CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211939Orig1s000

OTHER REVIEW(S)

OFFICE OF DEVICE EVALUATION

DIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL, RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES

GENERAL HOSPITAL DEVICES BRANCH

INTERCENTER CONSULT MEMORANDUM

Date	September 4, 2019
To	Adam Grafton, RPM CDER/OPQ/OPRO/DRBPMI/RBPMBI
Requesting Division	CDER/OPQ
From	Matthew Ondeck CDRH/ODE/DAGRID/GHDB
Through (Team Lead)	Rumi Young, Injection Team Lead CDRH/ODE/DAGRID/GHDB
Through (Branch Chief)	CAPT Alan Stevens CDRH/ODE/DAGRID/GHDB
Subject	Consult for Submission # NDA 211939 ICCR2018-04134 ICC1801025/Case #00006430
Recommendation	Device Constituents Parts of the Combination Product are Approvable

Digital Signature Concurrence Table	
Reviewer	
Team Lead	
Branch Chief	

1. Submission Overview

Table 1. Submission Information	
ICCR # (Lead)	ICCR2018-04134
ICCR SharePoint Link	SP link/Case #00006430
ICC tracking # (Lead)	ICC1801025
Submission Number	NDA211939
Sponsor	PFENEX, Inc.
Drug/Biologic	Teriparatide
Indications for Use	Treatment of postmenopausal women with osteoporosis at high risk for fracture Treatment of men and women with osteoporosis associated with sustained systemic glucocortocoid therapy at high risk for fracture
Device Constituent	Pen injector
Related Files	IND 129196 • ICC1800814 – Lening Shen was the previous lead CDRH reviewer and provided comments specific components of the application that would be needed from a device standpoint.

Table 2. Review Team	
CDER/CBER Lead Review Division	CDER/OPQ/OPRO
Submission RPM	Adam Grafton, RPM
Lead Device Reviewer	Matthew Ondeck CDRH/ODE/DAGRID/GHDB
The CDRH review is being managed under ICC #: ICC1801025	
Below is a list of the Discipline Specific ICCR#, ICC# and CON#. The CON# are under ICC1801025 in CTS.	

Discipline Specific Consults	Reviewer Name (Center/Office/Division/Branch)	ICCR #	ICC #	CON #
Quality Systems/Inspection	Payal Patel (CDRH/OC)	ICCR2018-04137 - SP Link	Same as lead	CON191373

Table 3. Important Dates		
Interim Due Dates	**Meeting Date**	**Due Date**
Filing	CMC: January 16, 2019 OND: January 19, 2019	January 19, 2019
74-Day Letter		
Mid-Cycle		May 15, 2019
Primary Review		August 20, 2019
Action Date		October 7, 2019

2. PURPOSE/BACKGROUND

2.1. Scope

The purpose of this consult to CDRH is to evaluate the approvability of the pen injector system that is to be used with the Teriparatide injection. The scope of this review is to evaluate and provide an approvability recommendation of the device related information that is needed to determine the safety and effectiveness of the combination product. The instructions that were issued in the consult state the following: "*Assess the adequacy of the Autoinjector system from the device perspective to support the approval of the NDA.*"

The subject submission is a 505(b) 2 application that is using NDA 021318, Forteo (Teriparatide) from Eli Lilly .

2.2. Prior Interactions

There is prior involvement with this combination product under the IND 129196. In consult ICC180081, Lening Shen was the previous lead CDRH reviewer and provided comments specific components of the application that would be needed from a device standpoint.

2.3. Indications for Use

Combination Product	Indications for Use
PF708 (Teriparatide Injection)	Treatment of postmenopausal women with osteoporosis at high risk for fracture. Treatment of men and women with osteoporosis associated with sustained systemic glucocortocoid therapy at high risk for fracture
Pen Injector	Delivery of Drug Product

3. ADMINISTRATIVE

3.1. Documents Reviewed

Document Title	Location
Reviewer's Guide for Combination Product (SN0001; 2018Dec07; Original Submission)	0001(1) 1.2
Container Closure System Pen	0001(1) 3.2.P.7
1.11.1 Quality Information Amendment	0004(4) 1.11.1
Justification of Specifications	0001(1) 3.2.P.5.6
Specifications	0001(1) 3.2.P.5.2
Analytical Procedures	0001(1) 3.2.P.5.3
Stability Summary and Conclusions	0001(1) 3.2.P.8.1
RPTX-0193 Summary of Performance Testing PF708 pen injector – (b) (4) May 2018	0001(1) 3.2.P.R
RPTX-0297 Biological Evaluation Report of Assembly Unit (b) (4)	0004(4) 3.2.P.R
RTP- 00049: PF708 Combination Product Version 4.0	0004(4) 3.2.P.R

BONSITY Draft User Manual	0001(1) 1.14.1.3
Quality Information Amendment	0023(23). 1.11.1
Quality Information Amendment	0024(24). 1.11.1
1111-information-amend-quality	0029(29).1.11.1

4. DEVICE DESCRIPTION AND PERFORMANCE REQUIREMENTS

4.1. General Device Description:

The following device is a pen injector comprised of the pre-filled PF708 - teriparatide injection (propriety name Bonsity), cartridge subassembly unit (CSU), and the dose mechanism sub assembly (DMS). The following information italicized in this section is taken from document Container Closure System -Pen [0001(1) 3.2.P.7].

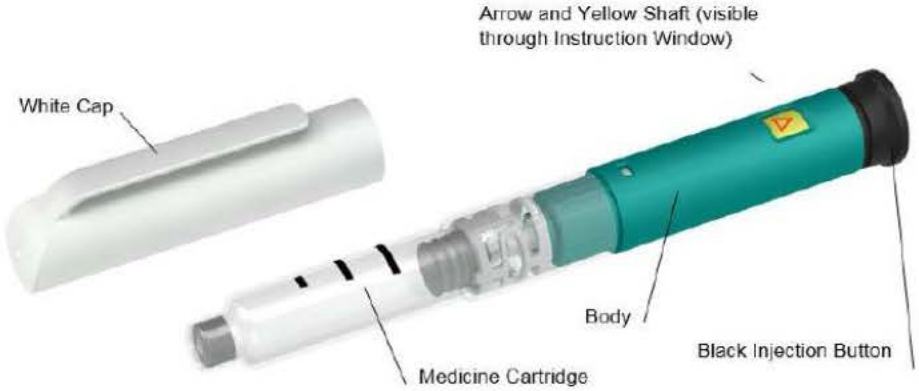
[redacted] (b) (4)

The PF708 drug product pen injector is then packaged and labeled into the PF708 Finished Drug Product (Pen Injector), which is stored at 2°C to 8°C.

The PF708 drug product pen injector is a manually operated "pull and push" type, fixed-dose, multiple-dose, single-patient use, disposable pen injector. It provides subcutaneous injection of multiple, 80-µL fixed doses of teriparatide formulation, that contain 20 mcg of teriparatide in each dose. The PF708 drug product pen injector is designed to administer the doses from an integrated, non-replaceable 3-mL cartridge pre-filled with drug product using commercially available pen needles. The PF708 pen injector contains (b) (4) *full doses. An active stop in the PF708 pen injector prevents the setting of any additional dose after delivery of t* (b) (4) *dose. The patient is instructed to use a dose daily for 28 days. The entire pen injector is to be disposed 28 days after first use.*

The PF708 drug product pen injector utilizes a sterile injection pen needle (not provided) that the user purchases independently upon recommendation by their healthcare provider. The commercially available needles (Becton Dickinson, 29 G to 31 G, Ultrafine pen needles) are compatible with both the RLD and the PF708 drug product pen injector. The PF708 drug product pen injector corresponds to system designation C of the International Organization for Standardization (ISO) 11608-1:2014, which describes a needle-based injection device with integrated non-replaceable container. In accordance with ISO 11608-3: 2012, "Needle-based injection systems for medical use - Requirements and test methods - Part 3: Finished Containers", the integrated, non-replaceable cartridge meets dimensional and performance requirements such that it fits and functions with the pen injector subassemblies to meet ISO 11608-1 performance requirements.

The following is an image of the subject pen injector:



The design is composed of several components. See below:

(b) (4)

Table 3.2.P.7-16. Subassemblies

Sub-assemblies	Description	Function
	Dosing Mechanism Subassembly	Enables dose setting and injection. Pushes forward the cartridge plunger. Gives visible and audible feedback during dose setting and injection.
	Cartridge Subassembly Unit	Cartridge holder: Holds the cartridge in its defined position. Includes the screw thread to attach the needle. Pen cap: Protects the cartridge from light and dust.

4.2. Summary Device Feature/Characteristics Table:

The summary device characteristic are provided below:

Device Characteristic	Subject ANDA Description/Spec
Injector Platform Name	PF708 (teriparatide (b) (4) injection
Priming Dose / Volume	No
Dose accuracy	80 µL
Injection Time	Manual
Injection tissue and depth of injection	Subcutaneous
Audible / visual feedback	Visual (line on injection button is visible pre-injection, not visible post-injection)
Visibility of medication container	Yes
Last Dose Specifications and Safety Features	Last dose – meets ISO 11608-1:2016
Needle Specifications • Length(s) • Gauge(s) • Connection type o ISO 11608-2:2012 o Prestaked	BD 29-31 G ultrafine pen needles ISO 11608-2:2012
Type of Use (e.g. single use, disposable, reusable, other)	Multiple doses, single use pen
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	Self Administration
Injection mechanism (e.g., manual piston, spring, gas, etc.)	(b) (4)
Method of actuation	Manual
Automated Functions	None
Residual Medication	Yes, 80 µL dose (fixed dose), 28 doses per pen
Delivered Volume spec (for single dose or selectable volume range for multidose pens)	meets ISO 11608-1:2016
Environments of use	Home/clinical use
Storage conditions and expiry	Stored in refrigerated conditions, 2°C to 8°C, with pen cap
Graduation marks / fill lines	Fill lines
Safety Features • Needle safety	N/A (Only needle caps for pen needles)

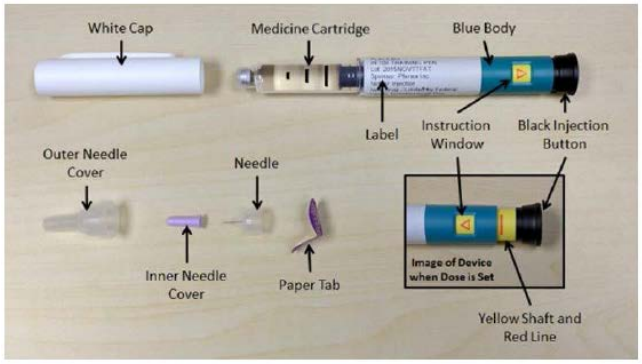
4.3. Steps For Device Use/Comparison to RLD Product:

To support the steps for using the device, the sponsor has provided the use steps and comparison of the RLD device:

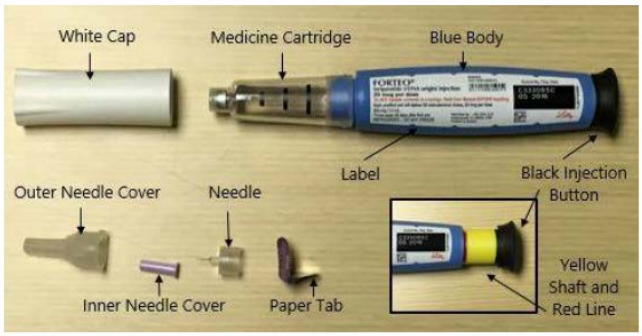
No assembly of PF708 drug product pen injector is required prior to use by the user the PF708 drug product pen injector is pre-assembled and pre-filled with drug product formulation. A priming step is not required prior to PF708 pen injector use. The sequence of steps for the user to administer a dose is:

- Prepare the injection site.
- Remove the white cap.
- Check pen injector, pen injector label, and medication.
- Remove paper tab from sterile needle and attach sterile needle to pen injector.
- Remove the outer needle cover from the sterile needle.
- Set the dose by pulling the black injection button until the red line appears and the red arrow in the instruction window points towards the needle end.
- Remove the inner needle coverInsert the needle into the injection site.
- Inject the dose by pressing down the black injection button until it stops and holding for a count of 5.
- Remove the needle from the injection site.
- Confirm dose completion by observing that the black injection button is pressed down all the way, the yellow shaft is hidden, and the red arrow in the instruction window points towards the injection button.
- Replace the inner needle cover.
- Remove and dispose of the needle.
- Replace the white cap and store pen injector in refrigerator. Do not freeze.

The sponsor states: *the PF708 Finished Drug Product (Pen Injector) is being developed as a therapeutic equivalent to Forteo.* Therefore, they have provided a physical/task comparison between the two devices. See the comparison between the two devices below. Note: since the submission is a 505(b)(2) and not a generic, I do not believe the devices need to be identical to support approval; however the sponsor appears to be supporting the usability of the device (Note: that the sponsor has already provided HF testing, which will be reviewed by CDER/DMEPA) with the comparisons provided below.



Upper Panel:
PF708



Lower Panel:
RLD

Figure 3.2.P.7-3. PF708 Pen Injector and Reference Listed Drug Pen Injector Comparison

The sponsor provided a physical and task comparison to the RLD injector:

Table 3.2.P.7-3. Physical Comparison to Reference Listed Drug

Attribute	Comparison	Conclusion
Pen body	Both pen injectors have the same general shape, though the RLD pen is more ovoid (see *Figure 3.2.P.7-1*).	Minor design differences and no risk to substitution
Pen cap	Both pen injectors have a white cap.	No design differences and no risk to substitution
Cartridge holder	Both pen injectors include a clear glass cartridge, enclosed in a transparent cartridge holder with 3 black lines. The shape of the PF708 cartridge holder is cylindrical compared to the RLD cartridge holder, which is more ovoid.	Minor design differences and no risk to substitution
Injection button	Similarities: Both pen injectors include a black injection button, a yellow shaft, and a red line. Minor design differences: The shape of the injector button on the PF708 pen injector is round compared to RLD's oval button shape. The PF708 pen has an instruction window that provides information on the status of the device, whether the dose is set (arrow pointing toward needle) or injected (arrow pointing toward black injection button). The added instructional element on the PF708 pen reinforces the state of the device; whether the device is ready to inject or that the complete dose has been delivered.	Minor design differences and no risk to substitution

RLD = reference listed drug.

Table 3.2.P.7-4. Task Comparison	
Reference Listed Drug	**PF708**
Prepare the injection site	Same
Remove PF708 pen injector cap	Same
Check device for medication, damage and expiration date	Same
Attach new needle and remove outer needle cover	Same
No priming	Same
Set dose	Same: red line and yellow shaft visible Minor design difference: Arrow points toward threaded end (for needle attachment) of pen injector in PF708 instruction window
Remove inner needle cover	Same
Injection to thigh or abdomen	Same
Confirm dose	Same: red line and yellow shaft are no longer visible Minor design difference: Arrow points toward black injection button in PF708 instruction window
Remove needle	Same
Recap pen injector	Same
Store pen injector in refrigerator	Same
Dispose pen injector 28 days after first use	Same

Reviewer Note:
Since the submission is a 505(b)(2) and not a true generic [505(j)], I do not believe the devices need to be identical to support approval; however the sponsor appears to support the usability of the device as demonstrated in the comparison.

Device Description Recommendation:
The Device Description is adequate

5. DESIGN CONTROL REVIEW

5.1. Design Review Summary

The review provided below is a check to ensure that adequate device related documentation has been provided for review:

Review Section:	Provided (Yes/No)	Location
Device Description • Drawings • Principle of Operation	Yes	Seq 0001(1) 3.2.P.7
Comparison to Clinical Use Device	Yes	Seq 0001(1) 3.2.P.7
Design Comparison to RLD Device	Yes	Seq 0001(1) 3.2.P.7
Design Control Documentation • Design input/output • EPRs • Traceability	 Yes Yes Yes	Seq 0001(1) 3.2.P.7
Design Verification		

• Primary verification • Stability verification • Shipping verification	Yes Yes	Seq 0001(1) 3.2.P.7, 3.2.R Seq 0001(1) 3.2.P.8.1 Seq 0001(1) 3.2.P.7, 3.2R
Design Validation • Clinical Comparison • Human Factors	 Yes Yes	 Seq 0001(1) 3.2.P.7 Seq 0001(1) 3.2.P.7, 5.3.5.4
Biocompatibility Information	Yes	Seq 0001(1) 3.2.P.7
Labeling	Yes	Seq 0001(1) 1.14.1.3
Risk Analysis	Yes	Seq 0001(1) 3.2.R (RPT-00139)
Lot Release Specifications	Yes	Seq 0001(1) 3.2.P.5.1.1

6. DESIGN VERIFICATION AND VALIDATION REVIEW

6.1. Summary of Design V&V Attributes

Design Verification / Validation Attributes	**Yes**	**No**	**N/A**
Validation of essential requirements covered by clinical and human factors testing	X		
To-be-marketed device was used in the pivotal clinical trial		X*	
Verification methods relevant to specific use conditions as described in design documents and labeling	X		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)	X		
Traceability demonstrated for specifications to performance data	X		

* See Section 6.2, where the changes between the clinical use device and commercial device are discussed.

Discipline -Specific Design Verification / Validation adequately addressed						
	Consult needed			Consultant	Attributes Acceptable	
	Yes	No	N/A		Yes	No
Engineering (Materials, Mechanical, General)		X		N/A	X	
Biocompatibility		X		N/A	X	
Sterility			X			
Software / Cybersecurity			X			
Electrical Safety / EMC			X			
Human Factors			X			
Quality Systems/Facilities	X			Payal Patel	X	

Standards / Guidance Conformance		**YES**	**NO**	**N/A**
Conformance to Standards	ISO 11608-1:2014 – Needle based injection systems – Requirements and Test Methods	X		
	ISO 11608-2:2012 – Needles	X		
	ISO 11608-3: 2012 Finished Containers	X		

	ISO 11608-4:2006 – Electronic and Electromechanical Pen Injectors			X
	ISO 11608-5:2012 – Automated Functions			X

*This table does NOT include discipline specific Guidance / Standards that may be applicable to the review

6.2. Design Validation Review

Design Validation Attributes	Yes	No	N/A
Phase I/II/III Study utilized the to-be-marketed device		X*	
Bioequivalence Study utilized to-be-marketed device			X
Simulated Actual Use Study utilized to-be-marketed device	X		

The sponsor states that minor modifications were made to the devices from the clinical version to the to be marketed version. They state the following changes were made:

(b) (4)

Summary of modifications

(b) (4)

The sponsor states that they have provided verification testing of the final finished version of the device to demonstrate that the product meets specification: *The design intent (specifically design input requirements) and design output specifications and performance remain the same, as confirmed in design verification testing.*

Reviewer Note:
The changes that were made to the device appear to be minor in nature and would not affect the EPRs of the device (dose accuracy, break/glide force, injection time, etc.). Since the changes that are listed above that were made to the clinical versions of the device do not appear to have any effect on the performance specifications of the device, the device design and performance specifications have been adequately validated by clinical testing.

Additionally, the device design was validated in formative and summative human factors testing, provided in 0001(1) 5.3.5.4 RPT-00149 – Human Factors Evaluation and Usability Summary Report. The full review of the human factors protocol and results is deferred to CDER/DMEPA.

