or OPF will consult Pharmacology/Toxicology on the safety of leachables/extractables, if deemed necessary, after the applicant responds to the identified deficiencies.

Pharmacology/Toxicology recommends that OLDP and/or OPF include the language in *Section 2 Internal Recommendation* to the applicant when requesting leachable studies for the generic teriparatide injection.

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[1] ANDA 211079 EDR Module 1.2 Cover Letter Original Submission;
\\cdsesub1\evsprod\anda211097\0000\m1\us\12-cover-letters\cover-letter-anda-2017-12-08.pdf
[2] RLD NDA 21318 Label Approved on August 30, 2013;
http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021318s036lbl.pdf
[3] ANDA 211097 EDR Module 3.2.P.2 Extractables Report Container Closure;
\\cdsesub1\evsprod\anda211097\0000\m3\32-body-data\32p-drug-prod\teriparatide-injectable-novocol\32p2-pharm-dev\pharmaceutical-development-6.pdf
[4] ANDA 211097 EDR Module 3.2.P.2 Extractables Report Manufacturing Equipment;
\\cdsesub1\evsprod\anda211097\0000\m3\32-body-data\32p-drug-prod\teriparatide-injectable-novocol\32p2-pharm-dev\pharmaceutical-development-7.pdf
[5] ANDA 211097 EDR Module 3.2.P.2 Risk Assessment Container Closure;
\\cdsesub1\evsprod\anda211097\0000\m3\32-body-data\32p-drug-prod\teriparatide-injectable-novocol\32p2-pharm-dev\pharmaceutical-development-8.pdf
[6] ANDA 211097 EDR Module 3.2.P.2 Risk Assessment Manufacturing Equipment;
\\cdsesub1\evsprod\anda211097\0000\m3\32-body-data\32p-drug-prod\teriparatide-injectable-novocol\32p2-pharm-dev\pharmaceutical-development-9.pdf
[7] Consult Request to DCR on February 22, 2018 in GDRP;
http://panorama.fda.gov/document/preview?versionID=5a9076aa0056b07ee1eee04b58ec45bb&ID=5a9076aa0056b07d854c9173a3d0c865

Note, that if nonclinical data are submitted in your response, it may impact the timelines of your application.

Melanie Mueller

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Date: 6/11/2018 01:13:26PM
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Robert Dorsam

Digitally signed by Robert Dorsam
Date: 6/11/2018 01:08:38PM
GUID: 5048c79e00001d1a860d88bc481f8883

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 211097

BIOEQUIVALENCE REVIEW(s)

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	211097	
Drug Product Name	Teriparatide Injection	
Strength(s)	20 mcg per dose (600 mcg/2.4 mL)*	
Applicant Name	Apotex Inc.	
Applicant Address	150 Signet Drive Toronto, Ontario Canada M9L 1 T9	
US Contact Name and US Mailing Address	Dr. Kiran Krishnan, SVP, Global Regulatory Affairs, 2400 North Commerce Parkway, Weston, Florida 33326	
US Contact Telephone Number	954-384-3986	
US Contact Fax Number	866-392-1774	
US Contact Email Address	kkrishna1@apotex.com	
Original Submission Date(s)	December 29, 2017	
Submission Date(s) of Amendment(s) Under Review	N/A	
First Generic	No	
Primary Reviewer	Manjinder Kaur, Ph.D.	
Secondary Reviewer	Suman Dandamudi, Ph.D.	
OSIS status	**Backlog, Year 1 and Year 2 ANDAs** ☐ Pending ☐ Complete ☐ N/A	**Post October 1, 2014 ANDAs** ☐ To Be Determined by OSIS ☐ Pending For Cause Inspection ☐ Complete ☒ N/A (Waiver/Deem Bioequivalent)
Waiver/Deem Bioequivalent	☒ Granted ☐ Tentatively granted ☐ Not granted ☐ N/A	
QC Dissolution	☐ Pending ☐ Adequate ☐ Inadequate ☒ N/A	
Formulation	☒ Adequate ☐ Inadequate	
Will Response to CR Result in a Reformulation?	☐ Possibly ☐ No ☒ N/A	
Deficiency Classification	☐ Major ☐ Minor/IR ☒ N/A (Review is adequate)	
Major Deficiency Theme	N/A	
Justification for Major Designation	N/A	
Overall Review Result	☒ Adequate ☐ Inadequate	

Product Specific Guidance (PSG) Referenced in Review	☒ **Recommended/Latest Revision Date: October, 2017** **RLD Number: NDA 021318** ☐ **N/A (no PSG available at time of review)**		
Revised/New Draft Guidance Generated as Part of Current Review	☐ **YES** ☒ **NO**		
Bioequivalence study tracking/supporting document #	**Study/test type**	**Strength**	**Review Result**
1	**Waiver**	20 mcg per dose (600 mcg/2.4 mL)	☒ **Adequate** ☐ **Inadequate**

*: RLD is expressed as 0.25 mg/mL or 250 mcg/mL

1 EXECUTIVE SUMMARY

Apotex Inc. has requested a waiver of in vivo bioequivalence (BE) study requirements under Section *21 Code of Federal Regulations (CFR) § 320.22(b)(1)* for its test product, Teriparatide Injection, USP, 20 mcg/dose (600 mcg/2.4 ml). The reference listed drug (RLD) product referenced in this application is FORTEO ® (teriparatide [rDNA origin]) Injection, 0.6 mg/2.4 mL (0.25 mg/mL) manufactured by Eli Lilly and Co. (NDA 021318, approved on June 25, 2008).

The active pharmaceutical ingredient (API), teriparatide, is a peptide with 34 amino acids. The API in the test product is of chemical synthesis origin, whereas the API in the reference product, FORTEO® is of recombinant-DNA (rDNA) origin.

To date, there is no product specific guidance available for Teriparatide Injection. However, there is draft guidance for a group of synthetic peptides referencing rDNA-sourced peptides as RLD i.e. Guidance for Industry: ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin[1].

Based on the information submitted, the test drug product contains the same active ingredient in the same concentration and dosage form as the RLD. The test product is qualitatively (Q1) and quantitatively (Q2) the same as the RLD product. The pH of three batches of the test product is 4.2 (batch #: D02100RDA), 4.3 (batch #: D02101RDA) and 4.3 (batch #: D02124RDA), respectively[2], which fall within the pH specification range of the RLD product (pH 3.8 – 4.5)[3]. Therefore, the Division of Bioequivalence III (DBIII) grants the waiver of *in vivo* BE study requirements for the test product, Teriparatide Injection, 600 mcg/2.4 mL (250 mcg/mL) as per *Section 21 CFR §320.22(b)(1)*[4].

The application is **adequate**.

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[1] https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm578365.pdf

[2] DARRTS, ANDA 211097, EDR 0, 3.2.P.5.4 Batch Analyses.
[3] NDA 021318, Amendment 0102 (Supplement 37) received 09/05/2013, Module 3.2.P.5.1, *Specifications*
[4] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=320.22

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information[5]

Test Drug Product and Strength(s)	Teriparatide Injection, 600 mcg/2.4 mL (250 mcg/mL)
Reference Standard (RS) and Strength(s)	Forteo® (Teriparatide Recombinant Human), 600 mcg/2.4 mL (250 mcg/mL)
RS Holder; NDA/ANDA Number; Approval Date	Eli Lilly and Company, NDA 021318, Approved: November 26, 2002
Reference Listed Drug (RLD) and Strength(s)	Same as the RS above
RLD Holder; NDA/ANDA Number; Approval Date	Same as the RS above

3.2 PK/PD Information[6]

Most recent RLD label (provide embedded document) Please check if an NG/G/J tube study is needed.	 021318s036lbl.pdf (Version revised 08/30/2013;)
Indication	Forteo is recombinant human parathyroid hormone analog (1-34), [rhPTH(1-34)] indicated for: • Treatment of postmenopausal women with osteoporosis at high risk for fracture • Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture

[5] Electronic Orange Book, Search Word: Teriparatide, Last accessed: 04/09/2018.
[6] Drugs@FDA, Search word: 050023, label approved on 12/18/2017, Last accessed: 03/18/2018.

	• Treatment of men and women with osteoporosis associated with sustained
Boxed warning	**WARNING: POTENTIAL RISK OF OSTEOSARCOMA** In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration. The effect was observed at systemic exposures to teriparatide ranging from 3 to 60 times the exposure in humans given a 20-mcg dose. Because of the uncertain relevance of the rat osteosarcoma finding to humans, prescribe FORTEO only for patients for whom potential benefits outweigh potential risk. FORTEO should not be prescribed for patients at increased baseline risk for osteosarcoma (e.g., those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, pediatric and young adult patients with open epiphyses, or prior external beam or implant radiation therapy involving the skeleton)
Bioavailability	Teriparatide is absorbed after subcutaneous injection; the absolute bioavailability is approximately 95% based on pooled data from 20-, 40-, and 80- mcg doses. The rates of absorption and elimination are rapid. The peptide reaches peak serum concentrations about 30 minutes after subcutaneous injection of a 20-mcg dose and declines to non-quantifiable concentrations within 3 hours.
Food Effect	N/A (Injection)
Tmax	The peptide reaches peak serum concentrations about 30 minutes after subcutaneous injection of a 20-mcg dose
Metabolism	Peripheral metabolism of PTH is believed to occur by non-specific enzymatic mechanisms in the liver followed by excretion via the kidneys.
Excretion	No excretion studies have been performed with teriparatide.
Half-life	The half-life of teriparatide in serum is 5 minutes when administered by intravenous injection and approximately 1 hour when administered by subcutaneous injection.
Maximum Daily Dose	20 mcg

3.3 OGD Recommendations for Drug Product

Source of most recent recommendations or provide the embedded document to the current draft guidance	https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM578365.pdf
Analytes to measure (in plasma/serum/blood):	N/A
Bioequivalence based on:	According to 21 CFR 320.22 (b)(1), a waiver of the requirement for the submission of evidence measuring in vivo bioavailability or demonstrating bioequivalence may be granted to a drug if (i) it is a parenteral solution intended solely for administration by injection,

	or an ophthalmic or otic solution; and (ii) contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.	
Waiver request of in-vivo testing:	Yes	
Summary of OGD or DB History	Approved ANDAs[7]:	None
	Pending ANDAs[8]:	Yes, there are two pending ANDAs (current ANDA and ANDA 208569)
	Controls[9],[10]:	Yes, There are many controlled correspondences for this drug product in Mercado and OGD database. Few of them are listed here. (Controls Nos.12-0761, #11-0333, 14-0442, 14-0387, 13-0511, 13-1003, 13-0044, 12-0561, 04-253 and 7390241 (**from current applicant**)
	Protocols[11]:	Yes (P150013[12])
	Pending Citizen Petitions and other legal and regulatory issues:[13]	☐ Yes ☒ No There is no policy alert for current test product even though there is a closed citizen petition by the innovator, Eli Lilly[14], [15]

[7] Electronic Orange Book, Search word: Teriparatide, Last accessed: 04/09/2018
[8] DARRTS, Search word: Teriparatide, Last accessed: 04/09/2018
[9] GDRP, Search word: Teriparatide, Last accessed: 04/09/2018
[10] OGD Division of Bioequivalence Controls Documents Tracking, Search word: Teriparatide, Last accessed: 04/09/2018.
[11] OGD Division of Bioequivalence Protocols Tracking, Search Word: Teriparatide, Last accessed: 04/09/2018
[12] \\cdsnas\ogd99\DIVBE\ProtocolFiles\P150013Protocol.pdf
[13] Please check DLRS policy updates in the link http://sharepoint.fda.gov/orgs/CDER-OGD/OGDP/DLRS/SitePages/Home.aspx, Last accessed: 04/02/2018.
[14] V:\DIVISION\BIO\BIO1\Email Reference\208569 Teriparatide Injection\Lilly petition\CP for 208569.msg
[15] V:\DIVISION\BIO\BIO1\Email Reference\208569 Teriparatide Injection\Lilly petition\FW Teriparatide Citizen Petition Final Response (issued 11317).msg

4 APPENDIX

4.1 Formulation Data

4.1.1 Composition of the Test Product[16, 17]

Strength (Label Claim):		250 mcg/mL (600 mcg/2.4mL)				
Component Grade	**Quality Standard**	**Function**	**Quantity per mL**	**RLD FORTEO™ (each mL contains)[1]**	**Quantity per vial (mg)**	**% w/v total unit dose**
Teriparatide	In-House	Active	0.250 mg	[redacted] (b) (4)		
Glacial Acetic Acid	USP	[redacted] (b) (4)	0.41 mg			
Sodium Acetate (Anhydrous)	USP		0.1 mg			
Mannitol	USP		45.4 mg			
Metacresol	USP		3 mg			
Water for Injection	USP-NF		q.s.			
Sodium Hydroxide	NF	pH Adjuster	q.s. to pH			
Hydrochloric Acid	NF	pH Adjuster	q.s. to pH			
[redacted]						
TOTAL:						**100.00%**

[1]Composition information is taken from the RLD labeling, FORTEO™ (teriparatide [rDNA origin]) Injection, [redacted] (b) (4) is considered to be Q1/Q2 with the RLD, FORTEO™ (teriparatide [rDNA origin]) Injection, 600mcg/2.4mL – NDA number 021318.

1 Page has been wittheld in full as b4 (CCI/TS) immediately following this page

[16] DARRTS, ANDA 211097, EDR 000, 2.3.P. Quality Overall Summary (WORD).
[17] DARRTS, ANDA 211097, EDR 000, 3.2.P.1: Description and composition of the drug product.

4.1.3 Comparison of Composition between the Test and RLD Products (Not to be released under FOIA)

Ingredients	Function	Test Formulation Quantity per mL (mg/mL)	RLD Formulation Quantity per mL (mg/mL)	Percentage Difference
Teriparatide	Active substance	0.250	(b) (4)	(b) (4)
Glacial acetic acid	(b) (4)	0.410		
Sodium Acetate*		0.10		
Mannitol		45.400		
Metacresol		3.000		
Hydrochloric acid	pH adjuster	q.s.		
Sodium hydroxide	pH adjuster	q.s.		
Water for injection				

(b) (4)

4.2 Reviewer's Comments:

- The proposed test product, Teriparatide Injection, 600 mcg/2.4 mL is supplied as a sterile, colorless, clear, solution for injection in a (b) (4) glass cartridge which is pre-assembled into a disposable delivery device (b) (4) for subcutaneous injection.

- The route of administration, dosage form, and strength of the test product are same as those of the RLD product.

- Based on the data submitted, the formulation of the test product is deemed qualitatively (Q1) and quantitatively (Q2) the same as that of the RLD product.

- The pH specification of RLD is 3.8 to 4.5[3]. The applicant proposed specifications for pH of its test product are also same i.e. 3.8-4.5[19].

- The pH of three batches of the test product, Teriparatide Injection, 600 mcg/2.4 mL ranges from 4.2 to 4.3, and thus is within the pH specification range of the RLD product.

- The RLD product does not have specifications for osmolality. However, the test product has osmolality specifications of (b) (4) (Analytical Procedures, Module 3.2.P.5.2.) which is in line with USP <785>.

[19] GDRP, ANDA211097, , M.3.2.P.5.4, \\cdsesub1\evsprod\anda211097\0000\m3\32-body-data\32p-drug-prod\teriparatide-injectable-novocol\32p5-contr-drug-prod\32p54-batch-analys\batch-analyses-1.pdf

- Per internal meeting discussions[20, 21], for generic drug-device combination product, Division of Clinical Research (DCR) will be responsible for reviewing threshold analyses/comparative use human factor (HF) study and consulting/coordinating with other groups as applicable (e.g. DLR, DMEPA, OGDP). Therefore, the review of threshold analyses/comparative use human factor (HF) study submitted by the applicant is deferred to DCR.

- Per the internal discussion between the Office of Bioequivalence (OB) and the Office of Research Standards (ORS)[22], in vitro BE studies, for example injection volume and injection depth, are not recommended.

- The potency of the test product is (97.6% - 100.2%). It is noted that the potency specification for RLD and test products is same (Not less than 90.0% and not more than 105.0% of label claim).

- OGD is in the process of developing a guidance to allow synthetic peptide drug products referencing NDA peptide drug products of rDNA origin using the 505(j) pathway.

- As per the Agency's current thinking about the development of synthetic peptide products referencing a recombinant is that in order to qualify for an ANDA pathway, the proposed products should first follow the following criteria:

  1. The impurity profile for the ANDA product, at a minimum, includes the same or a lower level of specified impurities common to the synthetic peptide and the RLD;
  2. Any new specified impurity in the ANDA product is no more than 0.5% of the drug substance and the applicant has provided justification for why each such impurity does not affect safety or effectiveness; and
  3. The submission otherwise meets the statutory and regulatory requirements for an ANDA, including, for example, that the submission includes information from physicochemical characterizations and biological evaluations to show that the active ingredient is the same as that of the RLD through a comparison of their properties (including, but not limited to, primary sequence, secondary structure and oligomer/aggregation states, and biological activities).

  Only if the criteria above are satisfied, the Agency will assess the Q1/Q2 of the proposed products versus the RLD.

  It should be noted that all the above mentioned criteria will be evaluated by OPQ.

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[20] V:\DIVISION\BIO\BIO1\Email Reference\208569 Teriparatide Injection\20170710 DBI Staff Meeting.ppt

[21] V:\DIVISION\BIO\BIO1\Email Reference\208569 Teriparatide Injection\Drug device combination product preso for OB (final).pptx

[22] V:\DIVISION\BIO\BIO1\Email Reference\208569 Teriparatide Injection\RE 208569 post-CR meeting request letter.msg, 08/30/2017

- From the bioequivalence perspective, the test product is considered to be Q1/Q2 to the RLD product.

- Therefore, per 21 CFR § 320.22 (b)(1), the waiver request for the test product, Teriparatide Injection, 600 mcg/2.4 mL (250 mcg/mL), is granted.

4.3 Detailed Regulatory History (If Applicable)

None

4.4 Consult Reviews

None

4.5 Additional Attachments

None

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:	211097
APPLICANT:	Apotex Inc.
DRUG PRODUCT:	20 mcg per dose (600 mcg/2.4 mL)

The Division of Bioequivalence III (DBIII) has completed its review and has no further questions at this time.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Nilufer M. Tampal, Ph.D.
Director, Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

4.6 Outcome Page

Completed Assignment for 211097 ID: 34653

Reviewer:	Kaur, Manjinder	**Date Completed:**
Verifier:	,	**Date Verified:**
Division:	Division of Bioequivalence	
Description:	Teriparatide Injection, 20 mcg per dose (600 mcg/2.4 mL)	

Items:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*
34653	12/29/2017	BIO	ANDA Original [1]	1	1
34653	12/29/2017	Parallel	Waiver Injectable (Per application) [1]	1	1
				Total:	5

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 211097

STATISTICAL REVIEW

STATISTICAL REVIEW AND EVALUATION

CONSULT REVIEW AMENDMENT

Consult Requester	Avani Bhalodia, PharmD, BCPS, FISMP, OMEPRM/DMEPA Millie Shah, PharmD, BCPS, FISMP, OMEPRM/DMEPA
Type of Consult	Review of comparative use human factors study report (sequence 0020 and 0025)
ANDA Number	ANDA 211097
Drug Name	Teriparatide Injection, USP, 20 mcg/dose (600 mcg/2.4 ml)
Applicant	Apotex, Inc.
Reference Listed Drug	Eli Lilly and Company, Inc's Forteo® (teriparatide [rDNA origin] injection) 20 mcg per dose (NDA 021318)
Indication	• Treatment of postmenopausal women with osteoporosis at high risk for fracture • Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture • Treatment of men and women with osteoporosis associated with sustained, systemic glucocorticoid therapy at high risk for fracture
Dates	Review Assignment Date: 12/3/2020 Information Request (IR) Date: 3/2/2021 IR Response Date: 3/9/2021 Completion Date: 6/3/2021
Biometrics Division **Primary Statistical Reviewer** **Secondary Statistical Reviewer**	 Yifan (Katie) Wang, Ph.D., DBVIII/OB/OTS/CDER Somesh Chattopadhyay, Ph.D., DBVIII/OB/OTS/CDER
Keywords	teriparatide prefilled pen (PFP), injection, comparative use human factors (CUHF) study, non-inferiority (NI), NI margin, block randomization, use success, crossover design, sample size, power, Tango method

1. BACKGROUND INFORMATION

This consult request from Division of Medication Error Prevention and Analysis (DMEPA) is to evaluate the comparative use human factors (CUHF) study results for the Teriparatide Injection USP, 20 mcg per dose (600 mcg/2.4 mL) (ANDA 211097) submitted by Apotex Inc. on 10/15/2020 (sequence 0020), and the Information Request (IR) response on 3/9/2021 (sequence 0025). The specific requests from DMEPA are to check if the sample size in this CUHF study was adequately powered, if the study design was statistically appropriate, and if the Applicant's conclusion was accurate regarding non-inferiority (NI) to draw use performance comparison between the proposed product and the Reference Listed Drug (RLD).

The RLD product, Forteo® (teriparatide) injection for treatment of osteoporosis by Eli Lilly and Co., was approved on 11/26/2002 under NDA 021318 (with Patent No. 7517334 expiring on 3/25/2025). Teriparatide prefilled pen (PFP) is a generic version of the Forteo® pen injector. (b) (4)

(b) (4)

Apotex, Inc. submitted a Threshold Analysis in the original submission of ANDA 211097 on 12/29/2017 to identify and assess differences in the design of the user interface of the device constituent part for its Teriparatide PFP in comparison to the Forteo® pen.

FDA commented in a Complete Response Letter dated 10/26/2018 that differences related to Teriparatide PFP's slimmer body, shape, and tactile/texture may have the potential to impact postmenopausal women with osteoporosis and elderly patients' abilities to safely and effectively operate the device (b) (4) and may affect how these users perform the critical task of daily dose injection. FDA suggested additional information or data may be warranted (such as data from a Comparative Use Human Factors Study) to further assess whether the identified differences in the user interface impact the clinical effect or safety profile when compared to the RLD.

