# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 211939Orig1s000

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 129196

**MEETING MINUTES**

Pfenex Inc.
Attention: Maria Feldman
Consultant, Regulatory Affairs
10790 Roselle Street
San Diego, CA 92121

Dear Ms. Feldman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PF708 (teriparatide injection).

We also refer to the meeting between representatives of your firm and the FDA on July 17, 2018. The purpose of the meeting was to discuss a proposed data package, format, and content to support filing and review of a 505(b)(2) new drug application (NDA).

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Samantha Bell, Regulatory Project Manager at (301) 796-9687.

Sincerely,

*{See appended electronic signature page}*

Theresa Kehoe, M.D.
Clinical Team Leader
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

**FOOD AND DRUG ADMINISTRATION**
CENTER FOR DRUG EVALUATION AND RESEARCH

# MEMORANDUM OF MEETING MINUTES

| | |
|---|---|
| **Meeting Type:** | B |
| **Meeting Category:** | Pre-NDA |
| **Meeting Date and Time:** | July 17, 2018, 11:00 A.M. to 12:00 P.M. |
| **Meeting Location:** | 10903 New Hampshire Avenue<br>White Oak Building 22, Conference Room: 1415<br>Silver Spring, Maryland 20903 |
| **Application Number:** | IND 129196 |
| **Product Name:** | PF708 (teriparatide injection) |
| **Proposed Indications:** | Treatment of postmenopausal women with osteoporosis at high risk for fracture<br>Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture<br>Treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture |
| **Sponsor/Applicant Name:** | Pfenex Inc. |
| **Meeting Chair:** | Theresa Kehoe, M.D. |
| **Meeting Recorder:** | Samantha Bell |

**FDA ATTENDEES**

Division of Bone, Reproductive, and Urologic Products:
Hylton V. Joffe, M.D., M.M.Sc., Director
Theresa Kehoe, M.D., Clinical Team Leader
Stephen Voss, M.D., Medical Officer
Jacqueline Karp, M.D., Medical Officer
Miyun Tsai-Turton, Ph.D., Pharmacology and Toxicology Reviewer
Margaret Kober, R.Ph., M.P.A., Chief, Project Management Staff
Samantha Bell, B.S., B.A., R.A.C., Regulatory Health Project Manager

Office of Pharmaceutical Quality (OPQ), Office of New Drug Products:
Mark Seggel, Ph.D., Acting CMC Lead
Donna Christner, Ph.D., Branch Chief
Avital Shimanovich, Ph.D., Microbiologist
Marla Stevens-Riley, Ph.D., Microbiologist

OPQ, Office of Biotechnology Products (OBP):
William Hallett, Ph.D., Team Leader, OBP

Office of Translational Sciences (OTS), Office of Clinical Pharmacology (OCP):
Peng Zou, Ph.D., Clinical Pharmacology Reviewer

Office of Surveillance and Epidemiology (OSE), Immediate Office:
Oyinolola Fashina, Project Manager

OSE, Office of Medication Error Prevention and Risk Management:
Denise Baugh, Safety Evaluator, Division of Medication Error Prevention and Analysis (DMEPA)
Lolita White, Pharm.D., Team Lead, DMEPA
Shannon Hoste, General Engineer for Human Factors, DMEPA
CDR Quynh Nhu Nguyen, M.S., Associate Director for Human Factors, DMEPA
Jacqueline Sheppard, Pharm.D., Risk Management Specialist, Division of Risk Management (DRISK)

Center for Devices and Radiological Health (CDRH), Office of Device Evaluation, General Hospital, Respiratory, Infection Control, and Dental Devices (DAGRID), General Hospital Devices Branch:
Lening Shen, B.S., M.B.A., General Engineer, Lead Reviewer
CDR Alan Stevens, Branch Chief
Carolyn Dorgan, Team Leader

Office of Scientific Investigations:
Roy Blay, Ph.D., Reviewer

**SPONSOR ATTENDEES**
Hubert C. Chen, M.D., Chief Medical and Scientific Officer
Mayda Mercado, Vice President, Global Quality
Keith Haney, Senior Director, Product Development
Jeff Allen, Ph.D., Senior Director, Analytical Services
Eric Cunningham, Associate Director, Process Characterization
Christine Thai, Associate Director, Device and Packaging
(b) (4), Consultant, Quality
(b) (4) Consultant, Regulatory Affairs
Maria Feldman, Consultant, Regulatory Affairs

## 1.0 BACKGROUND

Pfenex Inc. is developing PF708 as a proposed therapeutic equivalent to Forteo [teriparatide (rDNA) injection] (NDA 021318). The active ingredient in PF708 is teriparatide, a 34-amino

acid recombinant analog of human parathyroid hormone (rhPTH [1-34]). Pfenex is proposing to use a pen device that the Sponsor claims is similar to that of Forteo.

