

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125513Orig1s000**

**CHEMISTRY REVIEW(S)**



**First Approval for Indication**

**Recommendation: Approval**

**BLA 125513  
Review 1  
September 23, 2015**

<b>Drug Name/Dosage Form</b>	Asfotase alfa / injection
<b>Strength/Potency</b>	100 mg/mL (80 mg/0.80 mL) and 40 mg/mL ( (b) (4) , 18 mg/0.45 mL, 28 mg/0.70 mL, and 40 mg/1.0 mL)
<b>Route of Administration</b>	Subcutaneous
<b>Rx/OTC Dispensed</b>	RX
<b>Indication</b>	Treatment of Hypophosphatasia (HPP)
<b>Applicant/Sponsor</b>	Alexion Inc

**Product Overview**

Asfotase alfa is a fusion protein that includes a human recombinant tissue non-specific alkaline phosphatase (TNSALP), a polyaspartate domain that targets bone, and the Fc region of IgG1 to facilitate purification. TNSALP cleaves inorganic phosphate, which precipitates with calcium to form calcium phosphate that then becomes hydroxyapatite that gives bones strength and rigidity.

**Quality Review Team**

<b>DISCIPLINE</b>	<b>REVIEWER</b>	<b>BRANCH/DIVISION</b>
Drug Substance	Joslyn Brunelle	DBRR IV/OBP
DS (Complement Activation)	Mate Tolnay/Gerry Feldman	DBRR IV/OBP
Drug Product	Gunther Boekhoudt	DBRR IV/OBP
Immunogenicity	Frederick Mills/Gerry Feldman	DBRR IV/OBP
Facilities	Steven Fong/Peter Qiu	DIA/OPF
Microbiology	Candace Gomez-Broughton/Patricia Hughes	DMA/OPF
Labeling	Jibril Abdus-Samad	OBP
Business Regulatory Process Manager	Anita Brown	OPRO
Application Technical Lead	Cristina Ausin-Moreno	DBRR IV/OBP



**Multidisciplinary Review Team**

<b>DISCIPLINE</b>	<b>REVIEWER</b>	<b>OFFICE/DIVISION</b>
<b>RPM</b>	<b>Kevin Bugin/Lisa Pitts</b>	<b>DGIEP</b>
<b>Cross-disciplinary Team Lead</b>	<b>Anil Rajpal</b>	<b>DGIEP</b>
<b>Medical Officer</b>	<b>Carla Epps</b>	<b>DGIEP</b>
<b>Pharm/Tox</b>	<b>Sushanta Chakder/Dinesh Gautam</b>	<b>DGIEP</b>
<b>Clinical Pharmacology</b>	<b>Christine Hon/Yow-Ming Wang Justin Earp/Nitin Mehrotra</b>	<b>DGIEP</b>
<b>Statistics</b>	<b>Benjamin Vali/Yeh-Fong Chen</b>	<b>DB III</b>

- a. Names
  - i. Proprietary Name: Strensiq
  - ii. Non-Proprietary/USAN: asfotase alfa
  - iii. CAS name: Phosphatase, alkaline (synthetic human tissue-nonspecific isoenzyme ENB-0040) (1174277-80-5)
  - iv. INN Name: asfotase alfa
  
- b. Pharmacologic category: Human recombinant tissue non-specific alkaline phosphatase fusion protein

Submissions Reviewed:

<b>SUBMISSION(S) REVIEWED</b>	<b>DOCUMENT DATE</b>
STN 125513/0	3/31/2014
STN 125513/0002 (response to IR #1)	5/15/2014
STN 125513/0004 (response to IR #1)	7/30/2014
STN 125513/0005 (response to IR #2)	12/19/2014
STN 125513/0006 (final rolling submission)	12/23/2014
STN 125513/0011 (response to IR #3)	2/12/2015
STN 125513/0014 (response to IR #3, IR#4, and 74-day Letter)	3/13/2015
STN 125513/0017 (response to 74-day letter)	3/30/2015
STN 125513/0025 (response to 74-day letter, IR #5, and IR#6)	4/30/2015
STN 125513/0029 (response to IR#3 and IR#7)	6/1/2015
STN 125513/0031 (response to IR#5, IR#6, and IR#8)	6/30/2015
STN 125513/0035 (response to 74-day Letter)	7/27/2015
STN 125513/0036 (response to IR#5)	7/31/2015
STN 125513/0037 (response to IR #9)	8/13/2015
STN 125513/0038 (response to labeling and PMCs/PMRs issues)	8/14/2015
STN 125513/0039 (response to IR #10)	8/18/2015
STN 125513/0040 (response to IR #11)	8/21/2015
STN 125513/0042 (response to IR #12)	8/28/2015
STN 125513/0043 (response to Review Issue communicated during Late-Cycle Meeting)	9/3/2015



**QUALITY REVIEW BLA 125513 Strensiq (asfotase alfa)**



**Quality review Team – Signature Page**

<b>DISCIPLINE</b>	<b>REVIEWER</b>	<b>BRANCH/DIVISION</b>	<b>Signature</b>
Drug Substance (DS)	Joslyn Brunelle	Division of Biotechnology Review and Research IV	<p><b>Joslyn K. Brunelle -S</b></p> <p>Digitally signed by Joslyn K. Brunelle -S            DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000396541, cn=Joslyn K. Brunelle -S            Date: 2015.09.23 11:08:09 -0400</p>
DS (Complement Activation)	Mate Tolnay	Division of Biotechnology Review and Research IV	<p><b>Mate Tolnay -S</b></p> <p>Digitally signed by Mate Tolnay -S            DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300229347            Date: 2015.09.23 13:33:36 -0400</p>
Drug Product	Gunther Boekhoudt	Division of Biotechnology Review and Research IV	<p><b>Gunther H. Boekhoudt -S</b></p> <p>Digitally signed by Gunther H. Boekhoudt -S            DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000605472, cn=Gunther H. Boekhoudt -S            Date: 2015.09.23 10:50:05 -0400</p>
Microbiology	Candace Gomez-Broughton	Division of Microbiology Assessment	<p><b>Candace Y. Gomez-broughton -S</b></p> <p>Digitally signed by Candace Y. Gomez broughton -S            DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000640207            cn=Candace Y. Gomez broughton -S            Date: 2015.09.25 11:03:00 -0400</p>
Facilities	Steven Fong	Division of Inspectional Assessment	<p><b>Steven Fong -S</b></p> <p>Digitally signed by Steven Fong -S            DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Steven Fong -S            0.9.2342.19200300.100.1.1=2000287433            Date: 2015.09.24 08:42:28 -0400</p>
Immunogenicity	Frederick Mills	Division of Biotechnology Review and Research IV	<p><b>Frederick C. Mills -S</b></p> <p>Digitally signed by Frederick C. Mills -S            DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000737256            cn=Frederick C. Mills -S            Date: 2015.09.28 16:59:43 -0400</p>