Apotex Inc. submitted a general correspondence requesting a written response relevant to the post-complete response letter issued by the Agency (dated 10/26/2018) on 2/1/2019 and additional questions for clarification on 11/20/2019. The Agency made written responses to the questions in the general correspondence on 11/13/2019 and 1/30/2020.

Apotex Inc. submitted a response to the Complete Response Letter (dated 10/26/2018) in a question-and-answer format on 10/15/2020 with modified CUHF study protocols and results. According to the Applicant, as the situation related to COVID-19 in the United States at the time of initial study execution, the protocol was amended to allow for remote participation to assure participant safety, and avoid travel and close contact based on FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency (issued March 2020, Updated September 2020). The Applicant concluded that the differences in body size/shape and tactile/texture characteristics between the proposed product and the RLD are minor and will not impact the clinical effect or safety profile, and that the Teriparatide PFP device and the Forteo® device can be substituted under the conditions specified in the labeling.

In this submission, the Applicant submitted the study report (dated 10/8/2020), protocol Version A (dated 2/20/2020) and Version B (dated 8/11/2020) and the Statistical Analysis and Programming Plan (dated 9/9/2020).

FDA sent an IR with nine statistical and human factor questions to the Applicant on 3/2/2021. The Applicant submitted an IR response with datasets, randomization schedules, PASS software (sample size calculation) documentation and other supporting documents on 3/9/2021 (sequence 0025).

2. SUMMARY OF CUHF STUDY REPORT

2.1 Study Objective

The objective of the study is to demonstrate that differences in the user interface design of the Teriparatide PFP device (specifically, differences in the body shape, size and texture) do not negatively impact user performance when giving injections in comparison to the Forteo® device. Specifically, that the failure rate (the use error rate) for Teriparatide PFP is not worse than (i.e., not inferior to) the failure rate for Forteo®; a test of NI of the Teriparatide PFP relative to Forteo®. To support this goal, qualified participants conducted simulated injections using both the Forteo® PFP and Teriparatide PFP.

2.2 Study Design

This study has a crossover design with each participant being their own control stimulating self-injection using both the test and RLD products. According to the Applicant, the order of simulated injection was randomized across participants with either the Forteo® first followed by the Teriparatide, or vice versa. Participants were given the choice of participating in-person or remotely via web conference, and asked to choose their own administration site (either the thigh or abdomen) and give injections according to the randomization sequence into the injection pad strapped to their body with both injections on the same site.

For **in-person** testing, the moderator would be present in the room with the participant during the execution of the session.

For **remote** testing, a web conference would be set up with the participant in their own home and the moderator in another location as participants in this study are considered a vulnerable population and are more susceptible to COVID-19. Once an internet meeting connection was made between the moderator and the participant, the moderator would determine if the internet connection was sufficient to clearly see the injection process. The participant would be dismissed from the study if it was not possible to see the injection process or if there was a disruption of the internet connection during the testing; the participant would be replaced in order to achieve the target sample size. The participant would be asked to open "Box A" (needles, alcohol swabs, sharps bin, and an injection pad that is attached to the body for the simulated injection) and as per moderator instructions, start with (depending on the randomization scheme) either "Box B" (Teriparatide PFP and IFU) or "Box C" (Forteo® pen and IFU), followed by the other box.

Reviewer's Comments:

Page 10 of the study results report stated, "Some study sessions were conducted via web conference with the participant in their own home and the moderator in another location as participants in this study were considered a vulnerable population and are more susceptible to

COVID-19. Thus, participants were given the choice of participating in-person or remotely." However, the Applicant's study report did not specify the type of testing session each participant completed (e.g. in-person or remote). The Applicant was requested to clarify which participants participated in in-person sessions and which participants participated in remote sessions (e.g. provide participant IDs and indicate whether testing environment was an in-person or remote session). The Applicant provided the list of participant ID and testing environment in the IR response.

2.3 Randomization

According to the Applicant, each participant would complete two injections: one using the Forteo® pen and one using the Teriparatide pen. Subjects would first be stratified to either current or previous Forteo® users. For each stratum, a list of randomized testing sequences of either the RLD-test sequence or the test-RLD sequence will be generated by using block randomization with a block size of four (4). The recruiter who was assigned to booking the participant appointments was blinded to the randomization sequence and the randomization sequence was generated prior to any participant enrolling into the study. (*source: CUHF study protocol on 8/11/2020, page 14 of 24 of protocol /63 of 114 of CUHF study report*)

Reviewer's Comments:

The Applicant stated in the CUHF study report that the order of simulated injection of Forteo® and Teriparatide PFPs was block randomized stratified by user group (current or previous RLD users). However, the randomization schedule could not be located in the submitted materials. The Applicant provided their randomization schedule for each stratum (current users and previous users) in the IR response dated 3/9/2021 (sequence 0025). The randomization schedule is acceptable.

2.4 Sample Size

According to the Applicant, the sample size calculation was based on a NI Test for the Difference Between Two Correlated Proportions, performed in PASS 15, dependent on the following parameters:

- Alpha: chosen to be 0.05 for the one-sided comparison of a 90% confidence interval,
- Power: chosen to be 80%,

- NI margin D_{NI}: as the drug does not have a narrow therapeutic window and the consequence of an overall use error of the device is not considered to be serious, D_{NI} is chosen to be 0.15,
- Actual difference between devices: chosen to be 0, as both devices are considered to be equivalent in design and use,
- Standard Device Successful Usage Proportion P_S: 0.8667 was used based on a past study of previous and current Forteo® users in which 26 out of 30 users were successful in using the device,
- Nuisance Parameter, Matched Proportions: Defined as the proportion of subjects that either use both devices successfully or both devices as failures. This was chosen as 0.8667 based on the results of the past study with the assumption of a difference of 0 between the two devices.

		Generic Teriparatide		
		Pass	Fail	Total
RLD Forteo	Pass	0.8	0.0667	0.8667
	Fail	0.0667	0.0667	0.1333
	Total	0.8667	0.1333	1

The Applicant stated that a sample size of N=49 would be sufficient to provide 80.7% power based on the parameters above.

Reviewer's Comments:

The sample size calculation procedure in the study report was not clear. The Applicant was requested in the IR to provide the specific sample size calculation formulas besides the submitted parameters in the statistical analysis section. The Applicant provided the documentation of the PASS software that they used to find the sample size in the IR response.

1. *The Applicant stated that the "standard device successful proportion Ps: 0.8667 was used based on a past study of previous and current Forteo users in which 26 out of 30 users were successful in using the device" (quoted from the CUHF study protocol, Rev B, Page 18 of 24) but did not provide any reference or supporting evidence for this finding.*

2. *The Applicant assumed the concordance proportion (proportion of subjects who have the same outcomes, i.e., success or failure, for using the two devices) of 0.8667 in the sample size calculation. It is not made clear how this proportion translates to the assumed correlation in the Tango method that the Applicant eventually used for the NI analysis.*

3. *The Applicant's sample size of 49 is acceptable for the current settings in this CUHF study to attain 80% power. Please refer to Table 4 in Primary Analysis section in this review for reviewer's analysis results.*

2.5 Study Participants

Forty-nine (49) participants were recruited by phone using Participant Screener. There are two subpopulations of Forteo® users who might have dexterity and hand strength issues:

1. **Current** Self Administering Forteo® Users:
   a. Postmenopausal woman who are currently taking Forteo® and
   b. Elderly patients (including females and males, 65 years and older) currently taking Forteo®.
2. **Recent** Self Administering Forteo® Users:
   a. Postmenopausal woman, who for at least three weeks, within the past two years since time of screening, self-administered Forteo® and
   b. Elderly patients (including females and males, 65 years and older), who for at least three weeks, within the past two years since time of screening, self-administered Forteo®

Inclusion and exclusion requirements for study participants are:

Inclusion Criteria

- Diagnosed with osteoporosis.
- Post-menopausal female or male or female 65 years or older.
- Currently self-administering daily Forteo® injections for a **minimum of 3 weeks**.
- Previously self-administered daily Forteo® injections for a **minimum of three weeks within the past two years** (from date of screening).

Exclusion Criteria

- Difficulty reading and understanding English.
- A recent hand injury or medical condition (other than osteoporosis) that prevents use of an injection device via self-administration.
- An uncorrected visual impairment that prevents reading instructions.
- Personal association with or an immediate family member associated with a pharmaceutical or medical device company.

Table 1 below summarizes demographic information for the final sample of test participants. The participants were generally older, majority female, diagnosed with osteoarthritis, and had a range of hand dexterity ability (as measured by the Cochin Hand Function Scale).

Table 1: Demographic Summary

Participant IDs (b) (6)	Group	Age Range (Average Years)	Dominant Hand	Cochin Range (Median)	Gender
	Current Forteo® Users	50 - 79 (64.2)	Left: 3 Right: 24 Ambidextrous: 1	0 – 27 (0)	Female: 27 Male: 1
	Past Forteo® Users	46 - 75 (65.7)	Left: 3 Right: 18 Ambidextrous: 0	0 – 8 (0)	Female: 21 Male: 0

Source: Applicant's CUHF Study Report Table 1, Page 9 of 31.

Reviewer's Comments:

The study report was inconsistent in that it is proposing two subpopulations of current and past RLD users but requiring both conditions (currently RLD-use for a minimum of 3 weeks, and previously RLD-use for a minimum of three weeks within the past two years) in the inclusion criteria of the protocol (source: CUHF study protocol Rev B, Page 8-9 of 24). The Applicant confirmed in the IR response that one of the criteria had to be met, not both (IR response Page 8 of 16).

2.6 Data Collection

Each session was conducted in a one-on-one format and lasted up to 45 minutes. Participants were not trained prior to their test sessions but had access to the IFU for each device to reference it, if they chose to use it. The moderator did not compel them to review these materials. The moderator observed participant performance and comments for evidence of use-related issues. This was followed by a Post-Test Interview (PTI) that included a review of any use issue they encountered, and questions aimed at assessing their understanding of critical knowledge tasks relating to safe use of the product. Testing started on March 3, 2020 and finished on September 4, 2020. The sequence of activities for each session is outlined in Table 2 below.

Table 2: Sequence of Activities in Each Participant Session

Activity	Description
1. Participant Enrollment	The participant reviewed and signed an Informed Consent Form[5] prior to the session. The moderator asked the participant a set of background questions to verify they met the study inclusion criteria.
2. Study Introduction	The moderator read a study script, which introduced the study, and answered questions about the study at that time.
3. Simulated Injection 1	The participant was presented with the first of two injection scenarios; either the Forteo® scenario or the Teriparatide PFP scenario. The moderator observed the simulated injection and noted performance.
4. Break	A minimum 5-minute break was taken between injections. For in-person testing, the moderator took simple grip and pinch strength measurements using a dynamometer and a pinch gauge[6]. Both in-person and remote participants completed a Cochin Hand Function Assessment (questionnaire).
5. Simulated Injection 2	The moderator presented the participant with the second of the two injections scenarios; either the Forteo® scenario or the Teriparatide PFP scenario.
6. Use Error Interview	If the participant made one or more use errors on the critical tasks during either simulated-use scenario, the moderator interviewed the participant about the potential causes of the errors only after both simulated injections were completed.
7. Dismissal	Following the Use Error Interview (or if no use errors were made during the simulated-use scenarios) the participant was compensated for their participation and dismissed.

Source: Applicant's CUHF Study Report Table 2, Page 12 of 31.

2.7 Critical Tasks

Critical tasks are defined as tasks which, if performed incorrectly or not performed at all, would or could cause harm to the subject or user, where harm is defined to include compromised medical care. The Applicant identified 5 critical tasks in this study that were confirmed by the Agency via General Correspondence, including: pull out dose button to load the dose, place device against thigh or abdomen, push the injection button, hold the injection button down while delivering the medication, and hold in place to deliver the medication. The study moderator monitored participants during simulated injections for evidence of critical task use errors.

Table 3 describes each critical task, the definition of successful performance, and examples of potential task failures.

Table 3: Critical Tasks That May Be Affected by External Design

Critical Task	Definition of Successful Performance	Examples of Task Failures
1. Pull out dose button to load the dose.	User pulled the dose button out to load the dose.	• User was unable to pull the button out fully; unable to load the dose; no medication delivered. • User attempted to expel air or prime the device; loss of medication.
2. Place device against thigh or abdomen.	User placed the device against the thigh or abdomen.	• User was unable to place the device or hold in place securely; no medication given, or only partial dose delivered.
3. Push the injection button.	User pressed the injection button fully.	• User was unable to press the button fully; only partial dose delivered.
4. Hold the injection button down while delivering the medication.	User held the injection button down while completing Task 3.	• User was unable to maintain downward pressure on the button; only partial dose delivered.
5. Hold in place to deliver the medication.	User was able to hold the device in place while counting for the duration specified in the Instructions for Use (IFU) (a count of 5).	• User was unable to hold the device in place while counting; only partial dose delivered.

Source: Applicant's CUHF Study Report Table 3, Page 14 of 31.

2.8 Primary Endpoint

The Applicant stated that the endpoint for each injection was a binary, success/failure score. The participant's overall performance on a simulated injection was scored as a "success" if the participant completed each critical task without a use error, or as a "failure" if a use error was made on one or more of the critical tasks. The overall success rate for each device was the proportion of participants who had a successful injection with the device. The five critical tasks for completing an injection were scored for each simulated injection scenario. Task performance was scored using the following definitions:

- Success (S) – The participant successfully completed the task.
- Error (E) – The participant did not successfully complete the task, skipped, or omitted a task.
- Did not Attempt (DNA) – The participant did not attempt the task (e.g., a participant who did not remove the needle from a pen, did not therefore re-cap the pen after use; in this example, recapping the pen was not attempted and scored as "DNA").

2.9 Primary Analysis

The primary analysis for this study was to determine the difference between the proportion of successful usage of the generic Apotex Teriparatide device (b) (4) and the proportion of successful usage of the RLD Forteo® device (b) (4)

(b) (4)

The NI test was performed by comparing the lower bound of the 90% confidence interval (CI) for the difference in proportion of successful usage to D_{NI}. If the lower bound was not smaller than - D_{NI}, NI is demonstrated. The 90% CI was calculated using the Tango method for calculating confidence intervals for the difference in proportions in matched pairs (Tango 1998) developed by Rodriguez De Gil, et al (2013).

Reviewer's Comments:

The Applicant provided their justification for using 0.15 as the NI margin in their IR response. The Applicant's reasoning: FDA Product Specific Guidance for bioequivalence (BE) study with dichotomous clinical endpoint for non-NTI (narrow therapeutic index) drugs generally uses +/- 0.2 as the BE margin; FDA Guidance for CUHF study does not have a specified NI margin but an example with a margin of 0.10; since the CUHF study also uses dichotomous variables of user success/failure, and teriparatide is a non-NTI drug, the Applicant used the mid-point of 0.1 and 0.2, that is, 0.15 as their NI margin, and claimed that "even if the NI margin of 0.1 is required, the criterion for NI would have been met by the Apotex product" (Applicant's IR response, Page 4 of 16).

The Applicant's justification is not acceptable for the following reasons.

1. *The BE Guidance is not applicable for this study because: 1) a CUHF study compares the device use error or use success in a drug-device combination product, it does not compare drug products and 2) the purpose of a CUHF study is to show that the Test device is non-inferior to the RLD device in use error or use success, not BE. The Applicant should refer to the NI Guidance for more details about determining the NI margin.*

2. *The Applicant's statement that even a margin of 0.1 would have passed the NI test in the IR response appears to be a post-hoc justification. The Applicant should propose a NI*

margin that is clinically meaningful (i.e. how much additional use error is acceptable when applying the Test product compared to the RLD product) based on data from other studies of the RLD product. The Applicant's proposal should be reviewed and agreed upon by the FDA before the study is started.

Based on the reviewer's analysis presented in Table 4 below, a margin as small as 0.1 may be used in this CUHF study if the assumptions in the Applicant's settings are acceptable. For example, if the Applicant could provide evidence for the claimed RLD success rate of 0.8667, and assume the in-person correlation is 0.8 or higher (the Applicant did not consider this parameter), the margin of 0.1 with the Applicant's sample size 49 would attain 85% power with 90% confidence using the Tango method.

Table 4: Reviewer's Evaluation for NI Margin and Power (*N* = 49)

In-person Correlation	Margin	Power
0.7	0.08	0.5235
	0.10	0.7585
	0.12	0.8624
	0.15	0.9509
0.8	0.08	0.6098
	0.10	**0.8507**
	0.12	0.9307
	0.15	0.9849

Note: simulation results (5,500 times) are based on the Tango method with Applicant's current sample size 49 and 90% confidence, given the Test and RLD success rates are both 0.8667 according to the Applicant's claim.
Source: reviewer's analysis

2.10 Sensitivity Analysis

According to the Applicant, as a sensitivity analysis, the difference in proportion of successful usage and its 90% CI was calculated for the two subgroups of participants (i.e., in-person or remote testing). Given that a cross-over design was employed for the comparison of the test and RLD product, no significant impact of different testing environments was expected.

2.11 Results and Conclusions

The results of the primary and sensitivity analyses are presented in Table 4.

Overall, there was no difference in proportion of successful usage between the two products with the lower bound of the 90% CI (-0.0824, 0.0824) being larger than the Applicant's protocol-

defined NI margin of 0.15. Hence, according to the Applicant, NI of the test product to RLD was demonstrated.

The difference in proportion of successful usage between the two products and its 90% CI were also comparable between the two subgroups. The applicant concluded that no significant bias was introduced to the comparison of the test and RLD products due to the utilization of different testing environments (in-person and remote).

Table 5: Primary and Sensitivity Analysis Results

Category	N	Apotex Success/ Forteo® Success n (proportion)	Apotex Success/ Forteo® Failure n (proportion)	Apotex Failure/ Forteo® Success n (proportion)	Apotex Failure/ Forteo® Failure n (proportion)	Proportion Apotex Success P_T	Proportion Forteo® Success P_S	Actual Proportion Difference $P_T - P_S$	Proportion Difference 90% Confidence Interval (Lower, Upper)
Primary Endpoint Analysis									
Total	49	30 (0.6122)	2 (0.0408)	2 (0.0408)	15 (0.3061)	32 (0.6531)	32 (0.6531)	0.0000	(-0.0824, 0.0824)
Sensitivity Analysis									
In-Person Participants	17	11 (0.6471)	0 (0.0000)	1 (0.0588)	5 (0.2941)	11 (0.6471)	12 (0.7059)	-0.0588	(-0.2256, 0.0866)
Remote Participants	32	19 (0.5938)	2 (0.0625)	1 (0.0313)	10 (0.3125)	21 (0.6563)	20 (0.6250)	0.0313	(-0.0773, 0.1475)

Source: Applicant's CUHF Study Report Table 6, Page 21 of 31.

According to the Applicant, the data supports that the differences in device between the Teriparatide PFP and Forteo® are acceptable and that the Teriparatide PFP can be substituted to produce the same clinical effect and safety profile as Forteo® under the conditions specified in the labeling.

Reviewer's Comments:

1. (b) (4)

2. *If the NI margin of 0.1 is acceptable, this CUHF study passes NI for the Test product as compared to the RLD product in terms of use success. We still have concerns whether the study would pass if it were conducted fully in-person. Although not specified in the study report, the Applicant's sensitivity analysis results for in-person participants showed the Test product was inferior to the RLD product with the lower limit being -0.2256, which is smaller than the Applicant's margin of -0.15. However, the sample size of 17 is not adequate to draw a conclusion about NI in a subgroup.*

3. *No datasets were provided in the standard format in sequence 0020. The Applicant was requested in the IR to provide the demographic characteristics (e.g., sex, age, in-person or remote session, current or recent user, and administration site) and task level records following the data submission guideline at https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber. The Applicant submitted the subject level analysis dataset (adsl.xpt) and the tabulation dataset of critical task findings (ta.xpt) in their IR response.*

2.12 Handling of Missing Data

The Applicant mentioned in the table of analysis dataset that "if subject has missing data for any critical task then PPROTFL='N'; Else if subject completed the study in its entirety PPROTFL="Y"; Subject to additional adjudication" (*source: Statistical Analysis and Programming Plan, Page 11 of 23*). This is a part of the specifications for the analysis dataset, not a statement defining the per-protocol set in the document body. The Applicant needs to provide a clarification for their methods to handle missing data.

Reviewer's Comments:

The Applicant confirmed in the IR response that there was no missing data related to the user error assessment of each critical task for the determination of the primary endpoint of the study.

3. REVIEWER'S RESPONSE TO THE CONSULT

a) Comments for Internal Use (FDA)

For the CUHF study results of Apotex's Teriparatide Injection Pen submitted on 10/15/2020 in ANDA 211097 and the IR response submitted on 3/9/2021, we have the following comments.

1. The randomization schedule could not be located in the submitted materials in sequence 0020. The Applicant provided the randomization schedule for each stratum in the IR response in sequence 0025. The randomization schedule is acceptable.

2. The study report was inconsistent in that it is proposing two subpopulations of current and past RLD users but requiring both conditions in the inclusion criteria of the protocol. The Applicant confirmed in the IR response that one of the criteria had to be met, not both.

3. The Applicant's study report did not specify the type of testing session each participant completed (e.g. in-person or remote). The Applicant provided the list of participant ID and testing environment in the IR response.

4. The gender distribution in this study may not represent the intended user population. The Applicant stated that the study population was similar to the intended users. From the demographic information provided in this report, almost all study participants were females (48), and only one participant was male. We defer the decision of acceptability and appropriateness of the study population to DMEPA.

5. There was no clear statement about handling of missing data in the CUHF study report. The Applicant confirmed in the IR response that there was no missing data related to the use error assessment of each critical task for the determination of the primary endpoint in this study.

