CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218771Orig1s000

OTHER REVIEW(S)

MEMORANDUM

COMPARATIVE USE HUMAN FACTORS STUDY REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

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 03, 2024
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	NDA 218771
Product Name, Dosage Form, and Strength:	teriparatide injection, (b) (4) (250 mcg/mL)
Device Constituent:	Prefilled pen
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Almaject Inc. (Almaject)
FDA Received Date:	August 4, 2023
OSE TTT #:	2024-9688
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Associate Director of Human Factors:	Ariane O. Conrad, PharmD, BCACP, CDCES, FISMP

1 REASON FOR REVIEW

On August 4, 2023, Almaject submitted a new drug application (NDA) for teriparatide injection, (b) (4) (250 mcg/mL) as therapeutically equivalent (TE) to the listed drug (LD) Forteo (NDA 021318) through the 505 (b)(2) pathway. Almaject crossed-referenced the comparative use human factors study results (CUHF) previously submitted and reviewed under (b) (4) (b) (4) which is the focus of this review.[b] Of note, Almaject is an affiliated company of Alvogen, Inc; thus, Alvogen submitted a letter of authorization to authorize Almaject to "*rely upon or otherwise use*" all relevant modules of NDA 211939 for Bonsity.[cd]

2 BACKGROUND AND DISCUSSION

Teriparatide is a parathyroid hormone analog with a pre-filled pen device constituent part that is intended for the same indications as the LD Forteo:

- 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.

Alvogen Inc., previously submitted the following documentation for CUHF studies under NDA 211939 which is being referenced to Almaject's Teriparatide Injection, (b) (4) 505(b)(2) application pathway:

- Bonsity was approved under a new drug application (NDA) on October 4, 2019, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act.
- (b) (4)

(b) (4)

[b] Sachdeva, J. Reviewers Guide for Teriparatide injection NDA 218771. Morristown (MD); 2023 AUG 04.

[c] Sachdeva, J. Letter of Authorization for Almaject to cross reference to NDA 211939 Teriparatide injection. NDA 211939. Morristown (MD); 2023 JUL 27.

[d] Sachdeva, J. Cover Letter for Teriparatide injection NDA 218771. Morristown (MD); 2023 AUG 04.

(b) (4)

- (b) (4)
- On July 27, 2023, Alvogen submitted a letter of authorization, authorizing Almaject, Inc. to rely upon or otherwise use all relevant modules of NDA 211939 along with any amendments, supplements and annual reports in connection with their NDA.[i]
- On August 4, 2023, Almaject submitted NDA 218771 for teriparatide injection (b) (4) (b) (4) (250 mcg/mL) as TE to the LD Forteo (NDA 021318) through the 505 (b)(2) pathway. Almaject crossed-referenced the product description information and all studies including the CUHF study results submitted under (b) (4) (b) (4)

  Almaject indicated that the proposed product is the same as the FDA-approved product (teriparatide injection) under Alvogen, Inc.'s NDA 211939 in terms of product description, formulation, chemistry, manufacturing and controls information and the clinical and nonclinical studies. Almaject indicated that the only differences between the referenced Bonsity NDA 211939 and their proposed NDA 218771 are in the labeling and additional immunogenicity and analytical bridging studies to support a TE rating to the listed drug, Forteo.[k]

Regarding the user interface, specifically the instructions for use (IFU), carton labeling and container label, we note the only differences between the IFU, carton labeling, and container label used in the CUHF study and the proposed IFU, carton labeling, and container label are the differences in the product name (Bonsity *versus* Teriparatide), Applicant's name and contact information. We determined that these differences are minor; thus, they are unlikely to impact the results of the previously reviewed CUHF study. As such, we determined that our findings for

(b) (4)

[i] Sachdeva, J. Letter of Authorization for Almaject to cross reference to NDA 211939 Teriparatide injection. NDA 211939. Morristown (MD); 2023 JUL 27.

(b) (4)

[k] Sachdeva, J. Reviewers Guide for Teriparatide injection NDA 218771. Morristown (MD); 2023 AUG 04.

the CUHF results (b) (4) are appropriate to apply for NDA 218771. Thus, we maintain our determination that the CUHF study results confirm that the differences in the user interface between the proposed teriparatide PFP and Forteo pen are acceptable and that the proposed teriparatide PFP product can be substituted with the full expectation that it will produce the same clinical effect and safety profile as Forteo under the conditions specified in the labeling.[l] As such, we have no HF recommendations for this NDA.

Additionally, we note that the DMEPA 1 nomenclature and labeling review team evaluated product specific label and labeling under separate covers.[m n o]

3 CONCLUSION

Based on the aforementioned information, we maintain the CUHF study results (b) (4) confirm that the differences in the user interface between the proposed teriparatide PFP and Forteo pen are acceptable and that the proposed teriparatide PFP product can be substituted with the full expectation that it will produce the same clinical effect and safety profile as Forteo under the conditions specified in the labeling. As such, we have no HF recommendations for this NDA.

(b) (4)

[m] Yevgeniya, Y. Label and Labeling Packaging Review for teriparatide, injection, (b) (4) mcg (NDA 218771). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 DEC 22. TTT ID #.: 2023-5837.

[n] Yevgeniya, Y. Revised Label and Labeling Packaging Review for teriparatide, injection, (b) (4) mcg (NDA 218771). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 JAN 18. TTT ID #.: 2023-5837-1.