The FDA had a Pre-Investigational New Drug Application meeting with Pfenex to discuss their development plans on March 15, 2016.

Pfenex has conducted two clinical studies with PF708: a single-dose, 2-way crossover study (PF708-101) comparing the pharmacokinetics of PF708 and Forteo in healthy subjects, and a 24-week study (PF708-301) comparing the effects of PF708 and Forteo in osteoporosis patients.

Pfenex would like to discuss a proposed data package, format, and content to support filing and review of a 505(b)(2) NDA.

FDA sent Preliminary Comments to Pfenex on July 13, 2018.

## 2. DISCUSSION

***General FDA Comment*:** It is not clear from your meeting materials whether the to-be-marketed drug-device combination product is exactly the same as the drug-device combination product used in the studies supporting your NDA. Provide clarification on your proposed device.

***Discussion at the Meeting:***
Pfenex responded that the PF708-101 and PF708-301 clinical studies were conducted using the PF708 finished drug product (pen injector). See Questions 6 and 8 for additional discussion regarding testing to support the to-be-marketed device.

### 2.1. Nonclinical

***Question 1:* Does the Agency agree that the nonclinical information can be summarized only in Section 2.4 of the NDA for PF708?**

***FDA Response to Question 1:***
Yes. Nonclinical information can be summarized in Module 2.4, along with the safety information for the listed drug and any new nonclinical safety information identified during a literature search. Documents for Section 2.6 are not necessary. However, final study reports of all nonclinical studies and PDF files of all literature references should be included in Module 4.

***Discussion at the Meeting:***
There was no further discussion at the meeting.

***Question 2:*** ***Does Agency agree that the nonclinical toxicology and pharmacology studies, along with publicly available information, are sufficient to support the approval of PF708 under the 505(b)(2) pathway, with Forteo as the Reference Listed Drug?***

***FDA Response to Question 2:***
The Agency agrees that the 4-week bridging toxicology study, 6-week pharmacology study, and published literature are sufficient for a 505(b)(2) NDA submission. The adequacy of your nonclinical development program will depend on review of the final study reports, the adequacy of the data you plan to reference to support your product, and CMC characterization of impurities. In addition, if there is a difference in the impurity profiles (i.e. impurity, degradants, leachables) between your product and the US-approved listed drug, additional nonclinical studies may be required to assess these impurities

The sponsor mentions that they may reference a "Summary of Product Characteristics (SmPC)" in addition to Forteo Prescribing Information and published literature. Non-U.S. regulatory authority assessments and non-U.S. approved labeling may not be relied upon to support approval of a 505(b)(2) application. If the studies that were the basis of the non-U.S. conclusions have been published, an applicant may be able to rely on that literature.

Also refer to the FDA response to Question 8.

***Discussion at the Meeting:***
There was no further discussion at the meeting.

## 2.2. Clinical

***Question 3:*** Pfenex acknowledges that the review of the iPSP may not be completed at the time of the submission of the NDA. Does the Agency agree that the Sponsor may refer to the submission of the iPSP in Section 1.9 in the NDA submission, noting that it is currently under review with the Agency?

***FDA Response to Question 3:***
Any application submitted without an Agreed iPSP may be at risk for a refuse-to-file (RTF) action. We acknowledge receipt of your June 28, 2018, Agreed iPSP submission, which is currently under review. The goal date for response to this submission is July 28, 2018.

***Discussion at the Meeting:***
There was no further discussion at the meeting.

***Question 4:*** ***Does the Agency agree that the two clinical studies, PF708-301 and PF708-101, support the review and approval of the 505(b)(2) NDA for PF708 with Forteo as the Reference Listed Drug?***

***FDA Response to Question 4:***
The design of Study PF708-101 appears reasonable for providing a pharmacokinetic bridge to scientifically justify reliance on FDA's findings for Forteo as the listed drug. Whether Study PF708-101 and Study PF708-301 are adequate to support the scientific bridge to Forteo and for approval of your 505(b)(2) NDA for PF708 is a review issue.