6. No datasets were provided in the standard format in sequence 0020. The Applicant submitted the subject level analysis dataset (adsl.xpt) and the tabulation dataset of critical task findings (ta.xpt) in their IR response as requested.

7. The sample size calculation procedure in the study report was not clear. The Applicant provided the documentation of the PASS software that they used to find the sample size in the IR response.

8. The Applicant used a use success rate of 0.8667 for the RLD and claimed that it was based on "a past study" but did not provide any reference or supporting evidence for this claim.

9. The Applicant assumed the concordance proportion (proportion of subjects who have the same outcomes, i.e., success or failure, for using the two devices) of 0.8667 in the sample

size calculation. It is not made clear how this proportion translates to the assumed correlation in the Tango method that the Applicant eventually used for the NI analysis.

10. The justification for NI margin of 0.15 was not clear in the CUHF study report. The Applicant provided more details for their justification in their IR response arguing that because the equivalence margin for BE in the product-specific guidances for non-NTI drugs is 0.20, the NI margin of 0.15 in the CUHF study is justified. The justification referencing of the BE guidance is not acceptable due to the following reasons: 1) a CUHF study compares the device use error or use success in a drug-device combination product, it does not compare drug products and 2) the purpose of a CUHF study is to show that the Test device is non-inferior to the RLD device in use error or use success, not BE. The Applicant should refer to the NI Guidance for more details about determining the NI margin.

11. The Applicant's statement that even a margin of 0.1 would have passed the NI test in the IR response appears to be a post-hoc justification. The Applicant should propose a NI margin that is clinically meaningful (i.e. how much additional use error is acceptable when applying the Test product compared to the RLD product) based on data from other studies of the RLD product. The Applicant's proposal should be reviewed and agreed upon by the FDA before the study is started.

12. Given the current settings in this CUHF study (e.g., margin of 0.15, success rate of 0.8667), the Applicant's sample size of 49 is adequate to attain 80% power based on the reviewer's analysis.

13. Based on the reviewer's analysis, a margin as small as 0.1 may be used in this CUHF study if the assumptions in the Applicant's settings are acceptable. For example, if the Applicant could provide evidence for the claimed RLD success rate of 0.8667, and if assume the in-person correlation is 0.8 or higher (the Applicant did not consider this parameter), the margin of 0.1 with the Applicant's sample size 49 would provide 85% power with 90% confidence.

14. [redacted] (b) (4) Therefore, 0.1 may be accepted as the NI margin in this study also. [redacted] (b) (4) If the NI margin of 0.1 is acceptable, this CUHF study passes NI for the Test product as compared to the RLD product in terms of use success. We still have concerns whether the study would pass if it were conducted fully in-person. Although not specified in the study report, the

Applicant's sensitivity analysis results for **in-person** participants showed the Test product was inferior to the RLD product with the lower limit being -0.2256, which is smaller than the Applicant's margin of -0.15. However, the sample size of 17 is not adequate to draw a conclusion about NI for a subgroup.

15. The Applicant did not submit their CUHF study protocol at the study design stage for the Agency to review or make recommendations to the sample size or NI margin. Instead, they submitted the CUHF study report along with the protocol after the study was completed. Based on the reviewer's statistical analyses on the data provided, the NI could be demonstrated with a margin of 0.1 between the proposed generic combination product and its RLD in use error rates for the critical tasks impacted by changes in critical external design attributes, despite the issues mentioned above.

REFERENCES

FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency (issued March 2020, Updated September 2020).

Draft Guidance on Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA (January 2017).

FDA Guidance on Non-Inferiority Clinical Trials to Establish Effectiveness (November 2016).

Tango, T. (1998). Equivalence Test and Confidence Interval for the Difference in Proportions for the Paired-Sample Design. Statistics in Medicine, Vol 17: 891-908

Rodríguez de Gil P., Romano, J., Pham, T., Nguyen, D., Kromrey, J.D., Kim, E.S. (2013). CORR_P and TANGO: Interval Estimation for the Difference Between Correlated Proportions in Dependent Samples. South East SAS User Group Conference 2013. St. Petersburg, FL

APPENDIX A: ORIGINAL CONSULT REQUEST

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**			
TO *(Office/Division)*: OTS/DBVIII			FROM (*Name, Office/Division, and Phone Number of Requestor)*: Avani Bhalodia, OMEPRM/DMEPA, 301-796-5534	
DATE 12/03/20	IND NO. N/A	ANDA NO. 211097	TYPE OF DOCUMENT Human Factors Comparative Use Study Results	DATE OF DOCUMENT October 15, 2020
NAME OF DRUG Teriparatide	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE Jan 22, 2021
NAME OF FIRM: Apotex				

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☒ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

Please evaluate whether the submitted Comparative Use HF Study Results methodology for the Teriparatide Prefilled Pen (ANDA 211097) are acceptable.

Our specific requests are:
1) Are sample sizes adequately powered and study design statistically appropriate to draw use performance comparison between the two products?

2) If the sample size and study design are statistically appropriate, do you agree with the Applicant's conclusion regarding non-inferiority of the proposed product compared to the RLD?

3) Are there other considerations from a statistical review perspective that we have not covered in #1 and 2 above?

Please share your preliminary draft comments prior to finalizing your review.

(Note: we recently worked with Katie Wang and Somesh Chattopadhyay on another HF Comparative Use Protocol)

Link to the HF Report submission:
\\CDSESUB1\evsprod\anda211097\0020\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5354-other-stud-rep\apo-tcu2-vt-503\comparative-use-human-factors-study-apo-tcu2-vt-503.pdf

SIGNATURE OF REQUESTOR and DMEPA Point of Contact Avani Bhalodia	METHOD OF DELIVERY (Check all that apply) ☒ DARRTS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

YIFAN WANG
06/07/2021 04:32:21 PM
This is the stat review for the CUHF study report for ANDA 211097 Sequence 0020 and 0025.

SOMESH CHATTOPADHYAY
06/07/2021 04:34:03 PM

STATISTICAL REVIEW AND EVALUATION

CONSULT REVIEW

Consult Requester	Avani Bhalodia, PharmD, BCPS, FISMP, OMEPRM/DMEPA Millie Shah, PharmD, BCPS, FISMP, OMEPRM/DMEPA
Type of Consult	Review of comparative use human factors study report (sequence 0020)
ANDA Number	ANDA 211097
Drug Name	Teriparatide Injection, USP, 20 mcg/dose (600 mcg/2.4 ml)
Applicant	Apotex, Inc.
Reference Listed Drug	Eli Lilly and Company, Inc's Forteo® (teriparatide [rDNA origin] injection) 20 mcg per dose (NDA 021318)
Indication	• Treatment of postmenopausal women with osteoporosis at high risk for fracture • Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture • Treatment of men and women with osteoporosis associated with sustained, systemic glucocorticoid therapy at high risk for fracture
Dates	Review Assignment Date: 12/3/2020 Completion Date: 2/12/2021
Biometrics Division **Primary Statistical Reviewer** **Secondary Statistical Reviewer**	 Yifan (Katie) Wang, Ph.D., DBVIII/OB/OTS/CDER Somesh Chattopadhyay, Ph.D., DBVIII/OB/OTS/CDER
Keywords	Teriparatide Prefilled Pen (PFP), Injection, Comparative Use Human Factors (CUHF) Study, Non-inferiority, Randomization, Use Error Rate, Crossover Design

1. BACKGROUND INFORMATION

This consult request from Division of Medication Error Prevention and Analysis (DMEPA) is to evaluate the comparative use human factors (CUHF) study results for the Teriparatide Injection USP, 20 mcg per dose (600 mcg/2.4 mL) (ANDA 211097) submitted by Apotex Inc. on 10/15/2020. The specific requests from DMEPA are to check if the sample size in this CUHF study was adequately powered, if the study design was statistically appropriate, and if the Applicant's conclusion was accurate regarding non-inferiority to draw use performance comparison between the proposed product and the Reference Listed Drug (RLD).

The RLD product, Forteo® (teriparatide) injection for treatment of osteoporosis by Eli Lilly and Co., was approved on 11/26/2002 under NDA 021318 (with Patent No. 7517334 expiring on 3/25/2025). Teriparatide prefilled pen (PFP) is a generic version of the Forteo® pen injector. (b) (4)

(b) (4)

Apotex, Inc. submitted a Threshold Analysis in the original submission of ANDA 211097 on 12/29/2017 to identify and assess differences in the design of the user interface of the device constituent part for its Teriparatide PFP in comparison to the Forteo® pen.

FDA commented in a Complete Response Letter dated 10/26/2018 that differences related to Teriparatide PFP's slimmer body, shape, and tactile/texture may have the potential to impact postmenopausal women with osteoporosis and elderly patients' abilities to safely and effectively operate the device (b) (4) and may affect how these users perform the critical task of daily dose injection. FDA suggested additional information or data may be warranted (such as data from a Comparative Use Human Factors Study) to further assess whether the identified differences in the user interface impact the clinical effect or safety profile when compared to the RLD.

Apotex Inc. submitted a general correspondence requesting a written response relevant to the post-complete response letter issued by the Agency (dated 10/26/2018) on 2/1/2019 and

additional questions for clarification on 11/20/2019. The Agency made written responses to the questions in the general correspondence on 11/13/2019 and 1/30/2020.

Apotex Inc. submitted a response to the Complete Response Letter (dated 10/26/2018) in a question-and-answer format on 10/15/2020 with modified CUHF study protocols and results. According to the Applicant, as the situation related to COVID-19 in the United States at the time of initial study execution, the protocol was amended to allow for remote participation to assure participant safety, and avoid travel and close contact based on FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency (issued March 2020, Updated September 2020). The Applicant concluded that the differences in body size/shape and tactile/texture characteristics between the proposed product and the RLD are minor and will not impact the clinical effect or safety profile, and that the Teriparatide PFP device and the Forteo® device can be substituted under the conditions specified in the labeling.

In this submission, the Applicant submitted the study report (dated 10/8/2020), protocol Version A (dated 2/20/2020) and Version B (dated 8/11/2020) and the Statistical Analysis and Programming Plan (dated 9/9/2020).

2. SUMMARY OF CUHF STUDY REPORT

a) Study Objective

The objective of the study is to demonstrate that differences in the user interface design of the Teriparatide PFP device (specifically, differences in the body shape, size and texture) do not negatively impact user performance when giving injections in comparison to the Forteo® device. Specifically, that the failure rate (the use error rate) for Teriparatide PFP is not worse than (i.e., not inferior to) the failure rate for Forteo®; a test of non-inferiority of the Teriparatide PFP relative to Forteo®. To support this goal, qualified participants conducted simulated injections using both the Forteo® PFP and Teriparatide PFP.

b) Study Design

This study has a crossover design with each participant being their own control stimulating self-injection using both the test and RLD products. According to the Applicant, the order of simulated injection was randomized across participants with either the Forteo® first followed by the Teriparatide, or vice versa. Participants were given the choice of participating in-person or remotely via web conference, and asked to choose their own administration site (either the thigh

or abdomen) and give injections according to the randomization sequence into the injection pad strapped to their body with both injections on the same site.

For **in-person** testing, the moderator would be present in the room with the participant during the execution of the session.

For **remote** testing, a web conference would be set up with the participant in their own home and the moderator in another location as participants in this study are considered a vulnerable population and are more susceptible to COVID-19. Once an internet meeting connection was made between the moderator and the participant, the moderator would determine if the internet connection was sufficient to clearly see the injection process. The participant would be dismissed from the study if it was not possible to see the injection process or if there was a disruption of the internet connection during the testing; the participant would be replaced in order to achieve the target sample size. The participant would be asked to open "Box A" (needles, alcohol swabs, sharps bin, and an injection pad that is attached to the body for the simulated injection) and as per moderator instructions, start with (depending on the randomization scheme) either "Box B" (Teriparatide PFP and IFU) or "Box C" (Forteo® pen and IFU), followed by the other box.

a) Randomization

According to the Applicant, each participant would complete two injections: one using the Forteo® pen and one using the Teriparatide pen. Subjects would first be stratified to either current or previous Forteo® users. For each stratum, a list of randomized testing sequences of either the RLD-test sequence or the test-RLD sequence will be generated by using block randomization with a block size of four (4). The recruiter who was assigned to booking the participant appointments was blinded to the randomization sequence and the randomization sequence was generated prior to any participant enrolling into the study. (*source: CUHF study protocol on 8/11/2020, page 14 of 24 of protocol /63 of 114 of CUHF study report*)

b) Sample Size

According to the Applicant, the sample size calculation was based on a NI Test for the Difference Between Two Correlated Proportions, performed in PASS 15, dependent on the following parameters:

- Alpha: chosen to be 0.05 for the one-sided comparison of a 90% confidence interval,
- Power: chosen to be 80%,

- Non-inferiority margin D_{NI}: as the drug does not have a narrow therapeutic window and the consequence of an overall use error of the device is not considered to be serious, D_{NI} is chosen to be 0.15,
- Actual difference between devices: chosen to be 0, as both devices are considered to be equivalent in design and use,
- Standard Device Successful Usage Proportion P_S: 0.8667 was used based on a past study of previous and current Forteo® users in which 26 out of 30 users were successful in using the device,
- Nuisance Parameter, Matched Proportions: Defined as the proportion of subjects that either use both devices successfully or both devices as failures. This was chosen as 0.8667 based on the results of the past study with the assumption of a difference of 0 between the two devices.

		Generic Teriparatide		
		Pass	Fail	Total
RLD Forteo	Pass	0.8	0.0667	0.8667
	Fail	0.0667	0.0667	0.1333
	Total	0.8667	0.1333	1

The Applicant stated that a sample size of N=49 would be sufficient to provide 80.7% power based on the parameters above.

c) Study Participants

Forty-nine (49) participants were recruited by phone using Participant Screener. There are two subpopulations of Forteo® users who might have dexterity and hand strength issues:

1. **Current** Self Administering Forteo® Users:
   a. Postmenopausal woman who are currently taking Forteo® and
   b. Elderly patients (including females and males, 65 years and older) currently taking Forteo®.
2. **Recent** Self Administering Forteo® Users:
   a. Postmenopausal woman, who for at least three weeks, within the past two years since time of screening, self-administered Forteo® and
   b. Elderly patients (including females and males, 65 years and older), who for at least three weeks, within the past two years since time of screening, self-administered Forteo®

Inclusion and exclusion requirements for study participants are:

Inclusion Criteria

- Diagnosed with osteoporosis.
- Post-menopausal female or male or female 65 years or older.
- Currently self-administering daily Forteo® injections for a **minimum of 3 weeks**.
- Previously self-administered daily Forteo® injections for a **minimum of three weeks within the past two years** (from date of screening).

Exclusion Criteria

- Difficulty reading and understanding English.
- A recent hand injury or medical condition (other than osteoporosis) that prevents use of an injection device via self-administration.
- An uncorrected visual impairment that prevents reading instructions.
- Personal association with or an immediate family member associated with a pharmaceutical or medical device company.

Table 1 below summarizes demographic information for the final sample of test participants. The participants were generally older, majority female, diagnosed with osteoarthritis, and had a range of hand dexterity ability (as measured by the Cochin Hand Function Scale).

Table 1: Demographic Summary

Participant IDs	Group	Age Range (Average Years)	Dominant Hand	Cochin Range (Median)	Gender
(b) (6)	Current Forteo® Users	50 - 79 (64.2)	Left: 3 Right: 24 Ambidextrous: 1	0 – 27 (0)	Female: 27 Male: 1
	Past Forteo® Users	46 - 75 (65.7)	Left: 3 Right: 18 Ambidextrous: 0	0 – 8 (0)	Female: 21 Male: 0

Source: Applicant's CUHF Study Report Table 1, Page 9 of 31.

d) Data Collection

Each session was conducted in a one-on-one format and lasted up to 45 minutes. Participants were not trained prior to their test sessions but had access to the IFU for each device to reference it, if they chose to use it. The moderator did not compel them to review these materials. The moderator observed participant performance and comments for evidence of use-related issues. This was followed by a Post-Test Interview (PTI) that included a review of any use issues they encountered, and questions aimed at assessing their understanding of critical knowledge tasks

relating to safe use of the product. Testing started on March 3, 2020 and finished on September 4, 2020. The sequence of activities for each session is outlined in Table 2 below.

Table 2: Sequence of Activities in Each Participant Session

Activity	Description
1. Participant Enrollment	The participant reviewed and signed an Informed Consent Form[5] prior to the session. The moderator asked the participant a set of background questions to verify they met the study inclusion criteria.
2. Study Introduction	The moderator read a study script, which introduced the study, and answered questions about the study at that time.
3. Simulated Injection 1	The participant was presented with the first of two injection scenarios; either the Forteo® scenario or the Teriparatide PFP scenario. The moderator observed the simulated injection and noted performance.
4. Break	A minimum 5-minute break was taken between injections. For in-person testing, the moderator took simple grip and pinch strength measurements using a dynamometer and a pinch gauge[6]. Both in-person and remote participants completed a Cochin Hand Function Assessment (questionnaire).
5. Simulated Injection 2	The moderator presented the participant with the second of the two injections scenarios; either the Forteo® scenario or the Teriparatide PFP scenario.
6. Use Error Interview	If the participant made one or more use errors on the critical tasks during either simulated-use scenario, the moderator interviewed the participant about the potential causes of the errors only after both simulated injections were completed.
7. Dismissal	Following the Use Error Interview (or if no use errors were made during the simulated-use scenarios) the participant was compensated for their participation and dismissed.

Source: Applicant's CUHF Study Report Table 2, Page 12 of 31.

e) Critical Tasks

Critical tasks are defined as tasks which, if performed incorrectly or not performed at all, would or could cause harm to the subject or user, where harm is defined to include compromised medical care. The Applicant identified 5 critical tasks in this study that were confirmed by the Agency via General Correspondence, including: pull out dose button to load the dose, place

device against thigh or abdomen, push the injection button, hold the injection button down while delivering the medication, and hold in place to deliver the medication. The study moderator monitored participants during simulated injections for evidence of critical task use errors.

Table 3 describes each critical task, the definition of successful performance, and examples of potential task failures.

Table 3: Critical Tasks That May Be Affected by External Design

Critical Task	Definition of Successful Performance	Examples of Task Failures
1. Pull out dose button to load the dose.	User pulled the dose button out to load the dose.	• User was unable to pull the button out fully; unable to load the dose; no medication delivered. • User attempted to expel air or prime the device; loss of medication.
2. Place device against thigh or abdomen.	User placed the device against the thigh or abdomen.	• User was unable to place the device or hold in place securely; no medication given, or only partial dose delivered.
3. Push the injection button.	User pressed the injection button fully.	• User was unable to press the button fully; only partial dose delivered.
4. Hold the injection button down while delivering the medication.	User held the injection button down while completing Task 3.	• User was unable to maintain downward pressure on the button; only partial dose delivered.
5. Hold in place to deliver the medication.	User was able to hold the device in place while counting for the duration specified in the Instructions for Use (IFU) (a count of 5).	• User was unable to hold the device in place while counting; only partial dose delivered.

Source: Applicant's CUHF Study Report Table 3, Page 14 of 31.

f) Primary Endpoint

The Applicant stated that the endpoint for each injection was a binary, success/failure score. The participant's overall performance on a simulated injection was scored as a "success" if the participant completed each critical task without a use error, or as a "failure" if a use error was made on one or more of the critical tasks. The overall success rate for each device was the proportion of participants who had a successful injection with the device. The five critical tasks for completing an injection were scored for each simulated injection scenario. Task performance was scored using the following definitions:

- Success (S) – The participant successfully completed the task.
- Error (E) – The participant did not successfully complete the task, skipped, or omitted a task.
- Did not Attempt (DNA) – The participant did not attempt the task (e.g., a participant who did not remove the needle from a pen, did not therefore re-cap the pen after use; in this example, recapping the pen was not attempted and scored as "DNA").

g) Primary Analysis

The primary analysis for this study was to determine the difference between the proportion of successful usage of the generic Apotex Teriparatide device (P_T) and the proportion of successful usage of the RLD Forteo® device (P_S). The hypothesis test involved was as follows:

$$H_0: P_T - P_S < -D_{NI} \text{ versus } H_A: P_T - P_S \geq -D_{NI}$$

D_{NI} is the allowable margin by which P_T could be smaller than P_S. Rejecting the null hypothesis in favor of the alternative hypothesis supports the claim of non-inferiority of the test product to the RLD as defined by D_{NI}, where D_{NI} will be set as 0.15. The Type I error probability for the one-sided test (α) was set to 5%.

The non-inferiority test was performed by comparing the lower bound of the 90% confidence interval (CI) for the difference in proportion of successful usage to D_{NI}. If the lower bound was not smaller than - D_{NI}, non-inferiority is demonstrated. The 90% CI was calculated using the Tango method for calculating confidence intervals for the difference in proportions in matched pairs (Tango 1998) developed by Rodriguez De Gil, et al (2013).

h) Sensitivity Analysis

As a sensitivity analysis, the difference in proportion of successful usage and its 90% CI was calculated for the two subgroups of participants (i.e., in-person or remote testing). Given that a cross-over design was employed for the comparison of the test and RLD product, no significant impact of different testing environments was expected.

i) Results and Conclusions

The results of the primary and sensitivity analyses are presented in Table 4.

Overall, there was no difference in proportion of successful usage between the two products with the lower bound of the 90% CI (-0.0824, 0.0824) being larger than the Applicant's protocol-

defined non-inferiority margin of 0.15. Hence, according to the Applicant, non-inferiority of the test product to RLD was demonstrated.

The difference in proportion of successful usage between the two products and its 90% CI were also comparable between the two subgroups. The applicant concluded that no significant bias was introduced to the comparison of the test and RLD products due to the utilization of different testing environments (in-person and remote).