**QUALITY REVIEW BLA 125513 Strensiq (asfotase alfa)**



Immunogenicity and DS (Complement Activation) Team Lead	Gerry Feldman	Division of Biotechnology Review and Research IV	Gerald M. Feldman -S <small>c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000577813, cn=Gerald M. Feldman -S  Date: 2015.09.29 20:18:39 -04'00'</small>
Microbiology Team Lead	Patricia Hughes	Division of Microbiology Assessment	Patricia F. Hughestroot -S <small>Digitally signed by Patricia F Hughestroot S  DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300096547, cn=Patricia F. Hughestroot S  Date: 2015.09.28 16:26:34 -04'00'</small>
Facilities Team Lead	Peter Qiu	Division of Inspectional Assessment	Zhihao Qiu -S <small>Digitally signed by Zhihao Qiu -S  DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Zhihao Qiu -S, 0.9.2342.19200300.100.1.1=2000438274  Date: 2015.09.24 21:34:49 -04'00'</small>
Application Technical Lead and DS and DP Team Lead	Cristina Ausin-Moreno	Division of Biotechnology Review and Research IV	Cristina Ausin-moreno -S <small>Digitally signed by Cristina Ausin-moreno -S  DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011707091, cn=Cristina Ausin-moreno -S  Date: 2015.09.30 07:15:41 -04'00'</small>
DS, DP, and Immunogenicity Tertiary Reviewer	Michele Dougherty	Division of Biotechnology Review and Research IV	Michele Dougherty -S <small>Digitally signed by Michele Dougherty -S  DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0010556865, cn=Michele Dougherty -S  Date: 2015.09.30 08:35:42 -04'00'</small>

## Quality Review Data Sheet

### 1. LEGAL BASIS FOR SUBMISSION: 351(a)

### 2. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II	(b) (4)	(b) (4)	3	N/A (Not reviewed because sufficient information was included in the submission)	N/A	None

<sup>1</sup> Action codes for DMF Table: 1 – DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows: 2 – Reviewed previously and no revision since last review; 3 – Sufficient information in application; 4 – Authority to reference not granted; 5 – DMF not available; 6 – Other (explain under "Comments")

<sup>2</sup> Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

#### B. Other Documents: None

### 3. CONSULTS: None

## Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

##### a. Recommendation

The OPQ, CDER, recommends approval of STN 125513 for Strensiq (asfotase alfa) manufactured by Alexion, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Strensiq is well controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

##### b. Approval action letter language

- Manufacturing location:

- Drug substance – (b) (4)
- Drug product – (b) (4)

- Fill sized and dosage form – Single dose vials:

Asfotase alfa concentration	Extractable volume per vial	Amount of asfotase alfa per vial
40 mg/mL	0.45 mL	18 mg
	0.70 mL	28 mg
	1.0 mL	40 mg
100 mg/mL	0.80 mL	80 mg

- Dating period:

- Drug product – 24 months; 2-8°C
- Drug substance – (b) (4)
- For packaged products: Not packaged
- Stability option
  - For stability protocols:
    - We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

- Exempt from lot release

- Yes
- Rationale if exempted – specified product
  - Note: We exempt specified according to 601.2a

c. Benefit/Risk Considerations

Hypophosphatasia (HPP) is an unmet medical need and it is characterized by high morbidity and mortality. In May 2013, asfotase alfa was granted breakthrough designation for treatment of HPP in perinatal-, infantile-, and juvenile-onset phenotypes. The recommended dosage regimen is 2 mg/kg administered subcutaneously three times per week, or 1 mg/kg administered six times per week. The dose may be increased to 3 mg/kg three times per week for insufficient efficacy.

The overall control strategy includes control of raw materials, facilities and equipment, manufacturing process, and adventitious agents. The control strategy combined with (b) (4) release, and stability testing ensure process consistency and drug substance and drug product with appropriate quality attributes and free of adventitious agents.

Asfotase alfa contains intact Fc region (b) (4) and can potentially bind to C1q and trigger activation of the complement system. Because the adverse events reported during the clinical studies do not indicate instances of complement activation, it is not necessary to resolve this concern pre-licensure and the sponsor will develop an assay to evaluate the complement activating capacity of asfotase alfa to that of human IgG1 post licensure (see section I.B, below).

According to the clinical-pharmacology reviewers, (b) (4) affects the systemic exposure of asfotase alfa. (b) (4)

(b) (4) The manufacturing history indicates a significant variability (b) (4) in the asfotase alfa lots manufactured using the commercial process. To achieve greater control (b) (4), the sponsor should assess and implement a revised control strategy (b) (4). Because the information provided in the BLA shows that Alexion can consistently produce asfotase alfa that is safe, pure, and potent, the studies may be conducted post licensure as a Post Marketing Commitment (see section I.B, below).

**B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable**

Below are draft PMRs and PMCs that are being negotiated with the applicant.

**PMR 1:** Develop an assay to directly compare the complement activating capacity of asfotase alfa to that of human IgG1. The assay should be set up under conditions to readily detect complement activation by IgG1. A dose response curve to demonstrate the sensitivity of the assay is recommended

**PMR 2:** Develop a validated cross-reactive immunologic material (CRIM) assay for patients with hypophosphatasia (HPP) and test patient samples in a cohort of

untreated patients. Results should be correlated with antibody response (binding and neutralizing), genetic mutations, enzyme activity level and clinical outcome in patients who are receiving Asfotase alfa treatment.