[o] Yevgeniya, Y. Revised Label and Labeling Packaging Review for teriparatide, injection, (b) (4) mcg (NDA 218771). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 MAY 30. TTT ID #.: 2023-5837-1.

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/s/

OLUWAMUREWA OGUNTIMEIN
06/03/2024 05:45:03 PM

ARIANE O CONRAD
06/03/2024 06:00:33 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	May 31, 2024
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	NDA 218771
Product Name, Dosage Form, and Strength:	teriparatide injection, 600 mcg/2.4 mL (250 mcg/mL)
Applicant Name:	Almaject, Inc.
FDA Received Date:	May 31, 2024
TTT ID #:	2023-5837-2
DMEPA 1 Safety Evaluator:	Yevgeniya Kogan, PharmD, BCSCP
DMEPA 1 Associate Director for Nomenclature and Labeling:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

Almaject, Inc. submitted revised container label and carton labeling received on May 31, 2024 for teriparatide injection. The Division of General Endocrinology (DGE) requested that we review the revised container label and carton labeling for teriparatide injection (Appendix A) to determine if they are acceptable from a medication error perspective. We note that DGE sent Almaject, Inc. an Information Request (IR) on May 6, 2024 via email on behalf of CMC notifying the sponsor that the drug substance (b) (4) (b) (4) and removed (b) (4) as requested. The revisions reflect the removal (b) (4) as well as the recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

Almaject, Inc. implemented all of our recommendations and we have no additional recommendations at this time.

[a] Kogan,Y. Label and Labeling Review for teriparatide injection (NDA 218771). Silver Spring (MD): FDA, CDER, OSE, DMEPA1 (US); 2024 May 30. TTT ID: 2023-5837-1.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

YEVGENIYA M KOGAN
06/03/2024 03:44:05 PM

IDALIA E RYCHLIK
06/03/2024 04:35:54 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	May 30, 2024
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	NDA 218771
Product Name, Dosage Form, and Strength:	teriparatide injection, (b) (4) (250 mcg/mL)
Applicant Name:	Almaject, Inc.
FDA Received Date:	April 2, 2024
TTT ID #:	2023-5837-1
DMEPA 1 Safety Evaluator:	Yevgeniya Kogan, PharmD, BCSCP
DMEPA 1 Associate Director for Nomenclature and Labeling:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

Almaject, Inc. submitted revised container label and carton labeling received on April 2, 2024 for teriparatide injection. The Division of General Endocrinology (DGE) requested that we review the revised container label and carton labeling for teriparatide injection (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

Almaject, Inc. implemented all of our recommendations, however we have additional recommendations for Almaject, Inc to consider in order to further improve the carton labeling from a medication error perspective.

3 RECOMMENDATIONS FOR ALMAJECT, INC.

A. Carton Labeling

1. Relocate the statement "Date of first use __/__/__. Discard unused portion 28 days after first use" to the back panel to decrease the PDP clutter and increase the prominence of critical information.
2. The PDP includes redundant product information that is also located on the back panel and detracts the reader's attention from more important product information (e.g., proper name, strength)
    a. Remove the statement "Refrigerate/DO NOT FREEZE" from the PDP as it is already on the back panel.
    b. Remove the statement "DO NOT transfer content to syringe" from the PDP it is already on the back panel.
3. Adjust formatting of the PDP to assure the eye is drawn to the critical information first (e.g., move the product name and strength to the top half of the PDP) for ease of product identification.

[a] Kogan,Y. Label and Labeling Review for teriparatide injection (NDA 218771). Silver Spring (MD): FDA, CDER, OSE, DMEPA1 (US); 2023 Dec 22. TTT ID: 2023-5837.

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/s/

YEVGENIYA M KOGAN
05/30/2024 05:21:20 PM

IDALIA E RYCHLIK
05/31/2024 02:31:19 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

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

Memorandum

Date: May 16, 2024

To: Meghna M. Jairath, Regulatory Project Manager
Division of General Endocrinology Products (DGE)

LaiMing Lee, Associate Director for Labeling (DGE)

From: Meena Savani, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sapna Shah, Team Leader, OPDP

Subject: OPDP Labeling Comments for TERIPARATIDE injection, for subcutaneous use

NDA: 218771

Background:

In response to DGE's consult request dated May 15, 2024, OPDP has reviewed the proposed Prescribing Information (PI) and Medication Guide for original the NDA for TERIPARATIDE injection, for subcutaneous use.

PI and Medication Guide:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on May 6, 2024, and we do not have any comments at this time.

OPDP comments on the proposed Medication Guide/IFU will be sent under separate cover, as a combined OPDP and Division of Medical Policy Programs (DMPP) review.

Thank you for your consult. If you have any questions, please contact Meena Savani at 240-402-1348 or Meena.Savani@fda.hhs.gov.

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/s/

MEENA R SAVANI
05/16/2024 11:37:44 AM

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

PATIENT LABELING REVIEW

Date:	May 16, 2024
To:	Meghna Jairath, PharmD Regulatory Project Manager **Division of General Endocrinology (DGE)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Kelly Jackson, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meena Savani, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	Teriparatide Injection
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	NDA 218771
Applicant:	Almaject, Inc.