Table 4: Primary and Sensitivity Analysis Results

Category	N	Apotex Success/ Forteo® Success n (proportion)	Apotex Success/ Forteo® Failure n (proportion)	Apotex Failure/ Forteo® Success n (proportion)	Apotex Failure/ Forteo® Failure n (proportion)	Proportion Apotex Success P_T	Proportion Forteo® Success P_S	Actual Proportion Difference $P_T - P_S$	Proportion Difference 90% Confidence Interval (Lower, Upper)
Primary Endpoint Analysis									
Total	49	30 (0.6122)	2 (0.0408)	2 (0.0408)	15 (0.3061)	32 (0.6531)	32 (0.6531)	0.0000	(-0.0824, 0.0824)
Sensitivity Analysis									
In-Person Participants	17	11 (0.6471)	0 (0.0000)	1 (0.0588)	5 (0.2941)	11 (0.6471)	12 (0.7059)	-0.0588	(-0.2256, 0.0866)
Remote Participants	32	19 (0.5938)	2 (0.0625)	1 (0.0313)	10 (0.3125)	21 (0.6563)	20 (0.6250)	0.0313	(-0.0773, 0.1475)

Source: Applicant's CUHF Study Report Table 6, Page 21 of 31.

According to the Applicant, the data supports that the differences in device between the Teriparatide PFP and Forteo® are acceptable and that the Teriparatide PFP can be substituted to produce the same clinical effect and safety profile as Forteo® under the conditions specified in the labeling.

j) Handling of Missing Data

The Applicant mentioned in the table of analysis dataset that "if subject has missing data for any critical task then PPROTFL='N'; Else if subject completed the study in its entirety PPROTFL="Y"; Subject to additional adjudication" (*source: Statistical Analysis and Programming Plan, Page 11 of 23*). This is a part of the specifications for the analysis dataset, not a statement defining the per-protocol set in the document body. The Applicant needs to provide a clarification for their methods to handle missing data.

3. REVIEWER'S RESPONSE TO THE CONSULT

a) Comments for Internal Use (FDA)

For the comparative use human factors (CUHF) study results of Apotex's Teriparatide Injection Pen submitted on 10/15/2020 in ANDA 211097, we have the following comments.

1. The Applicant stated that the order of simulated injection of Forteo® and Teriparatide PFPs was block randomized stratified by user group (current or previous RLD users). However, the randomization schedule cannot be located in the submitted materials.
2. The sample size calculation procedure is not clear. The Applicant needs to provide the specific sample size calculation formulas besides the submitted parameters in the statistical analysis section.
3. The justification for non-inferiority margin of 0.15 is not clear.
4. No datasets have been provided including the demographic characteristics (e.g., sex, age, in-person or remote session, current or recent user, and administration site) and task level records.
5. There's no clear statement about handling of missing data in the report body. The Applicant only mentioned in the table of variables that "if subject has missing data for any critical task then PPROTFL='N'" (*source: Statistical Analysis and Programming Plan, Page 11 of 23*).
6. The gender distribution in this study may not represent the intended user population. The Applicant stated that the study population was similar to the intended users. From the demographic information provided in this report, almost all study participants were females (48), and only one participant was male. We defer the decision of acceptability and appropriateness of the study population to DMEPA.
7. The document is inconsistent in that it is proposing two subpopulation of current and past RLD users, but requiring both conditions (currently RLD-use for a minimum of 3 weeks, and previously RLD-use for a minimum of three weeks within the past two years) in the inclusion criteria of the protocol *(source: CUHF study protocol Rev B, Page 8-9 of 24)*.

b) Comments to be Conveyed to the External Applicant

We have the following comments regarding your Comparative Use Human Factors (CUHF) study report for Teriparatide prefilled pen (PFP) submitted in ANDA 211097 on 10/15/2020.

1. You mentioned the order of simulated injection of the test and RLD products was block randomized and stratified by user group. Please provide your randomization schedule.
2. Please provide detailed justifications for using the non-inferiority margin of 0.15.
3. Please provide your specific sample size calculation formulas in the statistical analysis section.

4. Please provide the dataset including the demographic characteristics (e.g., sex, age, in-person or remote session, current or recent user, and administration site) and task level records in the CDISC format.
5. Please clarify your handling of missing data in this study.
6. Please clarify the inclusion criteria in your protocol, as it is requiring both conditions (currently RLD-use for a minimum of 3 weeks, and previously RLD-use for a minimum of three weeks within the past two years) at the same time.

REFERENCES

FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency (issued March 2020, Updated September 2020).

Draft Guidance for Industry (January, 2017). Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA.

Tango, T. (1998). Equivalence Test and Confidence Interval for the Difference in Proportions for the Paired-Sample Design. Statistics in Medicine, Vol 17: 891-908

Rodríguez de Gil P., Romano, J., Pham, T., Nguyen, D., Kromrey, J.D., Kim, E.S. (2013). CORR_P and TANGO: Interval Estimation for the Difference Between Correlated Proportions in Dependent Samples. South East SAS User Group Conference 2013. St. Petersburg, FL

APPENDIX A: ORIGINAL CONSULT REQUEST

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**			
TO *(Office/Division)*: OTS/DBVIII			FROM (*Name, Office/Division, and Phone Number of Requestor)*: Avani Bhalodia, OMEPRM/DMEPA, 301-796-5534	
DATE 12/03/20	IND NO. N/A	ANDA NO. 211097	TYPE OF DOCUMENT Human Factors Comparative Use Study Results	DATE OF DOCUMENT October 15, 2020
NAME OF DRUG Teriparatide	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE Jan 22, 2021
NAME OF FIRM: Apotex				

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☒ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

Please evaluate whether the submitted Comparative Use HF Study Results methodology for the Teriparatide Prefilled Pen (ANDA 211097) are acceptable.

Our specific requests are:
1) Are sample sizes adequately powered and study design statistically appropriate to draw use performance comparison between the two products?

2) If the sample size and study design are statistically appropriate, do you agree with the Applicant's conclusion regarding non-inferiority of the proposed product compared to the RLD?

3) Are there other considerations from a statistical review perspective that we have not covered in #1 and 2 above?

Please share your preliminary draft comments prior to finalizing your review.

(Note: we recently worked with Katie Wang and Somesh Chattopadhyay on another HF Comparative Use Protocol)

Link to the HF Report submission:
\\CDSESUB1\evsprod\anda211097\0020\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5354-other-stud-rep\apo-tcu2-vt-503\comparative-use-human-factors-study-apo-tcu2-vt-503.pdf

SIGNATURE OF REQUESTOR and DMEPA Point of Contact Avani Bhalodia	METHOD OF DELIVERY (Check all that apply) ☒ DARRTS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

YIFAN WANG
06/01/2021 10:38:40 AM

SOMESH CHATTOPADHYAY
06/01/2021 10:39:51 AM

STATISTICAL REVIEW AND EVALUATION

CONSULT PROTOCOL REVIEW

Consult Requester	Millie Shah, OMEPRM/DMEPA
Type of Consult	Comparative use human factors study protocol review
ANDA Number	ANDA211097
Drug Name	Teriparatide Injection, USP, 20 mcg/dose (600 mcg/2.4 ml)
Applicant	Apotex, Inc.
Reference Listed Drug	Eli Lilly and Company, Inc's Forteo® (teriparatide [rDNA origin] injection) 20 mcg per dose (NDA 021318)
Indication	• Treatment of postmenopausal women with osteoporosis at high risk for fracture • Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture • Treatment of men and women with osteoporosis associated with sustained, systemic glucocorticoid therapy (daily dosage equivalent to 5 mg or greater of prednisone) at high risk for fracture
Dates	Review Assignment Date: 3/8/2019 Desired Completion Date: 4/19/2019
Biometrics Division **Primary Statistical Reviewer** **Secondary Statistical Reviewer**	 Yifan (Katie) Wang, Ph.D., DB VIII/OB/OTS/CDER Somesh Chattopadhyay, Ph.D., DB VIII/OB/OTS/CDER
Keywords	Teriparatide Prefilled Pen, Injection, Comparative Use Human Factors Study, Non-inferiority, Randomization, Use Error Rate, Crossover Design, Surrogate

1. BACKGROUND AND SUMMARY OF CONSULT REQUEST

Eli Lilly and Company, Inc.'s Forteo® (teriparatide [rDNA origin] injection) 20 mcg per dose was approved on 11/26/2002 (NDA 021318) for the treatment of postmenopausal women with osteoporosis at high risk for fracture and to increase bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture. On 7/22/2009 a supplemental application of Forteo® was approved for treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture. Forteo® is administered as a 20-microgram once-daily dose and is currently available in a 2.4 mL prefilled delivery device (the Forteo® pen) for subcutaneous injection in the home.

Apotex, Inc. submitted a Threshold Analysis in the original submission of ANDA 211097 on 12/29/2017 to identify and assess differences in the design of the user interface of the device constituent part for its Teriparatide prefilled pen (PFP) in comparison to the Forteo® pen.

FDA commented in the Complete Response Letter on 10/26/2018 that differences related to Teriparatide PFP's slimmer body, shape, and tactile/texture may have the potential to impact postmenopausal women with osteoporosis and elderly patients' abilities to safely and effectively operate the device (b) (4) and may affect how these users perform the critical task of daily dose injection. FDA suggested additional information or data may be warranted (such as data from a Comparative Use Human Factors Study) to further assess whether the identified differences in the user interface impact the clinical effect or safety profile when compared to the RLD.

(b) (4)

Apotex, Inc. submitted the Protocol for a Comparative Use Human Factors Study of Forteo® and Teriparatide Prefilled Pen on 2/1/2019.

Apotex states that the goal of this study is to establish the non-inferiority in use error rates of the Teriparatide PFP compared to Forteo®, such that any design differences between the devices can be concluded to not negatively impact user performance on critical tasks.[1]

This study focused on performance of two subpopulations of Forteo® users: postmenopausal woman diagnosed with osteoporosis and elderly patients (65 years or older). The test is a simulated-use test with an injection pad to simulate the injection site.

The Applicant proposed to include two user groups: RLD user group (self-administering daily RLD for a minimum of one month) and surrogate group (never took RLD, never self-administered an injectable medication). The Applicant plans to recruit surrogates if recruitment of sufficient number of RLD users to meet the overall sample size requirement is difficult. The surrogates will be trained how to use Forteo® pen by a nurse at site, and practice injections until the participant can perform injections safely and effectively. Following training, a 10-minute break will be given prior to completing the simulated comparison injections with RLD and the Test devices.

The protocol identified nine critical tasks that the applicant believes may be affected by external design attributes relating to (b) (4) interacting with pen user interface elements. The tasks are: pull off the cap, attach a needle, pull out dose button to load the dose, place device against thigh or abdomen, push the injection button, hold the injection button down while delivering the medication, hold in place to deliver the medication, remove the needle, and replace the pen cap.

This study has a cross-over design. The participants will simulate self-injections using both RLD and the test devices. The device instructions will be given along with the pens. The order of these two devices being used will be randomized. The same administration site location (either abdomen or thigh) will be used.

The Applicant stated that to gauge whether the use of the Test device may change after initial use (due to practice effects, for example), participants will complete two additional injections with the Test device after the initial RLD and Test injection scenarios. The sequences are shown as below.

Sequence #1	**Sequence #2**
Forteo®	Teriparatide PFP 1
Teriparatide PFP 1	Forteo®
Teriparatide PFP 2	Teriparatide PFP 2
Teriparatide PFP 3	Teriparatide PFP 3

[1] Protocol for a Comparative Use Human Factors Study of Forteo® and Teriparatide Prefilled Pen, Version 1, submitted on February 1, 2019 in ANDA 211097.

During completion of all four injections, the moderator will observe each participant's performance on each of the nine critical tasks and record whether an error was made on each task. The applicant defined error as "an instance in which a participant omits a task or performs the task in a way that could have resulted in harm or compromised medical care had the error arose in actual use." The applicant will aggregate a total number of errors per injection, with an error rate calculated as the number of errors divided by the total number of critical tasks.

The Applicant proposed to set the non-inferiority margin to 0.11, representing the smallest unit of error detectable as a difference in any given individual, i.e., a difference of 1 error over the total of 9 critical tasks; 1/9 = 0.11. The tests of hypotheses are:

$$H_0: ER_{T(Injection\ 1)} - ER_R > d$$

$$H_A: ER_{T(Injection\ 1)} - ER_R \leq d$$

and

$$H_0: ER_{T(Injection\ 3)} - ER_R > d$$

$$H_A: ER_{T(Injection\ 3)} - ER_R \leq d$$

where ER_T and ER_R are the error rates for the test and reference products, respectively.

The Applicant proposed to test each hypothesis with a 95% upper confidence bound. A mixed Analysis of Variance would be used including factors of subject, group, sequence and treatment.

The final sample would consist of approximately 60 participants, with no more than half surrogates.

The Applicant defined two study endpoints. The primary endpoint is to demonstrate non-inferiority with respect to the first user experience with the generic device (the Test injection 1). The secondary endpoint is with respect to the learned use with the generic device (the Test injection 3).

2. REVIEWER'S RESPONSE TO THE CONSULT

a) Comments for Internal Use (FDA)

To establish non-inferiority of the use error rates of the generic product to those of the RLD, the applicant proposed to use the following variable: Total number of errors divided by the total of nine critical tasks for each participant for each individual injection. This is a composite endpoint that combines all the critical tasks that the applicant has identified. The applicant then plans to use 0.11 (1/9) as the non-inferiority margin. However, the interpretation of this endpoint significantly deviates from the idea of comparing use error rate for each critical task individually. Moreover, the applicant plans to analyze the endpoint using a mixed model ANOVA (analysis of variance) where this discrete variable will be treated as a continuous variable. This will cause the interpretation of the endpoint and the determination of the non-inferiority margin to be more difficult.

We suggest an endpoint that would be consistent with principles of the draft guidance, would encompass all of the critical tasks we believe a comparative human factors study should assess for this proposed product, and would also evaluate the final outcome of the injection. To do this, we propose an endpoint that would be defined as a binary yes/no, for which success would be recorded for a given subject only when that subject successfully completes all the critical tasks we recommend a comparative human factors study for the Teriparatide PFP evaluate. If one or more of the identified critical tasks are not successfully completed, an overall use failure would be recorded for that subject. Once all subjects complete the study using the two devices, the rates for overall use success and overall use failure for the set of patients could be calculated for both devices and then compared. Please also submit the data about success/failure for each participant for each individual critical task evaluated. Because each subject has an overall use success or an overall use failure, the success and failure rates convey the complementary information. For example, once we know the overall use success rate, the overall use failure rate is exactly known and equal to the number one (1) minus the success rate. Although mathematically equivalent because they are complementary, we suggest using "overall use success rate" rather than "overall use failure rate" or "error rate" to avoid potential confusion with other uses of the term error.

b) Comments to be Conveyed to the Applicant

We have the following recommendations about your Comparative Use Human Factor study protocol for your Teriparatide PFP. Please update the protocol based on these recommendations and resubmit it for our review.

1. The use of surrogates for the primary analysis is not acceptable. The surrogates may not represent the patient population. You should recruit an adequate number of RLD users in the study.

2. The Agency will focus on the first injection in this study. A second and third injection is not necessary in this study, and we will not consider your proposed second and third Teriparatide PFP injections as they will be subject to learning and recency bias.

3. We note that you proposed to combine the critical tasks you identified by calculating the error rate using "the total number of errors divided by the total of nine critical tasks for each participant, for each individual injection". We suggest an endpoint that would be consistent with principles of the draft guidance, would encompass all of the critical tasks we believe a comparative human factors study should assess for your proposed product, and would also evaluate the final outcome of the injection. To do this, we propose an endpoint that would be defined as a binary yes/no, for which success would be recorded for a given subject only when that subject successfully completes all the critical tasks we recommend a comparative human factors study for the Teriparatide PFP evaluate. If one or more of the identified critical tasks are not successfully completed, an overall use failure would be recorded for that subject. Once all subjects complete the study using the two devices, the rates for overall use success and overall use failure for the set of patients could be calculated for both devices and then compared. Please also submit the data about success/failure for each participant for each individual critical task evaluated. Because each subject has an overall use success or an overall use failure, the success and failure rates convey the complementary information. For example, once we know the overall use success rate, the overall use failure rate is exactly known and equal to the number one (1) minus the success rate. Although mathematically equivalent because they are complementary, we suggest using "overall use success rate" rather than "overall use failure rate" or "error rate" to avoid potential confusion with other uses of the term error. Please propose and justify the non-inferiority margin based on the new primary endpoint recommended above.

4. Please provide justification for the sample size based on your targeted power.

5. Please provide more details about the randomization procedure in the protocol. Other than randomization, no efforts should be made to balance the proportion of subjects completing each sequence.

REFERENCES

Draft Guidance for Industry (January, 2017). Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA.

APPENDIX A: ORIGINAL CONSULT REQUEST AND OTHER SUPPORTING DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			**REQUEST FOR CONSULTATION**	
TO *(Office/Division)*: OTS/DBVIII			FROM *(Name, Office/Division, and Phone Number of Requestor)*: Millie Shah, OMEPRM/DMEPA	
DATE February 22, 2019	IND NO.	ANDA NO. 211097	TYPE OF DOCUMENT Human Factors Comparative Use Protocol	DATE OF DOCUMENT February 1, 2019
NAME OF DRUG Teriparatide Prefilled Pen	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE March 14, 2019
NAME OF FIRM: Apotex				

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL	☐ PRE-NDA MEETING	☐ RESPONSE TO DEFICIENCY LETTER
☐ PROGRESS REPORT	☐ END-OF-PHASE 2a MEETING	☐ FINAL PRINTED LABELING
☐ NEW CORRESPONDENCE	☐ END-OF-PHASE 2 MEETING	☐ LABELING REVISION
☐ DRUG ADVERTISING	☐ RESUBMISSION	☐ ORIGINAL NEW CORRESPONDENCE
☐ ADVERSE REACTION REPORT	☐ SAFETY / EFFICACY	☐ FORMULATIVE REVIEW
☐ MANUFACTURING CHANGE / ADDITION	☐ CONTROL SUPPLEMENT	☒ OTHER *(SPECIFY BELOW)*:
☐ MEETING PLANNED BY		

II. BIOMETRICS

☐ PRIORITY P NDA REVIEW	☐ CHEMISTRY REVIEW
☐ END-OF-PHASE 2 MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☒ OTHER (SPECIFY BELOW):
☐ OTHER (SPECIFY BELOW):	

III. BIOPHARMACEUTICS

☐ DISSOLUTION	☐ DEFICIENCY LETTER RESPONSE
☐ BIOAVAILABILITY STUDIES	☐ PROTOCOL - BIOPHARMACEUTICS
☐ PHASE 4 STUDIES	☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	☐ SUMMARY OF ADVERSE EXPERIENCE
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)	☐ POISON RISK ANALYSIS
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

Please comment on the appropriateness of the Applicant's proposed Statistical Plan for the human factors comparative use protocol to establish the non-inferiority in use error rates of the Teriparatide Prefilled Pen compared to that of Forteo.

Link to submission: \\cdsesub1\evsprod\anda211097\0015\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5354-other-stud-rep\apo2016teriparatidef1503\apo2016teriparatidef1503-report-body.pdf

SIGNATURE OF REQUESTOR Millie Shah	METHOD OF DELIVERY (Check all that apply) ☒ DARRTS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER Millie Shah	PRINTED NAME AND SIGNATURE OF DELIVERER

06/18/2013

Reference ID: 4398178

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

YIFAN WANG
11/11/2019 07:48:06 PM

SOMESH CHATTOPADHYAY
11/11/2019 07:53:44 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 211097

OTHER REVIEW(s)

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS

INTERCENTER CONSULT MEMORANDUM – STREAMLINED

Date:	3/17/2023		
To:	Erin Andrews		
Requesting Center/Office:	CDER/OPQ	Clinical Review Division:	Other
From:	Courtney Evans OPEQ/OHT3/DHT3C		
Through (Division): ***optional**	CAPT Alan Stevens, Assistant Director OPEQ/OHT3/DHT3C		
Subject:	Consult for Submission: Response to IR for ANDA 211097 has been received. SD #36 - Device Deficiency section item #1- #3 to be reviewed.		
Recommendation:	Approvable, see original reviewer's memo in Appendix A		

Digital Signature Concurrence Table		
Reviewer	**Team Lead (TL)**	**Division (optional)**
Courtney Evans -S	Digitally signed by Courtney Evans -S Date: 2023.04.17 22:49:09 -04'00'	Alan Stevens

1. SUBMISSION OVERVIEW

Table 1. Submission Information	
Consult Identification #	(b) (4)
Consult Request Link	
ICC tracking #	
Submission Number	ANDA 211097
Sponsor	Apotex Inc.
Drug/Biologic	Teriparatide Injection, USP, 20 mcg/dose (600 mcg/2.4 mL)
Indications for Use	Treatment of postmenopausal women with osteoporosis at high risk for fracture (b) (4) Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture
Device Constituent	Pen Injector
Related Files	N/A

2. CDRH REVIEW

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(b) (4)

Review **Recommendation** :	The sponsor has adequately responded to all IRs, therefore there no outstanding review areas. Recommend approval of this submission.