**PMC 1:** Evaluate the asfotase alfa manufacturing process and develop a control strategy [REDACTED] (b) (4) [REDACTED] (b) (4) that ensures consistent patient exposure. Provide detailed summaries of all data utilized to propose the revised control strategy [REDACTED] (b) (4).

**PMC 2:** To re-evaluate the [REDACTED] (b) (4) endotoxin limits for the [REDACTED] (b) (4) [REDACTED] (b) (4) after data from thirty batches is available and [REDACTED] (b) (4) to reflect manufacturing process capability.

## II. Summary of Quality Assessments

### A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 below is a summary of critical quality attributes and their control strategy that are relevant to both drug substance and drug product. For additional information see [Appendix A](#) for the Drug Substance Quality Review, [Appendix A-2](#) for the Drug Substance - Immunochemical Properties Review, [Appendix B](#) for the Drug Product Quality Review, and [Appendix C](#) for the Drug Substance and Drug Product Quality Review Addendum.



**QUALITY REVIEW BLA 125513 Strensiq (asfotase alfa)**



Table 1: Drug Substance API CQA Identification, Risk and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Enzymatic Assay (potency)	Directly linked to efficacy	Intrinsic to molecule	DS and DP release and stability testing	
Hydroxy Apatite (HA) binding assay (potency)	Directly linked to efficacy	Intrinsic to molecule	DS and DP release and stability testing	
PPI hydrolysis (potency)	Directly linked to efficacy	Intrinsic to molecule	DS and DP release and stability testing	
(b) (4) (potency)	Pharmacokinetics	(b) (4)	(b) (4) DS and DP release and stability testing	The sponsor will evaluate the feasibility of improving process capability to produce asfotase alfa with less variability (b) (4) (b) (4). <b>This will be addressed as a PMC.</b>
(b) (4)	Efficacy and safety	Introduced during manufacturing process and storage	(b) (4) (b) (4) DS and DP release and stability testing	
(b) (4)	Efficacy and safety	Introduced during manufacturing process and storage	(b) (4)	



QUALITY REVIEW BLA 125513 Strensiq (asfotase alfa)



			(b) (4) DS and DP release and stability testing	
(b) (4)	Directly linked to efficacy and MOA	Intrinsic to molecule	(b) (4)	
(b) (4)	Efficacy and safety	Intrinsic to molecule		
(b) (4)	Directly linked to efficacy and safety	Introduced during manufacturing process		
				Characterization, DS and DP release and stability testing
(b) (4)	Safety	Introduced during manufacturing process and storage	(b) (4) DS and DP release and stability testing	
Immunochemical properties	Safety	Intrinsic to molecule	Asfotase alfa contains intact Fc region (including a CH2 domain) and can potentially bind to C1q and trigger activation of the complement system  See <a href="#">Appendix A-2</a> for additional information	The applicant should develop an assay to directly compare the complement activating capacity of asfotase alfa to that of human IgG1. <b>This will be addressed as a PMC.</b>

## **B. Drug Substance: asfotase alfa Quality Summary**

### **CQA Identification, Risk and Lifecycle Knowledge Management**

Table 2 below is a summary of the identification, risk, and lifecycle knowledge management for drug substance CQAs that derive from the drug substance manufacturing process and general drug substance attributes. For additional information see [Appendix A](#) for the Drug Substance Quality Review, [Appendix B](#) for the Drug Product Quality Review, [Appendix C](#) for the Drug Substance and Drug Product Quality Review Addendum, [Appendix D](#) for the Microbiology Review and [Appendix D-2](#) for the Microbiology Review Addendum.



QUALITY REVIEW BLA 125513 Strensiq (asfotase alfa)



Table 2: Drug Substance CQA Identification, Risk, and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Endotoxin (b) (4)	Safety	(b) (4)	(b) (4) Controlled during (b) (4) release and stability testing (acceptance criterion (b) (4))	The applicant will re-evaluate (b) (4) limits for endotoxin after manufacturing 30 lots. <b>This will be addressed as a PMC.</b>
Bioburden (b) (4)	Safety	(b) (4)	Cleaning procedures, environmental control and monitoring, (b) (4) Controlled during release and stability testing (acceptance criterion (b) (4))	
(b) (4)				

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a. Description

Asfotase alfa is a soluble IgG1 Fc fusion glycoprotein composed of 2 identical polypeptide chains. Each polypeptide chain has 3 components: human tissue non-specific alkaline phosphatase (TNSALP), human immunoglobulin IgG1 Fc domain, and a deca-aspartate peptide (D10) used as a bone targeting domain. There are 2 disulfide bonds that link the polypeptide chains. Each polypeptide chain contains

(b) (4)

(b) (4)

Molecular weight analysis confirmed identity and demonstrated lack of significant levels of post-translational modifications other than (b) (4). For additional information see [Appendix A](#).

b. Mechanism of action

Hypophosphatasia is characterized by a deficiency of TNSALP enzymatic activity. TNSALP enables bone mineralization by locally cleaving inorganic pyrophosphate (Pi). Pi precipitates with calcium as calcium phosphate, which then mineralizes and becomes hydroxyapatite (HA). HA confers strength and rigidity to bones. For additional information see [Appendix A](#).

c. Potency Assay

The biological function is due to the tissue non-specific alkaline phosphatase (TNSALP) portion of the protein. TNSALP is an enzyme that catalyzes the hydrolysis of phosphomonoesters with release of inorganic phosphate and alcohol. Enzymatic activity is determined using a synthetic substrate (nitrophenyl phosphate - pNPP) and a natural substrate (pyrophosphate - PPI).

The sponsor claims that they developed an assay that measures the ability of asfotase alfa to bind to HA. However, the assay shows that bound asfotase alfa is active but does not provide information regarding the binding itself.

(b) (4)

(b) (4)

information is sufficient. For additional information see [Appendix A](#).

(b) (4)

(b) (4)



## f. Manufacturing process summary

The manufacture of asfotase alfa drug substance

(b) (4)

(b) (4)



(b) (4) is well controlled, microbial controls are in place and are adequate with a **PMC** to re-evaluate the (b) (4) endotoxin limits (b) (4), (b) (4) after 30 batches have been manufactured. For additional information see [Appendix A](#), [Appendix C](#), [Appendix D](#), and [Appendix D-2](#).