1 INTRODUCTION

On August 4, 2023, Almaject, Inc. submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 218771 for Teriparatide Injection. The reference listed drug is FORTEO (teriparatide) NDA 021318. The proposed indications are:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture or patients who have failed or are intolerant to other available osteoporosis therapy.
- 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.
- 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.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of General Endocrinology (DGE) on September 12, 2023, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for Teriparatide Injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft Teriparatide Injection MG and IFU received on August 4, 2023, and received by DMPP and OPDP on May 6, 2024.
- Draft Teriparatide Injection Prescribing Information (PI) received on August 4, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 6, 2024.
- Approved FORTEO (teriparatide) comparator labeling dated September 7, 2021.

3 REVIEW METHODS

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

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

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU is consistent with the PI

- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the IFU meets the criteria as specified in both the FDA Guidance for Useful Written Consumer Medication Information (published July 2006) and Instructions for Use-Patient Labeling for Human Prescription Drug and Biological Products (published July 2022)
- ensured that the MG and IFU are consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

KELLY D JACKSON
05/16/2024 12:56:21 PM

MEENA R SAVANI
05/16/2024 01:06:45 PM

MARCIA B WILLIAMS
05/16/2024 01:43:27 PM

LASHAWN M GRIFFITHS
05/16/2024 01:54:04 PM

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM
INJECTOR DEVICE

Date	4/29/2024
To:	OLUWAFUNMIKE AJOMALE
Requesting Center	CDER
From	Bingjie Liang OPEQ/OHT3/DHT3C
Through (Team)	Shruti Mistry, Assistant Director Injection Devices Team OPEQ/OHT3/DHT3C
Subject	ICCR # 00936438 ICC#2300706 Submission # NDA 218771 Sponsor: Almaject, Inc. Drug Name/Indication for Use: Teriparatide [rDNA origin] Injection, (b) (4) mL (0.25 mg/mL) for the 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 of fracture, and treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture.
Recommendation	The finished drug product functionality comparability with Forteo, i.e., dose accuracy, injection force and dose button pull force, have demonstrated that the two products have equivalent functionality performance.

Digital Signature Concurrence Table

Reviewer	Team
Bingjie Liang -S Digitally signed by Bingjie Liang -S Date: 2024.04.29 14:16:28 -04'00'	Shruti N. Mistry -S 2024.04.29 14:19:12 -04'00'

1. PURPOSE/BACKGROUND

This is original application. The sponsor is seeking approval through the 505(b)(2) pathway in order to bring to market a therapeutically equivalent version of Forteo ("Proposed Product") under the new provisions set forth in 21 U.S.C. § 355(j)(7)(A) that require FDA to make therapeutic equivalence determinations at approval for drug products approved through the 505(b)(2) pathway.

OPQ requests CDRH review for this NDA because this is a drug-device combination (Pen injector). The pen injector section references to NDA 211939, Sequence 0001 under a Letter of Authorization. The Device Constituents Parts of the Combination Product were approved for NDA 211939 in consult ICC1801025/Case #00006430 dated Sept 4, 2019, which reviewed sequence 0000 1.2 to sequence 0029.11.1. It is noted that reference to the proprietary name Bonsity does not apply to NDA 218771.

The following revisions would be applied in this application:

• Section 2.3.P.7.2.5.2 Summary of Shelf-life (Storage and Functional Durability) provides information for the long-term aging study to support (b) (4) (b) (4) 24 month shelf life of the assembled product (b) (4). Since this sequence submission, updated stability data has been submitted in RPTX-0193, Performance Testing Summary Report (NDA 211939, Section 3.2.P.7, Sequence 0104) to complete the study indicating all acceptance criteria was met. Reviewer note: This was submitted in the Annual Report (the reporting period: 10/4/2021 to 10/3/2022) received on 12/5/2022. The information was not reviewed per Panorama. The reviewer verified that the updated stability data met all acceptance criteria as the sponsor stated.

• Section 2.3.P.7.2.5.3 Summary of Material Requirements and Biocompatibility Data identifies the pen injector as "passing a biocompatibility evaluation per ISO 10993". Since this sequence submission, RPTX-0297, Biological Evaluation Report (Biocompatibility) of Subassembly Unit (b) (4) was provided in NDA 211939, Section 3.2.R.1.P, Sequence 0004 to support the claim of complying with ISO 10993. Reviewer note: This was reviewed in consult ICC1801025.

• Section 2.3.P.7.2.7 Design Validation identifies a human factors engineering study being completed. The study included a comparison (threshold analysis) to the RLD. Since this sequence's submission a final Comparative Use Human Factors Study (CUHF) Protocol and Report, including a Threshold Analysis Report for Teriparatide Pen Injector and Forteo (RLD), were submitted and accepted in NDA 211939, Section 5.3.5.4, Sequence 0075. This CUHF demonstrated the non-inferiority of the Teriparatide Pen-Injector to the Forteo Pen-Injector. The difference in the data provided in this section regarding the study users identified 15 subjects in the original validation study (sequence 0001), whereas sequence 0075's CUHF was performed with 55 participants (41 as current Forteo [RLD] users and14 current pen-injector users). Reviewer note: In (b) (4) (b) (4)

DMEPA 1 reviewed the CUHF report and concluded in COMPARATIVE USE HUMAN FACTORS STUDY REPORT dated July 20, 2021, that determine that the CUHF study results confirm that the differences in the user interface between the Bonsity PFP and Forteo pen are acceptable and that the proposed Bonsity PFP product can

be substituted with the full expectation that it will produce the same clinical effect and safety profile as Forteo under the conditions specified in the labeling.