---END OF REVIEW---

APPENDIX A (ORIGINAL REVIEWER MEMO)

Appears this way on original

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS

INTERCENTER CONSULT MEMORANDUM – STREAMLINED

Date:	12/15/2022		
To:	Erin Andrews		
Requesting Center/Office:	CDER/OPQ	Clinical Review Division:	Other
From:	Porsche Bennett OPEQ/OHT3/DHT3C		
Through (Division): ***optional**	CAPT Alan Stevens, Assistant Director OPEQ/OHT3/DHT3C		
Subject:	Consult for Submission: ANDA211097		

(b) (4)

(b) (4)

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	(b) (4)

Digital Signature Concurrence Table		
Reviewer	**Team Lead (TL)**	**Division (optional)**

1. SUBMISSION OVERVIEW

Table 1. Submission Information	
Consult Identification #	ICCR#
Consult Request Link ICC tracking #	(b) (4)
Submission Number	ANDA211907
Sponsor	Apotex Inc.
Drug/Biologic	Teriparatide Injection
Indications for Use	1)Treatment of postmenopausal women with osteoporosis at high risk for fracture. 2) Indicated to increase bone mass in men with primary or hypogonadal osteoporosis. 3) Treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy.
Device Constituent	Pen injector
Related Files	(b) (4) (Original Review: Shawn Shermer)

2. CDRH REVIEW

ICC Review Request from CDER/OPQ, Other:	Engineering: Review Complete response letter with Drug Product CDRH Device deficiency comments #1-6. SD #31 received 5/12/2022 (b) (4)
Device Presentation(s) being evaluated:	Pen injector
Objective of this Memo:	The objective of this memo is to provide approvability recommendation for adequacy of device constituent part based on the firm's response to the device (CDRH)

	complete response responses. This review will focus on CR responses 1-6 for the combination product and CR responses 1-3 for the facilities review. All non-device related CR responses are out of scope of this review as well as any other device aspects not included in the CR letter.
Review **Comments**:	The following is the submission history and FDA correspondence related to this submission: • Original ANDA received: December 29, 2017 • FDA feedback: Original CR letter issued to firm: October 26, 2018 • Firms' submission: CR response amendment: October 15, 2020 • FDA feedback: Subsequent CR response letter issued to firm: June 14, 2021 • Firm's post complete response letter meeting request #1: August 6, 2021 ○ (b) (4) ○ • Firm's post complete response letter meeting request #2: September 8, 2021 (Not device related) • Firms' post complete response letter meeting request #3: September 9, 2021 • (b) (4) • All CR deficiencies were reviewed considering the most recent CR deficiency included in the 06/14/21 CR letter, any additional correspondence between FDA and the firm prior to this CR response (i.e., meeting requests where agreements were made between FDA/CDRH and the firm), and finally considering the firm's CR response included in this submission.
Review **Recommendation**:	The following additional data and information is needed: 1. Performance of EPRs over the proposed shelf life 2. Performance of EPRs post simulated transportation 3. (b) (4) Therefore, the submission is not recommended to be approved at this time.

(b) (4)

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	[redacted] (b) (4)
Reviewer Comments	The firm's response is adequate.
Response Adequate:	☒ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

---END OF REVIEW---

Appendix 1: Previous CDRH Review Memo [redacted] (b) (4)

Appendix 2: FDA Post-CRL Meeting Request Preliminary Responses- 20210909

OFFICE OF DEVICE EVALUATION

DIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL, RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES

GENERAL HOSPITAL DEVICES BRANCH

INTERCENTER CONSULT MEMORANDUM

Date	4/29/2021		
To:	Erin Andrews; FDA/OC/CDER/OPQ/OPRO/DRBPMII/RBPMB3/		
Requesting Center/Office:	CDER/OPQ	**Clinical Review Division:**	Choose an item.
From	Shawn Shermer OPEQ/OHT3/DHT3C		
Through (Team)	Courtney Evans, Acting Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	Rumi Young, Acting Assistant Director, Injection Team OPEQ/OHT3/DHT3C		
Subject*	ANDA 211097, Teriparatide Injection (b) (4) [redacted]		
Recommendation	**Filing Recommendation Date:** Click or tap to enter a date. ☑ CDRH did not provide a Filing Recommendation ☐ Device Constituent Parts of the Combination Product are acceptable for Filing. ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5.4 for Deficiencies		
	Mid-Cycle Recommendation Date: Click or tap to enter a date. ☑ CDRH did not provide a Mid-Cycle Recommendation ☐ CDRH has no approvability issues at this time. ☐ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A.		
	Final Recommendation Date: 4/29/2021 ☐ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☑ Device Constituent Parts of the Combination Product are Not Approvable - See Section 15 for Complete Response Deficiencies*		

(b) (4) [redacted]

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)
Shawn M. Shermer -S8 Shawn M. Shermer -S8 2021.04.29 15:42:05 -04'00'		Rumi Young -S Digitally signed by Rumi Young -S Date: 2021.04.30 10:26:12 -04'00'

1. Submission Overview

Submission Information	
Submission Number	ANDA 211097
Sponsor	Apotex Inc.
Drug/Biologic	Teriparatide Injection
Indications for Use	Treatment of postmenopausal women with osteoporosis at high risk of fracture Increase bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture.
Device Constituent	Pen-Injector
Related Files	ANDA211097_Teriparatide_CDRH_Review (b) (4) doc RLD is Forteo NDA N021318

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(b) (4)

(b) (4)

(b) (4)

2. PURPOSE/BACKGROUND

2.1. Scope

Apotex, Inc. is requesting approval of Teriparatide Injection. The device constituent of the combination product is a pen injector.

CDER/OPQ has requested the following consult for review of the device constituent for the combination product: Review CR letter CDRH responses submitted by firm 10/15/2020 SD #22

This submission was previously reviewed by Peter Petrochenko in July 2018. Peter identified deficiencies that were sent to the sponsor in a COMPLETE RESPONSE LETTER dated 10/26/2018. **This is Peter's memo, in which, I have added in information related to the sponsor's response of the CR deficiencies. New information will be identified by being in a shaded box. Additionally, I utilized the spelling & grammar check for this document that did result in minor changes.**

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the sponsor's responses to the CDRH deficiencies.

The original review division will be responsible for the decision regarding the overall safety and effectiveness for

approvability of the combination product.

The SharePoint ICCR contained the following consult request:

> *Please review the firm's documentation of the studies they conducted to ensure that the multi-use injector pen device proposed to be used for their drug product functions in an identical manner to that of the innovator drug or RLD. Please review documentation of engineering-based studies, such as materials of construction, design and verification that the proposed device delivers the correct volume in a repeatable manner. Review of chemistry-based studies such as analytical method validation, microbiological method validation or extractables and leachables is not requested from CDRH. Sample pens, for both the RLD and proposed products, along with the accompanying needles, have been requested from the firm.*

The CDRH reviewer (Peter Petrochenko) performed an evaluation of the design of the device constituent parts of the Teriparatide Injection, USP 20 mcg per dose combination product. This evaluation covered the intended design and design control information for the subject device constituent part.

This review covered the following elements:

- Biocompatibility of the user contacting surfaces (b) (4)
- Inspection of test methods and results of bench top testing completed
- Inspection of stability testing completed on the device constituent part
- Review of risk analysis documentation and conclusions of safety

This review did not cover the following elements:

- Review of drug product
- Review of primary container closure-drug product interaction or biocompatibility/toxicology
- Usability and Human Factors of the combination product
- Manufacturing of the drug product
- Manufacturing of the device constituent part of the combination product

2.2. Prior Interactions

July 2018- Original ANDA reviewed by Peter Petrochenko.

2.3. Background

Teriparatide Injection is an osteoporosis medicine that increases the number of bone-forming cells and helps build new bone in the spine, as well as other bones like the ankle/foot, hip, arm, pelvis, ribs, and wrist. The device is intended to assist self-injecting adult patients without any upper age limit, healthcare providers, caregivers as well as third parties to deliver subcutaneous injections of Teriparatide. The average osteoporosis patient may have vision, hearing and/or fine motor skill impairments. Handicapped patients and mentally disabled patients are not considered as self-injecting users. Patients may be injection naïve or have limited to no experience performing self-injections. A physician prescribing the drug has to decide case by case, if the patient is capable of handling the device and acting as self-injecting user to assure that the patient's kinetic and cognitive abilities allow a safe handling of the pen.

2.4. Indications for Use

Combination Product	Indications for Use
Test: ANDA-	(b) (4)] indicated for: • Treatment of postmenopausal women with osteoporosis at high risk for fracture • Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture • Treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture
RLD Forteo: NDA-	FORTEO is indicated for the treatment of postmenopausal women with osteoporosis who are at high risk for fracture. These include women with a history of osteoporotic fracture, or who have multiple risk factors for fracture, or who have failed or are intolerant of previous osteoporosis therapy, based upon physician assessment (see BLACK BOX WARNING). In postmenopausal women with osteoporosis, FORTEO increases BMD and reduces the risk of vertebral and nonvertebral fractures. FORTEO is indicated to increase bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fracture. These include men with a history of osteoporotic fracture, or who have multiple risk factors for fracture, or who have failed or are intolerant to previous osteoporosis therapy, based upon physician assessment (see BLACK BOX WARNING). In men with primary or hypogonadal osteoporosis, FORTEO increases BMD. The effects of FORTEO on risk for fracture in men have not been studied. • FORTEO reduces the risk of vertebral fractures in postmenopausal women with osteoporosis. • FORTEO reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis. • FORTEO increases vertebral and femoral neck BMD in postmenopausal women with osteoporosis and in men with primary or hypogonadal osteoporosis. • The effects of FORTEO on fracture risk have not been studied in men.

3. ADMINISTRATIVE

3.1. Documents Reviewed

Document Title	Date - Version	Location in ANDA 211097
Description and composition of the drug product	DEC 2017 / 0000	3.2.P.1

Technical Considerations fo (b) (4) developed for Apotex Inc., and Intended for Use with Teriparatide Injection	Version 01 November 2017	3.2.P.7
(b) (4) Cytotoxicity Test Reports		
Finished Product Release	10 Nov 2017	3.2.P.5.1
Summary of Performance Testing	24.11.2017	3.2.P.7
Risk assessment of leachables and extractables from a drug delivery system	Final non-glp report: 17-00698-n1	3.2.P.2

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(b) (4)

5. CLINICAL DEVELOPMENT

5.1. Human Factors Studies

5.1.1. Formative Study

A formative study was conducted usin (b) (4) and/or the supporting materials,

5.1.2. Threshold Analysis

The threshold analysis was original conducted usin (b) (4)

6. DESIGN CONTROL REVIEW

6.1. Design Review Summary

6.1.1. Design Control Documentation Check

Design Control Requirement*	Signed/Dated Document Present		Submission Location
	Yes	No	
Design Requirements Specifications included in the NDA / BLA by the Combination Product Developer	X		Summary of Performance Testing, 3.2.P.7
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.	X		Summary of Performance Testing, 3.2.P.7
Risk Analysis supplied in the NDA / BLA by the Combination Product Developer		X	Deficiency 2b. This became **deficiency 31b** in the CR letter. The sponsor did not provide the risk analysis for their combination product. The provided the risk analysis from the manufacturer of the delivery device (b) (4)). **This deficiency is unresolved.**
Validation Data: Human factors	X		N/A
Clinical data		X	
Traceability Documentation		X	Summary of Performance Testing, 3.2.P.7 is acceptable in place of traceability documentation, as it traces the specifications by including an "acceptance criteria" column for each test

6.1.2. Design Control Review

(b) (4)

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(b) (4)

8. DISCIPLINE SPECIFIC SUB-CONSULTED REVIEW

N/A

(b) (4)

10. LABELING

10.1. Conformance to FDA Guidance "Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products"

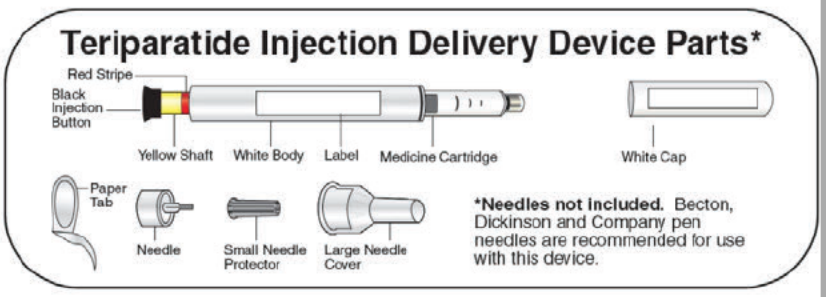
Labeling Element	Subject Device Labeling
Injector description, including name	Teriparatide Injection, USP
Intended use and indications for use	INDICATIONS AND USAGE (b) (4) • Treatment of postmenopausal women with osteoporosis at high risk for fracture (1.1) • Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture (1.2) • Treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture (1.3)
Type-of-use for the injector (e.g., personal, professional, single-use, reusable, labeled and sold for only one patient) a. Labeling should include appropriate warnings and precautions for the use conditions and patient population. For example, single-patient reusable injectors should include a warning to inform the user not to share the injector with other patients. b. Labeling on the injector itself should provide for space to allow healthcare provider to write the name of the specific patient for whom the injector is specified to avoid medication error. c. Labeling should include a prominent statement for "single patient use only" to avoid misuse and cross contamination.	(b) (4)
Intended patient population	yes
For general use injectors and those intended for use with a class/ family or a specific product line, sufficient labeling should be provided for the health care provider to determine what drug/biological product(s) is approved for administration by the injection method. As appropriate, this includes but is not limited to the following: a. Language stating the readily identifiable characteristics of the class, family or product line of drug or biological products approved for use with the injector; e.g., characteristics that are in the drug/biological product labeling, b. Language referring the user to the approved drug/biological labeling to determine if it is specifically approved for use with that type of injector and to obtain relevant dosing information, or c. Language indicating that the injector is for use in accordance with the approved labeling of the drug/biological product. d. List of brand name or list of name, type, and characteristics of drug/biological product that is specifically approved for use with the type of injector, method of injection, the dose range for the	N/A

injector, number of doses the injector delivers, single patient use or other conditions. e. Drug/biological product capability (e.g., single-dose-disposable, repeat dose disposable, single patient reusable or refillable, adjustable dose).	
Contraindications	----------CONTRAINDICATIONS---------- • Patients with hypersensitivity to teriparatide or to any of its excipients (4)
Warnings, limitations, and precautions, including incomplete dosing, overdosing, dosing site error (e.g., injection into the incorrect tissue), and cross-contamination	Warnings present consistent with the RLD labeling. (b) (4)
Safety and effectiveness data accrued with use of the injector	N/A – ANDA
Identification of any drug/biological product characteristics that are not compatible with the injector, if known	N/A – single drug product
Areas of the body appropriate for injection, including depictions with diagrams, and appropriate skin preparation prior to injection	"*Inject teriparatide injection one time each day in your thigh or abdomen (lower stomach area). Talk to a healthcare provider about how to rotate injection sites.*" 4 inject dose  Gently hold a fold of skin on your thigh or abdomen and insert the needle straight into your skin.  **Push in** black injection button until it stops. Hold it in and **count to 5 slowly. You must wait until the count of 5 to make sure you receive the correct dose.** Then pull the needle from the skin.
(b) (4)	
Directions for use, user instructions, and diagrams. As appropriate, this should include instructions for use of the injector that is consistent with the approved drug labeling instructions	Yes, see below
Assembly instructions and diagrams (e.g., how the drug/biological product is contained in the injector and the method for inserting the drug/biological product into the injector)	N/A – preassembled. Cap removal and needle guard removal instructions present (see below)
Maintaining sterility during injector assembly	N/A
Dose setting and administering an injection	N/A for dose setting – fixed dose Administration instructions present (see below)
How to ensure that the full dose is delivered	Yes, requires 5 second count during injection (see below).
How to ensure that a full dose remains in a reusable prefilled injector	N/A
Prevention of or remedy for incomplete or partial dosing or overdosing events	Red stripe on pull tab shown in instructions; 5 second instruction wait time (shown below)
The correct amount of pressure needed for an injection	"push in black injection button until it stops"
(b) (4)	

	(b) (4)
Labeling recommendations for sharps injury prevention features	No features present on this device or the RLD. Sufficient instructions provided for recapping and removing needle
Environmental conditions of use and storage	Keep in refrigerator at 2° to 8°C (36° to 46°F). Do NOT freeze.
(b) (4)	
Troubleshooting	Included (see below)
Life of the injector and critical components	Expiration dat (b) (4)

10.2. Package Labeling

The Device Parts shown in the user guide are included below on the left. The outside labeling of the pen itself (sticker) is shown on the right below.



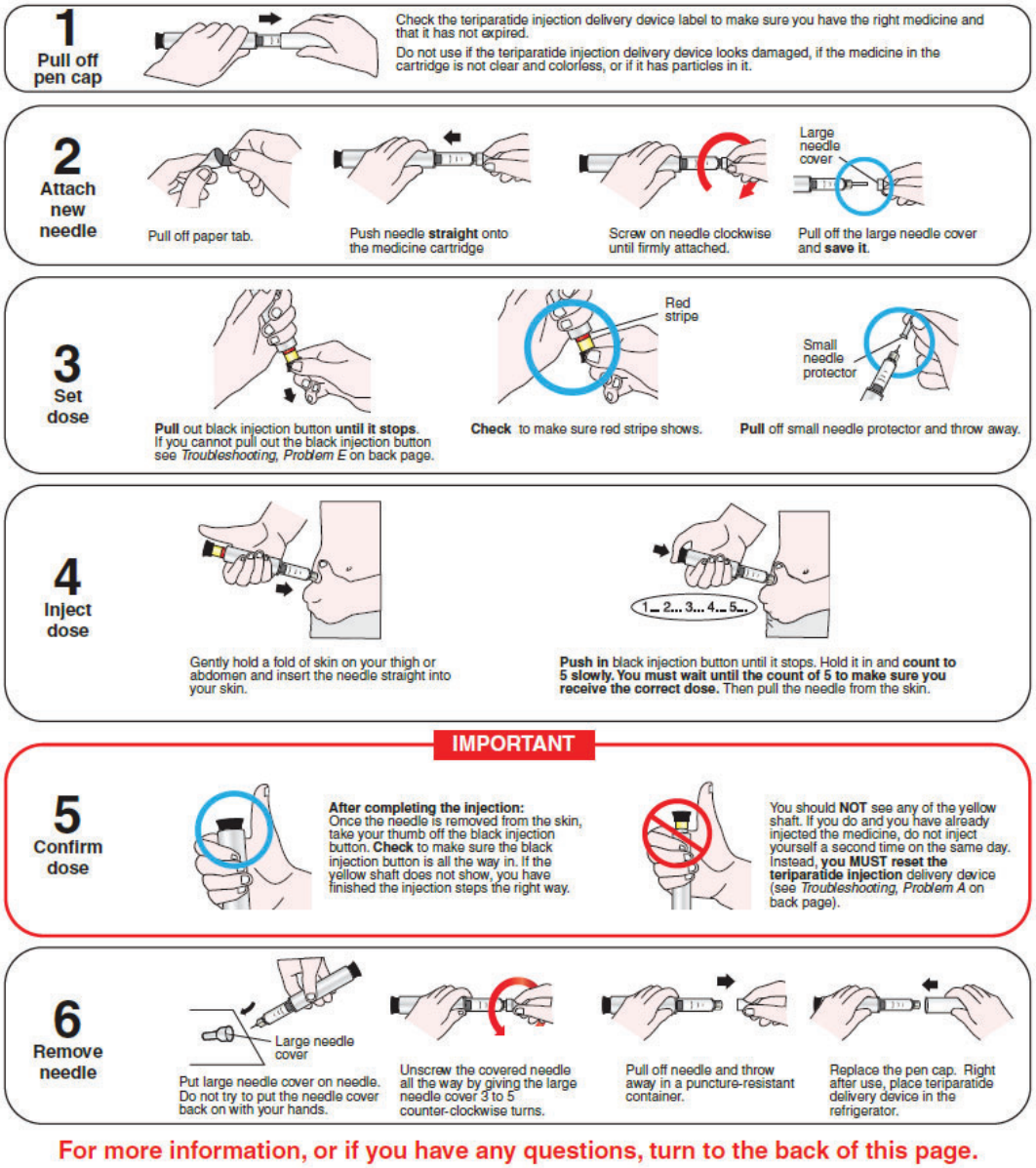
Wash your hands before every injection. Prepare the injection site as your healthcare provider instructed.

(b) (4)

10.3. User Manual

Instructions for use from the included user guide are shown below:

Wash your hands before every injection. Prepare the injection site as your healthcare provider instructed.



For more information, or if you have any questions, turn to the back of this page.

10.4. Troubleshooting, Warnings / Precautions from User Manual:

Troubleshooting

Problem	Solution
A. The yellow shaft is still showing after I push in the black injection button. How do I reset my teriparatide injection delivery device? 	To reset the teriparatide injection delivery device, follow the steps below. 1. **If you have already injected, DO NOT inject yourself a second time on the same day.** 2. Remove the needle. 3. Attach a new needle, pull off the large needle cover and save it. 4. Pull out the black injection button until it stops. Check to make sure the red stripe shows. 5. Pull off the small needle protector and throw away. 6. Point the needle down into an empty container. Push in the black injection button until it stops. Hold it in and **slowly count to five**. You may see a small stream or drop of fluid. **When you have finished, the black injection button should be all the way in.** 7. If you still see the yellow shaft showing, contact Apotex Corp (see Contact Information below) or your healthcare provider. 8. Put the large needle cover on the needle. Unscrew the needle all the way by giving the needle cover 3 to 5 counter-clockwise turns. Pull off the covered needle and throw away as instructed by your healthcare provider. Push the white cap back on, and put your teriparatide injection delivery device in the refrigerator. You can prevent this problem by **always using a NEW needle for each injection, and by pushing the black injection button all the way in and slowly counting to five**.
B. How can I tell if my teriparatide injection delivery device works?	The black injection button should be all the way in to show that the full dose of medicine has been injected from the teriparatide injection delivery device. Use a new needle every time you inject to be sure your teriparatide delivery device will work properly.
C. I see an air bubble in my teriparatide delivery device.	A small air bubble will not affect your dose and it will not harm you. You can continue to take your dose as usual.
D. I cannot get the needle off.	1. Put the large needle cover on the needle. 2. Use the large needle cover to unscrew the needle. 3. Unscrew the needle all the way by giving the large needle cover 3 to 5 counter-clockwise turns. 4. If you still cannot get the needle off, ask someone to help you.
E. What should I do if I have difficulty pulling out the black injection button?	**Change to a new teriparatide injection delivery device to take your dose as instructed by your healthcare provider.** When the black injection button becomes hard to pull out, this means there is not enough medicine in your teriparatide injection delivery device for another dose. You may still see some medicine left in the cartridge.