(b) (4)

(b) (4) According to the protocol,

(b) (4) bulk drug

substance lots will be placed under (b) (4) (b) (4) and (b) (4) (b) (4) stability conditions. The sponsor will submit a (b) (4) with (b) (4) (b) (4) of stability data prior to releasing the material. (b) (4) stability results will be included in the (b) (4). For additional information see [Appendix A](#).

g. Container closure

(b) (4)

(b) (4) the applicant performed a leachables evaluation of 6 DS lots monitored for 24 months. For additional information see [Appendix A](#) and [Appendix D](#).

h. Dating period and storage conditions

(b) (4)

### C. Drug Product: Strensiq Quality Summary

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes. For additional information see [Appendix B](#) for the Drug Product Quality Review, [Appendix D](#) for the Microbiology Review, and [Appendix D-2](#) for the Microbiology Review Addendum.



QUALITY REVIEW BLA 125513 Strensiq (asfotase alfa)



Table 3: Drug Product CQA Identification, Risk, and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Sterility (b) (4)	Safety risk to patients (infection) Efficacy (b) (4) (b) (4)	Accidental during fill, container closure failure	(b) (4) Sterility testing at release and stability; container closure integrity testing on stability	
Endotoxins (b) (4)	Safety, potential immunogenic reactions	Entire process	(b) (4) Controlled during release and stability testing.	
Container Closure Integrity (sterility assurance)	Failure in closure integrity may lead to contamination (loss of sterility) of DP or evaporation/leakage (impacting concentration or content)	Container design and control	Stability testing	
(b) (4)			Release and stability testing. Container closure integrity testing on	



QUALITY REVIEW BLA 125513 Strensiq (asfotase alfa)



	(b) (4)		stability	
Clarity and color (general)	Safety and efficacy	(b) (4)	Release and stability testing	
(b) (4)				
Leachables/ extractables (b) (4)	Safety	Manufacturing equipment and CCS	Risk assessment based on material characteristics, type of contact, and proximity to final product.  Extractables/leachables studies performed on CCS.	



**QUALITY REVIEW BLA 125513 Strensiq (asfotase alfa)**



pH (general)	Safety and efficacy	Formulation	Release and stability testing	
Osmolality (general)	Safety	Formulation	Release and stability testing	
Extractable volume (general)	Essential for dosing	Manufacturing Process	Release testing	
Identity (general)	Safety and efficacy	Intrinsic to molecule	Release testing	

- a. Potency and Strength  
Strensiq is supplied at two asfotase alfa concentrations, 40 mg/mL and 100 mg/mL. At the 40 mg/mL concentration, it is supplied as a single use vial at (b) (4) 0.45, 0.70, and 1.0 mL volumes containing (b) (4) 18, 28, and 40 mg of asfotase alfa respectively. At the 100 mg/mL concentration it is supplied in a single-use vial at 0.80 mL volume containing 80 mg of asfotase alfa.
- b. Summary of Product Design: Strensiq is supplied in single-use 2 mL vials
- c. List of Excipients: (b) (4) sodium chloride, (b) (4) dibasic sodium phosphate, (b) (4) (b) (4) monobasic sodium phosphate
- d. Reference material(s): the same reference material is used for drug substance and drug product
- e. Manufacturing Process  
The manufacturing process of drug product consists of (b) (4)  
(b) (4)
- The control strategy is appropriate to ensure (b) (4) consistently accurate (b) (4) and adequate critical quality attributes.  
For additional information see [Appendix B](#), [Appendix D](#), and [Appendix D-2](#).
- f. Container Closure  
The primary container closure system is a 2 mL Type I glass vial with a (b) (4) rubber stopper, (b) (4) and aluminium seal with a (b) (4) flip-off cap. Appropriate compatibility studies were performed for the container closure system. For additional information see [Appendix B](#), [Appendix D](#), and [Appendix D-2](#).
- g. Expiration Date & Storage Conditions: 24 months at 2-8°C
- h. List of co-packaged components, if applicable: None

#### D. Novel Approaches/Precedents: None

#### E. Any Special Product Quality Labeling Recommendations

Store at 2-8°C. Protect from light. Do not freeze or shake. Once removed from refrigeration it should be administered within one hour.

#### F. Establishment Information



QUALITY REVIEW BLA 125513 Strensiq (asfotase alfa)



OVERALL RECOMMENDATION:					
DRUG SUBSTANCE					
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	PRELIMINARY ASSESSMENT	INSPECTIONAL OBSERVATIONS	FINAL RECOMMENDATION
(b) (4)				VAI	Approval
					Facilities evaluation not required for this site
			Approval (2/3/2015)	NAI	Approval



**QUALITY REVIEW BLA 125513 Strensiq (asfotase alfa)**



MCB and WCB Storage Release and stability testing	Alexion Pharmaceuticals; Smithfield, RI	794325824/ 30006568549	Approval (2/3/2015)		Facilities evaluation for this site is not required for cell banking
<b>DRUG PRODUCT</b>					
<b>FUNCTION</b>	<b>SITE INFORMATION</b>	<b>DUNS/FEI NUMBER</b>		<b>INSPECTIONAL OBSERVATIONS</b>	<b>FINAL RECOMMENDATION</b>
(b) (4)			Approval (6/16/2015)	VAI	Approval
			Approval (2/3/2015)		Facilities evaluation not required for this site
DP release and stability testing	Alexion Pharmaceuticals; Smithfield, RI	794325824/ 30006568549	Approval (2/3/2015)	VAI	Approval
(b) (4)			Approval (2/3/2015)		Approval



QUALITY REVIEW BLA 125513 Strensiq (asfotase alfa)



<p>(b) (4)</p>	<p><b>Approval (2/3/2015)</b></p>		<p><b>Approval</b></p>
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### G. Facilities

The subject BLA proposes manufacture of Strensiq (asfotase alfa) DS at (b) (4). The most recent inspection was conducted (b) (4) by (b) (4) and resulted in the issuance of a 2-item FDA Form 483. The inspection was classified VAI. The PLI inspection took place on (b) (4) and the inspectors (from CDER-DMA and CDER-OBP) recommended NAI. On 09/22/2015, CDER/OPF/DIA rendered an approved decision for this facility.

