

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125513Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)



Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993

REVIEW ADDENDUM

Date: September 22, 2015
To: Administrative File, STN 125513
From: Candace Gomez-Broughton, Ph.D., CDER/OPQ/OPF/DMA/Branch IV
Endorsed: Patricia Hughes, Ph.D., Acting Branch Chief, CDER/OPQ/OPF/DMA/Branch IV
Subject: Original Biologic License Application
US License: 1743
Applicant: Alexion Pharma Inc.
Facility: **Drug Substance:** (b) (4)
(b) (4)
Drug Product: (b) (4)
(b) (4)
Product: STRENSIQ™ (asfotase alfa)
Dosage: sterile solution for subcutaneous injection (40 mg/mL and 100 mg/mL)
Indication: enzyme replacement therapy for patients with hypophosphatasia (HPP)
Due date: November 23, 2015

Recommendation: BLA 125513, as amended, is recommended for approval from a microbiology product quality perspective with the following post-marketing commitment:

To re-evaluate the (b) (4) endotoxin limits for the (b) (4) (b) (4) after data from thirty batches is available and (b) (4) to reflect manufacturing process capability.

This is an addendum to for the quality microbiology review memo entered into Panorama on 21 August 2015 for BLA 125513.

(b) (4)
Reviewer Question: Sample volume (b) (4) for the bioburden (b) (4) (b) (4) should be increased (b) (4). Please amend the BLA accordingly.

Sponsor's Response: The sample volume for the bioburden (b) (4) as described

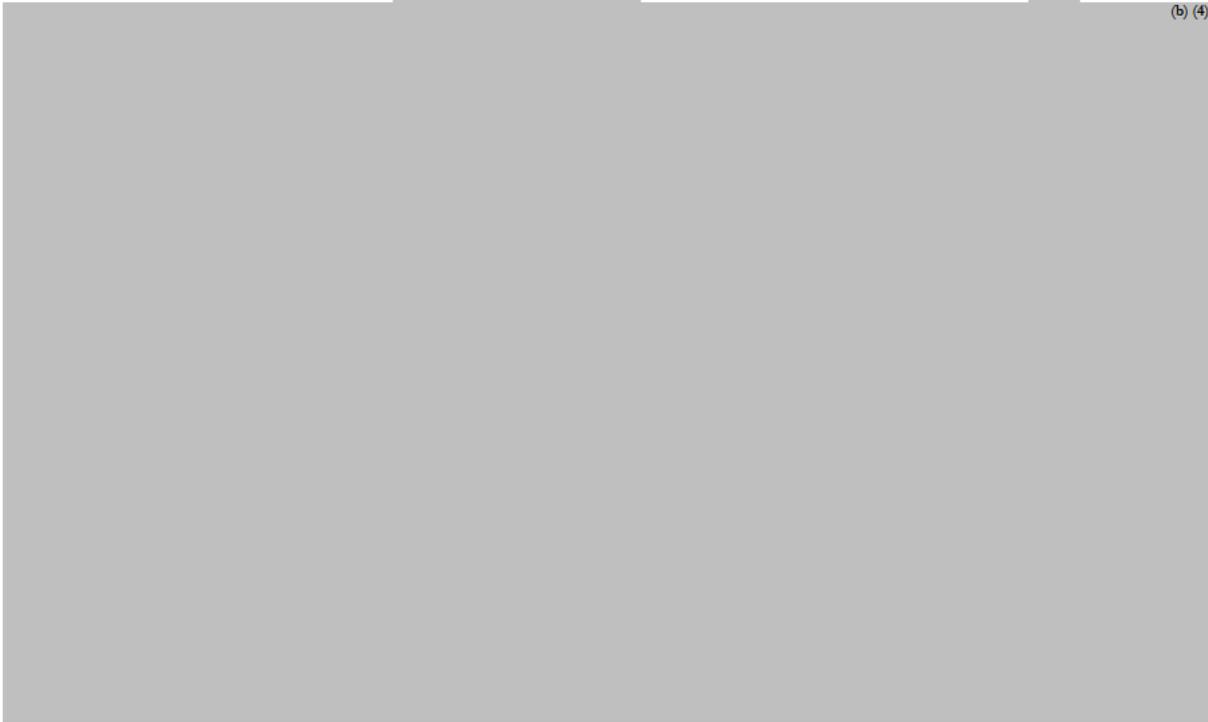
in section 3.2.S.2.2 Description of Manufacturing Process and Process Controls. It is described (b) (4) in Section 3.2.S.2.2.4 Step 3: (b) (4).