I have examined the critical tasks and related use errors associated with the injection steps of the device, since CDER/DMEPA will be conducting the primary HF review. One of the tasks shown below is task 22: "administer dose":

Table 8. Task Performance Summary

Task (Evaluation Method)	Untrained (n=46) – Session 1 Patients (PU), Caregivers (CU), and HCPs (HU)		Trained (n=34) – Session 2 Patients (PT), and Caregivers (CT)		Forteo–experienced (n=15) - Session 1 Untrained Patients (F)		Proposed Mitigations (and rationale)
	# UEs	Root Cause Analysis	# UEs	Root Cause Analysis	# UEs	Root Cause Analysis	
Task 22 – Administer dose (Observe Performance)	16	HU2 and PU3 did not hold for a count of 5. HU2 explained that is not common clinical practice. CU11 started counting to 5 as soon as needle is inserted based on experience with giving injections to husband. PU15, PU16, and PU19 could not deliver the dose because of failure in prior task (set the dose). They did not refer to the IFU. CU17 and CU1 attempted to give the injection twice with the needle cover on, resulting in no dose delivered. However, both participants believed they have delivered the full dose. CU1 indicated that he did not behave as he would at	0	N/A	4	F7 indicated she knew to hold for a count of 5 but had forgotten to do so. F9 recognized that she did hold for 5 seconds and not receive the full dose given that medication leaked from her pen after the injection. She indicated that she would wait until the next day to give another injection and make sure to hold for a count of 5 during her next injection. F11 couldn't complete due to failure in prior task - participant thought he was to go through the motions of giving an injection using the Pen injector without exposing needle and wasting drug – Study Artifact. F14 couldn't complete due to failure in prior task to remove inner needle cover. After receiving	Recommend updating graphics of the pen in IFU Steps 7a-7d to show plunger at the same place, since movement of the plunger is small. Add text box below step 7 "You may not see plunger moving. To confirm that your dose has been delivered, see Step 8". Clear information and a graphics are provided as a dedicated step in the IFU (Step 7C. Figure M) directing users to "Hold it in and count to 5 slowly. You must wait until the count of 5 to make sure the full dose has been delivered)." HCPs and Forteo-experienced users

It is of note that 16/46 untrained users and 4/15 Forteo (RLD product) expereinced users had issues with the injections. The most common errors appears to be the "hold for 5 seconds step (3 untrained and 2 Forteo experienced) or that users did not see the plunger in the device internals move. The sponsor states that they have provided updated labeling mitigations to state "you may not see the plunger moving" to confirm the dose. This mitigation appears adequate.

Reviewer Note:
The sponsor is not proposing to make any additional labeling/design mitigations to mitigate the risk of patients not receiving the full dose of drug due to not waiting 5 seconds after injection, as they state: "*Clear information and a graphics are provided as a dedicated step in the IFU (Step 7C. Figure M) directing users to "Hold it in and count to 5 slowly. You must wait until the count of 5 to make sure the full dose has been delivered).*" The corresponding labeling is shown below:

(b) (4)

Of note, the RLD product also has a 5 second wait time and nearly identical labeling. The sponsor has also provided a comparative task analysis which was included in Section 4.3 of the memo, which demonstrates that the use steps appear to be almost identical to the RLD product; therefore it is strange that the Forteo experienced users experienced trouble with holding the product 5 seconds, since the labeling/use step is nearly identical to the Forteo. Because of this I do not recommend any additional labeling mitigations and I defer the rest of the HF review to CDER/DMEPA

Design Validation Recommendation:
The design validation documentation is adequate.

6.3. Design Verification Review

The sponsor has provided design verification documentation in 0001(1) 3.2.P.7. A summary table is shown below:

Device Performance Requirement	Specification	Test Methods (3.2.P.5.2)	Primary Spec Verified (3.2.P.7)	Spec Verified to Expiry (3.2.P.8.3)	Spec Verified after Shipping (NOT PROVIDED)	Lot Release Specification Included (doc# 3.2.P.5.1)

Dose Accuracy	80 (b) (4) µL Number of dose delivered (b) (4)	Adequate	Yes	Yes	Yes	Yes
Injection Force	≤ (b) (4) N	Adequate	Yes	Yes	Yes	Yes
Dose Setting Force	Dose knob can be pulled out (lot release) > (b) (4) N	Adequate	Yes	Yes	Yes	Yes
Visual Feedback	• Line on dose knob is present when dose knob is pulled out • Triangle print is present when dose knob is pulled out	Adequate	No*	No*	No*	Yes

* See Section 6.3.4. Visual feedback is not provided as a primary verification method. Given that the ink on the red line and dose set (red triangle) will be very unlikely to be affected by aging or shipping, As long as this is measured at lot release through visual inspection, I do not believe that this needs to be verified through typical performance testing since the line is either present or not.

A description of the EPR specs, verification methods for each EPR and summary verification results are shown below. Of not in test report: RPTX-0193, the sponsor states all pen verification testing was completed with (b) (4) needles and that compatibility with other needles was completed with compliance to ISO 11608-2.

6.3.1. Dose Accuracy:

The dose accuracy specification is the same as the proposed RLD product, is aligned with the dose accuracy requirement for a fixed dose mulit-use pen injector ISO-11608-1:2015, and is the same dose specification used in the clinical testing. Also the dose specification includes that the product must administer (b) (4) doses; note: that the labeling states that there are 28 doses with the device. The sponsor states that dose accuracy must be verified in accordance with ISO 11608-1 in terms of reliability/confidence, but the product reliability requirement is (b) (4)% reliability with (b) (4)% confidence. Given that this drug is not an emergency use product, I believe that this specification/reliability requirements is reasonable..

Dose accuracy was measured as follows (001(1)3.2.P.5.2)):

For batch-release testing, 20 pens are tested for dose accuracy and the number of doses delivered. For stability samples, 10 pens are tested (stage 1), followed by an additional 10 pens (stage 2) if stage 1 acceptance criteria are not met. Dose accuracy is performed when the plunger is at the beginning, middle, and close to the end of the cartridge. When performing dose accuracy testing, count and report the number of doses from the pen injector (including doses dispensed to waste when moving the plunger forward and doses dispensed to waste after the final 3 weighed doses

Dispensed volume for each dose weight (report to 3 decimal places in mL) is calculated using the following equation:

$$V(\mu L) = \frac{W\ (mg)}{D\ (\frac{mg}{\mu L})}$$

Where:
W = Expelled solution weight
D = Measured density of the batch

Dose accuracy testing is completed with 5 mm 31 G needles. This is the smallest gauge and longest length needle and represents worst case dose accuracy testing. Therefore the needles tested are adequate.

The sponsor does not conduc (b) (4) dose measurements despite the device containing that many doses that they state that they conduct 3 total measurements for each of the first dose, middle, and last doses (9 in total). In between they state

that they dose the pen 10 times to move the plunger from first dose to middle, then 9 times to move from middle to last dose. These doses are not measured. This appears to be adequate given that they are bracketing their measurements to the first, middle dose, and last dose to support dose accuracy of all (b) (4) doses. They state that dose accuracy and number of doses will be completed as a part of release and stability testing.

Reviewer Note:
With a fill volume of (b) (4) mL and 80 µL per dose, the total doses per pen is (b) (4) doses. In an IR to the sponsor it was requested that they explain how the risk of an incomplete dose being administered at the final (b) (4) dose is mitigated. The stated:

(b) (4)

Given that the product includes set doses of (b) (4) mL, this is not a concern and there is a built in functionality that will not let the user pull out the dose button when completed. This is adequate.

The sponsor states that dose accuracy testing is completed with the final finished device. Summary testing is provided in accordance with ISO 11608-1 in test report Rptx-0193:

Primary Verification:

Table 3.2.P.7-5. Dose Accuracy Summary

Condition	Result (mL)[a,b]	Acceptance Criteria	Test Result
Cool atmosphere	Average = 0.081 mL UTL = 0.087mL LTL = 0.075 mL Post modification: Average = 0.080 mL UTL = 0.088 mL LTL = 0.073 mL	(b) (4)	Pass
Standard atmosphere	Average = 0.080 mL UTL = 0.085 mL LTL = 0.075 mL Post modification: Average = 0.080 mL UTL = 0.087 mL LTL = 0.074 mL	(b) (4)	Pass
Warm atmosphere	Average = 0.080 mL UTL = 0.084 mL LTL = 0.076 mL Post modification: Average = 0.082 mL UTL = 0.089 mL LTL = 0.074 mL	(b) (4)	Pass
Last dose (31st dose)	Average = 0.080 mL UTL= 0.083 mL LTL= 0.078 mL Post modification: Average = 0.080 mL UTL = 0.086 mL LTL = 0.076 mL	(b) (4)	Pass

Free fall	Average = 0.081 mL UTL= 0.085 mL LTL= 0.078 mL Post modification: Average = 0.082 mL UTL = 0.089 mL LTL = 0.077 mL	(b) (4)	Pass
Dry heat	Average = 0.081 mL UTL= 0.085 mL LTL= 0.077 mL	(b) (4)	Pass
Cold storage	Average = 0.081 mL UTL= 0.085 mL LTL= 0.078 mL	(b) (4)	Pass
Vibration	Average = 0.080 mL UTL= 0.084 mL LTL= 0.076 mL	(b) (4)	Pass

[a] = UTL = calculated upper tolerance limit to probability content (from ISO 11608-1).
LTL = calculated lower tolerance limit to probability content (ISO 11608-1).
[b] = Dose accuracy data summarized contains data prior to and after the modification referenced in *section 3.2.P.7.5*, confirming that the modification did not impact the essential performance of the PF708 pen injector. Dry heat, cold storage, and vibration dose accuracy testing was tested before the modifications. Since the raw material and gate location did not change, the repeated dose accuracy conditions were sufficient to verify the performance of the PF708 pen injector.

Stability Verification:

The sponsor also has presented stability data for dose accuracy with the pen injector to demonstrate that they can meet a 24 month shelf life.

Lot Number	Acceptance Criteria	(b) (4)	24-month
1628-018A001 (C0004D1)	Dose accuracy (volume)		80
	Dose accuracy (k-lower)		3.868
	Dose accuracy (k-upper)		4.081

[a] = CMO lot number listed with Pfenex lot number in parenthesis.

Reviewer Note:

The sponsor states the following regarding why the k upper and k lower are identical for dose accuracy testing in response to an IR:

(b) (4)

The sponsor should provide a summary of the risk based approach that considers why this level of reliabiltiy/confidence was used.

Update 9/4/2019:
The sponsor has provide the risk based rationale for the stability reliability for doses accuracy:

(b) (4)

The sponsor has provided a thought out risk based approach for why they have chosen (b) (4) % reliability/confidence for dose accuracy at stability. Given the low risk associated with a slightly lower reliability; i.e. (b) (4) % vs. (b) (4) % reliability, for lot release; I believe that the response is acceptable and a (b) (4) % reliability/confidence is acceptable for dose accuracy at stability.

Shipping Verification:
The sponsor states that performance testing after shipping validation testing in accordance with ASTM D4169-16 (as requested in deficiency #2 in Section 11.1, will be completed prior to commercial distribution of the drug product as required. Given that this testing would not be completed until August 2019, to demonstrate that the device will function to specification after shipping, the sponsor attempts to leverage existing EPR verification testing (test report Rptx-0193), where devices were shipped from (b) (4) in document: Seq 0001(1).3.2.P.7 – Container Closure System – Pen, table 3.2.P.7-12. This testing included verification of all device EPRs (Dose accuracy, injection force, Dose setting force). All dose accuracy testing passed the acceptance criteria. In response to a CDRH deficiency (Section 11.5, #1), they have supported the similarity of this shipping with a comparison of the shipping that the product will undergo and the packaging of the to-be marketed device. The packaging appears to be comparbable based on the sponsor's description of the device packaging and seems reasonable to leverage the design verification packaging to support the commercial packaging charactersitics. The comparison is below:

Description	Design Verification Shipment	Proposed Commercial Shipment
Primary – Carton	(b) (4)	(b) (4)
Shipper		
Pallet		
Shipping Conditions	2-8°C	2-8°C
ECT = Edge Crush Test; ID = Inner Dimensions		

In addition, the sponsor has described the types of "preconditioning" that the product would be exposed to during the shipping process (ground and air transport) from (b) (4) . These include shock, vibration, stacking, pressure. Also, the travel from (b) (4) is a longer distance that what would be inspected within the (b) (4) during shipping of the proposed product. I believe that the shipping that was used in the actual shipping study is

adeuqate to be leverageed, given that the sponsor justifies the comparability between the devices shipped to (b) (4) for design verification testing. The comparability includes a description of the primary/secondary packaging, packaging configurations used, and the types of preconditioning that the devices were exposed to during shipping.

After actual shipping, the sponsor provided dose accuracy verification testing was completed in accordance with ISO 11608-1, after free-fall and vibration and demonstrated that they meet specification. I believe that they have demonstrated that the device will meet the EPRs after shipping.

Reviewer Note:
Dose accuracy has been adequately verified through primary verification, stability/shelf life, and after actual shipping.

6.3.2. Injection Force

Prior to 6/3/2019, the sponsor was relying on break/glide force of the cartridge subassembly only as an EPR rather than break/glide force or injection force of the final finished pen injector (with drug product). In a response to the IR the sponsor had agreed to conduct injection force testing to stability.

The specification for injection force of the final finished combination product is (b) (4) N. A (b) (4) N force is relatively low, even for users with osteoporosis. While human factors validation testing doesn't necessarily validate the upper specification for injection force, I am less concerned because the force to inject of (b) (4) N is low.

The sponsor states that testing was completed using an injection speed of (b) (4) mm/min, which they states to a user depressing the plunger in approximately (b) (4). This appears reasonable.

The sponsor states that: *Injection Force testing was performed after shipping the PF708 Finished Drug Product (Pen Injectors) from (b) (4) to (b) (4)) as part of Design Verification. The PF708 Finished Drug Product (Pen Injectors) were packaged on a pallet and shipped using both ground and air transport (approximately (b) (4) miles).*

Primary Verification/Shipping:
The sponsor provided verification of injection force in test report Rptx-0193. This was used as primary verification of the device but this testing was completed after actual shipping. The sponsor states that: *Injection Force testing was performed after shipping the PF708 Finished Drug Product (Pen Injectors) from (b) (4) to (b) (4) (b) (4) as part of Design Verification. The PF708 Finished Drug Product (Pen Injectors) were packaged on a pallet and shipped using both ground and air transport (approximately (b) (4) miles).*

In addition, the sponsor has described the types of "preconditioning" that the product would be exposed to during the shipping process (ground and air transport) from (b) (4). These include shock, vibration, stacking, pressure. Also, the travel from (b) (4) is a longer distance that what would be inspected within the (b) (4) during shipping of the proposed product. I believe that the shipping that was used in the actual shipping study is adeuqate to be leveraged, given that the sponsor justifies the comparability between the devices shipped to (b) (4) for design verification testing. The comparability includes a description of the primary/secondary packaging, packaging configurations used, and the types of preconditioning that the devices were exposed to during shipping.

After actual shipping, the sponsor provided injection force verification testing and all testing passed the (b) (4) N specification. I believe that they have demonstrated that the device will meet the injection force after shipping.

Stability Verification:

The sponsor provided verification of injection force on 7/15/2019, in response to IRs sent to the sponsor. The sponsor has provided testing with devices aged to the shelf life of the product and all devices met the < (b) (4) N specification. See the summary testing below. The sponsor stated: *The acceptance criteria for injection force was et for all aged lots tested. There were no instances of an injection force measurement* ≥(b) (4) *N (range: 4.36- 12.79 N).*

Table 3. PF708 Finished Drug Product (Pen Injector) Injection Force and Dose Button Pull Force Data Supporting Specification

Lot	Age (months)	Injection Force	Pull Force
Lot 1544-045A001, 5°C	39M	Average: 9.6 ± 1.4 N k = 7.25 / pass	Average: 5.6 ± 0.7 N p = 0.01 / pass
Lot 1614-003A002, 5°C	37M	Average: 5.9 ± 0.7 N k = 21.61 / pass	Average: 5.4 ± 0.5 N p = 0.01 / pass
Lot 1542-200A001, 25°C (6M) then 5°C	43M	Average: 9.4 ± 1.1 N k = 9.70 / pass	Average: 6.1 ± 0.8 N p = 0.01 / pass
Lot 1544-045A001, 25°C (6M) then 5°C	39M	Average: 9.8 ± 1.5 N k = 6.61 / pass	Average: 5.7 ± 0.9 N p = 0.01 / pass
Lot 1614-003A002, 25°C (6M) then 5°C	37M	Average: 6.8 ± 1.1 N k = 12.01 / pass	Average: 5.5 ± 0.5 N p = 0.01 / pass

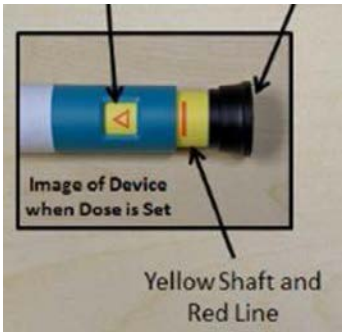
Reviewer Note:
The sponsor has adequately verified the injection force of the product.

6.3.3. Visual Feedback:

The sponsor states that the following are visual inspection/functional operation specifications that will be monitored at lot release (not conducted on stability samples) for the finished pen injector. These are the following:

Table 3.2.P.5.2-14. Visual and Functional Inspection Checklist	
1	Needle attaches to the pen
2	Dose knob can be pulled out
3	Line on dose knob is present when dose knob is pulled out
4	Triangle print is present when dose knob is pulled out
5	Dose knob can be pushed in
Note: Do not discard any initial doses. Visual and functional inspection is performed concurrently with dose accuracy test.	

Reviewer Note:
Given that the ink on the red line and dose set (red triangle) will be very unlikely to be affected by aging or shipping, I believe that it is reasonable that this is only inspected at lot release and not in stability testing. As long as this is measured at lot release through visual inspection, I do not believe that this needs to be verified through typical perforamnce testing since the line is either present or not.



6.3.4. Dose Setting Force:

The sponsor calls the dose setting force, the force that the user needs to pull back the dose knob of the device to essentially load the device prior to injection. See the image in the labeling below:

(b) (4)

Reviewer Note:
The sponsor does not appear to consider the force needed to pull back the actuation button to reset the device (dose setting force) as an performance requirement that needs to be verified through the shelf life.

Update 6/13/2019
In response to deficiency #3 in Section 11.4, the sponsor has agreed to include (b) (4) N at lot release testing upon Agency recommendation. The sponsor has provided this as a part of primary verification and after actual shipping but is not including after or stability. I believe that through responses to IRs in Section 11.3 and 11.4, the sponsor has provided assurance that dose setting force will be met through lot release testing to ensure that this specification is met. However, the sponsor did not provide information to demonstrate that this performance requirement would not change after shelf life.

Update 7/17/2019:

In an IR response dated 7/15/2019, the sponsor provided verification testing of the dose knob pullout force after aging to the product shelf life. See the summary testing below:

Table 3. PF708 Finished Drug Product (Pen Injector) Injection Force and Dose Button Pull Force Data Supporting Specification

Lot	Age (months)	Injection Force	Pull Force
Lot 1544-045A001, 5°C	39M	Average: 9.6 ± 1.4 N k = 7.25 / pass	Average: 5.6 ± 0.7 N p = 0.01 / pass
Lot 1614-003A002, 5°C	37M	Average: 5.9 ± 0.7 N k = 21.61 / pass	Average: 5.4 ± 0.5 N p = 0.01 / pass
Lot 1542-200A001, 25°C (6M) then 5°C	43M	Average: 9.4 ± 1.1 N k = 9.70 / pass	Average: 6.1 ± 0.8 N p = 0.01 / pass
Lot 1544-045A001, 25°C (6M) then 5°C	39M	Average: 9.8 ± 1.5 N k = 6.61 / pass	Average: 5.7 ± 0.9 N p = 0.01 / pass
Lot 1614-003A002, 25°C (6M) then 5°C	37M	Average: 6.8 ± 1.1 N k = 12.01 / pass	Average: 5.5 ± 0.5 N p = 0.01 / pass

Therefore, given that the sponsor has verified dose knob pull out force after shipping and aging to the shelf life and has included lot release testing, I believe that the current testing and control strategy is adequate to ensure maintenance of the dose knob pull out force after product release and up to the product expiry.