Clarify whether the to-be-marketed formulation and device were used in Study PF708-101 and Study PF708-301. If not, provide data to bridge the clinical batches and the to-be marketed drug-device combination product in your NDA.

***Discussion at the Meeting:***
Pfenex responded that the PF708-101 and PF708-301 clinical studies were conducted using the PF708 finished drug product (pen injector). See response under General FDA comment.

***Question 5: Does the Agency agree that the immunogenicity test method is acceptable?***

***FDA Response to Question 5:***
No, we do not agree. In your validation of your screening assay, described in document (b) (4), submitted October 26, 2017, the assay performance was assessed with positive controls used at a range of 250 ng/mL to 75.0 ng/mL. While this range of positive controls covers the low end of our expectation regarding sensitivity, it does not provide assurance that your assay works with strong positive samples. Additionally, your validation protocol indicates that you performed an assessment of a hook effect with Batch (b) (4) however, no data supporting this assessment was found. Provide information supporting your assay's capability to detect strong positives samples, and provide the data from Batch (b) (4) that was used to demonstrate the lack of a hook effect.

***Discussion at the Meeting:***
Pfenex will provide data that demonstrate the immunogenicity screening assay's capability to identify strongly positive samples, as well as data that support the lack of a hook effect with the Batch (b) (4) data in the validation report provided with the initial submission of the NDA. Pfenex confirmed they only titer patients who test positive in the screening assay. The FDA voiced a preference for titering all samples to ensure samples are within the assay's validated range.

## 2.3. Medical Device

***Question 6: Does the Agency concur with the proposed approach for design verification testing to support the to-be-marketed device?***

***FDA Response to Question 6:***
You have included a list of verifications testing including the following: requalification of the assembly process, dose button pull out force, injection force, dose accuracy (under various environmental conditioning) and overcome "stop last dose". We have noted that

break loose/glide force was not captured in this list. This is an essential performance requirement for the pen-injector and should be evaluated in addition to the listed attributes. However, without a description of the methods or reference to a standard or guidance document we cannot comment on whether these are appropriate. Please refer to the FDA Guidance titled Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products issued in June 2013 (https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm147095.pdf ) for specific standards and methods recognized by the Agency for Pen-Injectors.

In your NDA submission, verification testing documentation should include summary test results of established test methods for the product (e.g. recognized consensus standards, FDA Guidance, etc.) or complete verification test reports for unique or unrecognized test methods. All verification testing should be directly traced to the design inputs of the device constituent. Ensure that you utilize test methods and preconditioning that simulate the intended use of your product. Use a statistically significant sample size for verification testing. Provide valid justifications for the acceptability of any test results that do not pass its acceptance criteria.

As part of design verification, verify the Essential Performance Requirements (EPRs) with the to-be-marketed version of the device constituent and the intended drug product. However, if you plan to rely on verification testing conducted with a surrogate, provide a scientific rationale for the acceptability of the surrogate for the intended drug product (i.e. fluid characteristics, viscosity, etc.). If available, results of stability/shelf-life testing may be provided if the to-be-marketed version of the device constituent and intended drug product are used.

For pen-injectors, we expect the EPRs to include, at a minimum, the following:

- Dose Accuracy
- Break loose/Glide Force

Refer to the FDA Guidance titled Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products issued in June 2013 (https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm147095.pdf ) for more details.

***Discussion at the Meeting:***
See Discussion under Question 8 regarding essential performance requirements, dose accuracy and break loose/glide force.

***Question 7:*** ***Does the Agency agree with Pfenex's proposal to provide the human factors engineering/usability engineering report in the NDA and to provide additional information in response to any Agency comments to the protocols post-submission?***

***FDA Response to Question 7:***
Our review of your human factors (HF) validation study protocol entitled "Human Factors Validation Protocol" received on April 2, 2018, is in process and we plan to provide our comments by July 27, 2018. Address our comments prior to commencing your HF validation study. We agree with your proposal to provide the human factors validation study results in the NDA.