SATISFACTORY



Sponsor Response:

- a. Hold time studies were not completed (b) (4) based on the (b) (4) overall site strategy for establishing (b) (4) hold times across the facility. (b) (4)



- b. The sponsor has revised Section 3.2.S.2.5 Process Validation and/or Evaluation to list the correct media used in the hold studies.

SATISFACTORY



SATISFACTORY

Container Closure Integrity

The sponsor has submitted method validation reports and implementation plans for the Container Closure Integrity test to be used in lieu of sterility for drug product being placed on stability.

The sponsor has updated the applicable BLA section in Sequence 0035.

P.3.5 Control of Drug Product

P.3.5.1 Specification

Tables 1 and 2 were updated to list Container Closure Integrity as a test used for stability to be performed in lieu of sterility testing.

P.5.2 Release and Stability Analytical Procedures

Table 3 was updated to list CCIT as a test method used for asfotase alfa stability testing.

P.5.3 Validation of Analytical Procedures

Container Closure Integrity

Container closure integrity is assessed

(b) (4)

(b) (4)

The method was qualified (b) (4) to verify the capability of the test method to accurately differentiate between positive and negative controls (leak vs. no-leak).

(b) (4)

The acceptance criteria for the studies are listed below.

- All negative controls must pass
- All positive controls with (b) (4) defects must fail
- All positive controls with (b) (4) defects must fail

Results met all of the acceptance criteria. All positive controls failed the test with (b) (4). While all of the negative controls passed.

Reviewer comment: The (b) (4) method for container closure integrity is suitable for its intended use.

SATISFACTORY

SIGNATURES

Candace Y. Gomez-broughton -S

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Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: August 21, 2015
To: Administrative File, STN125513
From: Candace Gomez-Broughton, Ph.D., Microbiologist CDER/OPQ/OPF/DMA/Branch IV
Endorsed: Patricia Hughes, Ph.D. Acting Branch Chief CDER/OPQ/OPF/DMA/Branch IV
Subject: Original Biologic License Application
US License: 1743
Applicant: Alexion Pharma Inc.
Facility: **Drug Substance:** (b) (4)
(b) (4)
Drug Product: (b) (4)
(b) (4)
Product: STRENSIQ™ (asfotase alfa)
Dosage: sterile solution for subcutaneous injection (40 mg/mL and 100 mg/mL)
Indication: enzyme replacement therapy for patients with hypophosphatasia (HPP)
Due date: November 23, 2015

Recommendation for Approvability: BLA 125513, as amended, is recommended for approval from a microbiology product quality perspective with the following post-marketing commitment:

To re-evaluate the (b) (4) endotoxin limits for the (b) (4) (b) (4) after data from thirty batches is available and (b) (4) to reflect manufacturing process capability.

REVIEW SUMMARY

Asfotase alfa is a soluble IgG₁ fusion protein consisting of a soluble catalytic domain of human tissue non-specific alkaline phosphatase (TNSALP), human immunoglobulin G1 Fc domain, and a deca-aspartate peptide (D10) used a bone targeting domain and two amino acid linkers between the domains. The soluble domain of asfotase alfa provides the biological function by catalyzing the hydrolysis of phosphomonoesters with release of inorganic phosphate and alcohol. Asfotase alfa is expressed in a Chinese Hamster Ovary (CHO) cell line. (b) (4)

(b) (4) is contracted by the sponsor for asfotase alfa drug substance manufacturing.
(b) (4) is contracted by the sponsor for asfotase alfa drug product manufacturing.

The BLA was submitted in eCTD format.

ASSESSMENT

Amendments Reviewed For Drug Substance Quality Microbiology

- SDN 0025
- SDN 0031

S Drug Substance

S.1. General Information

The asfotase alfa drug substance is formulated as a solution consisting of 100 mg/mL protein, 25 (b) (4) sodium phosphate and (b) (4) sodium chloride.