Manufacture of Strensiq DP takes place at (b) (4). The most recent inspection took place on (b) (4) by (b) (4) and resulted in the issuance of a 2-item FDA Form 483. The inspection was classified VAI. This facility is approved based on the District recommendation.

Cell banking operations will occur at (b) (4) (b) (4) Alexion Pharmaceuticals, Smithfield, RI.

Testing/packaging operations will occur at:

- Alexion Pharma, Smithfield, RI (FEI 3006568549): facility approved based on file review.



For additional information see [Appendix E](#) for the Facilities Review and [Appendix E-2](#) for the Facilities Review Addendum.

### H. Lifecycle Knowledge Management

#### a. Drug Substance

##### i. Protocols approved

- (b) (4) (b) (4) DS lots will be placed on (b) (4) and (b) (4) (b) (4) (b) (4) stability conditions. The sponsor will submit a (b) (4) with (b) (4) of stability data prior to releasing the material. (b) (4) stability results will be reported in the (b) (4).
- Annual stability protocol
- Stability protocol (b) (4)

- ii. Outstanding review issues/residual risk
- iii. Future inspection points to consider

**b. Drug Product**

- i. Protocols approved
  - Annual stability protocol
  - Stability protocol [REDACTED] (b) (4)
- ii. Outstanding review issues/ [REDACTED] (b) (4) risk
- iii. Future inspection points to consider

In accordance with Alexion procedures, trending of release results is reviewed on an annual basis. Alexion commits to re-evaluate specifications after data from thirty [REDACTED] (b) (4) batches are available.

## Quality Assessment Summary Tables

**Table 1: Noteworthy Elements of the Application**

#	Checklist	Yes	No	N/A
<b>Product Type</b>				
1.	Recombinant Product	X		
2.	Naturally Derived Product		X	
3.	Botanical		X	
4.	Human Cell Substrate/Source Material		X	
5.	Non-Human Primate Cell Substrate/Source Material		X	
6.	Non- Primate Mammalian Cell Substrate/Source Material	X		
7.	Non-Mammalian Cell Substrate/Source Material		X	
8.	Transgenic Animal Sourced		X	
9.	Transgenic Plant Sourced		X	
10.	New Molecular Entity	X		
11.	PEPFAR Drug		X	
12.	PET Drug		X	
13.	Sterile Drug Product	X		
14.	Other _____			
<b>Regulatory Considerations</b>				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application (# _____)		X	
16.	Comparability Protocol(s)		X	
17.	End of Phase II/Pre-NDA Agreements		X	
18.	SPOTS (Special Products On-line Tracking System)		X	
19.	USAN Name Assigned	X		

20.	Other _____				
<b>Quality Considerations</b>					
21.	Drug Substance Overage			X	
22.	Design Space	Formulation		X	
23.		Process		X	
24.		Analytical Methods		X	
25.		Other		X	
26.	Other QbD Elements			X	
27.	Real Time Release Testing (RTRT)			X	
28.	Parametric Release in lieu of Sterility Testing			X	
29.	Alternative Microbiological Test Methods			X	
30.	Process Analytical Technology in Commercial Production			X	
31.	Non-compendial Analytical Procedures	Drug Product	X		
32.		Excipients		X	
33.		Drug Substance	X		
34.	Excipients	Human or Animal Origin		X	
35.		Novel		X	
36.	Nanomaterials			X	
37.	Genotoxic Impurities or Structural Alerts			X	
38.	Continuous Manufacturing			X	
39.	Use of Models for Release			X	
40.	Other _____				



## Appendices



## **BLA STN 125513**

**Product USAN name**  
**Asfotase alfa**

**Manufacturer**  
**Alexion**

**Joslyn Brunelle -DS**  
**Gunther Boekhoudt -DP**  
**Cris Ausin - TL**  
**Michele Dougherty - RC**



**OBP CMC Review Data Sheet**

1. **BLA#:** STN 125513
  
2. **REVIEW DATE:** August 5, 2015
  
3. **PRIMARY REVIEW TEAM:**  
**Medical Officer:** Carla Epps  
**Pharm/Tox:** Dinesh Gautam  
**Product Quality Team:** Joslyn Brunelle (DS), Gunther Boekhoudt (DP), Mate Tolnay (Fc portion only), Fred Mills (Immunogenicity)  
**BMT or Facilities:** Candace Gomez-Broughton and Steven Fong  
**Clinical Pharmacology:** Christine Hon, Justin Earp  
**Statistics:** Ben Vali  
**OBP Labeling:** Jibril Abdus-Samad  
**RPM:** Lisa Pitt and Kevin Bugin
  
4. **MAJOR GRMP DEADLINES**  
**Received:** December 23, 2014  
**Filing Meeting:** January 21, 2015  
**Mid-Cycle Meeting:** June 24, 2015  
**Primary Review Due:** August 8, 2015  
**Late Cycle Meeting:** September 2, 2015  
**Wrap-Up Meeting:** September 29, 2015  
**CDTL Memo Due:** September 25, 2015  
**PDUFA Action Date:** November 23, 2015
  
5. **COMMUNICATIONS WITH SPONSOR AND OND:**

<b>Communication/Document</b>	<b>Date</b>
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T-con with EMA	12/3/2014
Immunogenicity Pre-BLA Meeting	1/14/2014
Information Request #1	5/15/2014
Pre-BLA Meeting	7/8/2014
Information Request #2	11/26/2014
Information Request #3	1/27/2015
Team Meeting	2/19/2015



Appendix A: Drug Substance Quality Review: Office of Biotechnology Products

74-day Letter (Microbiology IR)	2/27/2015
T-con with Sponsor	3/5/2015
Information Request #4	3/6/2015
Team Meeting	3/11/2015
Information Request #5	4/17/2015
Information Request #6	4/20/2015
Team Meeting	4/21/2015
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Team Meeting	6/3/2015
Information Request #8	6/22/2015
Midcycle Meeting	6/24/2015
T-con with Sponsor	7/24/2015
Information Request #9	7/24/2015