***Discussion at the Meeting:***
Pfenex notified FDA that they have initiated the HF validation study because they expected any FDA comments would likely not substantially impact the study design. FDA noted that in 2016, Pfenex was advised to wait for comments before proceeding. FDA advised Pfenex to address our comments on the HF validation study protocol in the HF validation study report to be submitted as part of the original NDA application. FDA stated that acceptability of the study results will be a review issue.

## 2.4. Chemistry, Manufacturing, and Control (CMC)

***Question 8: Does the Agency concur that the proposed drug substance and drug product specifications are adequate to support the review and approval of the NDA for PF708?***

***FDA Response to Question 8:***
No, we cannot not agree at this time that the proposed drug substance specification is adequate to support review of the NDA. We have concerns with the acceptance criteria you have set for total oxidation products. (b) (4) . Judging from the limited information provided, it is unclear why (b) (4) are necessary. Provide information on the impurity levels measured in your drug substance and product batches, in particular the clinical trial batches. The adequacy of the final drug substance (DS) specification is a review issue, and setting impurity limits will involve consultations with the entire review team, including, for example, evaluation of data by the pharmacology/toxicology review team.

Also, add size-exclusion HPLC purity with a justified acceptance criteria to the drug substance specification.

With regard to the product specification, propose acceptance criteria for individual known impurities (e.g., oxidation products, deamidation products), or justify not including specific known impurities in the specification. To support the proposed acceptance criteria, the NDA should include detailed impurity profiles obtained at release and on stability.

The drug product specification should also include tests for agglomeration/oligomeric substances and for osmolality.

The specification for commercial release of the finished drug product should include the microbiological tests of sterility per USP <71> and bacterial endotoxins per USP <85>. The endotoxin specification should be based on the maximum patient dose per the USP <85> recommendation of not more than 5 EU/kg/hour. Additionally, because the drug product is an injectable multiple dose product, anti-microbial effectiveness should be demonstrated per USP <51>. Antimicrobial effectiveness testing per USP <51> should be performed on at least one batch at expiry as recommended in ICH Q1A(R2). Final determination of the adequacy of the information will be made during review of the application.

The cartridge specification should include a test for Break Loose and Glide Force, while the pen injector specification should include a test verifying function (i.e., number of doses delivered).

The overall acceptability of the product specification will be determined based on the totality of information submitted in the NDA.

Based on the information provided, there are discrepancies in the acceptance criteria listed for design verification and the drug product specifications. For the drug product, the specifications should be defined based on the essential performance requirements as described in our response to Question 6. Include, at a minimum, dose accuracy and break loose/glide force in the drug product specifications. If you intend to propose alternative control strategies for the essential performance requirements, we recommend requesting specific feedback regarding your strategy.

***Discussion at the Meeting:***
Pfenex discussed their testing strategy diagrammed in the attached response document. FDA reiterated the request to provide data to document and support the acceptance criteria for the total oxidation products. (b) (4) FDA disagreed and explained both are essential requirements needed and are consistently required specifications for other proposed pen injectors.

***Question 9: Does the Agency agree that the stability data package for the drug substance and for the drug product is adequate to support the review and approval of the NDA for PF708?***

***FDA Response to Question 9:***
No, we do not agree that the stability data package is sufficient to support review of the NDA.

The drug substance test acceptance limits for release and stability should be the same. In addition, revise the drug substance stability protocol to add the release test for product-related substances and impurities, with the same acceptance criteria. Report the measured

total of methionyl sulfoxides, largest other related impurity, and total impurities at each time point.

With regard to the drug product stability package, see the response to Question 8 for additional attributes that should, unless adequately justified, be evaluated on stability. For example, the impurity profiles should include individual known impurities.

The terms "drug product cartridge" and "finished drug product pen-injector" should be clearly defined in the application along with an explanation of which is being tested for sterility and endotoxin. The specification for commercial release of the finished drug product should include the microbiological tests of sterility per USP <71> and bacterial endotoxins per USP <85>, and finished drug product placed on the long-term stability program should include a test of sterility annually consistent with the ICH Q1A(R2) guidance.

Additionally, the stability data for the "drug product cartridge" lots placed under long term conditions in Section 19.2 has the units for endotoxin were listed as EU/mg protein, whereas the units listed on the specification for the "drug product cartridge" in Section 18.2 were EU/mL. This discrepancy should be addressed prior to the submission of the application. Final determination of adequacy of the stability program tests and testing timepoints will be made during review of the application.