This section is reviewed by the OBP reviewer.

S.2. Manufacture

S.2.1 Manufacturer(s)

The drug substance manufacturing, testing, and release sites are provided in the table below. Drug substance manufacturing will take place at (b) (4).

Facility	FEI Number	Responsibilities
(b) (4)		Drug substance manufacture
Alexion Pharmaceuticals Inc./Alexion Manufacturing Facility (ARIMF)	300658549	Release and stability testing

Reviewer comment: Compliance status of the facilities is assessed by the DIA reviewer. The DS manufacturing site was inspected on Sept. 9-13, 2014 and was NAI.

S.2.2. Description of Manufacturing Process and Process Controls

Asfotase alpha DS manufacturing process consists

(b) (4)

(b) (4)

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Reviewer comments: The manufacturing process has been adequately described. Microbial controls are in place. The microbial controls and hold times are discussed further in Section 3.2.S.2.4.

SATISFACTORY

S.2.3 Control of Materials

This section will be reviewed by OBP.

S.2.4 Controls of Critical Steps and Intermediates

Microbial (b) (4) controls for the asfotase alfa drug substance manufacturing process are summarized in the table below.

Process Step	Attribute	Acceptance Criteria
(b) (4)	Bioburden	(b) (4)
	Bioburden	
	Endotoxin	
	Bioburden	
	Endotoxin	
	Bioburden ((b) (4))	
	Endotoxin (b) (4)	
	Bioburden (b) (4)	
	Endotoxin (b) (4)	
	Bioburden (Cycle 1 and 2)	
	Endotoxin (Cycle 1 and 2)	
	Bioburden (b) (4)	
	Endotoxin (b) (4)	
	Bioburden	
	Endotoxin	
	Bioburden	
Endotoxin		

(b) (4)



Reviewer comment: The Sponsor's response to this information request will be reviewed in an addendum to this review memo.

S.2.5.9 Shipping Validation Studies

(b) (4)



Shipping validation studies were completed using three drug substances batches (280897, 284989, and 259248)

(b) (4)



(b) (4)

S.4 Control of Drug Substance

S.4.1 Specification

The bioburden and endotoxin release specifications for the asfotase alfa drug substance are as follows:

- Bioburden: (b) (4)
- Endotoxin (LAL): (b) (4)

S.4.2 Analytical Procedures

S.4.2.1.1 (b) (4) Bioburden USP <61>, Ph.Eur.2.6.12

Bioburden in (b) (4) samples is determined by (b) (4) method (USP <61> and Ph.Eur.2.6.12). (b) (4)

(b) (4) If growth is observed, bioburden is reported as either CFU/mL or CFU/10 mL.

S.4.2.1.8 (b) (4) Endotoxin USP <85>, Ph. Eur. 2.6.14, JP 4.01

The kinetic chromogenic Limulus Amoebocyte Lysate (LAL) assay is used to measure endotoxin in (b) (4) samples. (b) (4)

(b) (4) Results are reported in EU/mL.

S.4.2.2 Release and Stability Analytical Procedures

S.4.2.2.21 Bioburden USP <61>, Ph. Eur. 2.6.12, JP 4.05

The (b) (4) method is used for release testing and is completed as described in Section S.4.2.1.1.

S.4.2.2.2 Endotoxin USP <85>, Ph. Eur. 2.6.14

The LAL assay is used for determine endotoxin levels at release. The assay is completed as described in Section S.4.2.1.8.

S.4.3 Validation of Analytical Procedures

S.4.3.1 (b) (4) Analytical Procedures

S.4.3.1.1 Bioburden

The (b) (4) method was validated (b) (4)

(b) (4)

The sponsor states that the results for all samples types met acceptance criteria. (b) (4)

(b) (4) The sponsor will continue bioburden analysis (b) (4)

S.4.3.1.6 Endotoxin

The bacterial endotoxin concentration in drug substance samples is determined by using the kinetic chromogenic Limulus Amoebocyte Lysate (LAL) test. Validation studies were completed to demonstrate that this method is suitable (b) (4)

Qualification was completed on three lots of (b) (4) bulk drug substance samples. The sponsor provided the qualification report for endotoxin testing using (b) (4) reagent. The limit of detection was (b) (4). The sponsor also conducted tests to determine (b) (4)

(b) (4)

(b) (4). These results demonstrate that this method is suitable for testing bacterial endotoxin in drug substance (b) (4) samples. All acceptance criteria were met.