Cleaning and Storage

Cleaning Your Teriparatide Delivery Device

- Wipe the outside of the Teriparatide Delivery Device with a damp cloth.
- Do not place the Teriparatide Delivery Device in water, or wash or clean with any liquid.

Storing Your Teriparatide Delivery Device

- After each use, refrigerate the Teriparatide Delivery Device right away. Read and follow the instructions in the Medication Guide section "How should I store Teriparatide Injection?".
- Do not store the Teriparatide Delivery Device with a needle attached. Doing this may cause air bubbles to form in the medicine cartridge.
- Store the Teriparatide Delivery Device with the white cap on.
- Do not freeze Teriparatide Injection. If the Teriparatide Delivery Device has been frozen, throw the device away and use a new Teriparatide Delivery Device.
- If the Teriparatide Delivery Device has been left out of the refrigerator, do not throw the delivery device away. Place the delivery device back in the refrigerator and call Apotex at 1-800-706-5575.

Disposal of Pen Needles and Delivery Device

Disposal of Pen Needles and the Teriparatide Delivery Device

- Before throwing away the Teriparatide Delivery Device, be sure to remove the pen needle.
- Throw away your Teriparatide Delivery Device and used needles as instructed by your healthcare provider, local or state laws, or institutional policies.

Dispose of the Teriparatide Delivery Device 28 days after first use.

1st use date _____/_____/_____

Throw away after _____/_____/_____

Other Important Notes

- The Teriparatide Delivery Device contains 28 days of medicine.
- Do not transfer Teriparatide Injection to a syringe. This may result in you taking the wrong dose of medicine.
- Read and follow the instructions in the User Manual so that you use your Teriparatide Delivery Device the right way.
- Check the Teriparatide Delivery Device label to make sure you have the right medicine and that it has not expired.
- Do not use the Teriparatide Delivery Device if it looks damaged. Look at the Teriparatide medicine in the cartridge. If the medicine is not clear and colorless, or if it has particles, do not use it. Call Apotex if you notice any of these (see *Contact Information*).
- Use a new needle for each injection.
- During injection, you may hear one or more clicks – this is normal.
- The Teriparatide Delivery Device is not recommended for use by the blind or by those who have vision problems without help from a person trained in the proper use of the device.
- Keep your Teriparatide Delivery Device and needles out of the reach of children.

Contact Information

If you have questions or need help with your Teriparatide Delivery Device, contact Apotex at 1-800-706-5575 or your healthcare provider.

Marketed by: Apotex Corp.
Weston, Florida 33326, USA

Revised: March 2018

(b) (4)

(b) (4)

[redacted]

12.QUESTIONS FROM SPONSOR FOR TYPE A/B/C MEETING

N/A

13.INTERACTIVE REVIEW

Agency Information Request # (sent on XX/XX/XX) -
Sponsor Response (received on XX/XX/XX)

Reviewer Comments

Follow on Agency Information Request # (sent on XX/XX/XX) -
Sponsor Response (received on XX/XX/XX)

Reviewer Comments

Follow on Agency Information Request # (sent on XX/XX/XX) -
Sponsor Response (received on XX/XX/XX)

Reviewer Comments

[5] \\cdsesub1\evsprod\anda211097\0000\m3\32-body-data\32p-drug-prod\teriparatide-injectable-novocol\32p5-contr-drug-prod\32p52-analyt-proc\analytical-procedure-2.pdf

(b) (4)

ANDA 211097, Teriparatide Injection, USP 20 mcg per dose
Apotex, Inc.

Follow on Agency Information Request # (sent on XX/XX/XX) -
Sponsor Response (received on XX/XX/XX)

Reviewer Comments

Agency Information Request # (sent on XX/XX/XX)-

Sponsor Response (received on XX/XX/XX)

Reviewer Comments

(b) (4)

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(b) (4)

16. RECOMMENDATION

Deficiencies will be sent as part of the complete response (CR) letter.

16.1. Recommended Post-market commitments/post-market requirements

17. APPENDIX

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Kimberly McCullough

Digitally signed by Kimberly McCullough
Date: 9/09/2021 10:50:45AM
GUID: 525d9c4900038bd46a3ecdae8355361b

Date	4/30/2021		
To:	Erin Andrews; FDA/OC/CDER/OPQ/OPRO/DRBPMII/RBPMB3/		
Requesting Center/Office:	CDER/OPQ	**Clinical Review Division:**	Choose an item.
From	Shawn Shermer OPEQ/OHT3/DHT3C		
Through (Team)	Courtney Evans, Acting Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	Rumi Young, Acting Assistant Director, Injection Team OPEQ/OHT3/DHT3C		
Subject	ANDA 211097, Teriparatide Injection (b) (4)		
Recommendation	**Filing Recommendation Date:** Click or tap to enter a date. ☑ CDRH did not provide a Filing Recommendation ☐ Device Constituent Parts of the Combination Product are acceptable for Filing. ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5.4 for Deficiencies		
	Mid-Cycle Recommendation Date: Click or tap to enter a date. ☑ CDRH did not provide a Mid-Cycle Recommendation ☐ CDRH has no approvability issues at this time. ☐ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A.		
	Final Recommendation Date: 4/30/2021 ☐ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☑ Device Constituent Parts of the Combination Product are Not Approvable – Section 4 for Complete Response Deficiencies		

(b) (4)

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)

1. Submission Overview

Submission Information	
Submission Number	ANDA 211097
Sponsor	Apotex Inc.
Drug/Biologic	Teriparatide Injection
Indications for Use	Treatment of postmenopausal women with osteoporosis at high risk of fracture Increase bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture.
Device Constituent	Pen-Injector
Related Files	unknown

Contents

2. Purpose/Background

Apotex, Inc. is requesting approval of Teriparatide Injection. The device constituent of the combination product is a pen injector.

The ANDA 21097 (b) (4) Quality Review was completed by LCDR Phillip Lafleur. The sponsor provided a response to the deficiencies identified by LCDR Lafleur.

CDER/OPQ has requested the following consult for review of the device constituent of the combination product: Review CR letter CDRH responses submitted by firm 10/15/2020 SD #22

Background

Teriparatide Injection is an osteoporosis medicine that increases the number of bone-forming cells and helps build new bone in the spine, as well as other bones like the ankle/foot, hip, arm, pelvis, ribs, and

wrist. The device is intended to assist self-injecting adult patients without any upper age limit, healthcare providers, caregivers as well as third parties to deliver subcutaneous injections of Teriparatide. The average osteoporosis patient may have vision, hearing and/or fine motor skill impairments. Handicapped patients and mentally disabled patients are not considered as selfinjecting users. Patients may be injection naïve, or have limited to no experience performing self-injections. A physician prescribing the drug has to decide case by case, if the patient is capable of handling the device and acting as self-injecting user to assure that the patient's kinetic and cognitive abilities allow a safe handling of the pen.

Indications for Use

Combination Product	Indications for Use
Test: ANDA-	(b) (4) • Treatment of postmenopausal women with osteoporosis at high risk for fracture • Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture • Treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture
RLD Forteo: NDA-	FORTEO is indicated for the treatment of postmenopausal women with osteoporosis who are at high risk for fracture. These include women with a history of osteoporotic fracture, or who have multiple risk factors for fracture, or who have failed or are intolerant of previous osteoporosis therapy, based upon physician assessment (see BLACK BOX WARNING). In postmenopausal women with osteoporosis, FORTEO increases BMD and reduces the risk of vertebral and nonvertebral fractures. FORTEO is indicated to increase bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fracture. These include men with a history of osteoporotic fracture, or who have multiple risk factors for fracture, or who have failed or are intolerant to previous osteoporosis therapy, based upon physician assessment (see BLACK BOX WARNING). In men with primary or hypogonadal osteoporosis, FORTEO increases BMD. The effects of FORTEO on risk for fracture in men have not been studied. • FORTEO reduces the risk of vertebral fractures in postmenopausal women with osteoporosis.

	• FORTEO reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis. • FORTEO increases vertebral and femoral neck BMD in postmenopausal women with osteoporosis and in men with primary or hypogonadal osteoporosis. • The effects of FORTEO on fracture risk have not been studied in men.

(b) (4)

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OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS

INTERCENTER CONSULT MEMORANDUM – MEETING REQUEST

Date	7/15/2021		
To:	Erin Andrews; FDA/OC/CDER/OPQ/OPRO/DRBPMII/RBPMB3/		
Requesting Center/Office	CDER/OPQ		
From	Sreya Tarafdar OPEQ/OHT3/DHT3C		
Through (Team)	Suzanne Hudak, Acting Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *optional	CPT Alan Stevens, Assistant Director, Injection Team OPEQ/OHT3/DHT3C		
Subject	ANDA 211097 , Teriparatide Injection, USP 20 mcg per dose (b) (4)		
Recommendation	**Recommendation Date: 7/27/2021** ☑ CDRH has provided responses to the Sponsor questions ☐ CDRH has additional comments for the Sponsor ☑ CDRH has comments for the review division		

Digital Signature Concurrence Table		
Reviewer	**Team Lead (TL)**	**Division (*Optional)**

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	ANDA 211097
Sponsor	Apotex Inc.
Drug/Biologic	Teriparatide Injection, USP 20 mcg per dose
Indications for Use	*Treatment of postmenopausal women with osteoporosis at high risk for fracture *Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture
Device Constituent	Pen-Injector
Related Files	(b) (4)

Review Team		
Lead Device Reviewer	*Sreya Tarafdar*	
Discipline Specific Consults	**Reviewer Name (Center/Office/Division/Branch)**	**CON #**
N.A		

Important Dates	
Discipline-Specific Review Memos Due	
Final Lead Device Review Memo Due	07/27/2021
Interim Due Dates	**Meeting/Due Date**
Internal Meeting	07/23/21
Pre-Meeting Feedback Due	
WRO due	07/14/21

2. FINAL COMMENTS/RECOMMENDATION

2.1. Preliminary Feedback for the Sponsor

Question 4 a

If anything further is being requested for injection force (or if the previously submitted data for dispense force testing is what the Agency requires)?

FDA response: In your CRL Response submitted on October 15, 2020, you provided the dispense force in your Comparison Testing Report section 4.4. This is acceptable. No further information is required for injection force testing.

Question 4 b

For the "injection time" and "needle depth", is specific testing required for these parameters or is the Agency looking for an explanation similar to what has been outlined above. If specific testing is required, could the Agency please provide further clarity on the type of testing that is expected in response to this question.

FDA response: In your post- complete response letter meeting request (dated July 1, 2021) you have provided calculations to determine the injection time based on the equipment velocity for injection force testing and the travel path of the dose button. We typically require the sponsor to test the injection time and provide report/results and not determine it by calculations. But in your case, since the device is a manual and not automatic device and the injection time for manual pen-injectors is dependent upon the force applied on the dose button, no further specific testing are required at this point. We recommend you update the comparison table and include these parameters (injection time and extended needle length/depth of needle insertion) in the table and provide explanation/ justification similar to what has been outlined above, that it is a manual device.

(b) (4)

2.2. Comments to the Review Team

☐ CDRH does not have any further comments to convey to the review team.

☑ CDRH has the following comments to convey to the review team:

CDRH chooses to defer Question 1 from the sponsor to CDER to respond and provide a feedback. A little background on it is as follows:-

The complete response letter signed June 14, 2021, by Aaron Sigler, has a preamble or summary of the deficiencies at the beginning of the Drug Product (DP) section on Page 2 of 10. Aaron has justified classifying the Pharmaceutical quality deficiencies as MAJOR because of the following:

(b) (4)

This section was not written/drafted by CDRH. And we did not find any deficiency related to accelerated stability data in the drug Product section of the CRL. Since CDER drafted this section of the CRL, we would like to defer this question to CDER to respond to the sponsor. Could CDER please clarify if you are referring to the CDRH Device deficiency # 3 or any other accelerated stability data related to the drug product ?

TABLE OF CONTENTS

3. PURPOSE/BACKGROUND

Apotex, Inc. is requesting approval of Teriparatide Injection. The device constituent of the combination product is a pen injector.

CDER/OPQ has requested the following consult for review of the device constituent for the combination product:
SD #28 - Question #1, 4 & 5 in meeting request. Check SD #29 to see if addendum has a revision to question #1, 4 & 5.

This submission was initially reviewed by Peter Petrochenko in July 2018. Peter identified deficiencies that were sent to the sponsor in a COMPLETE RESPONSE LETTER dated 10/26/2018. The sponsor's response to Peter's issued CR deficiencies came in on 10/15/2020. The sponsor's response to the CR deficiencies was reviewed by Shawn Shermer in April 2021. Shawn identified follow-on deficiencies that were sent to the sponsor in a COMPLETE RESPONSE LETTER dated 06/14/21. The sponsor has sent in a meeting request letter dated June 24 and a second one (with additional questions) dated July 1 and posed some clarification questions. **This is a follow -up on Shawn's memo, in which, I have added provided feedback and responded to the sponsor's clarification questions pertaining to Shawn's issued CR deficiencies. New information/feedback will be identified by blue colored font.**

The goal of this memo is to provide a response/feedback to the sponsor for their clarification questions # 4 and 5 from their meeting request details_addendum 1.
Note: Request details on (b) (4) ***did not include Question 6 in the consult request. However, CDRH has provided response to Question 6 from the Sponsor's meeting request details _ addendum 1, since the Question 6 addresses clarifications following deficiency issued by Shawn Shermer.***

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.1. Scope

3.2. Prior Interactions

3.2.1. Related Files

(b) (4)

3.3. Background

Teriparatide Injection is used for treatment of osteoporosis that increases the number of bone-forming cells and helps build new bone in the spine, as well as other bones like the ankle/foot, hip, arm, pelvis, ribs, and wrist. The constituent device of the combination product is intended to assist adult patients in self-injecting without any upper age limit, healthcare providers, caregivers as well as third parties to deliver subcutaneous injections of Teriparatide. The average osteoporosis patient may have vision, hearing and/or fine motor skill impairments. Handicapped patients and mentally disabled patients are not considered as self-injecting users. Patients may be injection naïve or have limited to no experience performing self-injections. A physician prescribing the drug has to decide case by case, if the patient is capable of handling the device and acting as self-injecting user to assure that the patient's kinetic and cognitive abilities allow a safe handling of the pen

3.4. Indications for Use

Combination Product	Indications for Use
Test: ANDA-	(b) (4) • Treatment of postmenopausal women with osteoporosis at high risk for fracture • Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture • Treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture

RLD Forteo: NDA-	FORTEO is indicated for the treatment of postmenopausal women with osteoporosis who are at high risk for fracture. These include women with a history of osteoporotic fracture, or who have multiple risk factors for fracture, or who have failed or are intolerant of previous osteoporosis therapy, based upon physician assessment (see BLACK BOX WARNING). In postmenopausal women with osteoporosis, FORTEO increases BMD and reduces the risk of vertebral and nonvertebral fractures. FORTEO is indicated to increase bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fracture. These include men with a history of osteoporotic fracture, or who have multiple risk factors for fracture, or who have failed or are intolerant to previous osteoporosis therapy, based upon physician assessment (see BLACK BOX WARNING). In men with primary or hypogonadal osteoporosis, FORTEO increases BMD. The effects of FORTEO on risk for fracture in men have not been studied. • FORTEO reduces the risk of vertebral fractures in postmenopausal women with osteoporosis. • FORTEO reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis. • FORTEO increases vertebral and femoral neck BMD in postmenopausal women with osteoporosis and in men with primary or hypogonadal osteoporosis. • The effects of FORTEO on fracture risk have not been studied in men.
Pen-Injector	Delivery of the Drug Product

3.5. Materials Reviewed

Materials Reviewed	
Document	**Sequence/Module (s)**
(b) (4)	
addendum-1-meeting-request-details-pdf (1)	Seq 0027/SD 28/Mod 1.2
addendum-1-meeting-request-details-pdf (1)	Seq 0028/SD 29/Mod 1.2

(b) (4)

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 211097

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 211097

NOTIFICATION
WILL MISS GDUFA DATE

Apotex Corp.
U.S. Agent for Apotex Inc.
2400 North Commerce Parkway
Suite 400
Weston, FL 33326
Attention: Kiran Krishnan
Senior Vice President, Global Regulatory Affairs

Dear Kiran Krishnan:

This correspondence is in reference to the GDUFA Goal Date of May 17, 2023 for ANDA 211097, Teriparatide Injection USP, 600 mcg/2.4 mL (250 mcg/mL), Single-Patient-Use Prefilled Pens. It appears that we will not take an action by the GDUFA goal date identified above for this application, due to unresolved regulatory issues. Therefore, FDA is deferring action on your application until this issue can be resolved. We remain committed to continuing our assessment of the application and to take action as quickly as possible. You may contact me in 4-6 weeks for an updated status regarding this application. There is no further action required at this time.

If you have any questions, contact Regulatory Project Manager, Kimberly McCullough, at (240) 402-9021, Kim.McCullough@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Kimberly McCullough, BS, RPh, MBA

Regulatory Project Manager
Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

Kimberly McCullough

Digitally signed by Kimberly McCullough
Date: 5/17/2023 01:18:38PM
GUID: 525d9c4900038bd46a3ecdae8355361b

ANDA 211097

AMENDMENT ACKNOWLEDGEMENT
Standard
Minor

Apotex Corp.
U.S. Agent for Apotex Inc.
2400 North Commerce Parkway
Suite 400
Weston, FL 33326
Attention: Kiran Krishnan
Senior Vice President, Global Regulatory Affairs

Dear Kiran Krishnan:

This is in reference to your amendment received on February 17, 2023, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Teriparatide Injection, 600 mcg/2.4 mL (250 mg/mL) in prefilled delivery device (pen).

This amendment is subject to the provisions of the Generic Drug User Fee Amendments of 2022 (GDUFA III). FDA has made an initial determination that this is a standard minor amendment. The GDUFA goal date for review of this standard minor amendment is May 17, 2023. We also note that, consistent with the GDUFA III Commitment Letter, your information request/discipline review letter (IR/DRL) response extends the goal date for your ANDA.

GDUFA provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the reference listed drug (RLD) that occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current recommendations on demonstrating bioequivalence reflected in relevant product specific guidances.

As described in FDA's Draft Guidance for Industry, Cover Letter Attachments for Controlled Correspondences and ANDA Submissions, FDA recommends that you include the appropriate attachment(s) along with the cover letter for your submission to

help FDA ensure that your submission is properly triaged and assigned to the appropriate assessors. This will also ensure that submissions are effectively managed by FDA and acted upon within the performance review goal dates set by the Generic Drug User Fee Amendments.

If you have any questions, contact Kimberly McCullough, Regulatory Project Manager, at (240) 402 - 9021.

Sincerely,

{See appended electronic signature page}

Kimberly McCullough
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Kimberly McCullough

Digitally signed by Kimberly McCullough
Date: 2/25/2023 01:30:42PM
GUID: 525d9c4900038bd46a3ecdae8355361b

ANDA 211097

INFORMATION REQUEST
QUALITY

Apotex Corp.
U.S. Agent for Apotex Inc.
2400 North Commerce Parkway
Suite 400
Weston, FL 33326
Attention: Kiran Krishnan
SVP, Global Regulatory Affairs

Dear Kiran Krishnan:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on December 29, 2017, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Teriparatide Injection, USP, 20 mcg per dose (600 mcg/2.4 mL).

We also refer to your May 12, 2022 submission, containing complete response.

Reference is also made to any amendments submitted prior to the issuance of this letter.

We are reviewing the Quality section of your submission and request the following additional information/clarification and/or have the following comments:

QUALITY

(b) (4)

(b) (4)

C. Labeling Deficiency

1. Please add the sentence "*The molecular formula of teriparatide is* $C_{181}H_{291}N_{55}O_{51}S_2$" to the Description of your product labeling to be in line with the most recent RLD labeling.

(b) (4)

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(b) (4)

It has been determined that the quality assessment for this ANDA requires an additional technical consultation. Please note that the quality assessment of the ANDA cannot be fully completed until this technical consultation has been finalized. Therefore, additional requests for information and/or deficiencies may be issued based on the outcome of this technical consultation.

We request a complete written response, no later than February 20, 2023 in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. If you are responding to a late cycle information request[1], the goal date may be extended based upon the major or minor deficiencies included upon receipt of the response. The goal date assigned to the amendment may extend the review goal date for your current submission.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
QUALITY
MINOR

If you do not submit a complete written response by February 20, 2023, the listed information requests may be incorporated in a discipline review letter or complete response letter.

As described in FDA's draft guidance for industry *Cover Letter Attachments for Controlled Correspondences and ANDA Submissions*, FDA recommends that you include the appropriate attachment(s) along with the cover letter for your submission to help FDA ensure that your submission is properly triaged and assigned to the appropriate assessors. This will also ensure that submissions are effectively managed by FDA and acted upon within the performance review goal dates set by the Generic Drug User Fee Amendments.

If you have any questions, please contact Erin Andrews, Regulatory Business Process Manager, at erin.andrews@fda.hhs.gov or (240) 402 - 8578.

Sincerely,

{See appended electronic signature page}

Erin Andrews
Regulatory Business Process Manager
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

[1] Late cycle defined as IRs or DRLs issued after the mid-cycle of an original ANDA or less than 90 days from the goal date for any ANDA amendment.

Erin Andrews

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Date: 1/20/2023 03:06:29PM
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ANDA 211097

AMENDMENT ACKNOWLEDGEMENT
Standard
Minor

Apotex Corp.
U.S. Agent for Apotex Inc.
2400 North Commerce Parkway
Suite 400
Weston, FL 33326
Attention: Kiran Krishnan
Senior Vice President, Global Regulatory Affairs

Dear Kiran Krishnan:

This is in reference to an amendment to the Drug Master File (DMF) (b) (4) received on December 29, 2022, which is referenced in your abbreviated new drug application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Teriparatide Injection, 600 mcg/2.4 mL (250 mg/mL) in prefilled delivery device (pen).