The sponsor has provided primary level verification and testing and verification testing after shipping, in test report rptx-0193, to demonstrate that the dose knob pull out force is consistent and within specification. See summary results below. All testing passed. For the actual shipping testing protocol that was used, please see Section 6.3.1 and 6.3.2 where it was already described. The Force to set a dose passed the acceptance criteria.

Table 3.2.P.7-13. Operation Performance Summary

Attribute	Results	Acceptance Criteria	Test Result
Pen cap removal force	6.15 ± 0.66 N	(b) (4)	Pass
Needle attachment torque	See *Table 3.2.P.7-12*		Pass
Force to set a dose[a] (Pull injection button)	6.00 ± 0.48 N Post modification: 5.33 ± 1.02 N		Pass

As stated in the review note above, I believe that the current testing and control strategy is adequate to ensure maintenance of the dose knob pull out force. The summary testing is below:

Design Verification Recommendation:
The design verification documentation is adequate.

7. DISCIPLINE SPECIFIC SUB-CONSULTED REVIEW

7.1. Biocompatibility

The biocompatibility review was completed by lead reviewer Matthew Ondeck in accordance with the FDA Guidance: Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process".

The container closure and primary fluid path, including the needle, are deferred to CDER. The only portion of the device that is applicable to this review is the patient skin contacting components, which includes the subassemblies. See below:

For the biological evaluation the following components of the (b) (4) were considered:

Image	Part Name (Subassembly)	Material No.	Lot-No.	Reference No.	Remarks
					(b) (4)

The materials of construction are provided below:

The materials of the pen injector have met material and biocompatibility requirements.

Table 3.2.P.7-9. Materials of Construction

Component	Material	Patient Contact
	(b) (4)	Intact skin
		None
		None
		Intact skin
		Intact skin
		None
		None
		Intact skin
		None
		Intact skin
		None
		None
		Intact skin
		Intact skin

These components are evaluated for cytotoxicity, sensitization, and irritation endpoints in report RPTX-0297 0004(4) 3.2.R.

7.1.1. Cytotoxicity:

The sponsor has conducted cytotoxicity testing in accordance with ISO 10993-5. A summary is provided below:

For the endpoint Cytotoxicity, which is requested according to ISO 10993-1, the test system Elution Test in L929 cells was chosen. This test system is a choice for a proper risk assessment for a medical device on Cytotoxicity according to ISO 10993-1. The Cytotoxicity Elution Test is a suitable method according to ISO 10993-5.

The extraction has been performed for 24 ± 2 h at 37 ± 1 °C. The test items were extracted with the cell culture medium DMEM (Dulbecco's Modified Eagle Medium) supplemented with 10% fetal calf serum under agitation. In compliance with ISO 10993-12 the surface/volume ratio in the extraction was 3 cm²/mL.

L929 cells than were incubated for at least 24 hours with five different concentrations of the extracts: 100%, 66%, 44%, 30% and 20%. After incubation signs for cytotoxicity were examined using two different endpoints. Within the first endpoint, the microscopic grading, no reduced cell growth could be observed all over the dilution series of the extract. This result was confirmed by the second endpoint, the MTS- staining and measurement, since no distinct reduction of cell viability could be found all over the dilution series of the extract. Therewith the extract of the device Subassembly Unit (b) (4) showed no cytotoxic effects.

Reviewer Note:
The cytotoxicity testing appears to have been completed in accordance with ISO 10993-5 and the materials did not display any levels of cytotoxicity. This is adequate.

7.1.2. Irritation:

The sponsor has chosen the intracutaneous irritation testing in accordance with ISO 10993-10 with albino rabbits. A summary is provided below:

The items were extracted in accordance with the relevant guideline. The extraction has been performed for 72 ± 2 h at 37 ± 1 °C. The test items were extracted with physiological saline (0.9% NaCl) as polar extraction medium as well as with Cottonseed oil as a polar extraction medium under agitation. In compliance with ISO 10993-12 the surface/volume ratio in the extraction was 3 cm²/mL.

The test item extracts were injected intracutaneously to healthy, young adult female albino rabbits. The rabbits were inspected 24 ± 2, 48 ± 2 and 72 ± 2 hours after injection and the tissue reaction for erythema and edema were graded and finally calculated. As the results of this testing the polar as well as the non-polar extract of the device Subassembly Unit (b) (4) did not cause any intracutaneous reaction in the investigated rabbits within an observation period of 72 hours. Therewith the extracts of the device Subassembly Unit (b) (4) showed no irritating relevance.

Reviewer Note:
The irritation testing appears to have been completed in accordance with ISO 10993-10 and the materials did not display any levels of irritation. This is adequate.

7.1.3. Sensitization:

The sponsor has chosen the intracutaneous irritation testing in accordance with ISO 10993-10 and the Guinea Pig Maximization test (GPMT) . A summary is provided below:

The investigation (project No. 77896-11-147-2017100233) has been performed in the laboratories of (b) (4) with regard to ISO 10993-10 and in compliance with GLP regulations. The items were extracted in accordance with the relevant guideline. The extraction has been performed for 72 ± 2 h at 37 ± 1 °C. The test items were extracted with physiological saline (0.9% NaCl) as polar extraction medium as well as with

Cottonseed oil as apolar extraction medium under agitation. In compliance with ISO 10993-12 the surface/volume ratio in the extraction was 3 cm²/mL.

The test item extracts as well as the controls were administered to healthy, young adult albino guinea pigs of female sex by intradermal injection at the anterior dorsal region of the thorax. 7 days after intradermal induction gauze patches with polar and apolar extracts were attached to the same area. After 48 hours the patches were removed. 13 days after completion of the topical induction phase, the animals were challenged with the test item extracts by topical application to sites that were not treated during the induction stage. After 24 ± 2 hours the patches then were removed. The skin reactions were observed approximately 24 hours and 48 hours after removing the test material or controls and the skin reactions were scored. As the results of this testing the polar as well as the non-polar extract of the device Subassembly Unit (b) (4) did not cause any sensitization in the investigated guinea pigs within the observation period. Therewith the extracts of the device Subassembly Unit (b) (4) showed no sensitizing relevance.

Reviewer Note:
The sensitization testing appears to have been completed in accordance with ISO 10993-10 and the materials did not display any levels of sensitization. This is adequate.

Biocompatibility Recommendation:
The biocompatibility information is adequate

7.2. Quality System

The quality systems recommendation was completed by CDRH/OC reviewer Payal Patel. Her review was provided by email the lead CDRH review, Matthew Ondeck, on 2/11/2019. See her quality systems summary review:

Pfenex Inc. - Management Controls and Design Controls

The applicant states: This facility is compliant with the drug cGMPs (21 CFR 210 and 211) and complies with 21 CFR 4.4. (b)(1) ((b) (4) .)

Pfenex, Inc. is responsible for the release of PF708 drug product cartridge and finished drug product (pen injector). Pfenex, Inc; however they are only responsible for release and not manufacturing. Because they are not responsible for primary manufacturing responsibilities, an inspection will not be required. Pfenex is responsible for management controls, design controls, purchasing controls and CAPA per 21 CFR 4.4. They have not provided information on how they comply with Part 4.4 with respect to this combination product. Interactive deficiencies will be issued to request this information. See MC deficiencies (#2-5) in Section 11.3.

Reviewer Note:
The CDRH QS reviewer reviewed the QS related deficiency responses and found them to adequate to resolve the deficiencies.

Quality System Recommendation:
The Quality System Information is adequate.

7.3. Facilities/Inspections

The facilities inspection recommendation was completed by CDRH/OC reviewer Payal Patel. Her review was provided by email the lead CDRH review, Matthew Ondeck, on 2/11/2019. See her facilities review:

This portion of the consult for CON191373 - ICC1801025 (NDA 211939), is for a determination of device facility inspection.

Pfenex, Inc. – Combination Product Holder

Pfenex, Inc. is responsible for the release of PF708 drug product cartridge and finished drug product (pen injector). Pfenex, Inc; however they are only responsible for release and not manufacturing. Because they are not responsible for primary manufacturing responsibilities, an inspection will not be required. Pfenex is responsible for management controls, design controls, purchasing controls and CAPA per 21 CFR 4.4. The adequacy of their quality systems can be determined through a quality systems review. **No Inspection is required.**

PF708 Finished Pen Injector Assembly, Packaging, and Labeling Manufacturer

The applicant states: This facility is compliant with 21 CFR 210 and 211 and is certified to ISO 13485:2016 (excluding design controls.)

(b) (4)

The previous inspection was conducted on (b) (4) and found NAI for a PFS/Auto-injector system, the QSIT inspection was conducted covering CAPA and Production and Process Controls. **A device inspection of** (b) (4) **is not recommended at this time**.

(b) (4)

The QS regulations for devices applies to finished devices; therefore, they do not address subassembly manufacturers or manufactures that perform device related testing. I will be issuing IA deficiencies to the applicant (b) (4) for this; however, these other facilities do not need a PAI.

Facilies Recommendation:
A device inspection of [redacted] (b) (4)) is not required.

A device inspection of Pfenex, Inc. (DUNS: 013603710) is not required

8. RISK ANALYSIS

8.1. Risk Analysis Attributes

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	X		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	X		
Mitigations are adequate to reduce risk to health	X		
Version history demonstrates risk management throughout design / development activities	X		

8.2. Summary of Risk Analysis

The sponsor has provided a full device risk analysis (dFMEA) that appears to be in accordance with ISO 14971, with 1-5 scales for the individual failure modes severity, occurrence and ability to be identified by the user. They have identified failure modes that would result in patient risk and mitigations to these failure modes. Examples of these include the following (Note, that the sponsor has stated that the first bullet was the subject of a CAPA and resulted in design changes to the clinical version of the device). This is provided in 0004(4) 3.2.R RTPX-0297.

- Pen locking out due to partial dose and reset – [redacted] (b) (4)
- Patient receiving a partial dose at last dose – [redacted] (b) (4)
- Carton design is inadequate to withstand distribution – verification testing
- Repeated punctures of septum – verification testing
- Failure modes related to labeling – validation testing, labeling review
- Under-dose due to container breakage – vibration testing verification testing
- Forces needed to use device are too high – validation testing
- Device doesn't function at stability – verification testing
- Biocompatibility – testing

Reviewer Note:
[redacted] (b) (4)

(b) (4)

(b) (4) I believe that this is reasonable assurance and as low as possible risk levels that the device component would not lead to the given risks. I believe that this deficiency is resolved.

Risk Analysis Recommendation:
The risk analysis is adequate

9. LABELING

The following is the instructions for use:

(b) (4)

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

Reviewer Note:
The instructions for use appear reasonable for use of the device. Additionally, the sponsor has clarified that the indicated needles to be used with the product are included in the labeling. “Becton, Dickinson and Company pen needles from 29 to 31 gauge are recommended for use with this device”. Performance testing was completed with the (b) (4) needles; however the sponsor has provided compliance of the injector with ISO 11608-2, which is used as international standard for pen needles/injector compatibility. I believe that this is adequate.

Labeling Recommendation:
The labeling is adequate.

10.DESIGN TRANSFER ACTIVITIES – RELEASE SPECIFICATION

The following release specifications are included for the device constituent within eCTD Module 3.2.P.5.1:

Release specifications for Pen Injector:

Table 3.2.P.5.1-2. Release Specification of PF708 Finished Drug Product (Pen Injector)		
Test	**Acceptance Criteria**	**Analytical Procedure**
Dose accuracy		09D05-159
Visual inspection	(b) (4)	
	Attributes: • Line on dose knob is present when dose knob is pulled out • Triangle print is present when dose knob is pulled out	
Functional operation	(b) (4)	
	Attributes: • Needle attaches to pen • Dose knob can be pulled out • Dose knob can be pushed in	
Dose accuracy	Dose accuracy: (b) (4) µL[a] with k upper NLT (b) (4) and k lower NLT (b) (4) Number of doses delivered = (b) (4)	
Identification (teriparatide)	The ratio of the retention time of the teriparatide peak of the sample solution to that of the standard solution, as obtained in the assay, is (b) (4)	RP-HPLC USP monograph - Teriparatide Injection (b) (4) 1861)
Injection force and dose button pull force	Injection force: k ≥ (b) (4)	(b) (4) 0032-16100
	Dose button pull force: p < (b) (4),	
acc = accept; AQL = acceptable quality limit; NLT = not less than; rej = reject; RP-HPLC = reversed-phase-high performance liquid chromatography; USP = United States Pharmacopeia. [a] = (b) (4) [b] =		

Release specifications for Drug Cartridge:

Table 3.2.P.5.1-1. Release Specification of PF708 Drug Product Cartridge		
Test	**Acceptance Criteria**	**Analytical Procedure**
Container content for injections	No value less than (b) (4) mL	USP <697> (b) (4) 200764)
Break loose and sustaining glide force	Break loose force[a] ≤ (b) (4) N; V ≥ (b) (4)	(b) (4) 16100-1018-A
	Sustaining glide force[a] is ≤ (b) (4) N; V ≥ (b) (4)	
EU = endotoxin units; NMT=not more than; AQL = acceptable quality limit; LQL = limiting quality level; RP-HPLC = reversed-phase high-performance liquid chromatography; SE-HPLC = size-exclusion high-performance liquid chromatography; USP = United States Pharmacopeia [a] = (b) (4)		

Reviewer Note:
(b) (4) mL a (b) (4) per dose allows for (b) (4) doses to be administered. Additionally there is a device mechanism that doesn't allow the

user to administer the half dose when the product has been used.

Update 6/13/2019
In response to agency deficiencies 1 and 3 in Section 11.4, the sponsor has agreed to include injection force and button pull out force as lot release tests.

Update 7/17/2019:
The release specification tables for the product was updated by the sponsor on 7/15/2019 to include injection force and dose button pull out force. This is adequate.

Update 8/30/2019:
In response to an IR the Sponsor provided an update to the Injection Force and Dose button pullout force lot release specification to inlcude actual forces. See below:

Test	Acceptance Criteria	Analytical Procedure
Injection force and dose button pull force	Injection force: • k ≥ (b) (4) with • Average NMT (b) (4)	(b) (4) -0032-16100
	Dose button pull force: • p < (b) (4), with • Average NLT (b) (4) and NMT (b) (4)	
[a] = (b) (4)		

Table 3.2.P.7-13. Operation Performance Summary

Attribute	Results	Acceptance Criteria	Test Result
Injection force[a] (Push injection button)	First dose: 9.79 ± 0.62 N 2nd-(b) (4) dose: 7.49 ± 1.29 N Post modification: First dose: 9.48 ± 0.98 N 2nd-(b) (4) dose: 7.11 ± 1.52 N	(b) (4) N	Pass
Needle removal torque	See *Table 3.2.P.7-12*	No more than 2 samples ≥ (b) (4) N-mm	Pass
Pen cap attachment force	5.12 ± 0.59 N	(b) (4) N	Pass
[a] = (b) (4)			

They have updated Injection force and Dose button pull force to include forces, but they only include average forces. Therefore this could potentailly include three samples of (b) (4) N. It is noted in Seq0000.3.2.P.7 document: Container Closure System- Pen, that the sponsor lists the acceptance criteria for Force to Set a dose as (b) (4) N, with no mention of average. The sponsor should remove average as it masks the speicfic values of each pen.

Update 9/4/2019:

The sponsor has removed the "Average" statement from the forces and has included NMT or NLT. This is acceptable. See below:

Test	Acceptance Criteria	Analytical Procedure
Injection force and dose button pull force	Injection force: • (b) (4) •	(b) (4)0032-16100
	Dose button pull force: • (b) (4) •	
[a] = (b) (4)		

The lot release specification for dose accuracy was (b) (4) from ISO 11608-1 requirements of 97.5%/95% reliability/confidence to (b) (4)% reliability/confidence. It is uncler why this was done. In response to an IR the sponsor stated:

The PF708 lot release acceptance criteria are justified by a risk-based approach that considers both ISO 11608-1 parameters and the PF708 (teriparatide) therapeutic window and disease indication. This is congruent with the guidance provided in ISO 11608-1. Pfenex set the dose accuracy specification to a (b) (4)% confidence and (b) (4)% probability content for the PF708 product to be inclusive of all dose accuracy test conditions from the design verification.

I do not necessarily have an issue with the sponsor (b) (4) the reliability (b) (4)% from design verification to lot release, given that they have verified their device design in accordance with ISO 11608-1; however they should justify the (b) (4) in reliability specification with the risk based rationale that they state that used.

Update 9/4/2019:

The sponsor has provide the risk based rationale for the lot release reliability for doses accuracy:

(b) (4)

The sponsor has provided a thought out risk based approach for why they have chosen (b) (4)% reliability/confidence for dose accuracy at lot release. Given the low risk associated with a (b) (4) reliability; i.e. (b) (4)% reliability, for lot release; I believe that the response is acceptable and a (b) (4)% reliability/confidence is acceptable for dose accuracy at lot release.

Release Specifications Recommendation:
The release specifications are adequate.

11.INTERACTIVE REVIEW

11.1. IR #1 - 74 Day Letter Deficiencies: Issued 1/16/2019: Returned 2/28/2019

(b) (4)

[redacted]

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12.RECOMMENDATION

Device Constituents Parts of the Combination Product are Approvable

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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/

SAMANTHA S BELL
10/08/2019 03:31:45 PM

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

Enhanced Pharmacovigilance Plan

Date:	September 26, 2019
Reviewers:	Jenny Kim, PharmD, BCPS, Safety Evaluator Division of Pharmacovigilance II Peter Waldron, MD, Medical Officer Division of Pharmacovigilance II
Team Leader:	Lynda McCulley, PharmD, BCPS Division of Pharmacovigilance II
Deputy Division Director:	Ida-Lina Diak, PharmD, MS Division of Pharmacovigilance II
Product Name:	Bonsity (PF708; teriparatide)
Subject:	Enhanced pharmacovigilance plan for osteosarcoma
Application Type/Number:	NDA 211939
Applicant/Sponsor:	Pfenex
OSE RCM #:	2019-1871

1 INTRODUCTION

The Division of Pharmacovigilance (DPV) proposes an enhanced pharmacovigilance (EPV) plan for Bonsity NDA 211939 (PF708; teriparatide) to expand data collection methods and better characterize cases reporting osteosarcoma. Osteosarcoma following teriparatide exposure was identified in preclinical rat studies and remains an important potential risk that requires further evaluation. The quality of postmarketing reports is critical for appropriate evaluation of the relationship between the product and adverse events.[a] Therefore, DPV recommends that for all cases suggestive of osteosarcoma, the Sponsor make a reasonable attempt to obtain complete case details during initial and subsequent contact, and encourages the use of a trained medically qualified person to interview reporters.