S.4.3.2 Release and Stability Analytical Procedures

S.4.3.2.20.1 Bioburden (b) (4)

The bioburden test method used (b) (4) was qualified (b) (4)

(b) (4)

S.4.3.2. Bioburden (ARIMF)

The bioburden test method used at ARIMF was qualified (b) (4)

(b) (4)

S.4.2.21 Endotoxin

S.4.2.21.1 Kinetic Chromogenic Endotoxin (b) (4)

(b) (4). The study was completed in triplicate and all acceptance criteria were met for 100 mg/mL asfotase alfa samples. Recovery levels were between (b) (4) (acceptance criteria: recovery must be between (b) (4)).

S.4.2.21.2 Kinetic Chromogenic Endotoxin (ARIMF)

Both the 100 mg/mL and 40 mg/mL concentrations were tested (b) (4). Seven batches of 100 mg./mL concentration and six batches of 40 mg/mL concentration were tested. Results for the 100 mg/mL concentration ranged from (b) (4) and results from the 40 mg/mL samples ranged from (b) (4). All results met the acceptance criteria (b) (4).

S.4.4 Batch Analysis

Analytical data was provided for commercial process lots 332604, 333366, 335332, 338971, 341981, 379564, 381602, 381604, 411607, and 415567. Commercial lots were manufactured using the manufacturing process described in Section 3.2.S.2.2 Description of Manufacturing Process and Process Controls. Bacterial endotoxin results were (b) (4) and bioburden results were (b) (4).

S.4.5 Justification of Specification

The commercial specifications proposed in Section 3.2.S.4.1 Specification were derived from the original specifications in place for clinical studies and (b) (4) based on manufacturing experience. Justification provided in this section is based on manufacturing experience at the (b) (4) scale process. Trending of release results is reviewed by the Sponsor annually. In addition, the Sponsor commits to reevaluate DS specifications after data from thirty (b) (4) batches is available (b) (4).

The bioburden specification (b) (4) for release and stability was established based on manufacturing capability. No batches to date have exceeded the specification. The endotoxin specification was determined per the recommendation in the 1987 "Guidance for Validation of Limulus Amoebocyte Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices" (b) (4).

cGMP STATUS

The (b) (4) manufacturing facility located (b) (4) was inspected by reviewers Candace Gomez-Broughton, Ph.D., Joslyn Brunelle, Ph.D., and Leslie Rivera-Rosado, PhD. from (b) (4). No FDA form 483 was issued at the end of inspection. The inspection was classified as NAI.

CONCLUSION

I. Section 3.2.S of the BLA pertaining to microbial control of the drug substance manufacturing process was reviewed. The BLA, as amended, is recommended for approval from a CMC microbiology product quality perspective with the following post-marketing commitment:

To re-evaluate the (b) (4) endotoxin limits (b) (4) after data from thirty batches is available and (b) (4) reflect manufacturing process capability.

II. CMC product specific information and data should be reviewed by the OBP reviewer.

III. The drug substance manufacturing facility (b) (4) was inspected on (b) (4) (b) (4) and was classified as NAI.

P DRUG PRODUCT

P.1 Description and Composition of the Drug Product

Asfotase alfa drug product (DP) is supplied as a sterile aqueous solution at a concentration of either 40 mg/mL or 100 mg/mL in (b) (4) sodium phosphate, (b) (4) sodium chloride in a 2 mL glass vial. The 40 mg/mL concentration is supplied as a single-use vial at (b) (4) 0.45, 0.70, and 1.0 mL volumes at (b) (4) 18, 28, and 40 mg of asfotase alfa, respectively. The 100 mg/mL concentration is supplied at a 0.80 mL volume containing 80.0 mg of asfotase alfa in a single-use vial.

The container closure system includes a 2 mL Type 1 glass vial, a (b) (4) stopper (b) (4) and an aluminum seal with a (b) (4) flip-off cap for both presentations.