(b) (4)

• Table 2.3.P.7-6 provides description of the device subassemblies. Since this sequence submission, an additional (b) (4) was added to the dosing mechanism subassembly. This change made for other variants of (b) (4) manufactured by (b) (4) for multiple customers, and is not relevant to nor will it affect the approved IFU for the Alvogen/Almaject product as either or both (b) (4) (b) (4). For details, refer to NDA 211939, Section 3.2.P.7 in Sequence 0104. Reviewer note: The sponsor submitted an annual report in sequence 0104. In 3.2.P.7 Container Closure System, the sponsor stated that the change to the (b) (4) are minor and are being make as a result of continuous process improvement at the pre-assembly stage and (b) (4) (b) (4) manufactured by (b) (4). These minor changes were not assessed in NDA 211939.

The sponsor stated (b) (4) has performed a series of tests to ensure that the alterations to (b) (4) have no adverse impact to the safety or performance of the pen and it has been concluded that the alterations have no impact on the functional interfaces within the Dosing Mechanism and therefore do not affect the functionality of the pen, the changed (b) (4) has no impact on the final assembly process, and no impact on (b) (4) covered by the current pFMEA.

From a finished drug product pen assembly perspective in the manufacturing process at (b) (4), there was no change in the pen sub-assembly functional specifications and therefore no impact on the final drug product pen assembly process. The above changes are considered cosmetic in nature which will ultimately be masked by the label that is affixed on the final assembled pen.

The Design History Risk files were reviewed by Alvogen which concluded that the change will not impact Hazard Assessment, Use, or Design Failure Mode and Effect files. Further, the external appearance of the pen injector remains unchanged meaning no differences to the users and no additional threshold analyses are warranted.

It is also important to note that the addition of (b) (4) (b) (4) manufactured by (b) (4) for multiple customers, is not relevant to nor will it affect the approved IFU for the Alvogen product as either or both ((b) (4)) can be used as (b) (4) (b) (4).

Based on the above technical assessment, the sponsor stated there is no functional impact on the final assembled pen, the changes are considered minor and annual reportable in nature. The updated performance testing report (Report SPCX-00011) (10082024: (b) (4) Component Specification Dosing Mechanism) is provided in this module. (note: this change was not evaluated in Sequence 0104).

On 09/26/2023, Madhuri Patel from CDER DMEPA commented that the additional (b) (4) is internal change where the end user does not see, touch, or feel, and does not impact a task specified in the IFU, the generally would not except another CUHF study. We have no remaining concern for this change for NDA 218771,

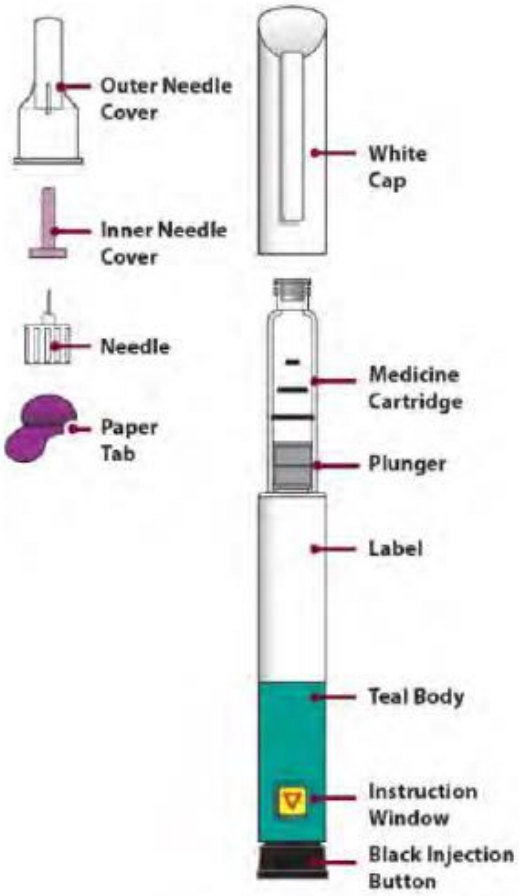
• Section 2.3.P.7.2.10 Quality System identified the current applicant's name, Pfenex, of NDA 211939 for this sequence. The description of the Quality Management System (QMS) in this section also applies to Almaject's QMS streamlined approach and therefore the content for QMS applies to Almaject in NDA 218771.Because Almaject is an affiliated company of Alvogen, Inc. and share company resources, including quality systems and documentation, the previous review on the QMS can be leveraged for NDA 218771.

The purpose of this consult is to evaluate the finished drug product (Pen Injector) functionality comparability with Forteo.

2. DEVICE DESCRIPTION

System and subsystem functional block diagram is provided in Figure 4.3.1.

4.3.1 System and Subsystem Functional Block Diagram



3. DEVICE PERFORMANCE REVIEW

The sponsor is seeking approval to bring to market a therapeutically equivalent version of Forteo. The sponsor simply refers Drug Product and Container Closure to NDA 211939, sequence 0001 but did not provide the pen injector functionality comparability with Forteo.

The following additional information request was sent to the sponsor through the CDER RPM on 11/17/2023. The sponsor requested the extension to respond from 11/27/23 to 11/29/2023. The extension request was granted on 11/27/2023.

- You are seeking approval through the 505(b)(2) pathway in order to bring to market a therapeutically equivalent version of Forteo ("Proposed Product"), We were unable to locate the finished drug product (Pen Injector) functionality comparability with Forteo. Please detail where in your submission you have included these data or provide the finished drug product functionality comparability with Forteo.