2 ENHANCED PHARMACOVIGILANCE PLAN

The goal of EPV is to better characterize cases of osteosarcoma reported with Bonsity by obtaining additional data including risk factors, diagnostic imaging, and other relevant clinical patient data. DPV requests the following EPV activities:

1. **Expedite reporting, as 15-Day alerts,** of all initial and follow-up reports suggestive of osteosarcoma to the FDA Adverse Event Reporting System (FAERS), regardless of expectedness of the event.
2. **Conduct report follow-up using a targeted questionnaire.** All reports should be reviewed by a medically qualified person. To ensure accurate communication of the diagnosis, request and submit a copy of the pathologist's report of the biopsy specimen, or a verbatim copy of this text. This is a critical component in evaluating these cases. While there may be situations in which this information may not be available, a reasonable attempt should be made to obtain the report. The following information should be included in the questionnaire
    i. Age and sex of the patient
    ii. Duration of Bonsity exposure
    iii. Time to onset of osteosarcoma
    iv. Risk factors including exposure to other possibly causative chemicals or drugs, history of therapeutic radiation exposure, history of Paget disease of bone and nonmalignant bone neoplasms, cancer history for all first-degree relatives
    v. Summary of pathology report of the biopsy specimen
    vi. Action taken with respect to Bonsity administration (e.g., discontinuation or product switch)

3. **Submit interval and cumulative analyses annually for 15 years** from the date of approval as part of the periodic safety report. Data should be analyzed from all sources. All aggregate data analysis should be conducted by a medically qualified person.

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[a]FDA Guidance for Industry: Good pharmacovigilance practices and pharmacoepidemiologic assessment. March 2005.

4. **Include the following in each periodic safety report submission:**
    - Causality assessment of all osteosarcoma cases
    - Identification of potential risk factors for osteosarcoma
    - Include the MedDRA search strategy for retrieving cases of osteosarcoma
    - Provide a line listing summarizing each case with the information requested in the targeted questionnaire

Please submit this protocol and targeted questionnaire for FDA review within 45 days from approval date. FDA will reassess this EPV program 15 years after the approval date of Bonsity.

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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:	September 23, 2019
To:	Hylton Joffe, MD Director **Division of Bone, Reproductive and Urologic Products (DBRUP)**
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:	Aman Sarai, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Jina Kwak 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):	BONSITY (teriparatide injection)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	NDA 211939
Applicant:	Pfenex, Inc.

1 INTRODUCTION

On December 7, 2018, Pfenex, Inc. (Pfenex) submitted for the Agency's review a original New Drug Application (NDA) for PF708 (teriparatide injection), 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 for facture, and treatment of men and women with osteoporosis assicaited with sustained systemic glucocorticoid therapy at high risk for fracture.

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 Bone, Reproductive and Urologic Products (DBRUP) on January 8, 2019 and January 4, 2019, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for BONSITY (teriparatide injection) for subcutaneous use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed August 29, 2019.

2 MATERIAL REVIEWED

- Draft BONSITY (teriparatide injection) MG and IFU received on December 7, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 9, 2019.
- Draft BONSITY (teriparatide injection) Prescribing Information (PI) received on December 7, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 9, 2019.
- Approved FORTEO (teriparatide injection) comparator MG dated August 30, 2013 and IFU dated May 19, 2007.

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. We reformatted the MG and IFU document using the Arial font, size 10.

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

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 3, 2019
Requesting Office or Division:	Division of Bone, Reproductive and Urologic Products (DBRUP)
Application Type and Number:	NDA 211939
Product Name and Strength:	Bonsity [a] (teriparatide) injection, 620 mcg/2.48 mL (250 mcg/mL)
Applicant/Sponsor Name:	Pfenex Inc.
FDA Received Date:	August 23, 2019
OSE RCM #:	2018-2619-1
DMEPA Safety Evaluator:	Ebony Whaley, PharmD, BCPPS
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised instructions for use (IFU), carton labeling, and container label received on August 23, 2019 for Bonsity. The Division of Bone, Reproductive and Urologic Products (DBRUP) requested that we review the revised instructions for use (IFU), carton labeling, and container label for Bonsity (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.[b]

2 CONCLUSION

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

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

[a] The proposed proprietary name Bonsity was conditionally approved on March 5, 2019.

[b] Whaley E. Human Factors Results and Label and Labeling Review for Bonsity (NDA 211939). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 AUG 28. RCM No.: 2018-2619 and 2018-2621.

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HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING 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 28, 2019
Requesting Office or Division:	Division of Bone, Reproductive and Urologic Products (DBRUP)
Application Type and Number:	NDA 211939
Product Type:	Combination Product
Drug Constituent Name and Strength	Bonsity[a] (teriparatide) injection, 620 mcg/2.48 mL (250 mcg/mL)
Device Constituent:	Pen injector with multi-dose cartridge
Rx or OTC:	Rx
Applicant/Sponsor Name:	Pfenex Inc.
Submission Date:	December 7, 2018; March 6, 2019; March 18, 2019; April 10, 2019; April 26, 2019; May 17, 2019
OSE RCM #:	2018-2619; 2018-2621
DMEPA Safety Evaluator:	Ebony Whaley, PharmD, BCPPS
DMEPA Team Leader:	Lolita White, PharmD
DMEPA Associate Director for Human Factors:	QuynhNhu Nguyen, MS

[a] The proposed proprietary name Bonsity was conditionally approved on March 5, 2019.

1. REASON FOR REVIEW

We reviewed the human factors (HF) validation study report and labels and labeling submitted under NDA 211939 for Bonsity (teriparatide) injection. This is a combination product with a proposed pen injector device constituent part that is intended for the treatment of postmenopausal women with osteoporosis at high risk for fracture, to increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture, and for the treatment of men and women with glucocorticoid-induced osteoporosis at high risk for fracture.

1.1. PRODUCT DESCRIPTION

Bonsity (teriparatide) injection is a multi-dose prefilled pen device containing 28 doses of Bonsity 20 mcg per dose. Bonsity is intended for subcutaneous administration by patients, caregivers, or healthcare providers once daily in the thigh or abdominal wall (see Appendix A).

1.2. REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

On July 2, 2018, we completed a review of the sponsor's HF validation study protocol.[b] We identified deficiencies in the proposed HF validation study protocol and communicated them to the sponsor.

(b) (4)

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.

[b] Baugh, D. Human Factors Protocol Review for Teriparatide injection IND 129196. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUL 2. RCM No.: 2017-1812-2.
c Hoste, S. Human Factors Protocol Review for Teriparatide injection IND 129196. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 NOV 5. RCM No.: 2018-1539
d Advice/Information Request for Teriparatide injection IND 129196. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUN 25.

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
Background Information on Human Factors Engineering (HFE) Process	C
Human Factors Validation Study Report	D
Information Requests Issued During the Review	E
Labels and Labeling	F

3. OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design, errors/close calls/use difficulties observed with critical tasks (Table 2), and our analysis to determine if the results support the safe and effective use of the proposed product.

3.1 SUMMARY OF STUDY DESIGN

The sponsor completed four simulated use HF validation studies (see Appendix D) which included a total of 95 participants representative of intended users in the following user groups: trained adult patients (n = 16), untrained adult patients (n = 15), untrained Forteo experienced adult patients (n = 15), trained caregivers (n = 18), untrained caregivers (n = 15), and untrained healthcare providers (n = 16).

- **Trained testing scenario**: Trained participants (e.g. adult patients, caregivers) completed a 30-minute training session and simulated injection under supervision of the trainer. Then following a minimum of 1-hour training decay, trained participants completed simulated use testing of the product (i.e. simulating one injection), in which they had access to the instructions for use (IFU) and carton labeling but were not explicitly instructed to use them. Following the simulated-use test, each participant was asked knowledge task questions.
- **Untrained testing scenario**: Untrained participants (e.g. adult patients, Forteo experienced adult patients, caregivers and healthcare providers) completed simulated use testing of the product, in which they had access to the IFU and carton labeling but were not explicitly instructed to use them. Following the simulated-use test, each participant was asked knowledge task questions. Then, after a 1-hour

learning decay, participants completed a second simulated use testing of the product but this time were asked to perform the task as instructed by the IFU (e.g. Guided IFU use). Following the second simulated-use test, each participant was asked to point to the specific location of information in the labeling when answering the knowledge task questions.

3.2 RESULTS AND ANALYSES

Table 2 describes the errors/close calls/use difficulties observed with critical tasks in the HF validation study, Applicant's analyses of the results, and DMEPA's analyses and recommendations.

TABLE 2: SUMMARY AND ANALYSES OF ERRORS/CLOSE CALLS/USE DIFFICULTIES OBSERVED WITH CRITICAL TASKS

Key: Untrained patients (PU), trained patients (PT), Forteo–experienced untrained patients (F), untrained caregivers (CU), trained caregivers (CT), and HCPs (HU).

First time use scenario: untrained and trained participants

Guided IFU use scenario: untrained participants only

Critical Tasks	Number of, Description of, and Subjective Feedback for Use Errors, Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
Identify the need to not inject more than 1x per day (Knowledge)	First time use scenario *n = 2 failures* - 2 participants stated that Bonsity could be administered multiple times a day according to the doctor's instructions. One of the two participants did not refer to the labeling. The other participant had prior experience with medications that are injected more than once and did not refer to the labeling.	- Both participants guessed their response instead of referring to the labeling. Therefore, no specific root cause was related to the product user interface.	The sponsor noted that the IFU and Medication Guide (MG) inform users "DO NOT inject more than one dose of Bonsity in the same day" and "Inject Bonsity one time each day", respectively. The sponsor also noted that the dose prescribed by the doctor (on the prescription), container label, and carton labeling will provide information regarding frequency of administration. The sponsor noted that the likelihood of harm relating to extra doses is low because the half-life of the product is short (~ 1 hour). The sponsor determined that no further mitigation is required.	Based on the sponsor's use-related risk analysis (URRA), the potential harm associated with administering more than 1 injection per day is administration of an extra dose. The sponsor indicated that it would take chronic overdoses (>5) in a short period of time for there to be a moderate change in pharmacokinetics with no significant clinical impact. We discussed the potential impact of extra doses with the clinical reviewer. The clinical reviewer noted that a one-time overdose, such as 2 to 4 extra doses at once, would not result in serious harm. However, the clinical reviewer noted chronic overdoses, such as routine administration of 2 doses per day, could potentially have clinically significant consequences including long-term hypercalcemia (with symptoms such as nausea, vomiting, constipation, lethargy and muscle weakness) or hypercalciuria. Our review of the study results did not identify subjective feedback that indicated that the labels and labeling should be improved to mitigate the risk of errors with this task. We note there is the potential for clinical harm if users administer the product more than once daily (e.g. in the case of chronic overdose). However, our review of the labels and labeling

TABLE 2: SUMMARY AND ANALYSES OF ERRORS/CLOSE CALLS/USE DIFFICULTIES OBSERVED WITH CRITICAL TASKS
Key: Untrained patients (PU), trained patients (PT), Forteo–experienced untrained patients (F), untrained caregivers (CU), trained caregivers (CT), and HCPs (HU).
First time use scenario: untrained and trained participants
Guided IFU use scenario: untrained participants only

Critical Tasks	Number of, Description of, and Subjective Feedback for Use Errors, Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
				finds the IFU informs users "DO NOT inject more than one dose of BONSITY in the same day" in the Important Information section. Additionally, the side panel of the carton labeling states "Preset dose: 20 mcg teriparatide once daily" and similar labeling statements appear on the reference product. As such, based on our overall assessment of the study results and user interface (e.g. labels and labeling), we find the residual risk acceptable and have no recommendations at this time.
Identify the need to not pull contents of cartridge into a syringe (Knowledge)	<u>First time use scenario</u> *n = 2 failures* - 1 participant said they did not know the correct response to the question without trying to find the answer in the labeling. The participant did not refer to the labeling. - 1 participant said it is common in practice to remove contents of cartridge if the pen injector is defective because medication is expensive. The participant did not refer to the labeling. <u>Guided IFU use scenario</u> *n = 1 use difficulty* - 1 participant knew to avoid pulling contents of cartridge into a syringe but could not find the information in the labeling.	- Both participants who did not provide the correct response, did not attempt to refer to labeling. In addition, one of the participants, indicated that their response was based on prior experience. - The participant who experienced use difficulty attributed the root cause to being unable to locate information in the IFU.	The sponsor noted that the IFU, MG, carton labeling, and container label have warning statements indicating "Do NOT transfer contents to a syringe". The sponsor also noted that the risk is also present in the reference product, and the Bonsity labeling includes statements identical to the reference product's labeling in multiple places. The sponsor determined that no further mitigation is required.	Based on the sponsor's risk assessment, the potential harm associated with administering the entire contents of the cartridge (800 mcg) in a single dose might cause "treatable transient effects" such as hypercalcemia, orthostatic hypotension, nausea, vomiting, dizziness and headache. We discussed the sponsor's assessment of potential harm with the clinical reviewer, and the clinical reviewer agrees with the sponsor's assessment. The clinical reviewer also noted that in the event of a one-time overdose of the entire contents of the cartridge, "it is anticipated that a transient hypercalcemic status…would return to physiological level within 24 hours after dosing". We note there is the potential for clinical harm if users fail this task, and we also note the study results identified the subjective feedback of one participant which indicated they could not locate

TABLE 2: SUMMARY AND ANALYSES OF ERRORS/CLOSE CALLS/USE DIFFICULTIES OBSERVED WITH CRITICAL TASKS
Key: Untrained patients (PU), trained patients (PT), Forteo–experienced untrained patients (F), untrained caregivers (CU), trained caregivers (CT), and HCPs (HU).
First time use scenario: untrained and trained participants
Guided IFU use scenario: untrained participants only

Critical Tasks	Number of, Description of, and Subjective Feedback for Use Errors, Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
				the information in the IFU. However, our review of the labels and labeling finds that the IFU informs users "**DO NOT** attempt to transfer BONSITY from the device provided to syringe or any other device" in the Important Information section. Additionally, the carton labeling and container label contain similar statements. We also note that similar statements appear on labeling of the reference product. As such, based on the overall assessment of the study results and user interface (e.g. labels and labeling), we find the residual risk acceptable and have no recommendations at this time.
Identify the need to use a new needle for each injection (Knowledge)	<u>Guided IFU use scenario</u> *n = 5 use difficulties/close calls* - 3 participants answered correctly but could not find the information in the labeling. - 2 participants answered correctly but had initial difficulty locating the information in the IFU. The participants indicated that they missed the information on the front the IFU (Step 9C) and continued reading the back of the IFU until they located the information.	- Three of the 5 participants were unable to find the information in the IFU and the sponsor stated that the participants knew the correct response without referring to the labeling. - Two of the 5 participants who experienced difficulty locating the information initially overlooked the associated step in the IFU and searched multiple sections before locating the information.	The sponsor stated that IFU Step 9C informs users not to reuse the needle. The sponsor also noted that the risk of re-using a needle is mitigated by the likelihood that the patient will likely feel more pain caused by a dull point (e.g. from a re-used needle) which would provide feedback to the user that a new needle is necessary for each use. The sponsor noted that the potential risk in reusing a	Based on the sponsor's URRA, the potential harm associated with reusing a needle is increased potential for clogging, painful injection/ discomfort, and infection. Our review of the study results identified user performance that indicated that the labeling should be improved to mitigate the risk of errors with this knowledge question and associated task. Specifically, we note that during the Guided IFU use scenario, some participants had difficulty finding the corresponding information in the IFU. Our review of the labels and labeling finds that the IFU Step 9c instructs users "**DO NOT** reuse needle". However, we note that the title of IFU Step 3 "(b) (4) could be improved to

TABLE 2: SUMMARY AND ANALYSES OF ERRORS/CLOSE CALLS/USE DIFFICULTIES OBSERVED WITH CRITICAL TASKS
Key: Untrained patients (PU), trained patients (PT), Forteo–experienced untrained patients (F), untrained caregivers (CU), trained caregivers (CT), and HCPs (HU).
First time use scenario: untrained and trained participants
Guided IFU use scenario: untrained participants only

Critical Tasks	Number of, Description of, and Subjective Feedback for Use Errors, Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
			needle is present in other similar marketed devices, including the reference product. The sponsor determined that no further mitigation is required.	more clearly indicate that a new needle should for each injection. This proposed revision would align IFU Step 3 with the reference product. **We provide specific IFU labeling recommendation #1 in Table 4.** Given that the modification is intended to clarify an IFU instruction and better aligns with the IFU labeling of a currently marketed product, we do not require additional human factors validation data.
Attach the needle (Observation)	First time use scenario *n = 1 failure* - 1 participant failed to fully attach the needle. Guided IFU use scenario *n = 3 use difficulties* - 3 participants initially attempted to screw the needle on in the wrong direction, but then self-corrected.	- The participant who failed to attach the needle turned the needle once to screw it on but did not firmly attach the needle to the pen injector. - Of the 3 participants that had use difficulty with this task: 1 participant said they were dyslexic and sometimes do things backwards, 1 participant said it was difficult to tell which was clockwise since the needle cap was not facing them, and 1 participant did not have additional RCA information.	The sponsor stated that the observed difficulties were associated with first time hands-on use. The sponsor noted that the user interface has adequate instructions and design. The sponsor determined that no further mitigation is required.	Based on the sponsor's risk assessment, the potential harm associated with failure to fully attach the needle is dose omission or needle stick injury. Our review of the study results identified user confusion with the IFU labeling. Specifically, one participant had difficulty determining which direction was clockwise due to the orientation of the pen injector (e.g. needle cap was not facing same direction [to the right] as depicted in the IFU). Our review of the labels and labeling finds that the IFU Step 3 includes instructions and graphics regarding how to attach the needle. We also note that the IFU for the reference product also includes similar instruction; however, the IFU for the reference product has a more prominent graphic for this task. As such, we find the proposed "attach the needle" IFU task could be

TABLE 2: SUMMARY AND ANALYSES OF ERRORS/CLOSE CALLS/USE DIFFICULTIES OBSERVED WITH CRITICAL TASKS
Key: Untrained patients (PU), trained patients (PT), Forteo–experienced untrained patients (F), untrained caregivers (CU), trained caregivers (CT), and HCPs (HU).
First time use scenario: untrained and trained participants
Guided IFU use scenario: untrained participants only

Critical Tasks	Number of, Description of, and Subjective Feedback for Use Errors, Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
				improved to mitigate the risk of medication errors leading to patient harm. **We provide specific IFU labeling recommendation #2 in Table 4.** Given that the modification is intended to clarify an IFU graphic, we do not require additional human factors validation data.
Set the dose (Observation)	First time use scenario *n = 19 failures* Of the total 19 participants who experienced use errors on the task, there were: - 14 participants who did not set dose until after already inserting needle into injection pad. The participants self-corrected after they felt no movement on the black injection button when attempting to administer the dose. - 3 participants who did not set the dose at all. - 1 participant who pulled the black injection button out to the point that the red stripe showed a little bit, but not entirely. This participant self-corrected after they could not feel any movement on the black injection button as they attempted to inject. - 1 participant who set the dose correctly but believed they must also	- Of the 14 participants who did not set the dose until after already to insert needle into injection pad: *3* did not open the IFU at all, *2* did not completely unfold the IFU where Step 5 was hidden, *6* were not closely following the IFU, *1* used one hand technique to set the dose, and *2* forgot to set the dose and were not following the IFU closely. - Of the 3 participants who did not set the dose at all, all three did not fully open the IFU (which led to Step 5 being concealed). - 1 participant did not pull the black injection button out completely - 1 participant thought they had to also dial to the correct dose	The sponsor noted that the IFU provides a dedicated step with information and a graphic to describe how to set the dose. The sponsor indicated that the pen injector is designed so that a dose cannot be delivered until the dose has been set (i.e. black injection button pulled all the way out). The sponsor also noted that participants were able to find their mistake in the IFU and correctly set the dose. The sponsor determined that no further mitigation is required.	Based on the sponsor's risk assessment, the potential harm associated with failure to properly set the dose is dose omission or delayed dose. Our review of the study results did not identify subjective feedback that indicated that the labels and labeling should be improved to mitigate the risk of errors with this task. We noted that the majority of the failures occurred where users initially failed the task but self-corrected after having difficulty with the subsequent use task, which demonstrated to us that users are able to overcome initial failure or difficulty with setting the dose. Our review of the labels and labeling finds that the IFU has a dedicated step for this task (IFU Step 5) which includes instructions and supporting graphics. We also note that the reference product also requires users to set the dose and the reference product's IFU labeling has similar IFU text and includes graphics for this step. Based on the HF study results indicating user self-correction