This amendment is subject to the provisions of the Generic Drug User Fee Amendments of 2022 (GDUFA III). FDA has made an initial determination that this is a standard minor amendment. The GDUFA goal date for review of this standard minor amendment is March 29, 2023.

GDUFA provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the reference listed drug (RLD) that occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current recommendations on demonstrating bioequivalence reflected in relevant product specific guidances.

As described in FDA's Draft Guidance for Industry, Cover Letter Attachments for Controlled Correspondences and ANDA Submissions, FDA recommends that you include the appropriate attachment(s) along with the cover letter for your submission to

help FDA ensure that your submission is properly triaged and assigned to the appropriate assessors. This will also ensure that submissions are effectively managed by FDA and acted upon within the performance review goal dates set by the Generic Drug User Fee Amendments.

If you have any questions, contact Kimberly McCullough, Regulatory Project Manager, at (240) 402 - 9021.

Sincerely,

{See appended electronic signature page}

Kimberly McCullough
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Kimberly McCullough

Digitally signed by Kimberly McCullough
Date: 1/05/2023 10:57:48AM
GUID: 525d9c4900038bd46a3ecdae8355361b

ANDA 211097

DISCIPLINE REVIEW LETTER
LABELING

Apotex Corp.
U.S. Agent for: Apotex Inc.
2400 North Commerce Parkway
Suite 400
Weston, FL 33326
Attention: Kiran Krishnan
Senior Vice President – Global Regulatory Affairs

Dear Sir:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on December 29, 2017, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Teriparatide Injection USP, 600 mcg/2.4 mL (250 mg/mL) Single-Patient-Use Prefilled Pens.

Reference is also made to any amendments submitted prior to the issuance of this letter.

The following comments have been identified by the Division of Labeling Review (DLR) based on your submission(s) on May 12, 2022. Prior to final approval, the proposed labeling should be clear and precise (grammar, spelling, and formatting) for end users, and accurately reflect the Reference Listed Drug (RLD) information to comply with FDA policies, laws, regulations (i.e., 21 CFR 314.94(a)(8)), official compendia, and relevant guidance.

1. PRESCRIBING INFORMATION
    a. HIGHLIGHTS OF PRESCRIBING INFORMATION: Revise Initial U.S. Approval to read, "Initial U.S. Approval: 1987" to be in line with the RLD.
    b. Section 16.1 How Supplied: To be in line with the RLD, revise to read:

        Teriparatide Injection is a clear and colorless solution, available as single-patient-use prefilled delivery device (pen) in the following package size:
        • 600 mcg/2.4 mL (250 mcg/mL) [containing 28 daily doses of 20 mcg] NDC 60505-6188-0
    c. 5.3 Risk of Urolithiasis: Revise the first sentence (b) (4) to read "…patients treated with teriparatide injection…"

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the Electronic Orange Book are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

If you would like to respond to these possible deficiencies before the end of this review cycle, we request a complete written response to this discipline review letter (DRL) no later than December 30, 2022. If you submit a written response during this review cycle, depending on the timing and/or the information contained in your response, we may not be able to consider your response before taking action on your application. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

DISCIPLINE REVIEW LETTER
LABELING
MINOR

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application. As contemplated in the Generic Drug User Fee Amendments of 2022 (GDUFA III)[1], these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified or additional deficiencies may be identified as we complete our review of your entire application.

[1] GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2023-2027 (available at https://www.fda.gov/media/153631/download).

Deficiencies addressed by applicants in a response to a DRL may appear in a Complete Response Letter (CRL) if FDA's review of the response has been deferred or if FDA has outstanding concerns after review of the response. The CRL will include all deficiencies that must be satisfactorily addressed before the ANDA can be approved.

If the applicant receives a CRL, but has already responded to some (or all) identified deficiencies in a DRL response, the applicant does not need to re-submit previously submitted information in a CRL amendment. However, the applicant should still submit a CRL amendment and should clearly identify the previously provided DRL response that renders its CRL amendment complete.

Additionally, please take note of the following if you choose to respond to these possible deficiencies before the end of this review cycle:

1. If your submission is a response to a Major DRL received by the due date (or any agreed-upon extension), FDA may classify the response as Major and assign an appropriate goal date for that amendment.
2. If you do not respond by the requested due date, FDA may defer review of your response.
3. FDA will strive to review your response during the review cycle in which it is received if such review can be completed during such review cycle. However, if the Agency determines that it cannot review the response before a goal date or if a complete response letter is otherwise ready to be issued, the review of your response may be deferred. When FDA defers review of your response, it will be reviewed during the next review cycle for the application.
4. If you are responding to a late cycle DRL[2], the goal date may be extended based upon the major or minor deficiencies included upon receipt of the response.
5. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as a major or minor amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

As described in FDA's draft guidance for industry *Cover Letter Attachments for Controlled Correspondences and ANDA Submissions*, FDA recommends that you include the appropriate attachment(s) along with the cover letter for your submission to help FDA ensure that your submission is properly triaged and assigned to the appropriate assessors. This will also ensure that submissions are effectively managed by FDA and acted upon within the performance review goal dates set by the Generic Drug User Fee Amendments.

[2] Late cycle defined as IRs or DRLs issued after the mid-cycle of an original ANDA or IRs or DRLs issued less than 90 days from the goal date of an ANDA amendment

If you have any questions, please contact Julie Call, Labeling Project Manager, at julie.call@fda.hhs.gov or 240-402-8598.

Sincerely,

{See appended electronic signature page}

Julie Call, PharmD, PMP
Labeling Project Manager
Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

Julie
Call

Digitally signed by Julie Call
Date: 12/22/2022 11:18:29AM
GUID: 525d9e9d00038c406bce70608a211ab1

ANDA 211097

AMENDMENT ACKNOWLEDGEMENT
Standard
Major

Apotex Corporation
U.S. Agent for Apotex Inc.
2400 North Commerce Parkway
Suite 400
Weston, FL 33326
Attention: Kirin Krishnan
Senior Vice President, Global Regulatory Affairs

Dear Kirin Krishnan:

This is in reference to your amendment received on May 12, 2022, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Teriparatide Injection, 600 mcg/2.4 mL (250 mg/mL) in prefilled delivery device (pen).

This amendment is subject to the provisions of the Generic Drug User Fee Amendments of 2017 (GDUFA II). FDA has made an initial determination that this is a standard major amendment. We acknowledge that you have requested a priority review for this submission. However, your submission does not meet the criteria in accordance with the Center for Drug Evaluation and Research's Manual of Policies and Procedures 5240.3, *Prioritization of the Review of Original ANDAs, Amendments, and Supplements.* If FDA determines that an inspection is not required to validate the information contained in this standard major amendment, the GDUFA goal date for review of this standard major amendment is January 11, 2023. If FDA determines that an inspection is required to validate the information contained in this standard major amendment, the GDUFA goal date for review of this standard major amendment is March 11, 2023. Two possible goal dates are provided because FDA is unable to determine if an amendment requires an inspection at the time of submission. FDA will make this determination during the assessment of the amendment. For information, see FDA's guidance for industry, *ANDA Submissions - Amendments to Abbreviated New Drug Applications Under GDUFA.*

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant’s responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after the

submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current recommendations on demonstrating bioequivalence reflected in relevant product specific guidances.

If you have any questions, contact Kimberly McCullough, Regulatory Project Manager, at (240) 402 - 9021.

Sincerely,

{See appended electronic signature page}

Kimberly McCullough
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Kimberly McCullough

Digitally signed by Kimberly McCullough
Date: 5/16/2022 10:49:32AM
GUID: 525d9c4900038bd46a3ecdae8355361b

ANDA 211097

POST-CRL MEETING REQUEST
PRELIMINARY RESPONSES

Apotex Corp.
U.S. Agent for Apotex Inc.
2400 North Commerce Parkway
Suite 400
Weston, FL 33326
Attention: Kiran Krishnan
Senior Vice President, Global Regulatory Affairs

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) received for review on December 29, 2017, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Teriparatide Injection, 600 mcg/2.4 mL (250 mg/mL) in prefilled delivery device (pen).

Further reference is made to our Meeting Request Granted –Teleconference letter dated July 21, 2021.

Enclosed are our preliminary responses to the questions contained in your post-complete response letter meeting request dated June 24, 2021 and July 2, 2021.

If you have any questions, call Kimberly McCullough, Regulatory Project Manager, at (240) 402 - 9021.

Sincerely,

{See appended electronic signature page}

Kimberly McCullough
Regulatory Project Manager
Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research

PRELIMINARY RESPONSES

Meeting Type:	Post-complete response letter meeting
Meeting Date and Time:	12 August 2021, 1:15 p.m.

The Agency provides the following preliminary responses and any additional comments in preparation for the discussion at the meeting scheduled above for your ANDA 211097. The responses do not reflect agreements, key issues, or action items. This information is shared to promote a collaborative and successful discussion at the meeting. If these answers and comments are clear to you and you determine that further discussion is not needed, you have the option of cancelling the meeting by contacting the Project Manager via email prior to the scheduled TCON date of August 12, 2021, 1:15 p.m. In that event, these responses will constitute the official meeting response. If you determine that discussion is needed for only some of the original questions, you have the option of updating the agenda. Your updated agenda should list the questions for discussion and the order of priority. Do not submit any new data or additional questions not presented in the original meeting package, as this information will not be addressed or discussed at the meeting.

(b) (4)

[redacted]

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Kimberly McCullough

Digitally signed by Kimberly McCullough
Date: 9/09/2021 10:50:45AM
GUID: 525d9c4900038bd46a3ecdae8355361b

ANDA 211097

POST-CRL MEETING REQUEST
PRELIMINARY RESPONSES

Apotex Corp.
U.S. Agent for Apotex Inc.
2400 North Commerce Parkway
Suite 400
Weston, FL 33326
Attention: Kiran Krishnan
Senior Vice President, Global Regulatory Affairs

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) received for review on December 29, 2017, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Teriparatide Injection, 600 mcg/2.4 mL (250 mg/mL) in prefilled delivery device (pen).

Further reference is made to our Meeting Request Granted –Teleconference letter dated July 21, 2021.

Enclosed are our preliminary responses to the additional clarifying questions contained in your post-complete response letter meeting request dated August 12, 2021.

If you have any questions, call Kimberly McCullough, Regulatory Project Manager, at (240) 402 - 9021.

Sincerely,

{See appended electronic signature page}

Kimberly McCullough
Regulatory Project Manager
Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research

CLARIFICATION of PRELIMINARY RESPONSE

Meeting Type:	Post-complete response letter meeting
Meeting Date and Time:	September 16, 2021, 11:15 a.m.

The Agency provides the following preliminary responses and any additional comments in preparation for the discussion at the meeting scheduled above for your ANDA 211097. The responses do not reflect agreements, key issues, or action items. This information is shared to promote a collaborative and successful discussion at the meeting. If these answers and comments are clear to you and you determine that further discussion is not needed, you have the option of cancelling the meeting by contacting the Project Manager via email prior to the scheduled TCON date of September 16, 2021, 11:15 a.m. In that event, these responses will constitute the official meeting response. If you determine that discussion is needed for only some of the original questions, you have the option of updating the agenda. Your updated agenda should list the questions for discussion and the order of priority. Do not submit any new data or additional questions not presented in the original meeting package, as this information will not be addressed or discussed at the meeting.

(b) (4)

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Kimberly McCullough

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ANDA 211097

POST-CRL MEETING REQUEST
PRELIMINARY RESPONSES

Apotex Corp.
U.S. Agent for Apotex Inc.
2400 North Commerce Parkway
Suite 400
Weston, FL 33326
Attention: Kiran Krishnan
Senior Vice President, Global Regulatory Affairs

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) received for review on December 29, 2017, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Teriparatide Injection, 600 mcg/2.4 mL (250 mg/mL) in prefilled delivery device (pen).

Further reference is made to our Meeting Request Granted –Teleconference letter dated July 21, 2021.

Enclosed are our preliminary responses to the questions contained in your post-complete response letter meeting requests dated June 24, 2021 and July 2, 2021.

If you have any questions, call Kimberly McCullough, Regulatory Project Manager, at (240) 402 - 9021.

Sincerely,

{See appended electronic signature page}

Kimberly McCullough
Regulatory Project Manager
Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research

PRELIMINARY RESPONSES

Meeting Type:	Post-complete response letter meeting
Meeting Date and Time:	12 August 2021, 1:15 p.m.

The Agency provides the following preliminary responses and any additional comments in preparation for the discussion at the meeting scheduled above for your ANDA 211097. The responses do not reflect agreements, key issues, or action items. This information is shared to promote a collaborative and successful discussion at the meeting. If these answers and comments are clear to you and you determine that further discussion is not needed, you have the option of cancelling the meeting by contacting the Project Manager via email prior to the scheduled TCON date of August 12, 2021, 1:15 p.m. In that event, these responses will constitute the official meeting response. If you determine that discussion is needed for only some of the original questions, you have the option of updating the agenda. Your updated agenda should list the questions for discussion and the order of priority. Do not submit any new data or additional questions not presented in the original meeting package, as this information will not be addressed or discussed at the meeting.

(b) (4)

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Kimberly McCullough

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Date: 8/06/2021 04:08:57PM
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ANDA 211097

INFORMATION REQUEST

Apotex Corp.
U.S. Agent for Apotex Inc.
2400 North Commerce Parkway
Suite 400
Weston, FL 33326
Attention: Kiran Krishnan
Senior Vice President Global Regulatory and Medical Affairs

Dear Sir:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on December 29, 2017, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Teriparatide Injection, 600 mcg/2.4 mL (250 mg/mL) in prefilled delivery device (pen).

Reference is also made to your amendment dated October 15, 2020.

Your submission remains under review, and we require additional information in order to complete our Clinical Consultation review.

We refer to your comparative use human factors (CUHF) study results report submitted on October 15, 2020. To better inform our review of your CUHF study results report, we request that you provide a response to the following within 2 business days:

(b) (4)

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

We request a complete written response no later than April 16, 2021 in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
CLINICAL

If you do not submit a complete written response by April 16, 2021, the listed information requests may be incorporated in a complete response letter.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

If you have any questions, please contact the Clinical Project Manager, at Nitin.Patel@fda.hhs.gov.

Please also confirm receipt of this letter.

Sincerely,

{See appended electronic signature page}

Nitin K. Patel, Pharm.D.
Clinical Project Manager
Division of Clinical Review
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Nitin K. Patel

Digitally signed by Nitin K. Patel
Date: 4/13/2021 10:36:33AM
GUID: 508da70c00028f695d87f612d0d4cbb6

ANDA 211097

INFORMATION REQUEST
QUALITY

Apotex Corp.
U.S. Agent for Apotex Inc.
2400 North Commerce Parkway
Suite 400
Weston, FL 33326
Attention: Kiran Krishnan
Svp, Global Regulatory Affairs

Dear Kiran Krishnan:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on December 29, 2017, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Teriparatide Injection, Solution USP, 20 mcg per dose (600 mcg/2.4 mL).

We also refer to your October 15, 2020 submission, containing complete response.

We are reviewing the Quality section of your submission and have the following comments and information requests:

(b) (4)

It has been determined that the quality assessment for this ANDA requires an additional technical consultation. Please note that the quality assessment of the ANDA cannot be fully completed until this technical consultation has been finalized. Therefore, additional requests for information and/or deficiencies may be issued based on the outcome of this technical consultation.

We request a prompt written response, no later than February 2, 2021 in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
QUALITY/DRUG PRODUCT BIOTECHNOLOGY

If you have any questions, please contact Erin Andrews, Regulatory Business Process Manager, at erin.andrews@fda.hhs.gov or (240) 402 - 8578.

Sincerely,

{See appended electronic signature page}

Erin Andrews, PharmD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Erin
Andrews

Digitally signed by Erin Andrews
Date: 1/27/2021 01:16:11PM
GUID: 52e7d3790000f03cf7ec38aacca759ed

ANDA 211097

GENERAL CORRESPONDENCE

Apotex Corp
U.S. Agent for Apotex Inc
2400 North Commerce Parkway, Suite 400
Weston, FL 33326
Attention: Kiran Krishnan
Senior Vice President, Global Regulatory Affairs

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) received for review on December 29, 2017, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Teriparatide Injection, 600 mcg/2.4 mL (250 mg/mL) in prefilled delivery device (pen).

We also refer to your general correspondence received on July 29, 2020.

The Division of Clinical Review (DCR) has reviewed your General Correspondence (GC) dated July 29, 2020, regarding proposed modifications to your Comparative Use Human Factors (CUHF) study protocol.

(b) (4)

- Since you have already submitted your CUHF study results on October 15, 2020 in a response titled, “Response to COMPLETE RESPONSE (CR) LETTER dated October 26, 2018,” your submission closes out this GC request.

If you have any questions, please contact the Clinical Project Manager, at Nitin.Patel@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}
Nitin K. Patel, Pharm.D.
Clinical Project Manager
Division of Clinical Review
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Nitin K. Patel

Digitally signed by Nitin K. Patel
Date: 12/16/2020 11:02:15AM
GUID: 508da70c00028f695d87f612d0d4cbb6

ANDA 211097

AMENDMENT ACKNOWLEDGEMENT
Standard
Major

Apotex Corp.
U.S. Agent for Apotex Inc.
2400 North Commerce Parkway
Suite 400
Weston, FL 33326
Attention: Kiran Krishnan
Senior Vice President Global Regulatory and Medical Affairs

Dear Sir:

This is in reference to your amendment received on October 15, 2020, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Teriparatide Injection, 600 mcg/2.4 mL (250 mg/mL) in prefilled delivery device (pen) .

This amendment is subject to the provisions of the Generic Drug User Fee Amendments of 2017 (GDUFA II). FDA has made an initial determination that this is a standard major amendment. We acknowledge that you have requested a priority review for this submission. However, your submission does not meet the criteria in accordance with the Center for Drug Evaluation and Research's Manual of Policies and Procedures 5240.3, *Prioritization of the Review of Original ANDAs, Amendments, and Supplements.* If FDA determines that an inspection is not required to validate the information contained in this standard major amendment, the GDUFA goal date for review of this standard major amendment is June 14, 2021. If FDA determines that an inspection is required to validate the information contained in this standard major amendment, the GDUFA goal date for review of this standard major amendment is August 14, 2021. Two possible goal dates are provided because FDA is unable to determine if an amendment requires an inspection at the time of submission. FDA will make this determination during the assessment of the amendment. For information, see FDA's guidance for industry, *ANDA Submissions - Amendments to Abbreviated New Drug Applications Under GDUFA.*

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant’s responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should

ensure your application addresses any changes to the RLD that occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current recommendations on demonstrating bioequivalence reflected in relevant product specific guidances.

If you have any questions, contact Kimberly McCullough, Regulatory Project Manager, at (240) 402 - 9021.

Sincerely,

{See appended electronic signature page}

Kimberly McCullough
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Kimberly McCullough

Digitally signed by Kimberly McCullough
Date: 10/20/2020 11:12:21PM
GUID: 525d9c4900038bd46a3ecdae8355361b

ANDA 211097

GENERAL CORRESPONDENCE
ADDITIONAL WRITTEN RESPONSES

Apotex Corp
U.S. Agent for Apotex Inc
2400 North Commerce Parkway, Suite 400
Weston, FL 33326
Attention: Kiran Krishnan
Senior Vice President, Global Regulatory Affairs

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) received for review on December 29, 2017, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Teriparatide Injection, 600 mcg/2.4 mL (250 mg/mL) in prefilled delivery device (pen).

We also refer to your general correspondence received on Feburary 1, 2019, requesting a written response relevant to the post-complete response letter issued by this office on October 26, 2018. We also refer to our response dated November 13, 2019 and the additional question submitted for clarification, received on November 20, 2019.

The enclosed document constitutes our written responses to the additional clarification question submitted on November 20, 2019 by e-mail.

If you have any questions, call Kimberly McCullough, Regulatory Project Manager at (240) 402-9021.

Sincerely,

Kimberly McCullough
Regulatory Project Manager
Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure:
Written Response

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Kimberly McCullough

Digitally signed by Kimberly McCullough
Date: 1/30/2020 06:50:16PM
GUID: 525d9c4900038bd46a3ecdae8355361b

ANDA 211097

PRE-SUBMISSION FACILITY CORRESPONDENCE
ELIGIBLE FOR FURTHER ASSESSMENT

Apotex Corp.
U.S. Agent for Apotex Inc.
2400 North Commerce Parkway, Suite 400
Weston, FL 33326
Attention: Kiran Krishman, Ph.D.
SVP, Global Regulatory Affairs

Dear Sir:

This is in reference to your Pre-Submission Facility Correspondence (PFC) received on June 27, 2019, for your abbreviated new drug application (ANDA) to be submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act for Teriparatide Injection, 600 mcg/2.4 mL (250 mg/mL) in prefilled delivery device (pen).

This PFC is subject to the provisions of the Food and Drug Administration Reauthorization Act of 2017 (FDARA) and the Generic Drug User Fee Amendments GDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018-2022 (GDUFA II Commitment Letter).

We acknowledge your request for a priority review of your ANDA. Based on the rationale in your PFC, your ANDA preliminarily appears to meet the criteria for a priority review per the Center for Drug Evaluation and Research's Manual of Policies and Procedures 5240.3, *Prioritization of the Review of Original ANDAs, Amendments, and Supplements* (Prioritization MAPP). Therefore, your PFC is eligible for further assessment.

You should determine your ANDA submission date with reference to Section 801 of FDARA and the GDUFA II Commitment Letter. If the ANDA is submitted earlier than 60 days after submission of the PFC, the ANDA generally will not be eligible for the shorter goal date.