In the response received on 11/28/2023 in sequence 0006, the sponsor provided the dose accuracy analysis of Alvogen/Almaject Teriparatide Injection test results and compares them statistically against FORTEO®. However, the sponsor did not provide other two Essential Performance Requirements (EPRs), i.e., Injection Force and Dose Button Pull Force. The following additional information was sent to the sponsor through the CDER RPM on 12/15/2023 and the sponsor was granted the response extension from 12/22/2023 to 1/15/2024 due to being short-staffed during the holiday at the contact lab. The response was received on 1/12/2024 in sequence 0008.

- In the 11/28/2023 response, you provided the analysis of dose accuracy performance of Almaject Teriparatide Injection and compared them statistically against FORTEO®. However, you did not provide the functional comparability for other Essential Performance Requirements, i.e., Injection Force, to ensure that the subject product meets its intended use to support interchangeability with the pen injector used in the reference listed drug (RLD) FORTEO®. Please provide the Almaject Teriparatide Pen Injector functional comparability of Injection Force and Dose Button Pull Force, which are included in the release specification, with FORTEO®, and refer to the FDA Guidance titled Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products issued in June 2013 (https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm147095.pdf) for more details.

3.1 Dose Accuracy comparability with Forteo

The finished product dose accuracy specification is shown below. For batch-release testing, 20 pens, 9 doses per pen (3 beginning, 3 middle, and 3 end of pen) are tested for dose accuracy.

Dose accuracy: (b) (4) µL[a] with k upper NLT (b) (4) and k lower NLT Number of doses delivered = (b) (4)

In the consult ICC1801025 for NDA 211939, it was stated that the proposed dose accuracy specification is the same as the RLD product. The lot release specification was lowered from (b) (4) requirements of (b) (4)% reliability/confidence to (b) (4)% reliability/confidence based on the risk-based justifications. Considering the two major aspects of the product, i.e., indication and duration of therapy, a (b) (4)% probability content will not change the overall risk/benefit assessment versus the (b) (4)% probability content. I agree that a (b) (4)% reliability/confidence is acceptable for dose accuracy at lot release.

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or the analysis of FORTEO® Dose Accuracy, 12 pens are used, 6 pens from two different lots and 31 doses from each pen. The data is provided in Attachment 1.

For the analysis of Alvogen/Almaject Teriparatide Pen Injector Dose Accuracy, 320 pens are used, 20 pens from 16 different lots, and 9 doses from each pen (First 3 doses, middle 3 doses, and last 3 doses). The data is provided in Attachment 2.

The statistical summary for FORTEO and the subject device are shown in Diagrams 2 and 5. (b) (4)

(b) (4)

Diagram 2: FORTEO® Historgram and Statistical Summary

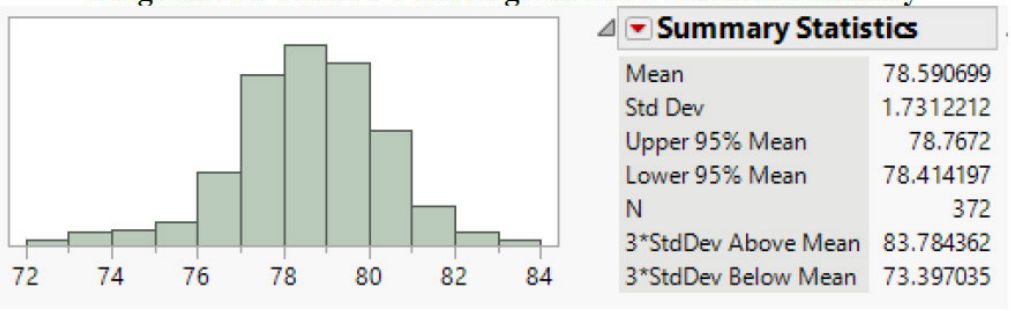
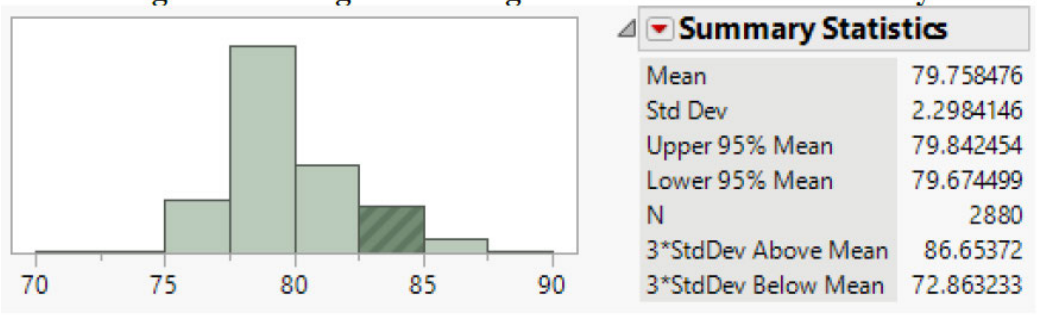


Diagram 5: Alvogen's Historgram and Statistical Summary



The two-sided tolerance limit factors, k, for FORTEO and the subject devices are determined based upon the confidence level ((b)(4)%), probability content ((b)(4)%) and the number of measurements by (b) (4). The population satisfies the requirements for the dose accuracy as shown in the following table, where mean – (k x std dev) ≥ PLSL and mean + (k x std dev) ≤ PUSL for FORTEO and the subject devices, respectively.