TABLE 2: SUMMARY AND ANALYSES OF ERRORS/CLOSE CALLS/USE DIFFICULTIES OBSERVED WITH CRITICAL TASKS
Key: Untrained patients (PU), trained patients (PT), Forteo–experienced untrained patients (F), untrained caregivers (CU), trained caregivers (CT), and HCPs (HU).
First time use scenario: untrained and trained participants
Guided IFU use scenario: untrained participants only

Critical Tasks	Number of, Description of, and Subjective Feedback for Use Errors, Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
	dial to the correct dose and accidentally expelled medication. <u>Guided IFU use scenario</u> *n = 1 close calls* - 1 participant almost did not set the dose. The participant's IFU was folded and the participant self-corrected when they read Step 6 and felt that something was missing.	- For the participant who experienced the close call, their IFU was folded and concealed Step 5.		after initial failure and based on our review of the labeling, we find the residual risk acceptable and have no recommendations at this time.
Knows the pen injector is ready to deliver dose (Knowledge)	<u>First time use scenario</u> *n = 5 failures* - 4 Forteo experienced participants did not state all the visual cues that indicate that the pen injector is ready to deliver a dose (e.g. showing the red stripe on the yellow shaft and/or instruction window showed an arrow pointing towards the needle). The sponsor noted that in the debrief session, the participants were able to identify the correct demonstration pen injector given the choice of a pen injector that was set to deliver a dose and another pen injector that had already delivered a complete dose (see row below). - 1 participant did not indicate the visual cues. The participant responded that, "If everything was	- Regarding the 4 participants who did not respond to the knowledge task question correctly during the first time use scenario, the participants did not use the information in the IFU to respond to the question. - Regarding the fifth participant who did not respond to knowledge task question correctly during the first time use scenario, the IFU instruction was concealed due to the IFU being folded. The sponsor also noted that the use of open ended questions may not elicit a specific, desired response.	The sponsor stated that the IFU provides a dedicated step with information and graphic to describe how to set the dose. The sponsor also noted that participants were able to correctly identify the correct demonstration pen injector when given the choice of a pen injector that was set to deliver a dose and another pen injector that had already delivered a complete dose. The sponsor determined that no further mitigation is required.	Based on the sponsor's risk assessment, the potential harm associated with the user being unaware whether the pen injector is ready to deliver a dose is delayed dose or dose omission. Our review of the study results did not identify subjective feedback that indicated that the labels and labeling should be improved to mitigate the risk of errors with this task. Our review of the labels and labeling finds that the IFU Step 5 informs users to "**Check** to make sure red stripe shows. Additionally, the instruction window will show an arrow pointing towards the needle end of the device..." and the IFU also includes a supporting graphic. We note that although the reference product does not include all the same visual indicators (e.g. the arrow is pointed towards the needle), the reference product requires users to perform a task to

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First time use scenario: untrained and trained participants
Guided IFU use scenario: untrained participants only

Critical Tasks	Number of, Description of, and Subjective Feedback for Use Errors, Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
	properly put on, the pen injector would be ready to deliver a dose." The sponsor noted that the IFU was not completely unfolded and IFU Step 5 was hidden. <u>Guide IFU use scenario</u> *n = 2 failures* - 2 participants did not respond correctly. One of the two participants repeated the same failure as with the first-time use scenario and did not use the information in the IFU to respond to question. The other participant indicated that the device is ready to deliver a dose if the device is not cloudy or out of date and if the black injection button is pulled out.	- Regarding the 2 participants who did not answer this knowledge task question correctly during the Guided IFU use scenario, 1 participant did not refer to the IFU and 1 participant provided a partially correct response (did not list all visual cues).		confirm the device is set (e.g. that the red stripe is visible) prior to administering the dose. Additionally, we note that users did not indicate confusion with the arrow visual indicator for the proposed device. We acknowledge that some study participants did not respond correctly to this knowledge task question. However, we also note that those participants did not attribute their confusion or incorrect response to the labeling or confusion with the arrow (e.g. the arrow is the main user interface component that differs between the proposed product and the reference product). As such, based on our review of the study results and user interface, we find the residual risk acceptable and have no recommendations.
Debrief question #1: Please tell me which device is ready to deliver a dose? Please point to the portions of the device that tells	*n = 1 failure* - 1 participant did not respond correctly. The participant was not aware that the arrow orientation changes and instead believed that there should only be one arrow and that arrow should be pointed towards the black injection button, indicating that it needs to be pushed all the way down.	The sponsor did not provide additional RCA information.	The sponsor did not proposed mitigations.	Based on the sponsor's risk assessment, the potential harm associated with the user being unaware whether the pen injector is ready to deliver a dose is delayed dose or dose omission. Our review of the study results did not identify subjective feedback that indicated that the labels and labeling should be improved to mitigate the risk of errors with this task. However, we note one participant indicated confusion regarding the

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First time use scenario: untrained and trained participants
Guided IFU use scenario: untrained participants only

Critical Tasks	Number of, Description of, and Subjective Feedback for Use Errors, Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
you it is ready to deliver a dose.				visual indicator (i.e. arrow) on the device. We note that the reference product also requires users to confirm the device is set and ready to deliver the dose with similar indicators (e.g. that the red stripe is visible). Our review of the labels and labeling finds that the IFU Step 5 adequately informs to "**Check** to make sure red stripe shows. Additionally, the instruction window will show an arrow pointing towards the needle end of the device..."" and also includes a supporting graphic. As such, based on our review of the study results and user interface, , we find the residual risk acceptable and have no recommendations.
Remove the inner needle cover (Observation)	<u>First time use scenario</u> *n = 4 failures* - 2 participants did not remove inner needle cover. The participants did not refer to the instructions because they thought it would be similar to injections they had given before. - 1 participant did not remove inner needle cover and thought the needle would pierce through the inner needle cover. - 1 participant failed this task due to a use error with the prior task (remove outer needle cover).	- Of the 4 participants who failed to remove the inner needle cover: 2 participants did not refer to the IFU, 1 participant believed the needle would pierce through the inner needle cover, and 1 participant failed to remove the outer needle cover. - Of the 4 participants who had close calls or use difficulties during the first time use scenario: 1 participant believed the inner cover was a	The sponsor noted that participants were able to complete the task correctly when instructed to follow the IFU. The sponsor noted that the user interface has adequate instructions and design. The sponsor determined that no further mitigation is required.	Based on the sponsor's risk assessment, the potential harm associated with not removing the inner needle cover is dose omission. Our review of the study results for the four use failures with this task indicate that the failures are attributed to mental model for three failures and one participant failed because they did not complete the prior task (remove outer needle cover). All other use errors with this task were close calls/use difficulty with self-correction. Our review of the labels and labeling finds that the IFU Step 6 informs users to "**Pull** small inner

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First time use scenario: untrained and trained participants
Guided IFU use scenario: untrained participants only

Critical Tasks	Number of, Description of, and Subjective Feedback for Use Errors, Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
	n = 4 close calls/use difficulties - 3 participants initially did not remove the inner needle cover and later self-corrected. One of the three participants said they thought the inner needle cover was a needle shield for needle phobic patients. - 1 participant initially unscrewed the needle and then realized they only meant to remove the inner needle cover. The participant screwed the needle back on and removed the inner needle cover correctly. <u>Guided IFU use scenario</u> *n = 1 close call/use difficulty* - 1 participant started to unscrew needle from pen injector instead of removing inner needle cover. They self-corrected and removed inner needle cover.	needle shield, 1 participant unintentionally unscrewed the needle, and the sponsor did not provide RCA for the other 2 participants. - Regarding the participant who experienced use difficulty during the Guided IFU use scenario, the participant unintentionally unscrewed the needle.		needle protector and throw it away" and also includes a supporting graphics. We also note that the reference product also requires users to remove the inner needle cover and the reference product's IFU labeling includes instruction and a supporting graphic. As such, we find the residual risk acceptable and have no recommendations at this time.
Insert the needle straight into the skin on the thigh or abdomen (Observation)	<u>First time use scenario</u> *n = 2 failures* - 1 participant inserted the needle at a 45-degree angle and stated that they were nervous. - 1 participant inserted needle at "steep angle". The participant stated	- Of the 2 participants who failed this task during the first time use scenario: 1 participant was nervous, and 1 participant had prior experience with Forteo and followed the instructions	The sponsor noted that IFU Step 7 and Figure K provide clear information and graphics regarding inserting the needle into the skin.	Based on the sponsor's URRA, the potential harm associated with not correctly inserting the needle straight into the skin is leakage at the injection site with an intradermal injection and reduced therapeutic effect due to losing some drug product.

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First time use scenario: untrained and trained participants
Guided IFU use scenario: untrained participants only

Critical Tasks	Number of, Description of, and Subjective Feedback for Use Errors, Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
	the doctor told them to use a slight angle with Forteo. <u>Guided IFU use scenario</u> *n = 1 failure* - 1 participant inserted the needle at an "extreme angle". The participant indicated that they would recline the patient if at home (in the testing scenario, the mannequin was sitting upright). The sponsor considers this a study limitation.	from the physician who prescribes their Forteo. - Regarding the participant who failed this task during the Guided IFU use scenario, the sponsor attributed the participant's performance to study artifact due to use of an injection pad on a mannequin (unable to recline).	The sponsor determined that no further mitigation is required.	Our review of the study results did not identify subjective feedback that indicated that the labels and labeling should be improved to mitigate the risk of errors with this task. Our review of the labels and labeling finds that the IFU Step 7A contains instructions and a graphic to instruct users regarding how to insert the needle. We also note that the reference product's IFU has similar instruction and an associated graphic and we are unaware of any postmarketing reports of confusion. As such, we find the residual risk acceptable and have no recommendations at this time.
Administer dose (Observation)	<u>First time use scenario</u> *n = 20 failures* - 8 participants gave more than one dose in a row. The participants were unsure if the full dose had been delivered because they expected the plunger to move down to the next black line on the cartridge or that the device would inject all of the medicine at once. Six of these 8 participants also believed the pen injector was one-time use. Additionally, one of the 8 participants did not refer to the IFU.	- Of the 20 participants who failed this task during the first time use scenario: *6* participants expected plunger movement and also believed the pen injector was one-time use, *4* participants failed to remove the inner needle cover in a previous task and did not refer to the IFU, *3* participants failed to set the dose in a previous task, *2* participants did not hold for a count of 5, *2* participants expected	The sponsor noted that IFU Step 7C and Figure M instruct users to "Hold it in and count to 5 slowly. You must wait until the count of 5 to make sure the full dose has been delivered)." The sponsor determined that a missed dose or extra doses would not result in serious harm to the patient due to the nature of the therapy. The sponsor also noted that the extra dose	Based on the sponsor's risk assessment, failure to properly administer the dose might result in underdose and leaking from pen or injection site. We also note that failures with this task might result in overdose, underdose or dose omission. We note the sponsor indicates that it would take chronic dose omissions or overdoses (>5) for there to be a moderate change in pharmacokinetics with no significant clinical impact. However, per our discussion with the clinical reviewer, chronic overdoses, such as routine administration of 2 doses per day, could potentially have clinically significant consequences including long-term hypercalcemia (with symptoms such as nausea, vomiting,

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First time use scenario: untrained and trained participants

Guided IFU use scenario: untrained participants only

Critical Tasks	Number of, Description of, and Subjective Feedback for Use Errors, Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
	- 5 participants (HU2, PU3, CU11, F7, and F9) did not hold for a count of 5. Specifically, 2 participants (CU11 and F7) started counting to 5 before the they pressed the black injection button all the way down. CU11 said they previously gave an injection to their spouse that way and did not refer to the IFU. F7 indicated they knew to hold for a count of 5 but had forgotten to do so. HU2 said they did not count to 5 because it is not common in their clinical practice. - 3 participants could not deliver the dose because of failure with a previous task (set the dose). - 4 participants failed this task due to failure remove inner needle cover in a previous task, which resulted in no dose delivered. None of these participants referred to the IFU. One of the 4 participants also indicated that they didn't behave as they would at home because they were participating in simulated use and would use the IFU the first several times. Another one of the 4 participants believed they were only going through the motions of a giving an injection (vs. simulated use).	plunger movement, *1* participant performed based on prior experience and did not refer to the IFU, 1 participant forgot to hold for a count of 5, and *1* participant stated holding to a count of 5 is not common in their clinical practice. - Of the 2 participants who failed this task during the Guided IFU use scenario: 1 participants did not read the IFU and the sponsor did not provide additional RCA for the other participant.	errors did not occur in the Guide IFU use scenario. The sponsor noted that some participants gave multiple doses expecting to see the plunger move, thinking that they were to deliver the entire contents of the cartridge. The sponsor also noted that drug product leakage (i.e. wet injection) was only observed for 1 participant failure. The sponsor noted that HCPs and Forteo experienced users tended perform based on their own individual, previous experiences. The sponsor attributes the failures in which users administered more than one dose to inattention to dosing requirements and first time use. Additionally, in response to the failures, the sponsor updated the IFU graphics of the pen to	constipation, lethargy and muscle weakness) or hypercalciuria (potentially predisposing patients to urolithiasis). Our review of the study results noted several participants expected the plunger to move significantly and/or the medication cartridge to empty completely; this led to participants administering more than 1 dose. We note the design of the cartridge and we also note that the slight movement of the plunger is the same with the proposed Bonsity device as with the reference product. We also note that several other failures with this task occurred due to participants not holding down injection for count of 5 or not removing the inner needle cover prior to attempting to administer the dose. We note the aforementioned tasks are the same with the proposed Bonsity device as with the reference product. We also note that study artifact may have contributed to users administering multiple doses. For example, a patient receiving an injection via self-administration or caregiver administration may "feel" the dose being administered which would mitigate confusion regarding whether the dose was administered. However, in the HF validation testing, users injected into an injection

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First time use scenario: untrained and trained participants
Guided IFU use scenario: untrained participants only

Critical Tasks	Number of, Description of, and Subjective Feedback for Use Errors, Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
	Guided IFU use scenario *n = 2 failures* - 2 participants did not hold for a count of 5. One of the 2 participants said they did not read instructions carefully because it seemed obvious that the medicine should be delivered to the body as soon as the black button had been pushed down fully. Neither failure resulted in a wet injection.		more accurately represent the plunger movement after injection. The sponsor revised IFU Steps 7a-7d to show plunger at the same place, since movement of the plunger is small. Additionally, the sponsor added a text box below Step 7 to indicate "You may not see plunger moving…". The sponsor determined that the revision is a minor clarification that does not required HF validation.	pad; as such, users may have been more likely to administer extra doses to confirm dose delivery. Our review of the labels and labeling finds that the IFU Step 7C contains instructions and a graphic to instruct users to hold the injection for a count of 5. We also note that the reference product's IFU has similar instruction and an associated graphic for the task of holding the injection for a count of 5. We note that in the response to the use errors and subjective feedback, the sponsor revised the graphics for IFU Steps 7a-7d to accurately represent the plunger position before, during, and after injection. We also note the sponsor did not validate the revisions; however, in this particular instance, we have determined that these changes can be implemented without additional validation testing data to be submitted for review. . We note that several failures occurred with this task; however, this task is not unique to the already marketed reference product. We also note the user interface components related to performance of this task (e.g. cartridge, injection button) and the overall for administering the dose are similar for the proposed Bonsity device as compared to the reference product. We lastly note that participants who failed this task did not convey confusion with the user interface

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First time use scenario: untrained and trained participants
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Critical Tasks	Number of, Description of, and Subjective Feedback for Use Errors, Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
				component (e.g. arrow) that differs between the proposed device and the reference product. We note there is the potential for clinical harm if users administer the product more than once daily (e.g. in the case of chronic overdose). However, based on our overall assessment of the study results, user interface, and the sponsor's proposed mitigations, we find the residual risk acceptable and do not propose mitigations at this time.
Confirm complete dose has been delivered (Knowledge) Correct answer: indicate that the black injection button should be all the way down or instruction window should show an arrow pointing towards the black injection button or yellow shaft not showing	<u>First time use scenario</u> *n = 9 failures* - 9 participants (PU10, CU4, CU13, CU15, HU3, HU6, HU10, F2, and F11) did not respond correctly (e.g. did not indicate that the black injection button should be all the way down or instruction window should show an arrow pointing towards the black injection button or yellow shaft not showing). Six of the 9 participants (PU10, CU4, CU13, CU15, HU3, and HU6) indicated that there are no visual indicators to tell them that a full dose has been delivered. HU10 believed that a full dose is delivered when the plunger goes down to the first line on the medication cartridge because that is what the participant	- Of the 9 participants who did not correctly answer this knowledge task question during the first time use scenario: 1 participant misunderstood IFU Step 7 and based their answer on previous experience with the reference product, 1 participant did not refer to the IFU and based their answer on previous experience with the reference product, 1 participant believed the device was one time use and did not refer to the IFU, and the sponsor did not provide additional RCA information	The sponsor noted that IFU Step 8 provides information and graphics regarding how to visually confirm that the full dose has been delivered. The sponsor noted that participants tended to answer based on their previous experience rather than referencing the IFU. The sponsor also noted that all the participants were able to identify then pen injector that had delivered a complete dose. As noted in the row above, the sponsor also revised	Based on the sponsor's risk assessment, the potential harm associated with not accurately confirming that the dose has been delivered is underdose (e.g. if the user is unaware of end of dose indicators). We also note that not accurately confirming that the dose has been delivered might also result in overdose or dose omission. Our review of the study results indicated one participant was confused by the IFU. We note that other participants were not aware of the visual indicators that indicate that a dose has been delivered. Our review of the labels and labeling finds that the IFU Step 8 contains instructions and a graphic to instruct users on how to confirm the dose has been delivered. We note the in response to user performance on this knowledge task question, the

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First time use scenario: untrained and trained participants

Guided IFU use scenario: untrained participants only

Critical Tasks	Number of, Description of, and Subjective Feedback for Use Errors, Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
	thought IFU Steps 7a - 7d illustrated. F2 believed that a full dose was delivered when the plunger went down and a small bubble formed at the tip of the needle and did not refer to the IFU. F11 believed that a full dose was delivered when the medication reservoir was empty because they thought the device was one time use only and did not refer to the IFU. The sponsor also noted that F2 and F11 tended to answer based on previous experience rather than referring to the IFU. <u>Guided IFU use scenario</u> *n = 2 failures* - 1 participant did not respond correctly. They did not refer to the instruction even though the moderator reminded them to. - 1 participant believed that a full dose was delivered after counting to 5. They did not refer to the IFU.	for the remaining 6 participants. - - Of the 2 participants who did not correctly answer this knowledge task question during the Guided IFU use scenario, both did not refer to the IFU.	the graphics in IFU Step 7 and also included the text box "You may not see plunger moving. To confirm that your dose has been delivered, see Step 8." Additionally, in a 5/17/19 response to IR, the sponsor noted in addition to the visual indicators accepted for response to this knowledge task question, several of the participants also indicated that "a dose is delivered when you count to 5". The sponsor noted that 3 of the 9 untrained participants that failed this task had confirmed they received a complete dose by stating they counted to 5. As such, the sponsor considers that "counting to 5" as an alternate action that confirms the dose has been delivered.	sponsor revised the IFU Step 7 to include clarifying statements (i.e. "You may not see plunger moving. To confirm that your dose has been delivered, see Step 8."). We also note the sponsor did not validate the revisions. In this particular instance, we have determined that these changes can be implemented without additional validation testing data to be submitted for review We acknowledge that several participants did not correctly respond to this knowledge task question; however, we note that the reference product also requires users to confirm the dose has been delivered (e.g. yellow shaft no longer visible, which is also an indicator for the proposed product). Although the reference product does not include an arrow as a visual indicator on the device to assist in dose confirmation, none of the results indicate that the inclusion of the arrow as a visual indicator appear to confuse participants. We note that the proposed device has visual cues (e.g. arrow changing direction, black injection button down) and an auditory cue (e.g. click at the end of the injection) to indication that the injection is complete. We also note that users are instructed to count to 5 to ensure doses is delivered; as such, users of the proposed device have multiple methods of feedback to ensure the dose has been delivered. Based on our review of