Results from cartridge functionality testing (e.g., break loose and glide force) and pen-injector functionality testing (e.g., dose accuracy, number of doses delivered) should be included in the stability reports.

Provide documentation that ensures that the to-be-marketed version of the combination product maintains the essential performance requirements as described in the Agency's response to Question 6 up to the labeled date of expiry and after actual and/or simulated shipping.

If you plan to use a test subject other than the to-be-marketed version, list the differences in the design and provide a risk-based assessment demonstrating how the differences do not significantly impact the product's essential performance requirements. Stability/shelf-life testing and shipping studies may be incorporated into design verification testing.

***Discussion at the Meeting:***

Pfenex stated they would be proposing a (b) (4)-month retest period for the drug substance and a 24-month expiration dating period for the rug product. Pfenex noted that they are in the process of validating the tests for product-related impurities using the USP Teriparatide Injection method. Some of these new data were summarized and presented at the meeting (see attached response to Question 9). Pfenex proposed inclusion of additional stability data following their submission of the NDA targeted for August 2018. FDA stated that all supportive stability data be included at the time of NDA submission. Submission of additional information during the review cycle could prompt an extension of the user fee goal date or may not be reviewed by FDA when reaching a decision on the application.

FDA asked Pfenex to summarize the available drug substance stability data obtained using the in-house method and the USP monograph method in tabular form for FDA to review and address in a post-meeting comment (see Post-Meeting Comments below).

FDA also asked Pfenex to include an assay for meta-cresol content to the drug product stability protocol.

Post-Meeting Comment:
The information contained in TABLE 3: DRUG SUBSTANCE STABILITY DATA INTENDED TO BE INCLUDED IN THE NDA SUBMISSION in the July 24, 2018, communication should provide adequate information on the batches manufactured prior to transfer of (b) (4) We request that both impurities methods be performed on lots 16-0003 and 16-0902 at the timepoints indicated and at each stability timepoint after that to provide additional information comparing the two methods. We also request that both methods be used for release of the first batch manufactured in the new (b) (4) See the Post-Meeting Comment for Question 11.

***Question 10:*** ***Does the Agency agree that process validation data for the drug substance, drug product, and the combination product are not required to be submitted in the NDA or during the review of the NDA?***

***FDA Response to Question 10:***
Yes, we agree that process validation data for the drug substance, drug product, and the combination product are not required to be submitted in the NDA or during the review of the NDA. However, as you have noted, process validation must be completed prior to marketing.

As stated in the briefing package, all information and studies outlined in the 1994 Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products are required at the time of submission of the application. Additionally, because this is a multiple dose product, antimicrobial effectiveness testing studies per USP <51> should also be provided at the time of submission of the application. Final determination of the adequacy of the sterility assurance information will be made during review of the application.

Typically, device component and finished combination product manufacturing processes should be validated prior to inspection. However, you may provide the process validation protocol in the NDA submission along with a justification that there is low risk associated with the fact that the validation will not be complete at the time of inspection.

Submit extractables and leachables data for the finished product in the NDA submission. Leachables should be measured through the end of shelf-life.

Refer to 2011 Guidance for Industry - Process Validation: General Principles and Practices

at https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm070336.pdf.

***Discussion at the Meeting:***
There was no further discussion at the meeting.

***Question 11:*** ***Commercial drug substance will be manufactured in the same equipment as for the clinical batches, but*** (b) (4) ***of the same manufacturer. Does the Agency agree that the plan to support the proposed commercial manufacturing site is adequate?***

***FDA Response to Question 11:***
In general, the plan appears reasonable. However, clarify what supporting batch release and stability data for batches manufactured at the commercial site will be submitted in the NDA.

***Discussion at the Meeting:***
Pfenex confirmed (b) (4) and they are currently in the process of analyzing PPQ lots which is scheduled to be completed at the end of the year. FDA raised concern regarding the availability of release data following (b) (4) as USP limits could be impacted. FDA also reminded Pfenex that all facilities should be ready for inspection at the time of NDA submission.

Post-Meeting Comment:
A facility should be ready for inspection at submission because inspection can occur any time during the review cycle. If the FDA inspects and finds the proposed commercial (b) (4) still under qualification and not ready for inspection, this would be an approvability issue. Submit the NDA after the new manufacturing (b) (4) is ready for inspection.