	Subject device	FORTEO
specification (µl)	(b) (4)	
PLSL (µl)		
PUSL (µl)		
mean (µl)	79.758476	78.590699
std dev	2.2984146	1.7312212
pen	320	12
dose/pen	9	31
total doses	2880	372
k	(b) (4)	
mean - (k x std dev)		
mean + (k x std dev)		

Notes: P_{LSL} - Lower specification limit; P_{USL} - Upper specification limit

The sponsor also conducted the statistical analysis in Diagrams 3 and 6 and concluded that the dose accuracy of FORTEO and the subject devices are within (b) (4)% error margin and (b) (4)% confidence interval.

Diagram 3: FORTEO® Statistical Test Equivalence to (b) (4)uL ((b) (4)% error margin (b) (4)% CI)

Diagram 6: Alvogen Statistical Test Equivalence to (b) (4) µL (b) (4)% error margin. (b) (4)% CI)

The sponsor provided the comparative use human factor study to evaluate user performance of the critical tasks impacted by the differing external critical design attributes. This report number QF-71-03-51 is included in Attachment 3. The review of the human factors is deferred to CDER/DMEPA.

3.2 Injection Force and Dose Button Full force

The finished drug product (Almaject's Pen Injector) functionality comparability of Injection force and Dose Button Full force with FORTEO® is provided in the technical assessment report, ALV-23-RP-054 in section 5.3.5.4 in sequence 0008.

3.2.1 Injection force comparability with Forteo

The specification for injection force of the final finished combination product is (b) (4) N, which was adequately verified per section 6.3.2 of the consult ICC1801025 for NDA 211939.

For the analysis of FORTEO® Injection Force, 20 pens are used, and 10 measurements from each pen. Data capture details are recorded in (b) (4) 20498 (Attachment 3).

For the analysis of Alvogen/Almaject Injection Force, 24 pens are used, 8 pens from 3 different lots, and 10 measurements from each pen. The data is provided in Attachment 4 – 7.

The summary statistics of FORTEO and the subject devices are shown in Diagrams 12 and 13. The mean of the injection force for the subject devices is comparable to that for FORTEO.

Diagram 12: FORTEO® Histogram and Statistical Summary

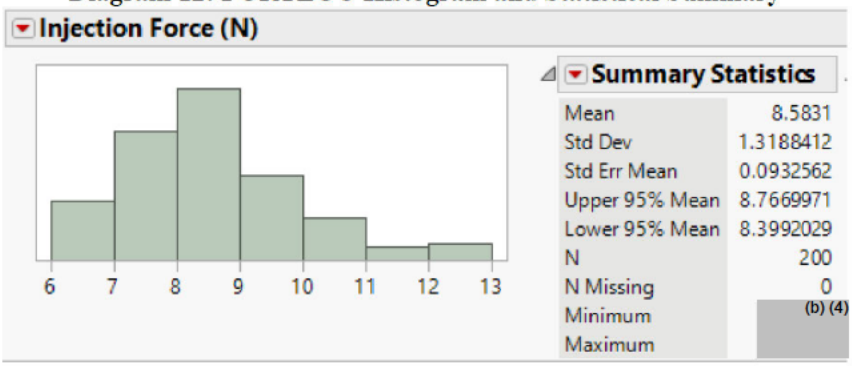
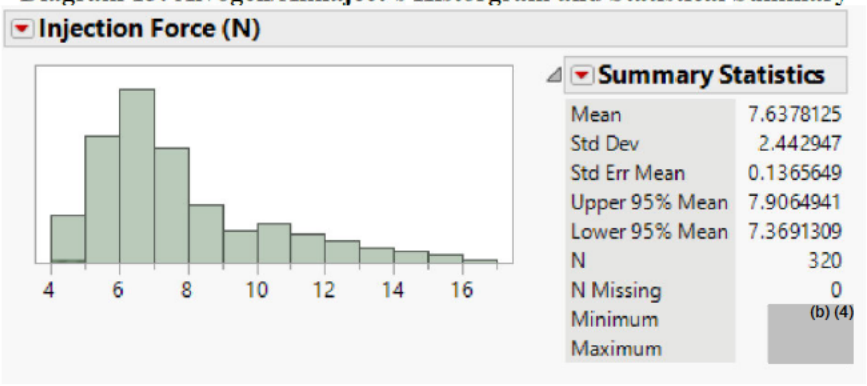


Diagram 13: Alvogen/Almaject's Historgram and Statistical Summary



The one-sided tolerance limit factors, k, for FORTEO and the subject devices are determined based upon the confidence level (b) (4)%), probability content (b) (4)%) and the number of measurements by (b) (4). The population satisfies the requirements for the injection force as shown in the following table, where mean + (k x std dev) ≤ PUSL for FORTEO and the subject devices, respectively.

	Subject device (b) (4)	FORTEO®
specification (N)		
mean (N)	7.6378125	8.5831
std dev	2.442947	1.3188412
pen	24	20
measurement/pen	10	10
total measurements	240	200
k@ (b) (4) % Probability (b) (4) % Confidence	(b) (4)	
mean + (k x std dev)		
acceptance criteria	pass	pass

3.2.2 Dose Button Pull force comparability with Forteo

The specification for Dose Button Pull Force is not more than (b) (4) N for release testing per the consult ICC1801025 for NDA 211939.

For the analysis of FORTEO Dose Button Pull Force, 20 pens are used, and 10 measurements from each pen. Data capture details are recorded in (b) (4) 20498 (Attachment 3).