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				the study results and user interface, we find the residual risk acceptable and do not have recommendations at this time.
Remove the used needle from the pen injector (Observation)	First time use scenario *n = 11 failures* - 4 participants did not remove the used needle from the pen injector. One of the 4 participants said they reuse their needles because they inject 6 times a day and would only change the needles every few days. Another one of the 4 participants said they were nervous, but they knew the needle was supposed to be one-time use. The remaining 2 participants did not refer to the IFU. - 4 participants received moderator assistance in removing the needle due to safety concerns. One of the 4 participants could not find the outer needle cover and attempted to use the inner needle cover to remove needle, which bent the needle. Two of the 4 participants attempted to remove the used needle without the outer needle cover. The remaining participant held the device with the needle facing to the left and turned the covered needle counterclockwise (wrong direction).	- Of the 11 participants that failed this task during the first time use scenario: 2 participants did not refer to the IFU, 2 participants attempted to remove the needle without the outer needle cover, 2 participants turned the outer needle cover in the wrong direction, 1 participant said they typically re-use needles, 1 participant was nervous, 1 participant had difficulty locating the outer needle cover and attempted to use the inner needle cover to remove the needle, 1 participant did not attempt this task due to failure in a prior task, and 1 participant did not attempt this task due to study artifact. - Of the 11 participants that had use difficulties or close calls with this task during the first time use scenario: 4	The sponsor noted that IFU Step 9 Figures P, Q, R, and S illustrate how to scoop the needle cover and arrows for direction to rotate needle to remove. The sponsor also noted that the use errors were associated with first time hands-on use by both untrained users in Session 1 (first time use scenarios) or trained participants. The sponsor stated that in Session 2 (guided IFU scenario), the untrained users avoided this error. The sponsor also noted there were no direct use errors associated with experienced Forteo users. The sponsor determined that no further mitigation is required.	Based on the sponsor's use-related risk analysis, the potential harm associated with not properly removing the used needle is 1) an accidental needle stick injury, 2) a needle stick to another person could cause serious irreversible harm by transfer of unknown bloodborne pathogens, and 3) storing Bonsity with needle attached in subsequent steps resulting in contamination. The IFU also indicates that storing Bonsity with the needle attached (due to not removing used needle from pen) may cause air bubbles to form in the cartridge. Our review of the study results identified subjective feedback that did not specifically indicate that the labels and labeling should be improved to mitigate the risk of errors with this task. Our review of the labels and labeling finds that the IFU Step 9 contains instructions and graphics to instruct users on how to remove the needle using the outer needle cover. We note the IFU for the reference product also includes similar instruction; however, the IFU for the reference product has more prominent graphic (e.g. arrow indicating the direction to turn the needle). We

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First time use scenario: untrained and trained participants

Guided IFU use scenario: untrained participants only

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	- 1 participant attempted to remove the needle by twisting the outer needle cover in the wrong direction, gave up, and stored the pen injector in the refrigerator with pen cap on and needle attached. - 1 participant did not attempt this step due to failure in prior task. - 1 participant did not attempt this step because they thought they were only supposed to go through the motions of giving an injection (study artifact). First time use scenario *n = 11 use difficulties/close calls* - 4 participants initially attempted to twist it off in the wrong direction. For two of the 4 participants, this led to the needle coming off. - 3 participants initially did not give turn outer needle cover enough times or did not use enough force. - 1 participant attempted to remove needle with the inner needle cover (based on how their other device worked). -	participants initially turned the needle in the wrong direction, 3 participants did not turn outer needle cover enough times/with enough force, 1 participant attempted to remove needle using inner needle cover, 1 participant initially stored device with pen cap and needle attached, 1 participant did not press the outer needle cover on completely, and 1 participant turned outer needle cover in wrong direction. - Of the 4 participants that had use difficulties or close calls with this task during the Guided IFU use scenario: 2 participants twisted the outer needle cover in the wrong direction, 1 participant did not turn outer needle cover enough times, and 1 participant twisted the outer needle cover in the wrong direction and also did not turn it enough times. -		find that revision of the arrow graphic to increase prominence might help mitigate the risk of failures with this task (e.g. clarify the direction to turn the needle to remove it). We acknowledge the risk of infection or needle sticks are not unique to the proposed product; **however, based on failures and subjective feedback for this step, we provide specific IFU labeling recommendation #3 in Table 4.** Given that the modification is intended to increase the prominence of an IFU graphic, we do not require additional human factors validation data.

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First time use scenario: untrained and trained participants
Guided IFU use scenario: untrained participants only

Critical Tasks	Number of, Description of, and Subjective Feedback for Use Errors, Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
	- 1 participant initially stored the pen injector with pen cap on and needle attached. - 1 participant did not initially press the outer needle cover on all the way before attempting to unscrew the needle. - 1 participant initially held the device with the needle facing the left and turned the cover in the wrong direction. <u>Guided IFU use scenario</u> *n = 4 use difficulties/close calls* - 2 participants initially twisted the covered needle in the wrong direction. - 1 participant initially did not turn the covered needle enough times. - 1 participant turned the covered needle one time in the correct direction and then attempted to turn it in the wrong direction.			
Dispose of the used needle in the sharps container (Observation)	<u>First time use scenario</u> *n = 16 failures* - 8 participants disposed of the needle in the trash instead of the sharps container. Two of the 8 participants indicated that the trash can looked like the puncture resistant container	Of the 16 participants that failed this task during the first time use scenario: 3 participants' performance was due to study artifact, 2 participants misinterpreted the IFU graphic of the sharps	The sponsor noted that IFU Step 9C, Figure T indicates how to correctly dispose of the needle. The sponsor also noted that the IFU has a Q&A section that discusses disposal.	Based sponsor's URRA, the potential harm associated with not disposing of the needle in an appropriate container is an accidental third-party needle stick with potential for injection by unknown bloodborne pathogens.

TABLE 2: SUMMARY AND ANALYSES OF ERRORS/CLOSE CALLS/USE DIFFICULTIES OBSERVED WITH CRITICAL TASKS

Key: Untrained patients (PU), trained patients (PT), Forteo–experienced untrained patients (F), untrained caregivers (CU), trained caregivers (CT), and HCPs (HU).

First time use scenario: untrained and trained participants

Guided IFU use scenario: untrained participants only

Critical Tasks	Number of, Description of, and Subjective Feedback for Use Errors, Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
	shown in the IFU. Another two of the 8 participants said they did not see a sharps container. One of the 8 participants said that was what the nurse taught them to do with Forteo. One of the 8 participants said they placed the used needle in the carton and dispose of the carton because they would not want to go through the trouble of disposing the sharps container once it is full. One of the 8 participants stated that they did not take the same caution and care that they would at home because this was a simulated study (study artifact). The remaining participant did not have an explanation for why they threw the used needle in the trash. - 6 participants did not dispose of the used needle in the sharps container because they never removed the needle (failure with previous task). One of the 6 participants indicated they reuse their needles and only change the needle every few days because they inject six times a day. One of the 6 participants said they were nervous, but they understand that the needle was one-time use.	container as a trash can, 2 participants did not see the sharps container, 2 participants did not remove the needle in previous task, 2 participants did not remove the needle in the prior task and also did not refer to the IFU, 1 participant did not remove the needle and said they reuse their needles, 1 participant did not remove the needle and said they were nervous, 1 participant referred to previous instruction from their nurse (negative transfer), 1 participant noted they did not want to go through trouble of disposing the sharps container, and 1 participant did not have additional RCA information Of the 2 participants that had close calls with this task during the first time use scenario, the sponsor attributed both close calls to inattention to instructions.	The sponsor noted that participants tended to respond based on their individual experiences rather than the IFU and that the issue of proper needle disposal is inherent with all pen injectors. The sponsor determined that no further mitigation is required.	Our review of the study results identified study artifact and mental model as contributing factors to use performance on this task; however, the subjective feedback also indicated that the labels and labeling could be improved to mitigate the risk of errors with this task. Specifically, we note that two participants indicated that that the trash can in the simulated us scenario looked like the sharps container depicted in the IFU, which might indicate that the sharps container graphic should be improved. Our review of the labels and labeling finds that the IFU Step 9c provides instructions and a graphic to describe the needle disposal process. However, we note the IFU graphic only shows a cropped view of a sharps container and could be improved. **We acknowledge that this risk of needle stick injury is not unique for this product; however, based on the subjective feedback we provide specific IFU labeling recommendation #4 in Table 4.** Given that the modification is intended to clarify an IFU graphic, we do not require additional human factors validation data.

TABLE 2: SUMMARY AND ANALYSES OF ERRORS/CLOSE CALLS/USE DIFFICULTIES OBSERVED WITH CRITICAL TASKS

Key: Untrained patients (PU), trained patients (PT), Forteo–experienced untrained patients (F), untrained caregivers (CU), trained caregivers (CT), and HCPs (HU).

First time use scenario: untrained and trained participants

Guided IFU use scenario: untrained participants only

Critical Tasks	Number of, Description of, and Subjective Feedback for Use Errors, Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
	Two of the 6 participants did not refer to the IFU. - 1 participant disposed the needle in the trash because it was closer than the sharps container; but if they were at home, they would have walked over to the sharps (study artifact) - 1 participant did not remove the needle because they thought were just supposed to go through the motions of giving an injection using the pen injector (study artifact). <u>First time use scenario</u> *n = 2 close calls* - 2 participants initially threw the used needle in the trash, caught their error, retrieved the needle from the trash, and threw it in the sharps container. <u>Guided IFU scenario</u> *n = 7 failures* - 3 participants (CU8, PU14, and CU13) disposed of the needle in the trash instead of the sharps container. PU14 and CU13 said they did not see a sharps container. CU13 further indicated that they felt comfortable	Of the 7 participants that failed this task during the Guided IFU use scenario: 4 participant had the same failures as in the first time use scenario, 2 participants did not see the sharps container in the study environment, and 1 participant believed they did not need to use the sharps container since they did not have children at home. -		

TABLE 2: SUMMARY AND ANALYSES OF ERRORS/CLOSE CALLS/USE DIFFICULTIES OBSERVED WITH CRITICAL TASKS
Key: Untrained patients (PU), trained patients (PT), Forteo–experienced untrained patients (F), untrained caregivers (CU), trained caregivers (CT), and HCPs (HU).
First time use scenario: untrained and trained participants
Guided IFU use scenario: untrained participants only

Critical Tasks	Number of, Description of, and Subjective Feedback for Use Errors, Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
	throwing needles in the trash at home because they don't have small kids. - 4 participants repeated the same failures as in the first time use scenario.			
Replace the white cap (Observation)	<u>First time use scenario</u> *n = 1 failure* - 1 participant did not replace the white cap and did not use the IFU. <u>First time use scenario</u> *n = 5 use difficulties/ close calls* - 3 participants almost did not replace the white cap. One of the 3 participants said they did not initially remember there was a white cap. Another one of the 3 participants said they did not realize they needed to complete this step until they re-read the IFU. The remaining participant threw the white cap in the trash, realized the mistake, and retrieved it from the trash; the participant said they were being absentminded - 2 participants initially placed the device in the refrigerator without the white cap on and then self-corrected. One of the 2 participants said they	- Regarding the failure that occurred during the first time use scenario, the participant did not refer to IFU. - Regarding the 5 use difficulties/close calls that occurred during the first time use scenario, 3 participant initially forgot to complete the task or were unaware of the task, 1 participant did not read the instructions, and 1 participant did not have additional RCA information. - Regarding the failure that occurred during the Guide IFU use scenario, the participant forgot to complete the task. - Regarding the use difficulty/close call that occurred during the Guided IFU use scenario, the	The sponsor noted that IFU Step 10A, Figure U directs the user to put the white cap back on the device before storing in the refrigerator in Step 10B. (b) (4) [redacted] The sponsor also noted that the design and use of the cap is similar to other marketed injection devices including the reference product.	Based on the sponsor's use-related risk analysis, the potential harm associated with not recapping the device is microbial contamination of the septum of device. In addition, we discussed the risk of microbial contamination with the MO; the MO noted that (b) (4) [redacted] provides additional mitigation for the concern for growth of microbes should the cap not be replaced. Our review of the study results did not identify subjective feedback that indicated that the labels and labeling should be improved to mitigate the risk of errors with this task. Our review of the labels and labeling finds that the IFU Step 10 informs users to "Push white cap back on (Figure U)" and also includes a supporting IFU graphic. We also note that the reference product also requires users to replace the white cap and the reference product's IFU labeling has similar IFU instruction and a similar graphic for this step.

TABLE 2: SUMMARY AND ANALYSES OF ERRORS/CLOSE CALLS/USE DIFFICULTIES OBSERVED WITH CRITICAL TASKS
Key: Untrained patients (PU), trained patients (PT), Forteo–experienced untrained patients (F), untrained caregivers (CU), trained caregivers (CT), and HCPs (HU).
First time use scenario: untrained and trained participants
Guided IFU use scenario: untrained participants only

Critical Tasks	Number of, Description of, and Subjective Feedback for Use Errors, Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
	did not initially read the instructions for this task. The sponsor did not provide additional detail for the other participant. <u>Guided IFU use scenario</u> *n = 1 failure* - 1 participant did not replace white cap due to forgetting. <u>Guided IFU use scenario</u> *n = 1 use difficulty/close call* - 1 participant initially mistook the outer needle cover for the white cap.	participant mistook one device component for another. -		As such, we find the residual risk acceptable and have no recommendations at this time.
Store the used pen injector in the refrigerator (Observation)	<u>First time use scenario</u> *n = 7 failures* - 4 participants stored the pen injector in the refrigerator with the white cap on and the needle attached due to failure to complete a prior task (i.e. did not remove the needle). Additionally, PU16 did not refer to the IFU. HU16 said they were nervous. For PU16, the sponsor noted that the IFU was folded, hiding the direction to remove the needle. - 2 participants failed this task due to study artifact. One of the 2 participants stored used pen injector with the pen cap on and the needle	- Of the 7 participants who failed this task: 4 participants did not complete the prior task of removing the needle (of these, 1 did not refer to the IFU, 1 had IFU folded and step was hidden, and 1 was nervous), 2 participants' performance was attributed to study artifact, and 1 participant did not refer to the IFU. -	The sponsor indicated that IFU Step 10B, Figure U directs the user to "Always store the device in the refrigerator with the white cap on right after use (Figure V)". The sponsor also indicated that the Medication Guide states "Keep your Bonsity delivery device in the refrigerator…". The sponsor revised the IFU text in the Storage Information and the phrase	Based on the sponsor's use-related risk analysis, the potential harm associated not storing the device in the refrigerator is degradation/reduced potency of the product from temperature or light. Our review of the study results did not identify subjective feedback that indicated that the labels and labeling should be improved to mitigate the risk of errors with this task. Our review of the labels and labeling notes that finds the sponsor revised the Storage Information section of the IFU after the HF validation study in the Storage Information section from "(b) (4) [redacted] to "Always store the device

TABLE 2: SUMMARY AND ANALYSES OF ERRORS/CLOSE CALLS/USE DIFFICULTIES OBSERVED WITH CRITICAL TASKS

Key: Untrained patients (PU), trained patients (PT), Forteo–experienced untrained patients (F), untrained caregivers (CU), trained caregivers (CT), and HCPs (HU).

First time use scenario: untrained and trained participants

Guided IFU use scenario: untrained participants only

Critical Tasks	Number of, Description of, and Subjective Feedback for Use Errors, Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
	attached and noted thought they were just supposed to go through the motions of giving an injection . The other participant indicated that "this is like acting and you would not be in my kitchen". - 1 participant did not store the device in the refrigerator and left the device with the needle attached and no white cap, on the table. The participant did not refer to the IFU.		[redacted] (b) (4) " was deleted to indicate that the device should always be stored in refrigeration	in the refrigerator with the white cap on". We find this revision does not require HF validation because it clarifies a task and does not change or provide additional instructions for use. We also note that the IFU Step 10 informs users "Always store the device in the refrigerator with the white cap on right after use". Additionally, our review of the carton labeling and container label notes the label and labeling instruct users to "Refrigerate/Do not freeze". However, we find that the information on the container label should be revised to increase the prominence of this important storage information. **We provide specific container label recommendation #1 in Table 4.** Given that the modification is intended to increase the prominence on information on the container label, we do not require additional human factors validation data.

3.3 ANALYSIS OF ESSENTIAL/NON-CRITICAL TASKS

We acknowledge that there were use-related issues (e.g. use errors, close calls, or use difficulties) on non-critical/essential tasks (e.g. identify need to not store pen in freezer, check that that pen injector is not damaged, check that the liquid in the medication cartridge is clear, store device in refrigerator before the first use) submitted in the HF study results report . However, our review of the subjective feedback and root cause analyses did not generate any concerns from a medication error perspective and we find the risks are mitigated to an acceptable level. Thus, we did not include these non-critical tasks within this review.

3.4 LABELS AND LABELING

Tables 3 and 4 below include the identified medication error issues with the submitted label and labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 3: Identified Issues and Recommendations for Division of Bone, Reproductive, and Urologic Products			
	Identified Issue	**Rationale for Concern**	**Recommendation**
Full Prescribing Information			
1.	In Section 16.1 How Supplied, the National Drug Code (NDC) number is denoted by a placeholder.	NDC number should be listed per 21 CFR 201.57(c)(17).	We recommend the sponsor revise to the PI to include the actual NDC number.

Table 4: Identified Issues and Recommendations for Pfenex Inc. (sent to sponsor on 8/19/19)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
Instructions for Use (IFU)			
1.	IFU Step 3 should be further clarified to indicate a new needle should be used with each injection.	User confusion regarding the needle might increase the risk of users attempting to re-use a needle for subsequent injections. The results and subjective feedback collected during your HF validation studies indicated that for the knowledge task question "Identify the need to use a new needle for each injection" , 5 participants had difficulty or close calls locating the information in the IFU.	Revise header of IFU Step 3 from "(b) (4) to "Attach new needle".
2.	The graphic in IFU Step 3 depicting the direction to turn the needle lacks clarity.	User confusion regarding how to attach the needle might increase the risk of dose omission or delayed dose. The results and subjective feedback collected during your HF validation studies indicated that for the task "Attach the needle", 1 participant failed the task and 3 participants had difficulty with the task. Specifically, we note that 1 participant indicated that they had difficulty determining which direction was clockwise due to the orientation of the pen injector (e.g. needle cap was not facing them as in the IFU).	Revise the arrow in the IFU Step 3 graphic depicting the direction to turn the needle to more clearly indicate the direction to turn the needle (e.g. increase the circumference and/or prominence of the arrow graphic).