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

The preservative-free asfotase alfa DP is aseptically filled into vials which are closed with (b) (4) stoppers and sealed with aluminum seals. The strategy for microbial control includes the following:

(b) (4)

[Redacted] (b) (4)

P.2.5.1 Container Closure Integrity Study (CCIT)

The container closure integrity test method validation will be reviewed in a separate addendum.

P.3 Manufacture

P.3.1 Manufacturers

The drug product manufacturing and testing sites are provided in the table below. Drug product manufacturing will be completed at [Redacted] (b) (4)

Facility	FEI Number	Responsibilities
[Redacted] (b) (4)		
Alexion Pharmaceuticals Inc./Alexion Manufacturing Facility (ARIMF)	3006568549	Release and stability testing
[Redacted] (b) (4)		

Reviewer comment: Compliance status of the facilities is assessed by the DIA facility reviewer.

P.3.2 Batch Formula

Each drug product batch consists of one drug substance batch which is at a concentration of 100 mg/mL. [Redacted] (b) (4)

P.3.3 Description of Manufacturing Process and Process Controls

The liquid asfotase bulk drug substance is [Redacted] (b) (4) a 100 mg/mL concentration. Drug product strengths are produced at concentrations of 100 mg/mL and 40 mg/mL. [Redacted] (b) (4)

[Redacted] A summary of the drug product manufacturing process is provided in the Figure 1 shown below.

Figure 1: Asfotase Alfa Drug Product Manufacturing Schematic Process



P.3.3.1 Manufacturing Process Steps





P.3.4 Controls of Critical Steps and Intermediates

Process controls used to ensure microbial quality during manufacturing are listed below:

Critical Process Control	Acceptance Criteria
(b) (4) Bioburden	(b) (4)
(b) (4) Integrity Testing	(b) (4)
(b) (4) Hold Time	(b) (4)

The drug product manufacturing process is continuous from formulation and storage. (b) (4)

Reviewer comment: The manufacturing process has been adequately described.

SATISFACTORY



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(b) (4)

P.5 Control of Drug Product

P.5.1 Specification

The drug product release specification for both concentrations of drug product include (b) (4) (b) (4) by the LAL method and “No growth” for sterility test by the USP/EP method. Container closure integrity testing will completed in lieu of sterility testing for DP lots placed on stability.

P.5.2 Analytical Procedures

P.5.2.1 (b) (4) Analytical Procedures

The (b) (4) method (USP <61>, Ph.Eur.2.6.12) is used to measure bioburden (b) (4) (b) (4)

P.5.2.2 Release and Stability Analytical Procedures

Sterility is tested at release using the (b) (4) method described in USP <71> and Ph.Eur. (b) (4) Results are reported as “No Growth” is there is no microscopic growth following incubation.

Endotoxin is measured at release using the method described previously in 3.2.S.4.2.2.22.

P.5.3 Validation of Analytical Procedures

P.5.3.1.2 (b) (4) Bioburden

The (b) (4) method was validated by testing the ability to recover microorganisms present in (b) (4) samples (b) (4) (b) (4)

(b) (4) . The acceptance criterion (b) (4) (b) (4)

(b) (4) meets acceptance criteria.

P.5.3.2.1 Endotoxin

Kinetic Chromogenic Endotoxin (b) (4)

(b) (4)

Six lots of asfotase alfa DP were used in the LAL method validation studies. Two lots of the 100 mg/mL concentration and four lots at the 40 mg/mL concentration. (b) (4)

(b) (4)

(b) (4) Results show (b) (4)
 (b) (4) which meets the acceptance criteria (b) (4)

Kinetic Chromogenic Endotoxin (b) (4)

(b) (4)

(b) (4) The validation studies were completed using 2 lots of 40 mg/mL DP and 1 lots of 100 mg/mL drug product. Results (b) (4) met acceptance criteria and are summarized in the table below.

Table 7: Summary of Kinetic Chromogenic Endotoxin Qualification (b) (4)

Parameter	Acceptance Criteria	Validation Results
(b) (4)		

P.5.3.2.2 Sterility

Three batches of drug product were used for the sterility test method qualification. The sterility test was done in the presence or absence of drug product. Microbial recovery in drug product samples were compared to positive control media. Challenge organisms included those listed in USP <71>:

- *S. aureus* (ATCC 6538)
- *P. aeruginosa* (ATCC 9027)
- *B. subtilis* (ATCC 6633)
- *C. sporogenes* (ATCC 11437)
- *C. albicans* (ATCC 10231)
- *A. brasiliensis* (ATCC 16404)

Results show comparable growth in the presence and absence of the drug product.