For the analysis of Alvogen/Almaject Teriparatide Injection Dose Button Pull Force, 32 pens are used, 8 pens from 3 different lots, and 10 measurements from each pen. The data is provided in Attachment 4 - 7.

The summary statistics for the dose button pull force of FORTEO® and the subject devices are shown in Diagrams 9 and 10. The mean of the dose button pull force of the subject device is comparable to that of FORTEO.

Diagram 9: FORTEO® Histogram and Statistical Summary

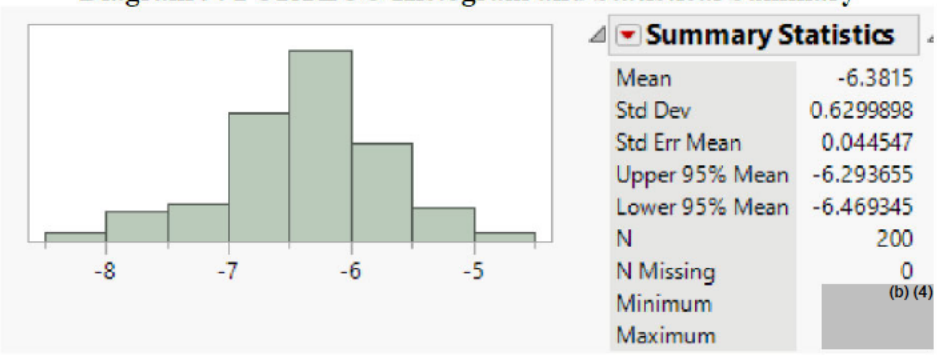
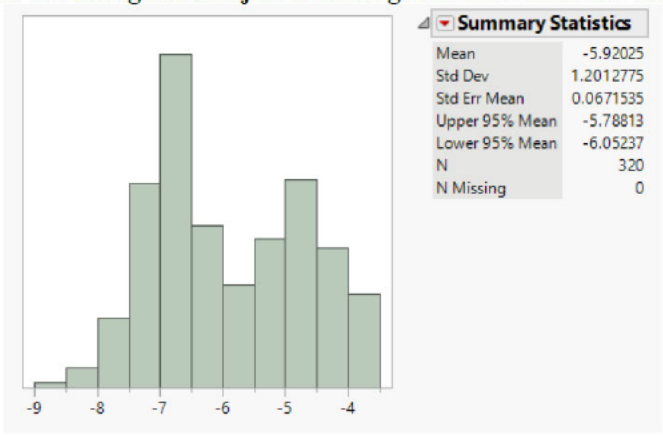


Diagram 10: Alvogen/Almaject's Historgram and Statistical Summary



The one-sided tolerance limit factors, k, for FORTEO and the subject devices are determined based upon the confidence level (b) (4) %), probability content (b) (4) %) and the number of measurements by (b) (4). The population satisfies the requirements for the Dose Button Pull Force as shown in the following table, where mean + (k x std dev) ≤ PUSL for FORTEO and the subject devices, respectively.

	Subject device	FORTEO®
specification (N)	(b) (4)	
mean (N)	5.92025	6.3815
std dev	1.2012775	0.6299898
pen	32	20
measurement/pen	10	10
total measurements	320	200
k@ (b) (4) % Probability (b) (4) % Confidence	(b) (4)	
mean + (k x std dev)		
acceptance criteria	pass	pass

The finished drug product functionality comparability with Forteo, i.e., dose accuracy, injection force and dose button pull force, have demonstrated that the two products have equivalent functionality performance.

<<END OF REVIEW>>

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

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 18, 2024
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	NDA 218771
Product Name, Dosage Form, and Strength:	teriparatide injection, (b) (4) (250 mcg/mL)
Applicant/Sponsor Name:	Almaject, Inc.
TTT ID #:	2023-5837-1
DMEPA 1 Safety Evaluator:	Yevgeniya Kogan, PharmD, BCSCP
DMEPA 1 Acting Team Leader:	Madhuri R. Patel, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label received on January 10, 2024 for teriparatide injection. The Division of General Endocrinology (DGE) requested that we review the revised container label for teriparatide injection (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Kogan,Y. Label and Labeling Review for teriparatide injection (NDA 218771). Silver Spring (MD): FDA, CDER, OSE, DMEPA1 (US); 2024 December 22. TTT ID No.: 2023-5837.

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MADHURI R PATEL
01/18/2024 05:14:02 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

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:	December 22, 2023
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	NDA 218771
Product Name, Dosage Form, and Strength:	teriparatide injection, (b) (4) (250 mcg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Almaject, Inc.
FDA Received Date:	August 4, 2023
TTT ID #:	2023-5837
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP
DMEPA 1 Acting Team Leader:	Madhuri R. Patel, PharmD

1. REASON FOR REVIEW

As part of the approval process for teriparatide injection, the Division of General Endocrinology (DGE) requested that we review the proposed prescribing information (PI), Instruction for Use (IFU), medication guide (MG), and container label and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

NDA 218771 is a 505(b)(2) NDA and the listed drug product is Forteo, NDA 021318.

The sponsor, Almaject is an affiliated company of Alvogen, Inc. which sponsored studies to support the therapeutic equivalent designation between Forteo® and Almaject's Teriparatide Injection, (b) (4). On July 27, 2023 Alvogen submitted a letter of authorization, authorizing Almaject, Inc. to rely upon or otherwise use all relevant modules of NDA 211939 along with any amendments, supplements and annual reports in connection with their New Drug Application.