Table 4: Identified Issues and Recommendations for Pfenex Inc. (sent to sponsor on 8/19/19)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
3.	The graphic in IFU Step 9b lacks clarity regarding the direction to turn the needle.	User confusion regarding the direction to turn the needle might result in wrong technique errors. The results and subjective feedback collected during your HF validation studies indicated that for the first time use scenario for the task "Remove the used needle from the pen injector", 11 participants failed the task and 11 participants had close calls or use difficulties.	Revise the graphic in IFU Step 9B to more specifically indicate the direction to turn the needle to remove it (e.g. increase the circumference/ prominence of the arrow graphic).
4.	The graphic in IFU Step 9c depicts a cropped graphic of a sharps container, which lacks clarity.	User confusion regarding proposal disposal of used needles might result in needle stick injury. The results and subjective feedback collected during your HF validation studies indicated that for the first time use scenario for the task "Dispose of the used needle in the sharps container", 16 participants failed to properly dispose of the used needle in the sharps container. Specifically, 2 participants indicated that the trash can in the study environment appeared similar to the puncture resistant container (i.e. sharps container) shown in the IFU.	Consider revising the IFU Step 9c graphic so that it provides a full depiction of a sharps container.
Container Label			

Table 4: Identified Issues and Recommendations for Pfenex Inc. (sent to sponsor on 8/19/19)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
1.	The storage statement on the container label is not prominent.	Lack of prominence of the storage information may contribute to deteriorated drug errors . The results and subjective feedback collected during your HF validation studies indicated that in the first time use scenario, 7 participants failed to properly store the pen injector in the refrigerator with the white cap and needle attached.	Increase the prominence of the word "Refrigerate" on container label (e.g. bolding, boxing, or other means to increase prominence).
2.	The container label does not contain an Rx only statement.	The Rx only statement is required on the drug label by Section 503(b)(4)(A) of the Federal Food, Drug, and Cosmetic Act.	Revise the container label to include an Rx only statement.
3.	The container label does not have a linear barcode.	The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible.	Include a linear barcode on the container label as required per 21 CFR 201.25(c)(2). Additionally, the barcode should be oriented lengthwise along the label to ensure it can be properly scanned (e.g. if the barcode wraps around the curvature of the pen injector, it will not be scannable).
4.	The expiration date format is not defined.	Lack of clarity regarding the expiration date might contribute to confusion and deteriorated medication errors.	Identify the format for the expiration date you intend to use. We recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug

Table 4: Identified Issues and Recommendations for Pfenex Inc. (sent to sponsor on 8/19/19)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
			package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.[e]
5.	The container label does not include the NDC number.	An NDC number is requested, but not required, on drug labels per 21 CFR 201.2. The NDC number should be provided for Agency review.	Revise the container label to include the NDC number.
6.	The route of administration is not prominent.	The route of administration is critical information that should be prominently displayed on the principal display panel (PDP).[f]	Revise the label to increase the prominence of the intended route of administration.
Carton Labeling			
1.	The Rx only statement is too prominent.	The Rx Only statement may draw attention away from important product identifying information on the PDP (e.g. product strength)	Reduce the prominence of the Rx only statement so that it does not appear with equal prominence as important identifying information on the PDP.
2.	The NDC number is denoted by a placeholder	The NDC number should be provided for Agency review.	Revise the carton labeling to include the NDC number.

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

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

Table 4: Identified Issues and Recommendations for Pfenex Inc. (sent to sponsor on 8/19/19)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
3.	The carton labeling does not include the net quantity.	The net quantity of contents statement is required per 21 CFR 201.51.	Revise the carton labeling to include a net quantity statement (e.g. 1 prefilled pen) on the PDP and ensure it is located away from the product strength.
4.	The carton labeling does not include the expiration date.	The expiration date is required per 21 CFR 201.17.	Revise the carton labeling to include the expiration date. We recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.[g]
5.	The carton labeling does not include the lot number.	The lot number is required per 21 CFR 201.10(i)(1).	Revise the carton labeling to include the lot number and ensure the lot number is clearly differentiated from the expiration date.
6.	The product has a different expiration date after the patient first uses the pen injector.	The proposed product has a different expiration date after first using the pen injector and the carton labeling should have a set space and format for the user to record	Revise the statement "(b) (4)" to "Date of first use __/__/__. Discard unused portion 28 days after first use" in bold font. The "__/__/__" statement will alert the users to write

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

Table 4: Identified Issues and Recommendations for Pfenex Inc. (sent to sponsor on 8/19/19)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
		the date of first use to mitigate the risk of deteriorated drug errors.	a complete date (month, day, and year) on the carton labeling.
7.	The carton labeling does not include a human-readable and machine-readable (2D data matrix barcode).	In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act. The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively.	We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling.[h]

[h] The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

4. CONCLUSION AND RECOMMENDATIONS

The results of the HF validation study identified failures, close calls, and use difficulties with critical and essential tasks. We provide recommendations to decrease risk of medication error with the intended use of the proposed product. Our evaluation of the proposed label and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 3 for the Division and Table 4 for the Applicant. We note that the Division conveyed Table 4 to the applicant/sponsor on August 19, 2019[i] and we recommend that the revisions are implemented along with additional revisions proposed by the sponsor. In this particular instance, we have determined that that these changes can be implemented without additional validation testing to be submitted for review.

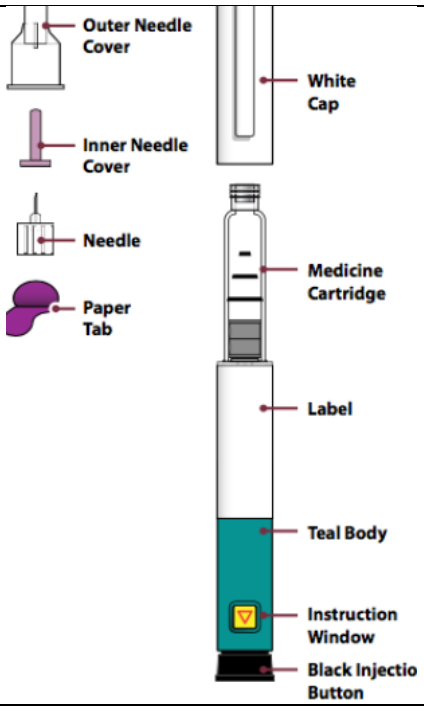
[i] Information Request for Teriparatide injection NDA 211939. Silver Spring (MD): FDA, CDER, OND, DBRUP (US); 2019 AUG 19. https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af8050f2b7&_afrRedirect=2818678787820065

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for Bonsity that Pfenex Inc submitted on March 6, 2019.

Table 5. Relevant Product Information	
Initial Approval Date	N /A
Therapeutic Drug Class or New Drug Class	Parathyroid Hormone Analog
Active Ingredient	teriparatide (b) (4)
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 Glucocorticoid-Induced Osteoporosis at High Risk for Fracture
Route of Administration	subcutaneous
Dosage Form	injection solution
Strength	(b) (4) mcg/(b) (4) mL
Dose and Frequency	20 mcg subcutaneously once a day injected into the thigh or abdominal wall
How Supplied	Multi-dose prefilled delivery device (pen) for subcutaneous injection containing 28 daily doses of 20 mcg. The BONSITY delivery device (pen) is available in the following package size: - 2.48 mL prefilled delivery device
Storage	- The BONSITY delivery device should be stored under refrigeration at 2°C to 8°C (36°F 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 BONSITY if it has been frozen.

Container Closure/Device Constituent	
Intended Users	Patients, caregivers, HCP
Intended Use Environment	Home or healthcare setting

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On July 2, 2019, we searched the L:drive and AIMS using the terms, teriparatide and NDA 211939, to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified 3 previous reviews[jkl], and we confirmed that our recommendations were either implemented or considered.

APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The background information can be accessible in EDR via:
\\cdsesub1\evsprod\nda211939\0012\m5\53-clin-stud-rep\535-rep-effic-safety-stud\osteoporosis\5354-other-stud-rep\rpt-00149\rpt-00149.pdf

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessible in EDR via:

- HF validation study results summary report:
  \\cdsesub1\evsprod\nda211939\0012\m5\53-clin-stud-rep\535-rep-effic-safety-stud\osteoporosis\5354-other-stud-rep\rpt-00149\rpt-00149.pdf
- HF validation study (patients, caregivers, HCP):
  \\cdsesub1\evsprod\nda211939\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\osteoporosis\5354-other-stud-rep\study-0190\report-body.pdf
- Supplemental HF validation study (Forteo-experienced patients):
  \\cdsesub1\evsprod\nda211939\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\osteoporosis\5354-other-stud-rep\study-0191\report-body.pdf
- Supplemental HF validation study addendum:
  \\cdsesub1\evsprod\nda211939\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\osteoporosis\5354-other-stud-rep\study-0258\report-body.pdf

[j] Baugh, D. Review of Threshold Analysis, Label, and Labeling for Teriparatide Injection, IND 129196. Silver Spring, MD. Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis; 2017 Nov 22. RCM No.: 2017-1812.
[k] Baugh, D. Review of Threshold Analysis, Label, and Labeling (Amendment) for Teriparatide Injection, IND 129196. Silver Spring, MD. Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis; 2019 Jan 26. RCM No.: 2017-1812-1.
[l] Hoste, S. Human Factors Protocol Review for Teriparatide injection IND 129196. Silver Spring, MD. Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis; 2018 NOV 5. RCM No.: 2018-1539.

- HF validation study addendum: \\cdsesub1\evsprod\nda211939\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\osteoporosis\5354-other-stud-rep\study-0259\report-body.pdf

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On March 6, 2019, we sent an Information Request (IR) to the sponsor requesting the injection time specification, a breakdown of untrained patient participants and whether they had pen/autoinjector experience, side-by-side comparison of IFU used in the HF validation testing vs. the intend-to-market IFU, and other clarifying HF information. The sponsor responded on March 18, 2019:
\\cdsesub1\evsprod\nda211939\0008\m1\us\111-information-amendment\1113-information-amend-clinical.pdf
\\cdsesub1\evsprod\nda211939\0008\m5\53-clin-stud-rep\535-rep-effic-safety-stud\osteoporosis\5354-other-stud-rep\rpt-00149\5354-comparison.pdf

On April 5, 2019, we sent an IR to the sponsor requesting detailed participant performance data and subjective feedback data for the tasks Set dose and Administer dose and requesting a clarification regarding a post-validation revision. The sponsor responded on April 10, 2019:
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\\cdsesub1\evsprod\nda211939\0012\m5\53-clin-stud-rep\535-rep-effic-safety-stud\osteoporosis\5354-other-stud-rep\rpt-00149\rpt-00149.pdf

On April 22, 2019, we sent an IR to the sponsor requesting additional root causes analysis information for the failures with the tasks Set Dose and Administer Dose, justification regarding the sponsor's determination not to validation IFU revisions made after HF validation testing, and clarification regarding participant response to a debrief question. The sponsor responded on April 26, 2019:
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On May 13, 2019, we sent at IR to the sponsor requesting additional participant performance information for the task Set Dose and detail about other similar marketed pen injector products. The sponsor responded on May 17, 2019:
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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,[m] along with postmarket medication error data, we reviewed the following Bonsity labels and labeling submitted by Pfenex Inc.

- Container label received on 12/7/2018
- Carton labeling received on 12/7/2018
- Instructions for Use (image not shown) received on 3/6/2019
  - EDR link: \\cdsesub1\evsprod\nda211939\0001\m1\us\draft-user-manual.docx
- Prescribing Information (Image not shown) received on 3/6/2019
  - EDR link: \\cdsesub1\evsprod\nda211939\0006\m1\us\114-labeling\draft\labeling\draft-pi-bonsity.docx

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

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08/29/2019 04:58:20 PM

Memorandum of Review

STN:	505(b)(2) NDA211939 Original,
Subject:	**Consult: Immunogenicity Review**
Submission Date:	12/07/2018
Review/Revision Date:	4/26/2019, 8/15/2019
Primary Reviewer:	Haoheng Yan, MD, PhD (Immunogenicity assays) Product Quality Reviewer, OPQ/OBP/DBRR IV
Secondary Reviewer:	Fred Mills, PhD Staff Scientist, OPQ/OBP/DBRR IV
Applicant:	PFenext, Inc
Product:	PF708
Indications:	Osteoporosis
Consult Due Date:	8/29/2019

Summary

PF708, teriparatide injection, a 34 amino acid recombinant analog of human parathyroid hormone (rhPTH[1-34]), for the treatment of osteoporosis with high risk of fracture. PF708 is developed as a proposed therapeutic equivalent to Forteo® (teriparatide (b) (4) injection) for subcutaneous injection (NDA 021318; approved November 26, 2002). The applicant developed an anti-drug antibody (ADA) assay, which includes screening, confirmatory and cross reactivity (endogenous PTH1-84) assays. The ADA assay uses a direct ELISA format (with protein A/G as detection agent). All patient samples were tested with the ADA screening assay, the screening positive samples were tested in the PTH1-34 confirmatory assay and the PTH1-84 cross reactivity assay. All PTH1-34 confirmed positive samples were tested in a cell based neutralizing antibody assay. Overall, both ADA and NAb assay are appropriately validated and adequate the intended use. Eight samples from 4 patients were tested positive for the ADA against PTH1-34, none of which cross reacted with endogenous PTH1-84 or showed neutralizing activity to PTH1-34.

Consult:

This is a New Original NDA with immunogenicity data. DBRUP is requesting OBP to review the immunogenicity portion of the application.

Current Forteo® label:

Immunogenicity — In the clinical trial, antibodies that cross-reacted with teriparatide were detected in 3% of women (15/541) receiving FORTEO. Generally, antibodies were first detected following 12 months of treatment and diminished after withdrawal of therapy. There was no evidence of hypersensitivity reactions or allergic reactions among these patients. Antibody formation did not appear to have effects on serum calcium, or on bone mineral density (BMD) response.

Clinical Immunogencity Finding

Study PF708-301, daily 20mg s.c. for 24 weeks is the main comparatively clinical study with immunogenicity sample testing. Two (2.3%) PF708-treated patients and 2 (2.2%) Forteo-treated patients had detectable ADA during the study. For PF708, 1 patient (b) (6)) had detectable levels of ADA at weeks 1, 4, 12, and 24. An additional patient (b) (6)) had detectable levels of ADA at weeks 12 and 24. For Forteo, 2 patients (b) (6)) had detectable levels at week 12 only (see table below).

Subject	Time Point	Batch Number	Sample ID	Raw Response Individual	Mean Response Value	% CV	Mean > In-Study CP	Neutralizing Result	Comment	In-Study CP
(b) (6)	Day 84	1	T7946720141	188319 203659	195989	5.5	Yes	Negative		123426
	Day 84	1	T7908437804	131693 152561	142127	10.4	Yes	Negative		123426
	Day 84	1	T7946170150	149591 168985	159288	8.6	Yes	Negative		123426
	Day 168	1	T7908922402	138064 166422	152243	13.2	Yes	Negative		123426
	Day 7	1	T7912595594	162827 145295	154061	8.0	Yes	Negative		123426
	Day 28	1	T7933559720	132065 113220	122642	10.9	No	Positive		123426
	Day 84	1	T7913120778	162510 131824	147167	14.7	Yes	Negative		123426
	Day 168	1	T7908389901	161850 154006	157928	3.5	Yes	Negative		123426

The applicant states: "PF708-related ADA findings were low in titer and resolved during follow-up, without apparent correlation with AEs of special interest or SAEs."

Review

- Unless otherwise noted, figures and tables in this review are copied directly from the submission.
- The review sequence of the individual aspect of the assay validation may not follow the exact sequence in the submission.
- The "guidance" cited in the review refers to the "Guidance for Industry: Immunogenicity Testing of Therapeutic Protein Products —Developing and Validating Assays for Anti-Drug Antibody Detection, January 2019" https://www.fda.gov/media/119788/download
- The reviewer's comments are shown in italic fond.

- An information request (IR) was sent to the applicant on May 30, 2019, the response was received the on 7/1/2019. The response was integrated into the context of the review.

Testing Strategy

The sponsor uses a tiered approach to detect anti-drug antibody (ADA) in clinical samples. Samples are first tested in an ADA screening assay, samples that screened positive are tested in a confirmatory assay. Confirmed positive sample are tested for titer and neutralizing antibody (NAb).

Reviewer's Comment: *The sponsor's approach to evaluate ADA is adequate (per the guidance).*

Anti-drug Antibody Binding Assay:

Validation Results (Validation Report No. RPTX-0051, Version 3.0) and Reviewer Assessment for ADA assay.

Validation Parameter	**Validation Report No. RPTX-0051, Version 3.0**	***Reviewer Comment***
Contract Research Organization	(b) (4)	*N/A*
Assay principle	ELISA using plates coated with PF708 or Forteo. ADA were detected using Protein A/G Peroxidase Conjugate. Samples were read by a colorimetric plate reader.	*Only PF708 coated plates were used in clinical testing.*
Sample Pretreatment (Acid dissociation, beads…)	None	*N/A*
Positive control (PC)	Rabbit PF708 Anti-Drug Polyclonal Antibody	*N/A*
PC Dose Curve and Hook Effect	No hook effect detected up to 1250ng/mL PC.	*N/A*
LPC1	100ng/mL	*LPCs were appropriate set based on the assay sensitivity, LPC1, LPC2 and HPC were used as PC in the clinical testing.*
LPC2	75ng/mL	
HPC	250ng/mL	
Matrix and NC	Normal human serum, prepared from 50 human serum lots used for cut point determination.	*Acceptable*
Screening cut- point (SCP): SCP: 1.6662 x NC (normal human serum) In study SCP: 1.0945 x NC	Determined from 50 individual lots of human serum, analyzed 3 times, each on different days, by 2 different analysts, resulting in 6 datasets. SCP was determined using parametric method by [median+1.654 x 1.4826 x MAD], MAD: median absolute deviation The in-study SCP was determined	*The applicant did provide data or statistical analysis on how the in study SCP were determined. An IR was sent requesting the information. In the response, the applicant stated that assay results (OD) from all 180 pre-dose samples were used to calculate in-study SCP. The log transformed OD values were found to be normally*

	using pre-dose patient samples.	*distributed. The in study SCP was calculated using the formula listed in the adjacent cell. The response is acceptable,and the in study SCP is acceptable*.*
Confirmatory cut-point (CCP): %Inhibition=100 x (1 - (PF 708 fortified sample response/unfortified sample response)) =12.8%	CCP was determined using the same dataset as SCP determination at 0.1% false positive rate	*The confirmatory cut point is acceptable.*
Titer Cut Point (TCP)	Same as SCP	*Acceptable*
Sensitivity	62.5ng/mL	*Acceptable*
Assay Drug tolerance	Assay can detect 75 ng/ml of PC in the presence of 0.100nM of on-board PF708	*The drug half life is ~1 hr. Since the samples were draw before dosing, assay is not required to tolerate on-board drug.*
Interference by hPTH	Assay can detect 75 ng/ml of PC in the presence of 1000ng/mL hPTH	*The endogenous PTH1-84 are less than 1ng/mL (data provided in IR6). The results are acceptable.*
Precision	HPC, LPCs and NC %CV for 15 runs, all intra- and inter- assay %CV <15%	*Acceptable*
Selectivity	10 lots of human serum, 20 lots of Osteoporotic Human Serum spiked with 60ng/mL, all are positive	*Acceptable*
Stability	• 24 hours at ambient temperature under white light • 6 freeze thaw cycles Recoveries were are all between 90-110%	*Acceptable*
Hemolysis	5% whole blood spiked sample were tested with HPC, LPC. No false positive or negative were tested in 5% whole blood spiked samples.	*Acceptable*
Assay Acceptance Criteria	%CV for each replicate for scored positive samples ≤20.0% 0.5 x Validation Mean ≤ OD of NC ≤ 2.0 x Validation Mean 0.7576 ≤ LPC1 ≤ 1.4054 0.6144 ≤ LPC1 ≤ 1.1472 HPC ≤ 1.6038	*The acceptance criteria were based on statistical analysis of the results from 18 validation runs using mean* $\pm t_{(0.01,\, n-1)}$ *x SD. The assay acceptance criteria are acceptable.*