(b) (4) FDA requests that batch release data on a lot manufactured (b) (4) be submitted in the original NDA submission, not in an amendment during the review cycle.

## 2.5. Regulatory

***Question 12:*** (b) (4)

***FDA Response to Question 12:***

(b) (4)

***Discussion at the Meeting:***
There was no further discussion at the meeting.

***Question 13:*** ***Does the Agency agree with the proposed plan for providing limited individual CRFs and patient narratives in the NDA?***

***FDA Response to Question 13:***
This plan to provide CRFs for each patient who died, had a serious adverse event, or discontinued study due to an adverse event during any of the clinical studies is acceptable.

***Discussion at the Meeting:***
There was no further discussion at the meeting.

***Question 14:*** ***Does the Agency agree that the REMS for PF708 is not required?***

***FDA Response to Question 14:***
At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to conclusively determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks. However, based on the information currently available, we do not believe that a REMS will be necessary. We will make a final determination for the need for a REMS during the review of your application.

***Discussion at the Meeting:***
There was no further discussion at the meeting.

***Question 15:*** ***Because the study population in PF708-101 was healthy subjects and in PF708-301 was patients with osteoporosis, does the Agency agree that integrated safety (ISS) and efficacy (ISE) analyses are not necessary?***

***FDA Response to Question 15:***
We agree with the proposal for a narrative Summary of Clinical Safety in section 2.7.4 without a more detailed ISS. We agree that section 2.7.3 and ISE are not necessary.

***Discussion at the Meeting:***
There was no further discussion at the meeting.

***Question 16:*** ***Does the Agency agree that the content of the proposed draft prescribing information is sufficient for filing and review of the NDA for PF708?***

***FDA Response to Question 16:***
We remind you that your product's prescription labeling must conform to the Physician Labeling Rule (PLR) and the Pregnancy and Lactation Labeling Rule (PLLR).

***Discussion at the Meeting:***
There was no further discussion at the meeting.

***Question 17:*** ***Does the Agency agree with the proposed structure and format of the datasets for both clinical and nonclinical studies?***

***FDA Response to Question 17:***
In your NDA submission, include the pharmacokinetic analysis dataset and pharmacokinetic parameter dataset for Study PF708-101 and Study PF708-301 in SAS Transport (.xpt) format.

***Discussion at the Meeting:***
There was no further discussion at the meeting.

***Question 18:*** ***Does the Agency agree with the content and organizational structure of the NDA described in the Table of Contents?***

***FDA Response to Question 18:***
Your proposal appears reasonable.

***Discussion at the Meeting:***
There was no further discussion at the meeting.

**Combination Product comments:**
Your proposed teriparatide pen injector is a combination product subject to 21 CFR Part 4 "Current Good Manufacturing Practice Requirements for Combination Products" accessible at: https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products. Related final guidance, "Current Good Manufacturing Practice Requirements for Combination Products, January 2017" is accessible at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM429304.pdf.

Compliance with 21 CFR Part 4:
As such, current good manufacturing practices (cGMP) requirements for combination products are applicable to each constituent part (drug and device) of the combination product. However, as reflected in the final rule on CGMPs for combination products (21 CFR Part 4), manufacturers have the option to demonstrate compliance both with the drug CGMP regulations (21 CFR Parts 210, 211) and with the device quality system (QS) regulation (21 CFR Part 820) through a streamlined approach. If utilizing a streamlined approach, you must demonstrate compliance with either the drug CGMPs or the QS regulation in its entirety and also with those provisions specified in Part 4 from the other of these two sets of requirements. Alternatively, you may demonstrate compliance with both the drug CGMPs and QS regulation in their entirety (non-streamlined approach).

Information to include in NDA Form 356h:
List the manufacturing facilities for the combination product and its constituent parts and identify what activities occur at each site (e.g., assembly, filling, sterilization, packaging other) involving which constituents parts (e.g., drug only, device only, both drug and device). For facilities that have manufacturing activities for both drug and device constituent parts, you should identify which CGMP operating system is being used at the site for the combination product (streamlined or non-streamlined) and if it is a streamlined system, whether it is a drug-CGMP-based or QS-regulation-based system.