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STN 125513/0004 (response to IR #1)	7/30/2014	Yes
STN 125513/0005 (response to IR #2)	12/19/2014	Yes
STN 125513/0006 (final rolling submission)	12/23/2014	Yes
STN 125513/0011 (response to IR #3)	2/12/2015	Yes
STN 125513/0014 (response to IR #3, IR#4, and 74-day Letter)	3/13/2015	Yes
STN 125513/0017 (response to 74-day letter)	3/30/2015	Yes
STN 125513/0025 (response to 74-day letter, IR #5, and IR#6)	4/30/2015	Yes
STN 125513/0029 (response to IR#3 and IR#7)	6/1/2015	Yes
STN 125513/0031 (response to IR#5, IR#6, and IR#8)	6/30/2015	Yes
STN 125513/0035 (response to 74-day Letter)	7/27/2015	Yes
STN 125513/0036 (response to IR#5)	7/31/2015	Yes



7.ADMINISTRATIVE

Signature Block

Name and Title	Signature and Date
<p>Michele Dougherty, Ph.D.</p> <p>Acting Review Chief</p> <p>Office of Biotechnology Products</p> <p>Division of Biotechnology Review and Research IV</p>	
<p>Cristina Ausin-Moreno, Ph.D.</p> <p>Acting Team Leader</p> <p>Office of Biotechnology Products</p> <p>Division of Biotechnology Review and Research IV</p>	
<p>Joslyn Brunelle, Ph.D.</p> <p>Drug Substance Primary Reviewer</p> <p>Office of Biotechnology Products</p> <p>Division of Biotechnology Review and Research IV</p>	



TABLE OF CONTENTS

3.2.S.1.2 Structure..... 35

3.2.S.1.3 General Properties ..... 37

3.2.S.2 Manufacture..... 37

3.2.S.2.1 Manufacturer(s) ..... 37

3.2.S.2.2 Description of Manufacturing Process and Process Controls..... 38

    3.2.S.2.2.1 Batch and Scale Definition..... 38

    3.2.S.2.2.2 Cell Culture and (b) (4) ..... 39

    3.2.S.2.2.3 Purification and Modification Reactions..... 44

    3.2.S.2.2.4 Filling, Storage, and Transportation..... 54

3.2.S.2.3 Control of Materials..... 54

    3.2.S.2.3.3 Source, History, and Generation of the Cell Substrate..... 55

    3.2.S.2.3.4 Cell Banking System, Characterization, and Testing..... 56

3.2.S.2.4 Controls of Critical Steps and Intermediates ..... 63

3.2.S.2.5 Process Validation and/or Evaluation..... 75

3.2.S.2.6 Manufacturing Process Development..... 77

3.2.S.3 Characterization..... 80

    3.2.S.3.1 Elucidation of Structure and Other Characteristics ..... 80

3.2.S.4 Control of Drug Substance ..... 99

3.2.S.4.1 Specification and 3.2.S.4.5 Justification of Specification ..... 99

3.2.S.4.2 Analytical methods and 3.2.S.4.3 Validation of methods..... 106

3.2.S.4.4 Batch Analysis ..... 143

3.2.S.5 Reference Standard..... 144

3.2.S.6 Container Closure ..... 151

3.2.S.7 Stability..... 152

3.2.S.7.1 Stability summary and conclusions ..... 152

3.2.S.7.2 Post approval stability protocol and stability commitment..... 153

3.2.A.2 Appendix Adventitious Agents Safety Evaluation..... 157

## DESCRIPTION OF DRUG SUBSTANCE

### S. DRUG SUBSTANCE

#### 3.2.S.1.2 Structure

Asfotase alfa is a soluble IgG1 Fc fusion glycoprotein composed of 2 identical polypeptide chains. Each polypeptide chain has 3 components: human tissue non-specific alkaline phosphatase (TNSALP), human immunoglobulin IgG1 Fc domain, and a deca-aspartate peptide (D10) used as a bone targeting domain. There are 2 disulfide bonds that link the polypeptide chains. In addition, each polypeptide chain contains [REDACTED] (b) (4) [REDACTED]. The amino acid sequence and graphic representation of the asfotase alfa structure is below in Figure 1.



Appendix A: Drug Substance Quality Review: Office of Biotechnology Products

**Figure 1: Asfotase Alfa Amino Acid Sequence**



## Appendix A: Drug Substance Quality Review: Office of Biotechnology Products

**3.2.S.1.3 General Properties****Table 1: General Properties of Asfotase Alfa**

Property	Result
Number of Amino Acids <sup>1</sup>	(b) (4)
Theoretical Molecular Weight <sup>2</sup>	
Chemical Formula	
Isoelectric (pI) range	
Extinction Coefficient at <sup>(b) (4)</sup> nm <sup>1</sup>	

The biological function is due to the tissue non-specific alkaline phosphatase (TNSALP) portion of the protein. TNSALP is an enzyme that catalyzes the hydrolysis of phosphomonoesters with release of inorganic phosphate and alcohol. Enzymatic activity is determined using a synthetic substrate (nitrophenyl phosphate - pNPP) and a natural substrate (pyrophosphate - PPI).

**Table 2: Specific Activity and Kinetic Data for Asfotase Alfa Drug Substance**

Property	Result
Specific Activity	(b) (4)
Alkaline Phosphatase Enzyme Kinetic Parameters	
Hydroxyapatite (HA) Binding	

**3.2.S.2 Manufacture****3.2.S.2.1 Manufacturer(s)**

Manufacture of Drug Substance, Raw material testing, <sup>(b) (4)</sup> testing:

<sup>(b) (4)</sup>

Storage of Cell Banks, Release and Stability Testing:

Alexion Pharmaceuticals Inc.

Alexion Manufacturing Facility (ARIMF)

100 Technology Way

Smithfield, RI 02917

FEI #3006568549



**3.2.S.2.2 Description of Manufacturing Process and Process Controls**

**3.2.S.2.2.1 Batch and Scale Definition**

Each Drug Substance (DS) batch is manufactured

(b) (4)

(b) (4)

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Appendix A: Drug Substance Quality Review: Office of Biotechnology Products



**3.2.S.2.5 Process Validation and/or Evaluation**

Process validation was performed on four consecutive drug substance batches manufactured between 2012-2013. The manufacturing process was  (b) (4) outlined above in Section 3.2.S.2.2.