Reviewer Questions: The following requests were made on 27 February 2015:

1. In Table 1 of the BLA Presubmission/Cover letter (dated March 31, 2014), it was stated that the data from the Container Closure Integrity method validation studies would be submitted with Wave 3. However, the data has not been submitted. Provide the Container Closure Integrity method validation study data or provide a time line for submitting the data.
2. Provide the study report for the Rabbit Pyrogen Test.

The sponsor responded on 13 March 2015 (Sequence 0014) by submitting the Rabbit Pyrogen Test Report. Drug product lots 3-FIN-1730, 3-FIN-1747, and 3-FIN-1831 were manufactured using the commercial process and subjected to the rabbit pyrogen test. The results show that the drug product is non-pyrogenic.

Reviewer comment: The container closure integrity test method validation was recently submitted to the Agency on 28 July 2015 (Sequence 0035). The review of the method validation will be discussed in an addendum to this review.

P.5.4 Batch Analysis

Batch analysis for batches manufactured (b) (4) is provided in this section. Results related to the microbial quality of the drug product batches met acceptance criteria. Results of the sterility test met USP/Ph.Eur requirements and endotoxin levels were (b) (4) for each batch. Lots manufactured using the commercial processes are described in the following tables:

Table 1: Summary of Asfotase Alfa Drug Product Commercial Process Batches (100 mg/mL)

Drug Product Lot	Manufacturer	Date of Manufacture	Concentration	Drug Substance Batch	Intended Batch Use
3-FIN-1474	(b) (4)	(b) (4)	100 mg/mL	280897	Clinical, Stability, Process Validation, Commercial
3-FIN-1475	(b) (4)	(b) (4)	100 mg/mL	284989	Clinical, Stability, Process Validation, Commercial
3-FIN-1476	(b) (4)	(b) (4)	100 mg/mL	332604	Clinical, Stability, Process Validation, Commercial
3-FIN-1831	(b) (4)	(b) (4)	100 mg/mL	333366	Clinical, Stability, Process Validation, Commercial
3-FIN-1926	(b) (4)	(b) (4)	100 mg/mL	335332	Clinical, Commercial
3-FIN-2012	(b) (4)	(b) (4)	100 mg/mL	379564	Clinical, Commercial
140168	(b) (4)	(b) (4)	100 mg/mL	381604	Clinical, Stability, Commercial

Table 2: Summary of Asfotase Alfa Drug Product Commercial Process Batches (40 mg/mL)

Drug Product Lot	Manufacturer	Date of Manufacture	Concentration	Drug Substance Batch	Intended Batch Use
3-FIN-1485	(b) (4)	(b) (4)	40 mg/mL	259248	Clinical, Stability, Process Validation, Commercial
3-FIN-1483	(b) (4)	(b) (4)	40 mg/mL	259248	Clinical, Stability, Process Validation, Commercial
3-FIN-1747	(b) (4)	(b) (4)	40 mg/mL	338971	Stability, Process Validation
3-FIN-1729	(b) (4)	(b) (4)	40 mg/mL	338971	Stability, Process Validation
3-FIN-1484	(b) (4)	(b) (4)	40 mg/mL	335332	Clinical, Stability, Process Validation, Commercial
3-FIN-1730	(b) (4)	(b) (4)	40 mg/mL	335332	Clinical, Stability, Process Validation, Commercial
3-FIN-1927	(b) (4)	(b) (4)	40 mg/mL	341981	Clinical, Commercial
3-FIN-2013	(b) (4)	(b) (4)	40 mg/mL	381602	Clinical, Commercial
140165	(b) (4)	(b) (4)	40 mg/mL	381602	Clinical, Stability, Commercial
140167	(b) (4)	(b) (4)	40 mg/mL	381602	Clinical, Commercial
140169	(b) (4)	(b) (4)	40 mg/mL	381602	Clinical, Stability, Commercial

P.5.6 Justification Of Specifications

Release and end of shelf life specifications for sterility are set according to USP <71>. The acceptance criterion complies with the compendial requirements.