Alovogen Inc., has previously submitted the following documentation for human factors study under NDA 211939 which is being referenced to Almaject's Teriparatide Injection, (b) (4) 505(b)(2) application pathway:

- Bonsity was approved under a new drug application (NDA) on October 4, 2019 pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act.
- (b) (4)

(b) (4)

(b) (4)

- An information request was submitted to Almaject, Inc. on November 11, 2023 requesting the sponsor to provide finished drug product functionality as compared with FORTEO. Almaject, Inc. responded on November 28, 2023 providing information to demonstrate the interchangeability of teriparatide Pen Injector with the RLD FORTEO device.

2. MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E- N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3. CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI), Instruction for Use (IFU), medication guide (MG), , container label and carton labeling, may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Almaject, Inc.

(b) (4)

4. RECOMMEDATIONS FOR DIVISION OF GENERAL ENDOCRINOLOGY (DGE)

Table 2. Identified Issues and Recommendations for Division of General Endocrinology (DGE)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	The "prefilled" description is missing when describing the pen.	Elimination of "prefilled" could lead to confusion of the device characteristics (i.e., requirement of cartridge)	In Section 3 and 16 consider revising (b) (4) (b) (4) to "single-patient-use prefilled pen(s)".
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	Incomplete description of dosage form.	A description of identifying characteristics of the dosage form is required for the end user to be able to assess product integrity.	Include the description of the dosage form (e.g. "clear and colorless solution"). 21 CFR 201.57©(17)(iii).
2.	We note the carton labeling provides specification of needle size (29-31 gauge). However, this information is not located in the PI.	Inconsistency between the carton and the PI on needle size recommendation.	Consider clarifying/elaborating on needle size in PI and/or IFU
Medication Guide (MG)			
1.	The section "What is Teriparatide Injection?" houses the following statement "Teriparatide injection should not be used in children and young adults whose bones are still growing"	This statement can be missed when consumer looks to section "who should not use Teriparatide injection?" Possibility of inappropriate patient group receiving this medication.	Consider moving the statement from section "What is Teriparatide Injection?" to "Who should not use Teriparatide injection?"
Instructions for Use (IFU)			
	Inconsistent disposal instructions. Some say "after 28 days" which are not in line with PI and MG which say "28 days after first use"	"Dispose device after 28 days" can be interpreted in a variety of ways such (e.g., 28 days of use, 28 days after first receiving the medication, etc.,)	Please consider consistent disposal instructions throughout the labeling as "Dispose of the device 28 days after first use".

5. RECOMMENDATIONS FOR ALMAJECT, INC.

Table 3. Identified Issues and Recommendations for Almaject, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s)			
1.	As currently presented, there is no space for end-user to write the beyond-use date which is the date the product must be discarded.	Since the product has a different beyond-use date after first use, the container label should have a designated space and format for the end-user to write the beyond-use date to minimize the risk of deteriorated drug medication errors	We recommend including space for the end-user to write beyond-use date on the container label after the following statement "Throw away 28 days after first use". For example: "Throw away 28 days after first use. Date of first use ___/___/___.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table presents relevant product information for teriparatide injection that Almaject, Inc. submitted on 8/4/2023, and the listed drug (LD).

Table 4. Relevant Product Information for Listed Drug and teriparatide injection

Product Name	FORTEO[e]	teriparatide injection
Initial Approval Date	11/26/2002	n/a
Active Ingredient	Teriparatide	
Indication	• Treatment of postmenopausal women with osteoporosis at high risk for fracture or patients who have failed or are intolerant to other available osteoporosis therapy. • 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. • 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.	
Route of Administration	subcutaneously	
Dosage Form	Injection	
Strength	600 mcg/2.4 mL (250 mcg/mL)	
Dose and Frequency	20 mcg once daily	
How Supplied	a clear and colorless solution, available as single-patient-use prefilled delivery device (pen)	(b) (4)
Storage	refrigeration at 2° to 8°C (36° to 46°F)	
Container Closure	Prefilled pen	Pen

[e] FORTEO [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 11/26/2021. [cited 11/24/2023]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021318Orig1s056lbl.pdf .

APPENDIX B. PREVIOUS DMEPA REVIEWS

On November 14, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, "teriparatide", "NDA 218771", and "NDA 211939". Our search identified no previous reviews since the date of our last search on October 18, 2022. [f]

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[g] along with postmarket medication error experiences with similar products, we reviewed the following teriparatide labels and labeling submitted by Almaject, Inc..

- Container label(s) received on August 4, 2023
- Carton labeling received on August 4, 2023
- Instructions for Use received on August 4, 2023, available from \\CDSESUB1\EVSPROD\nda218771\0001\m1\us\114-labeling\draft\labeling\almaject-teriparatide-user-manual-draft.pdf
- Medication Guide received on August 4, 2023, available from \\CDSESUB1\EVSPROD\nda218771\0001\m1\us\114-labeling\draft\labeling\almaject-teriparatide-med-guide-draft.pdf
- Prescribing Information received on August 4, 2023, available from \\CDSESUB1\EVSPROD\nda218771\0001\m1\us\114-labeling\draft\labeling\almaject-teriparatide-pi-draft.pdf

[f] Howard, C. Label and Labeling Review for product name (NDA 211939/S-004). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 10/18/2022. OSE RCM No.: 2022-333.

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

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