Appendix A: Drug Substance Quality Review: Office of Biotechnology Products

(b) (4)



***Reviewer comment:***

*The sponsor provided the data for all process parameters for all four process validation batches (332604, 333366, 335332, 338971). Overall, the data is within the acceptable ranges for each process parameter.*

(b) (4)



## Appendix A: Drug Substance Quality Review: Office of Biotechnology Products

(b) (4)

Overall, the manufacturing history at the (b) (4) scale includes approximately 19 DS lots. This is significantly more experience than the Agency would expect a sponsor of an Orphan Drug (with a small patient population) to have at the BLA stage. This demonstrates that the drug substance manufacturing process (b) (4) can consistently produce asfotase alfa drug substance. In summary, I conclude that process validation is acceptable.

**3.2.S.2.6 Manufacturing Process Development**

(b) (4)

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Appendix A: Drug Substance Quality Review: Office of Biotechnology Products

(b) (4)  
(b) (4) the sponsor wanted to avoid any excipient related issues with a drug meant for subcutaneous injection. Sodium chloride was used to (b) (4). Drug substance stability was evaluated (b) (4)

**Reviewer comment:**

*The stability data (reviewed in section 3.2.S.7) indicates that the product is stable for up to 24 months when stored at 2-8 °C. Therefore, there are no issues (b) (4).*

**3.2.S.3 Characterization**

**3.2.S.3.1 Elucidation of Structure and Other Characteristics**

Characterization studies used batch 260464 (b) (4) to evaluate asfotase alfa (b) (4)

(b) (4)

**Reviewer comment:**

*The BLA provides complete characterization for only one lot (260464) of the (b) (4) scale. However, the comparability study between the (b) (4) scales submitted under the IND 100619 was very extensive. Overall, the comparability study included release testing, the majority of the extended characterization assays summarized in this review, and forced degradation studies (b) (4). The study included 5 lots from the (b) (4) process and 5 lots from the (b) (4) process. The data can be found in the manufacturing process development section 3.2.S.2.6.*

*The Fc portion will be reviewed by Mate Tolnay. One of the concerns with an Fc region is that it could activate the complement system. The FDA requested that Alexion develop an (b) (4) assay to assess the potential for complement activation; this will be a postmarketing requirement. See Mate’s Review in [Appendix A-2](#).*

The **identity** of asfotase alfa was analyzed using 5 different analytical methods. (b) (4)

(b) (4)



Appendix A: Drug Substance Quality Review: Office of Biotechnology Products



(b) (4)

**Reviewer comment:**



(b) (4)

(b) (4) Overall, Alexion followed the Agency's recommendations and the assays appear adequate to analyze biological activity of asfotase alfa. More detailed information on the assay validation for release and stability testing can be found in Section 3.2.S.4.2.

*Of note, the number of lots tested using the physiologically relevant substrate is limited. Therefore, the data with which to set the specification for this assay is limited. The Agency acknowledged this during the CMC meeting in November 2013.*

*In summary, the characterization of asfotase alfa is adequate. Where appropriate, orthogonal methods were used to evaluate asfotase alfa characteristics.*

Appendix A: Drug Substance Quality Review: Office of Biotechnology Products

3.2.S.3.2 Impurities

The following product related impurities have been observed as summarized below in Table 45.

**Table 45: Summary of Asfotase Alfa Product Related Impurities**

Impurity	Analytical Method
(b) (4)	

**Reviewer comment:**

*Product related impurities are monitored at release and stability.*

(b) (4)

(b) (4)

(b) (4) impurities were identified in the asfotase alfa manufacturing process.

(b) (4)

(b) (4) Based on an impurity clearance assessment using drug substance batches 280897 and 284989, Alexion concluded that the impurities pose minimal risk to patient safety and no routine testing is necessary. This assessment was based on the impurity safety factor (ISF) method. It is based on worst case assumptions

(b) (4)

(b) (4)



Appendix A: Drug Substance Quality Review: Office of Biotechnology Products



(b) (4)

**Reviewer comment:**

*Alexion has demonstrated that either very low levels of impurities are present*

(b) (4)

(b) (4)

(b) (4)





Appendix A: Drug Substance Quality Review: Office of Biotechnology Products

(b) (4)

Overall, I agree with the sponsor's assessment that no further (b) (4) analysis or acceptance criteria are necessary (b) (4)

(b) (4)



Appendix A: Drug Substance Quality Review: Office of Biotechnology Products



(b) (4)

Appendix A: Drug Substance Quality Review: Office of Biotechnology Products

3.2.S.4 Control of Drug Substance

3.2.S.4.1 Specification and 3.2.S.4.5 Justification of Specification

**Table 1: Asfotase Alfa Drug Substance Clinical and Proposed Commercial Specifications**

Test	Clinical Acceptance Criteria	Proposed Commercial Acceptance Criteria Presented in Original BLA	Updated Proposed Commercial Acceptance Criteria
Appearance (Visible Particles, Color, Clarity)	(b) (4)	Few small translucent or white particles, Colorless to slightly yellow	Few small translucent or white particles may be present, Colorless to slightly yellow
	Clear, slightly opalescent or opalescent	(b) (4) Clear, slightly opalescent or opalescent	(b) (4) Clear, slightly opalescent or opalescent
Osmolality	(b) (4)	(b) (4)	(b) (4)
pH	7.2 – 7.6	7.2 – 7.6	7.2 – 7.6





Appendix A: Drug Substance Quality Review: Office of Biotechnology Products

(Continued)

Test	Clinical Acceptance Criteria	Proposed Commercial Acceptance Criteria Presented in Original BLA	Updated Proposed Commercial Acceptance Criteria
------	------------------------------	---	---

(b) (4)			
---------	--	--	--

**Reviewer comments:**

This section includes my analysis of Alexion’s proposed specifications. I included control charts/graphs that Alexion provided in their submission in order to illustrate the ranges used in clinical studies, where appropriate.