Endotoxin specification is set at (b) (4) which is based on the (b) (4) threshold for parenteral products, a maximum human dose of (b) (4) mg of drug.

P.7 Container Closure System

The asfotase drug product container closure system consists a 2 mL Type I glass vials with a (b) (4) stopper, (b) (4) and aluminum seal with (b) (4) flip-off cap. The same system is used for the 40 mg/mL and 100 mg/ mL drug product concentrations. All components are supplied by (b) (4)

P.8 Stability

Stability protocols include long-term storage under the recommended storage conditions (2-8°C), accelerated (23-27°C), and stressed (b) (4) storage studies. The drug product lots currently on stability includes lots manufactured at full scale at the proposed commercial manufacturing site as well as clinical lots. All of the drug product lots were manufactured using the commercial

container closure system. The sponsor proposes an expiry of 24 months for drug product stored at 2-8°C.

Commitments for post approval stability are provided below:

- The first three commercial lots at each drug product concentration will be placed on stability to confirm expiry
- No less than one lot of commercial product at each concentration per year will be placed on stability
- Results of post-approval stability studies will be reported in updates
- And confirmed stability result outside of the approved drug substance specification will be thoroughly investigated for impact to both drug substance and drug product lots

Reviewer comments: The sponsor has submitted the protocol and method validation for a container closure integrity test to be completed in lieu of sterility for drug product placed on stability. The method will be reviewed and discussed in a separate addendum.

SATISFACTORY

CONCLUSION

- I. The drug product section of the BLA is recommended for approval from a sterility assurance and microbiology product quality perspective.
- II. CMC product specific information and data should be reviewed by the OBP/DMA reviewer.
- III. No additional inspectional follow-up items were identified.

FDA Information Request for STN 125513/0 Microbial Quality

Section S.2.2 Description of Manufacturing Process and Controls

(b) (4) bioburden data should be obtained (b) (4)
(b) (4) **Please implement bioburden monitoring** (b) (4).

Section S.2.4 Control of Critical Steps and Intermediates

1. (b) (4) limits for endotoxin (b) (4) appear to be high for these steps in the process. Provide justification for these limits or lower the limits in accordance with process capability.
2. Please submit the protocol report for the (b) (4) Hold Time studies.
3. Provide information on the disposition of (b) (4) batch 338971 which had a bioburden result of (b) (4). This result is more than three times the acceptance criteria of (b) (4).

4. Specify in BLA section S.2.4 what quality assessments will performed (b) (4) and specify that (b) (4) will not be conducted (b) (4).

Section S.2.5 Process Validation and/or Evaluation

1. Will endotoxin samples be collected (b) (4) during routine manufacturing? An acceptance criterion of (b) (4) was described in Section S.2.2 however, the acceptance range provided in Section S. 2.5.1.3.3 Table 10 is listed as (b) (4).
2. Section S.2.5.1.3.3 Table 10 lists the (b) (4) bioburden acceptable range as (b) (4) while Section S.2.2 states that the acceptance criterion is (b) (4) Please amend the BLA to reflect the appropriate acceptance criteria.
3. Please submit endotoxin results for samples collected (b) (4) during process validation.

(b) (4)

Sample volume (b) (4) for the bioburden (b) (4) should be increased (b) (4) Please amend the BLA accordingly.

(b) (4)

Section P.2.5.1 Container Closure Integrity Study (CCIT)

Provide microbial growth promotion acceptance criteria for the microbial ingress test.

Section P.3.5 Process Validation and (or) Evaluation

Please provide a description of the (b) (4) qualification studies.

(b) (4)

(b) (4)

Your response submitted to the Agency on 30 April 2015

(b) (4) was inadequate.

(b) (4)

(b) (4). Please amend the BLA accordingly.

SIGNATURES

Candace Y. Gomez-
broughton -S

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cn=Candace Y. Gomez-broughton -S
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ou=HHS, ou=FDA, ou=People,
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00096547, cn=Patricia F.
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Date: 2015.08.21 15:18:37
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