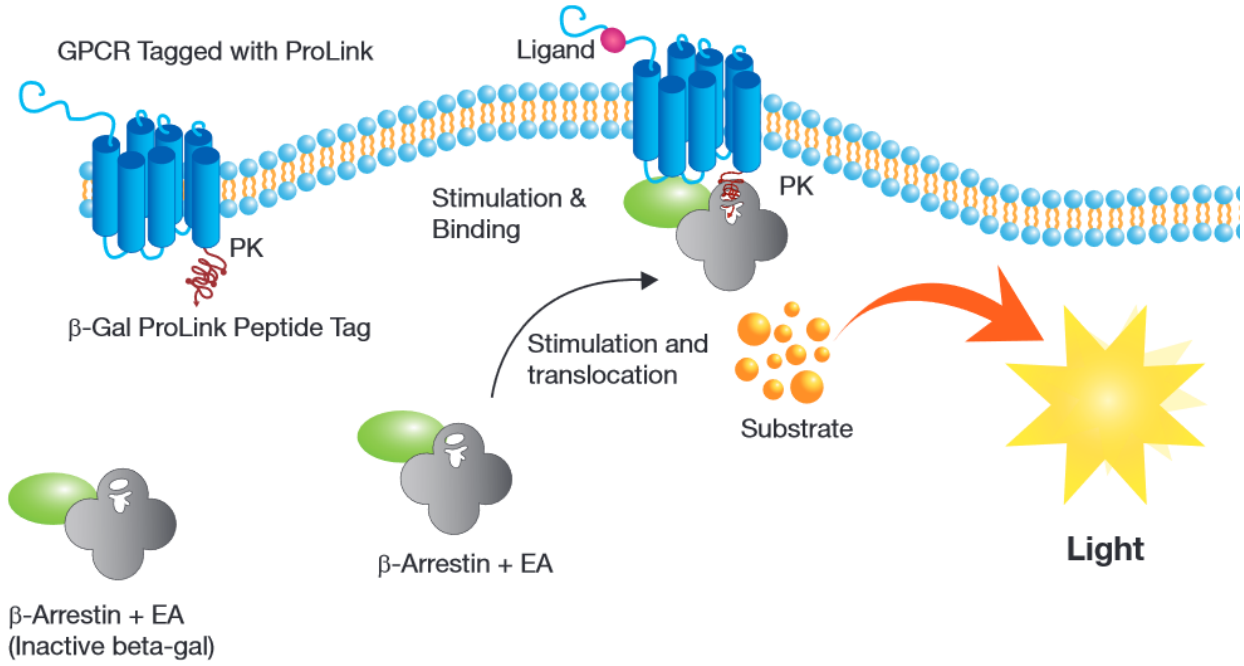
***** When assay CP is adjusted, the values of certain assay parameters such as precision, selectivity and drug tolerance would change accordingly in the validation exercise. Compared to a validation SCP: 1.6662 x NC, the in study SCP: 1.0945 x NC would increase the value of precision, selectivity and drug tolerance to better values. Therefore we did not request these parameters to be recalculated in the validation report.

The applicant did not provide assay performance for testing ADA cross reactivity to endogenous PTH 1-84 in the assay validation. In the IR response, the applicant stated that samples tested positive in the ADA screening assay were further tested for cross reactivity using excess PTH1-84 (competitive inhibition). The results were provided in Table 5 of the report for ELISA Determination of Anti-Human Parathyroid Hormone (PTH) 1-34 Antibodies in Human Serum (CA19926-02). The PTH1-84 %inhibition for all ADA screening positive samples was <12%.

Reviewer's Comment: a*lthough the applicant did not provide a cut point for PTH1-84 cross reactivity, the low levels of inhibition strongly suggest that there are no samples cross reactive to PTH1-84.*

Neutralizing Antibody Assay:

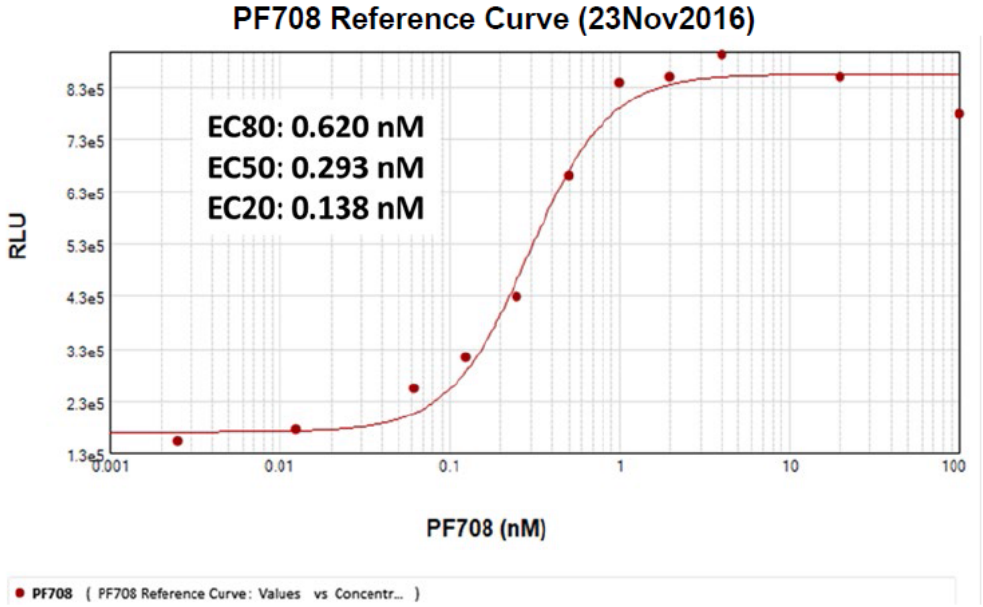
The applicant used a commercial PTH cell based assay, PathHunter® PTH Bioassay Kit, from Discover X, Fremont CA. It detects interaction of β-Arrestin with the activated GPCR (G Protein Coupled Receptor) designated PTH1R- the classical PTH receptor expressed at high levels in bone and kidney. This interaction is detected using β-galactosidase (β-gal) enzyme fragment complementation. In this system the GPCR is fused in frame with a small, 42 amino acid fragment of β -gal called ProLink™ and co-expressed in cells stably expressing a fusion protein of β-Arrestin and the larger, N-terminal deletion mutant of β-gal (called enzyme acceptor or EA). Activation of the GPCR stimulates binding of β-Arrestin to the ProLink-tagged GPCR and forces complementation of the two enzyme fragments of β-galactosidase, resulting in the formation of an active β-gal enzyme. This action leads to an increase in enzyme activity that can be measured using chemiluminescent PathHunter Bioassay Detection Reagents". (See illustration below copied from the PathHunter Kit user manual)



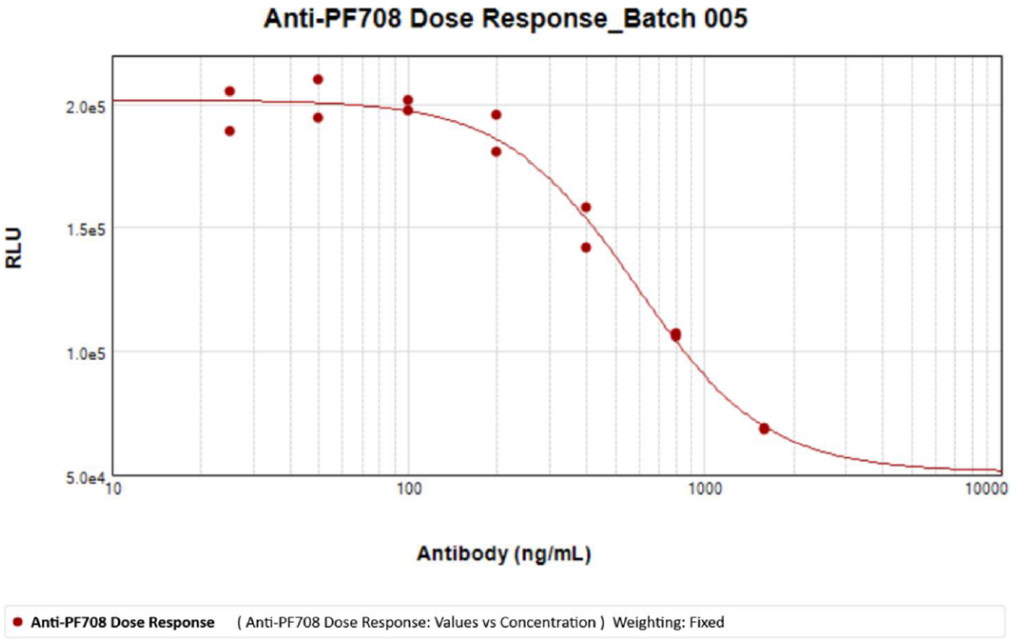
Reviewer's Comment:

The PathHunter kit measures the activation of the GPCR receptor by the ligand (PTH), which reflects the molecular mechanism of action for PTH. Therefore it is an appropriate assay format

for the NAb assay as long as it PF708 can activate the receptor too. In the IR response, the applicant confirmed that PF708 was used the activator in the assay. In addition, the applicant provided PF708 dosing curve (see below) to support the PF708 concentration at 0.5nM used in the assay was within the linear range of the dosing curve (per guidance).



The PathHunter PTH Bioassay Kit is a quantitative assay based on dilution curves. The applicant adapted the assay to a qualitative assay using a single agonist concentration. We requested the applicant provide a NAb assay dose response curve for neutralizing antibody control vs luminescence signal to support the suitability of the such adaptation. In the IR response, the applicant provided multiple dosing curves, demonstrating that the assay luminescence signal is dependent on the concentration of the neutralizing antibody control and dynamic range is ~200ng/mL to 1000ng/mL. The response is acceptable, and the assay design is acceptable.



Validation Results (Validation Report No. RPTX-0022, Version 2.0) and Reviewer Assessment for NAb assay.

Validation Parameter	Validation Report No. RPTX-0051, Version 3.0	Reviewer Comment
Contract Research Organization	(b) (4)	*A commercial bioassay kit, PathHunter® PTH Bioassay Kit, from Discover X, Fremont CA, is used.*
Positive control (PC)	Rabbit PF708 Anti-Drug Antibody ((b) (4)) Mouse Anti-Human PTH Monoclonal Antibody ((b) (4))	*Rabbit polyclonal PF708 Anti-Drug Antibody were used in the clinical study.*
PC Dose Curve and Hook Effect	Not provided	
LPC1	1000ng/mL (Rabbit polyclonal PC)	*The level of LPCs were appropriate based on the assay sensitivity*
LPC2	700ng/mL (Rabbit polyclonal PC)	
Matrix and NC	Normal human serum,	
Cut- point (CP): **Validation CP (vCP):** 0.83 x NC (normal human serum) **In study SCP:** NC - 41163	Determined from 30 individual lots of human serum, analyzed 3 times, each on different days, by 2 different analysts, resulting in 6 datasets. vCP was determined using parametric method by [median+1.654 x 1.4826 x MAD], MAD: median absolute deviation of the log(luminescent response)	*The applicant did provide data or statistical analysis on how the in study SCP were determined. In addition, the entire NAb assay validation report was based on the CP of 0.83xNC, the assay performance at the new in study was not provided. An IR was sent requesting the information. See additional information in the text below the table.*

	CP factor=vCP/mean NC The in-study SCP was determined using pre-dose patient samples.	
Sensitivity	Monoclonal PC: ~50ng/mL Polycolonal PC: ~800ng/mL	*These results were obtained by the reviewer from the PC concentration at which 5/5 runs scored positive in the serial dilution runs (Table 4, 5). At 400ng/mL polyclonal PC, 4/5 runs were positive.*
Assay Drug tolerance	Assay can detect 700 ng/ml of PC in the presence of 0.100nM of on-board PF708	*The drug half life is ~1 hr. Since the samples were draw before dosing, assay is not required to tolerate on-board drug.*
Interference by hPTH (PTH1-84)	Assay can tolerate PTH1-84 up to 0.1nM	*Level of endogenous PTH1-84 are likely to interfere assay signal, and the level of PTH1-84 in the patients' samples might be significantly different from its level in NegC. An IR was sent requesting the applicant to evaluate assay performance under the influence of different levels of PTH1-84. See IR response in the text below the table.*
Precision	11 runs in total Intra- assay precision %CV <20% (LPC1 and LPC2 and NC), Inter- assay %CV=29% (LPC1 and LPC2 and NC)	*Assay precision is deemed acceptable give that this is a cell-based assay. See response to IR and discussion below.*
Selectivity	10 lots of human serum, 10 lots of Osteoporotic Human Serum spiked with 700ng/mL and 1000ng/mL PC, all are positive	*Acceptable*
Stability	• 24 hours at ambient temperature under white light • 6 freeze thaw cycles Recovery are all between 85-110%	*Acceptable*
System Suitability	%CV for each replicate for scored positive samples ≤20.0% 0.5 x Validation Mean (67915)≤ OD of at least one NC ≤ 2.0 x Validation Mean (271658) 4664≤ LPC1 ≤ 128453 6314 ≤ LPC1 ≤ 158171	*The acceptance criteria were based on statistical analysis of the results from 11 validation runs using mean* $\pm t_{(0.01, n-1)}$ *x SD. The assay acceptance criteria are acceptable.*

In study CP:

The in study CP was calculated from the luminescent results of 30 predose samples, each sample was tested for 3 times and the results were collected as 3 datasets. All 3 datasets were found to be

normally distributed. In study cut point was calculated using a parametric method [median+1.654 x 1.4826 x MAD, yielding a 5% false positive rate] and then normalized with mean of NC.

Because the data are normally distributed, a parametric method is justified. Additional scaling using a 1.4826 factor targets a 5% false positive rate (more conservative than the recommended 1% false positive rate). Therefore, the response is acceptable.

The applicant submitted a validation addendum for assay sensitivity, selectivity and precision at the in-study cut point of "NC – 41163". Assay sensitivity is at 518ng/mL and 51ng/mL by anti-PF708 polyclonal and anti-PTH monoclonal PCs, respectively.

The observed sensitivities are within the expected range for cell-based NAb assays. Thus the assay sensitivity is acceptable.

Assay selectivity was determined using 10 lots of human serum, 10 lots of osteoporotic human serum spiked with 700ng/mL and 1000ng/mL polyclonal PC. All spiked normal serum samples were tested positive, 8/10 700ng/mL PC spiked osteoporotic human serum were positive and 9/10 spiked osteoporotic human serum were positive.

The assay is able to capture positive responses in almost all spiked samples. Therefore, the assay selectivity is acceptable.

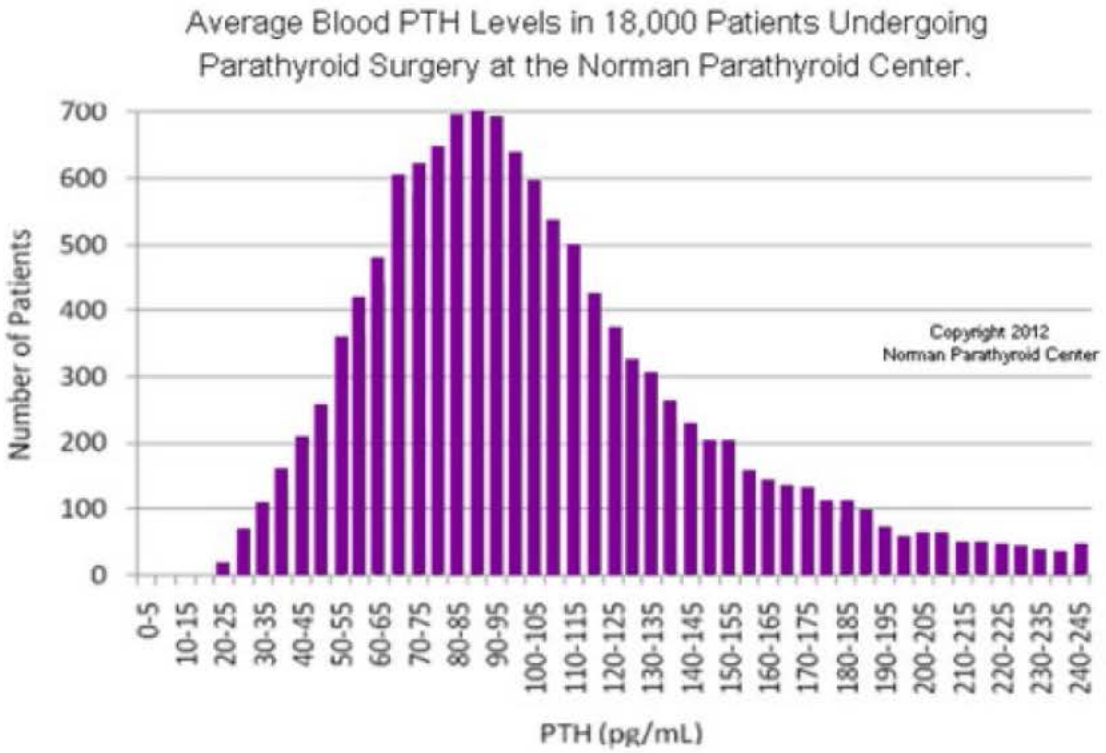
The applicant normalized data (signal-NC) to calculate the assay precision. The intra- and inter-assay precision are <24% and <31% for both PCs at 700ng/mL and 1000ng/mL.

Per guidance, "the intra-assay and inter-assay precision as expressed by percent coefficient of variation (%CV) is expected to be lower than 20%. However, it may be higher in some assay formats such as cell-based assays." Considering the NAb assay is a cell-based assay, the precision reported is acceptable.

PTH708 interference:

The established drug tolerance is up to 0.100 nM (assay can detect 700ng/mL PC in the presence of 0.1nM PF708) PF708. The applicant states that because the intact PTH 1-84 exerts its biological functions by through its active domain in the first 34 amino acids, it is concluded that the current NAb assay can tolerate the endogenous PTH 1-84 up to 0.100 nM, which is equivalent to 942 pg/mL. Based on the average blood PTH levels in patients undergoing parathyroid surgery published online by Norman Parathyroid Center (https://www.parathyroid.com/hyperparathyroidismdiagnosis.htm), it is unlikely for a subject in the clinical trial to have serum PTH higher than 942 pg/mL.

Given this justification, the response is acceptable.



Information Request sent to the applicant on May 30, 2019:

(b) (4)

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M E M O R A N D U M

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

DATE: 2/8/2019

TO: Division of Bone, Reproductive and Urologic Products
Office of Drug Evluation IV

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 211939

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the sites listed below. The rationale for this decision is noted below.

Rationale

Covance Clinical Research Unit, Inc.: This site is permanently closed. The Office of Regulatory Affairs (ORA) inspected the site in November 2015. The inspection was conducted under the following submission: BLA 125509.

The final classification for the inspection was No Action Indicated (NAI).

The pharmacokinetic (PK) study under the BLA 125509 was conducted within 2.5 years of the PK study under the current submission (NDA 211939).

(b) (4)

OSIS inspected the site in (b) (4). The inspection was conducted under the following submission: (b) (4)

The final classification for the inspection was No Action Indicated (NAI).

Therefore, based on the outcome of the previous inspection and the rationale described above, an inspection is not warranted at this time.

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	Covance Clinical Research Unit, Inc.	617 Oakley Street, Evansville, IN
Analytical	(b) (4)	(b) (4)

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ANGEL S JOHNSON
02/21/2019 10:32:53 AM