After submission of your ANDA, FDA will determine whether the ANDA meets the criteria described in the Prioritization MAPP. Additionally, you should submit a signed certification statement in your submission stating that no changes have been made to the pre-submitted facility information. In order to remain eligible for an eight-month priority review GDUFA goal date, the ANDA must meet the criteria in the Prioritization MAPP and the information submitted in the PFC must remain unchanged in the ANDA amendment, apart from the limited exceptions specified in Section 801 of FDARA.

If you have questions, contact Kimberly McCullough, Regulatory Project Manager, at (240) 402-9021.

Sincerely,

{See appended electronic signature page}

Kimberly McCullough
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Kimberly McCullough

Digitally signed by Kimberly McCullough
Date: 7/09/2019 11:37:50AM
GUID: 525d9c4900038bd46a3ecdae8355361b

ANDA 211097

POST-CRL MEETING REQUEST
PRELIMINARY RESPONSES

Apotex Corp.
U.S. Agent for Apotex Inc.
2400 North Commerce Parkway, Suite 400
Weston, FL 33326
Attention: Kiran Krishnan
Senior Vice President, Global Regulatory Affairs

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) received for review on December 29, 2017, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Teriparatide Injection, 600 mcg/2.4 mL (250 mg/mL) in prefilled delivery device (pen).

Further reference is made to our Meeting Request Granted –Teleconference letter dated November 30, 2018.

Enclosed are our preliminary responses to the questions contained in your post-complete response letter meeting request dated November 9, 2018.

If you have any questions, call Kimberly McCullough, Regulatory Project Manager at (240) 402-9021.

Sincerely,

{See appended electronic signature page}

Kimberly McCullough
Regulatory Project Manager
Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research

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U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20903
www.fda.gov

Kimberly McCullough

Digitally signed by Kimberly McCullough
Date: 12/22/2018 12:08:35AM
GUID: 525d9c4900038bd46a3ecdae8355361b

ANDA 211097

DISCIPLINE REVIEW LETTER

Apotex Corp.
U.S. Agent for: Apotex Inc.
2400 N. Commerce Parkway
Suite 400
Weston, FL 33326
Attention: Kiran Krishnan, Ph.D.
Senior Vice President – Global Regulatory Affairs

Dear Dr. Krishnan:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on December 29, 2017, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Teriparatide Injection, 600 mcg/2.4 mL (250 mg/mL) in prefilled delivery device (pen).

We have concluded the Bioequivalence review of this ANDA and have not identified any deficiencies at this time. However, please be advised that we may have concerns relating to your human factors study.

Please note that we are providing this preliminary determination to you before a complete review of your entire application. As contemplated in the Generic Drug User Fee Amendments of 2017 (GDUFA II) Commitment Letter[1], this preliminary determination does not reflect a complete review of your application and should not be construed as such. In addition, this determination does not necessarily reflect input from supervisory levels. You should be aware that this determination may be modified as we complete our review.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

[1] GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at: https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf).

If you have any questions, please contact Nitin K. Patel, Clinical Project Manager, at Nitin.Patel@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Nitin K. Patel, Pharm.D.
Clinical Project Manager
Division of Clinical Review
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Nitin K.
Patel

Digitally signed by Nitin K. Patel
Date: 6/28/2018 01:12:33PM
GUID: 508da70c00028f695d87f612d0d4cbb6

ANDA 211097

DISCIPLINE REVIEW LETTER

Apotex Corp.
U.S. Agent for Apotex Inc.
2400 North Commerce Parkway
Suite 400
Weston, FL 33326
Attention: Dr. Kiran Krishnan
SVP, Global Regulatory Affairs

Dear Dr. Kiran Krishnan:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on December 29, 2017, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Teriparatide Injection USP, 20 mcg per dose (600 mcg/2.4 mL).

We have concluded the Quality review of this ANDA and have identified the following initial deficiencies:

(b) (4)

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(b) (4)

Your ANDA referenced drug master file (DMF) (b) (4). This DMF was found inadequate to support your submission and a deficiency letter was sent to the DMF holder.

If you would like to respond to these initial deficiencies before the end of this review-cycle, we request a complete written response to this discipline review letter no later than July 30, 2018. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

DISCIPLINE REVIEW LETTER
QUALITY

If you do not submit a complete written response by July 30, 2018, these initial deficiencies may be incorporated in a complete response letter.

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application. As contemplated in the Generic Drug User Fee Amendments of 2017 (GDUFA II) Commitment Letter[1], these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified as we complete our review of your entire application.

If you respond to these issues during this review cycle, depending on the timing of your response, we may not be able to consider your response before taking action on your application.

If you have any questions, please contact Tristen Cook, Regulatory Business Process Manager, at (240) 402-5934.

Sincerely,

{See appended electronic signature page}

Tristen Cook
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

[1] GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at:https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf).

Tristen Cook

Digitally signed by Tristen Cook
Date: 6/27/2018 09:50:35AM
GUID: 58c8475e01d086e16fa31170175bd273

ANDA 211097

INFORMATION REQUEST

Apotex Corp.
U.S. Agent for Apotex Inc.
2400 North Commerce Parkway, Suite 400
Weston, FL 33326
Attention: Kiran Krishnan

Dear Kiran Krishnan:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on December 29, 2017, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Teriparatide Injection USP, 600 mcg/2.4mL (250 mcg/mL) prefilled pens.

Your submission remains under review, and we require drug product samples in order to complete our Clinical Consultation review.

We request at least 5 samples of the proposed product, and at least 3 samples of the RLD. The proposed product should be affixed with the to-be-marketed immediate container label, or a label that closely resembles the to-be marketed product. For the proposed product, samples with a mocked label, i.e., non-commercially produced, depicting the actual label in both size, shape and font would be acceptable. Whenever possible for the test product, please remove the active drug and replace it with placebo (or a viscosity matched mimic) to prevent accidental drug exposure during evaluation of the test product. Not needed for the RLD samples.

The requested samples should be mailed to the following address:

Nitin K. Patel, Pharm.D.
Senior Regulatory Project Manager
Division of Clinical Review
Office of Generic Drugs
Center for Drug Evaluation and Research, FDA
Bldg. 75, Room 2510
10903 New Hampshire Ave,
Silver Spring, MD 20993

We request a response no later than March 19, 2018.
This request is separate from any request for samples that may come to you from the Office of Pharmaceutical Quality.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
CLINICAL
REFERENCE # 21194937

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

If you have any questions, please contact the Clinical Project Manager, at Nitin.Patel@fda.hhs.gov.

Please also confirm receipt of this letter.

Sincerely,

Nitin K. Patel, Pharm.D.
Clinical Project Manager
Division of Clinical Review
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 211097

DISCIPLINE REVIEW LETTER

Apotex Corp.
U.S. Agent for: Apotex Inc.
2400 N. Commerce Parkway
Suite 400
Weston, FL 33326

Attention: Kiran Krishnan, Ph.D.
Senior Vice President – Global Regulatory Affairs

Dear Dr. Krishnan:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on December 29, 2017, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Teriparatide Injection, 600 mcg/2.4 mL (250 mg/mL) in prefilled delivery device (pen).

We have concluded the Labeling review of this ANDA and have identified the following initial deficiencies:

(b) (4)

2. CARTON LABELING

(b) (4)

   b. Please confirm that the lot number and expiration date will appear on the carton labeling.

3. MEDICATION GUIDE
   Add the phonetic spelling of the established name in the Title in accordance with 21 CFR 208.20(b)(1).

4. USER MANUAL
   a. Throughout the User Manual labeling, please revise to use red text to increase prominence of the important information (e.g., paragraph beginning with “The teriparatide injection delivery device contains…”, “Do

not transfer teriparatide injection…", "Wash your hands…" among other things) in accordance with the RLD.

b. We recommend that you include the title of each step (e.g., 1 Pull off pen cap, 2 Attach new needle, etc.) to be inside the box to clearly delineate each step. We refer you to the RLD.
c. Troubleshooting section: Please add a blue colored boxing around the paragraph beginning with "You can prevent this problem by always using a NEW needle…" to increase prominence of the important information and to be in accordance with the RLD.
d. Include the revision date.

If you would like to respond to these initial deficiencies before the end of this review-cycle, we request a complete written response to this discipline review letter no later than March 20, 2018. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

DISCIPLINE REVIEW LETTER
LABELING
REFERENCE # 20991197

If you do not submit a complete written response by March 20, 2018, these initial deficiencies may be incorporated in a complete response letter.

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application. As contemplated in the Generic Drug User Fee Amendments of 2017 (GDUFA II) Commitment Letter[1], these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified as we complete our review of your entire application.

If you respond to these issues during this review cycle, depending on the timing of your response, we may not be able to consider your response before taking action on your application.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

[1] GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at: https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf).

If you have any questions, please contact Julie Call, Labeling Project Manager, at julie.call@fda.hhs.gov or 240-402-8598.

Sincerely,

{See appended electronic signature page}

Julie Call, PharmD
Labeling Project Manager
Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

Julie
Call

Digitally signed by Julie Call
Date: 3/06/2018 02:43:58PM
GUID: 525d9e9d00038c406bce70608a211ab1

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 211097

INFORMATION REQUEST

Apotex Inc.
c/o Apotex Corp
Attention: Kiran Krishnan
SVP, Global Regulatory Affairs
2400 North Commerce Parkway
Suite 400
Weston, FL 33326

Dear Kiran Krishnan:

Please refer to your Abbreviated New Drug Application (ANDA) dated December 29, 2017, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Teriparatide Injection, Solution USP, 20 mcg/dose.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response, no later than March 2, 2018, in order to continue our evaluation of your ANDA.

A. **Other**

1. In your submission, you have provided a statement that the 21CFR 820.20 procedures as they relate to the subject submission are in compliance requirements of the regulation. However, you have not provided a summary of the management control procedures to support the fulfillment of the requirement of 21CFR 4.4(b)(1). In addition, it is not clear from your submission which firm has ultimate responsibility for the combination product. Please provide a summary of the organizational structure of all firms involved in the development and manufacture of the combination product and explain how all levels of the organization are controlled (i.e. agreements).

2. In your submission, you provided the document "Technical Considerations for (b) (4), developed for Apotex Inc., and Intended for Use with Teriparatide Injection". This document addresses design considerations for the combination product; however, upon review of the document, several items of additional information are required to address the requirements of 21CFR 820.30.

a. In your submission, you provided documentation of the design process which indicates that (b) (4) developed the design. However, it is not clear whether this firm is responsible for addressing the requirements of 21CFR 820.30. Please clarify which firm is responsible for development and implementation of design control procedures for the combination product.
b. Please explain how you utilized the design control process to develop the combination product under review and provide a description of your design control procedures. The procedures description must include how requirements for design and development planning, design input, design output, design review, design verification, design validation, design transfer, design changes, and design history file are fulfilled. Provide a copy or a summary of the plan used to design the combination product.
c. In your submission, you have noted that elements of design verification/validation are not completed, including biocompatibility, and pen cap compatibility with needles. Please clarify the status of those activities, and clarify if any additional verification/validation is required because of the change. Please also state when all verification/validation activities will be completed.

Please note, as with the other items, the statement of compliance with the 820.30 regulation is not adequate to address the requirement. Documentation as requested above is needed to review compliance to 21CFR 4.4(b)(1)

3. In your submission, you have provided a statement of conformity with 21CFR 820.50. However, you have not provided a summary of procedures related to supplier controls. Please provide a summary of the procedure(s) for purchasing controls. The summary should:
    a. Describe your supplier evaluation process and describe how it will determine type and extent of control you will exercise over suppliers.
    b. Define how you maintain records of acceptable suppliers and how you address the purchasing data approval process.
    c. Explain how you will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use.

    Please explain how the procedure(s) will ensure that changes made by contractors/suppliers will not affect the final combination product. Provide a description of how you apply the purchasing controls to the suppliers/contractors used in the manufacturing of the combination product. (e.g., through supplier agreement).

    Please provide these procedures as they relate to all facilities that are subject to 21CFR 820.50, including finished device/combination product contract manufacturers.

4. In your submission, you have provided a statement of conformity with 21CFR 820.100. However, you have not provided a summary of relevant procedures that satisfy this requirement. Please summarize the procedure(s) for your Corrective and Preventive Action (CAPA) System. The CAPA system should require:

a. Identification of sources of quality data and analysis of these data to identify existing and potential causes of nonconforming practices and products;
b. Investigation of nonconformities and their causes;
c. Identification and implementation of actions needed to correct and prevent recurrence of nonconformities; and
d. Verification or validation of the actions taken.

Please summarize these procedures as they relate to all facilities that are affected by implementation of the CAPA system including contract specification developers and contract manufacturers.

If you do not submit a complete response by March 2, 2018, the review will be closed and the listed deficiencies will be incorporated in a COMPLETE RESPONSE correspondence.

Please note, if information or data submitted exceeds the data requested in the IR/ECD this may result in conversion to a Tier 2 Unsolicited Amendment (i.e., an amendment with information not requested by FDA).

If the submitted data is determined to be a tier 2 unsolicited amendment, this may affect the goal date.

All items listed on this Information Request shall be addressed in its entirety, any partial or incomplete response will not be reviewed and the same deficiency list will be issued to you again as part of the Complete Response Letter issued by OGD. Please note that a commitment to address an item in the future is not considered satisfying the Information Request.

Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
QUALITY

If you have any questions, please contact Tristen Cook, Regulatory Business Process Manager, at 240-402-5934.

Sincerely,

{See appended electronic signature page}

Tristen Cook
Regulatory Business Process Manager
Office of Program and Regulatory Operations

Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Appears this way on original

Tristen Cook

Digitally signed by Tristen Cook
Date: 2/16/2018 02:53:31PM
GUID: 58c8475e01d086e16fa31170175bd273

ANDA 211097

PARAGRAPH IV ACKNOWLEDGEMENT
ANDA RECEIPT

Apotex Corp.
U.S. Agent for Apotex Inc.
2400 North Commerce Parkway, Suite 400
Weston, FL 33326
Attention: Kiran Krishnan

Dear Kiran Krishnan:

This is in reference to your abbreviated new drug application (ANDA) submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). The Food and Drug Administration (FDA or the Agency) has made a threshold determination that this ANDA is substantially complete. This ANDA is received for review.

NAME OF DRUG: Teriparatide Injection USP, 600 mcg/2.4mL (250 mcg/mL) prefilled pens

DATE OF APPLICATION: December 29, 2017

DATE (RECEIVED) ACCEPTABLE FOR REVIEW: December 29, 2017

Reference is made to the information request dated February 8, 2018 and to any amendments thereafter.

You have filed a paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and section 505(j)(2)(A)(vii)(IV) of the FD&C Act. Please note that you must comply with the notice requirements, as outlined below.

NOTICE OF CERTIFICATION

You must send notice of your paragraph IV certification on or after the date you receive this paragraph IV acknowledgment letter from FDA, but not later than 20 days after the date of the postmark, as defined in 21 CFR 314.3, on this paragraph IV acknowledgment letter.

Send notice by U.S. registered or certified mail, return receipt requested, or by a designated delivery service (as described in 21 CFR 314.95(g)) to each of the following persons:

(1) Each owner of the patent(s) or the representative(s) designated by the owner to receive the notice.

(2) The holder of the approved new drug application (NDA) under section 505(b) of the FD&C Act for the listed drug that is claimed by the patent and for which the applicant is seeking approval, or, if the NDA holder does not reside or maintain a place of

business within the United States, the NDA holder's attorney, agent, or other authorized official.

An applicant may send notice by an alternate method only if FDA has agreed in advance that the method will provide an acceptable form of documentation.

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the FD&C Act, and the notice must include, but is not limited to, the following information:

(1) A statement that FDA has received an ANDA submitted by the applicant containing any required bioavailability or bioequivalence data or information.
(2) The ANDA number.
(3) A statement that the applicant has received the paragraph IV acknowledgment letter for the ANDA.
(4) The established name, if any, as defined in section 502(e)(3) of the FD&C Act, of the proposed drug product.
(5) The active ingredient, strength, and dosage form of the proposed drug product.
(6) The patent number and expiration date of each listed patent for the reference listed drug alleged to be invalid, unenforceable, or not infringed.
(7) A detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid, unenforceable, or will not be infringed. The applicant must include in the detailed statement:
    a. For each claim of a patent alleged not to be infringed, a full and detailed explanation of why the claim is not infringed.
    b. For each claim of a patent alleged to be invalid or unenforceable, a full and detailed explanation of the grounds supporting the allegation.
(8) If the applicant alleges that the patent will not be infringed and the applicant seeks to preserve the option to later file a civil action for declaratory judgment in accordance with section 505(j)(5)(C) of the FD&C Act, then the notice must be accompanied by an offer of confidential access to the ANDA for the sole and limited purpose of evaluating possible infringement of the patent that is the subject of the paragraph IV certification.
(9) If the applicant does not reside or have a place of business in the United States, the name and address of an agent in the United States authorized to accept service of process for the applicant.

See 21 CFR 314.95.

DOCUMENTATION OF TIMELY SENDING AND RECEIPT OF NOTICE

Within 30 days after the last date on which notice was received by a person described in 21 CFR 314.95(a), you must submit an amendment to this ANDA with the following:

- In accordance with 21 CFR 314.95(b)(3), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that the notice met the content requirements under 314.95(c). A copy of the notice itself need not be provided to the Agency.

- In accordance with 21 CFR 314.95(e), provide documentation that the notice was sent on a date that complies with the timeframe required by 314.95(b) or (d) and a dated printout of the entry for the reference listed drug in FDA's "Approved Drug Products With Therapeutic Equivalence Evaluations" that includes the patent that is the subject of the paragraph IV certification. FDA will accept, as adequate documentation of the date the notice was sent, a copy of the registered mail receipt, certified mail receipt, or receipt from a designated delivery service (as described in 314.95(g)). FDA will accept as adequate documentation of the date of receipt a return receipt, signature proof of delivery by a designated delivery service, or a letter acknowledging receipt by the person provided the notice. An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.
- A designation on the cover page of the submission should clearly state "PATENT AMENDMENT".

NOTIFICATION OF FILING OF LEGAL ACTION

You must submit an amendment to your ANDA within 14 days of the filing of any legal action filed within 45 days of receipt of the notice of paragraph IV certification by any recipient. See 21 CFR 314.107(f)(2). The notification to FDA of the legal action must include:

(1) The ANDA number.
(2) The name of the ANDA applicant.
(3) The established name of the drug product or, if no established name exists, the name(s) of the active ingredient(s), the drug product's strength, and dosage form.
(4) A statement that an action for patent infringement, identified by court, case number, and the patent number(s) of the patent(s) at issue in the action, has been filed in an appropriate court on a specified date.

If a legal action is not filed within 45 days of receipt of the notice of paragraph IV certification by any recipient, please submit an amendment to your ANDA immediately after the 45 day period elapses stating that no legal action was taken by each person provided notice.

NOTIFICATION OF COURT ACTIONS OR WRITTEN CONSENT TO APPROVAL

You must submit an amendment to your ANDA within 14 days of the date of entry by the court of an action described in the following list, the date of appeal or expiration of the time for appeal, or the date of written consent to approval, as applicable. See 21 CFR 314.107(e). The amendment must include, as applicable:

(1) A copy of any judgment by the court (district court or mandate of the court of appeals) or settlement order or consent decree signed and entered by the court (district court or court of appeals) finding a patent described in 314.107(b)(3) invalid, unenforceable, or not infringed, or finding the patent valid and infringed.
(2) Written notification of whether or not any action by the court has been appealed within the time permitted for an appeal.
(3) A copy of any order entered by the court terminating the 30-month or 7½-year period as described in 314.107(b)(3)(i), (b)(3)(ii), (b)(3)(vii), or (b)(3)(viii).

(4) A copy of any written consent to approval by the patent owner or exclusive patent licensee described in 314.107(b)(3)(vi).
(5) A copy of any preliminary injunction described in 314.107(b)(3)(v) and a copy of any subsequent court order lifting the injunction.
(6) A copy of any court order pursuant to 35 U.S.C. 271(e)(4)(A) ordering that an ANDA may be approved no earlier than the date specified (irrespective of whether the injunction relates to a patent described in 314.107(b)(3)).

If you have further questions, you may contact the Patent and Exclusivity Team at CDER-OGDPET@fda.hhs.gov.

This originial ANDA is subject to the provisions of the Generic Drug User Fee Amendments of 2017 (GDUFA II). The GDUFA goal date for review of this standard review ANDA is October 28, 2018.

A drug with a name recognized in the USP National Formulary (USP–NF) generally must comply with applicable compendial standards or the drug will be deemed adulterated, misbranded, or both. (See section 501(b) and 502(e)(3)(b) and (g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act); also 21 CFR 299.5(a) and (b)). Such drugs must also comply with compendial standards for strength, quality, and purity, unless labeled to show all respects in which the drug differs or they will be deemed adulterated. (See section 501(b) of the FD&C Act and 21 CFR 299.5(c)). If the proposed specifications for your product do not conform with an applicable official USP monograph, you are advised to contact USP upon receipt of this Acknowledgement Letter to initiate a monograph revision through the USP Pending Monograph Process (PMP). Please note that initiation of the PMP does not mean that the proposed specifications will necessarily be approved by FDA; revisions to the USP monograph will be contingent upon FDA approval of the proposed specifications in this application.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

Please identify any related communications with the ANDA number referenced above. If you have any questions, contact Dat Doan, Project Manager Team Leader, at Dat.Doan@FDA.HHS.GOV[1] or 240-402-8926. We also recommend that you sign up for Generic Drug e-mail updates,[2] which provide updates and information generally related to generic drug regulation.

Sincerely,

{See appended electronic signature page}

Bankim Patel, RPh
Team Leader
Division of Filing Review
Office of Regulatory Operations
Office of Generic Drugs

[1] A secure email address is recommended for applicants to utilize when communicating with the Agency. If you have not already established a secure email with FDA, you may send a request for a secure email address to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications. Formal regulatory submissions must be submitted according to FDA regulations and current guidances.

[2] https://service.govdelivery.com/accounts/USFDA/subscriber/new?topic_id=USFDA_476

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Bankim Patel

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