Information to include in your NDA application: If you are using a drug-CGMP-based system, demonstrate compliance with the following provisions from the QS regulation. Provide the following information in your marketing application with respect to these requirements. You are not required to provide this information, but we encourage you to do so. Its review will enable the agency to determine whether inspection is needed with respect to these requirements and, if so, to enhance the efficiency of this inspection. Using the eCTD format, this information should be provided in Section 3.2.P.3.

- Management Responsibility (21 CFR 820.20)

Provide a summary of how your firm's management has established responsibility to assure that the combination product is manufactured in compliance with all applicable CGMP requirements (see 21 CFR Part 4). Also, provide a description of the functions and responsibility of each facility involved in the manufacturing of the combination product and its constituent parts.

- Design Control, General (21 CFR 820.30)

Explain how you utilized the design control process to develop the combination product under review and provide a description of your design control procedures. The description must include how requirements for design and development planning, design input, design output, design review, design verification, design validation, design transfer, design changes, and design history file are fulfilled. Provide a copy or a summary of the plan used to design the combination product.

- Purchasing Controls (21 CFR 820.50)

Provide a summary of the procedure(s) for purchasing controls. The summary should:

a. Describe your supplier evaluation process and describe how it will determine the type and extent of control you will exercise over suppliers.
b. Define how you maintain records of acceptable suppliers and how you address the purchasing data approval process.
c. Explain how you will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use.

Explain how the procedure(s) will ensure that changes made by contractors/suppliers will not affect the final combination product. Provide a description of how you apply the purchasing controls to the suppliers/contractors used in the manufacturing of the combination product. (e.g., through supplier agreement).

- Corrective and Preventive Action (21 CFR 820.100)

Summarize the procedure(s) for your Corrective and Preventive Action (CAPA) System. The CAPA system should require:

a. Identification of sources of quality data and analysis of these data to identify existing and potential causes of nonconforming practices and products;
b. Investigation of nonconformities and their causes;
c. Identification and implementation of actions needed to correct and prevent recurrence of nonconformities; and
d. Verification or validation of the actions taken.

- Installation (21 CFR 820.170) and Servicing (21 CFR 820.200)

If installation and service requirements apply based on the type of device constituent part included in your combination product, provide the following information :

*Installation*: a summary of how your firm has established installation, inspection instructions, and test procedures for the installation of the combination product.

*Servicing*: a summary of how your firm has established and maintained instructions and procedures for performing and verifying that servicing of the combination product meets the specified requirements.

eCTD information for combination products:
Refer to the eCTD guidance where Section 5 includes information on location of combination product information:
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm.

***Discussion at the Meeting:***
There was no further discussion at the meeting.

## 3.0 ADDITIONAL INFORMATION

### PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action. For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

### PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pd).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

## 505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry, *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for a listed drug, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug. You should establish a "bridge" between your proposed drug product and each listed drug upon which you propose to rely to

demonstrate that your proposed product is sufficiently similar to the listed drug such that reliance is scientifically justified. A demonstration of similarity to the listed drug may include, for example, comparative physico-chemical tests and bioassay, nonclinical data (which may include bridging toxicology studies), pharmacokinetic (PK)/pharmacodynamic (PD) data, and clinical data (which may include an assessment of immunogenicity).

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) (e.g. by trade name(s)) described in the published literature.

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug or published literature describing a listed drug (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug or on published literature. In your proposed 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of supporting information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature, we also encourage you to include that information in the cover letter for your marketing application in a table similar to the one below.

| **List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature** | |
|---|---|
| **Source of information (e.g., published literature, name of listed drug)** | **Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)** |
| *1. Example: Published literature* | *Nonclinical toxicology* |

| | |
|---|---|
| *2. Example: NDA XXXXXX "TRADENAME"* | *Previous finding of effectiveness for indication A* |
| *3. Example: NDA YYYYYY "TRADENAME"* | *Previous finding of safety for Carcinogenicity, labeling section B* |
| *4.* | |

## OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf.

## 4.0 ISSUES REQUIRING FURTHER DISCUSSION

The FDA advised inclusion of additional CMC data prior to submission of the NDA.

## 5.0 ACTION ITEMS

| Action Item/Description | Owner | Due Date |
|---|---|---|
| Meeting Minutes | FDA | August 16, 2018 |

## 6.0 ATTACHMENTS AND HANDOUTS

Response to Comments_129196_SN0024_16Jul2018.pdf

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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.**

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/s/

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THERESA E KEHOE
08/06/2018