1. (b) (4)

(b) (4)

The sponsor states that “trending of release results is reviewed on an (b) (4) basis. Alexion commits that the drug substance specification will be reevaluated (b) (4) (b) (4) process is available and will be (b) (4) further if appropriate.” This is acceptable.

2. March 13, 2015 amendment, Alexion agreed to revise the peptide mapping specification as below. This is acceptable.

(b) (4)
---------

#### 3.2.S.4.4 Batch Analysis

There are 12 drug substance lots from the (b) (4) scale and 11 drug substance lots from the (b) (4) scale used in clinical studies. Overall, there is release data from 16 lots of the (b) (4) (commercial) scale.

***Reviewer comment:***

*This is covered under Section 3.2.S.4.1 where the specifications are evaluated.*

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Appendix A: Drug Substance Quality Review: Office of Biotechnology Products



(b) (4)

***Reviewer comment:***

The sponsor provided stability data [redacted] (b) (4),  
[redacted] (b) (4) The data support an initial 2 year expiry, [redacted] (b) (4). This is  
acceptable.

## Appendix A: Drug Substance Quality Review: Office of Biotechnology Products

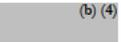
**3.2.S.6 Container Closure**

The drug substance container closure is a <sup>(b) (4)</sup> container. The <sup>(b) (4)</sup>



<sup>(b) (4)</sup>. These were evaluated under a leachable study.

***Reviewer comment:***

*I agree with the sponsor's assessment; the leachable data indicates the risk to the patient is low. The drug substance container closure is acceptable. <sup>(b) (4)</sup> containers are commonly used in manufacturing of biologics.*



### 3.2.S.7 Stability

#### 3.2.S.7.1 Stability summary and conclusions

Stability studies for drug substance include long term storage at (b) (4) and accelerated conditions (b) (4)

(b) (4) Table 2 and 3 summarize the batches of DS placed on stability. In summary, the evaluation includes 10 drug substance batches (b) (4) up to (b) (4) ( (b) (4) ). The sponsor is requesting a (b) (4) shelf-life for drug substance.

(b) (4)

## Appendix A: Drug Substance Quality Review: Office of Biotechnology Products

(b) (4)

**Reviewer comment:**

The data supporting real time stability is very extensive. I conclude the data support a (b) (4) shelf-life for drug substance stored at (b) (4)

Note that forced degradation studies were performed on 100mg/mL drug product batches. The DS and DP are both at the same 100mg/mL concentration and formulation. DP manufacturing consists of a (b) (4), so this is acceptable. See section 3.2.P.8 for more information on the forced degradation studies.

## 3.2.S.7.2 Post approval stability protocol and stability commitment

The following is copied directly from the submission:



Appendix A: Drug Substance Quality Review: Office of Biotechnology Products

(b) (4)

(b) (4)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Center for Drug Evaluation and Research – Food and Drug Administration

Office of Biotechnology Products / Office of Pharmaceutical Quality

BLA: 125513

DATE: July 10, 2015

FROM: Mate Tolnay, Ph.D. LIB/OBP/DBRR IV

THROUGH: Gerald Feldman, Ph.D. Chief, LIB, OBP/DBRR IV

PRODUCT: STRENSIQ™ (Asfotase alfa)

**Summary and recommendation**

Asfotase alfa contains a functional IgG1 Fc region which can potentially engage and activate the complement system. The complement activation assay used by Alexion, considered insensitive by FDA, detected no complement activation. Alexion was advised to directly compare the complement activating capacity of asfotase alfa to that of human IgG1. FDA noted a specific assay format that could be used. Alexion stated the feasibility of such an assay will be assessed and committed to provide an update by end of 3Q of 2015. A PMC to compare the complement activating capacity of asfotase alfa to that of human IgG1 is recommended. If asfotase alfa binds complement more strongly than human IgG1, further studies might be necessary.

*The following review consists of selected text edited from the original IND submission. All Tables and Figures are copied from the submission, and then edited. Reviewer’s comments are distinguished by use of italic font.*

**3.2.S.3.1 Elucidation of Structure and Other Characteristics**

**1.3. Immunochemical Properties**

Asfotase alfa contains an intact Fc region and can potentially bind to Fc receptors and thereby activate the complement system. The potential of asfotase alfa to activate complement in serum samples was evaluated [redacted] in human serum samples. This assay measured the levels of [redacted]



(b) (4) Alexion will assess the feasibility of an assay to compare the complement activation potential of asfotase alfa to that of human IgG1. Alexion commits to provide an update to the Agency by end of 3Q2015.

*Reviewer comment: Alexion stated that asfotase alfa does contain a CH2 domain and committed to assess the feasibility of an assay to compare the complement activation potential of asfotase alfa.*

***Reviewer Summation:***

*Based on my overall risk assessment, it is acceptable to evaluate the complement activating capacity of asfotase alfa as part of a PMC.*

## **BLA STN 125513**

**STRENSIQ (asfotase alfa)**

**Drug Product**

**Alexion**

**Reviewer: Gunther Boekhoudt**

**LC/TL Reviewer: Cris Ausin**

**Division of Biotechnology Review and Research IV**

## Appendix B: Drug Product Quality Review: Office of Biotechnology Products

**OBP CMC Review Data Sheet**1. **BLA#: STN 125513**2. **REVIEW DATE: August 5, 2015**3. **PRIMARY REVIEW TEAM:**

Clinical TL: Anil Rajpal  
Clinical Reviewer: Carla Epps  
Clinical Pharmacology TL: Yow-Ming Wang  
Clinical Pharmacology: Christine Hon  
Clinical Pharmacometrics: Justin Earp  
Product Quality TL: Cris Ausin  
Product Quality Reviewer (Drug Substance): Joslyn Brunelle, Mate Tolnay  
Product Quality Reviewer (Drug Product): Gunther Boekhoudt  
Product Quality Reviewer (Immunogenicity): Fred Mills  
Product Quality Labeling Reviewer: Jibril Abdus-Samad  
Micro TL: Patricia Hughes  
Micro Reviewer: Candace Gomez-Broughton  
Facilities Reviewer: Steven Fong  
Immunogenicity: Fred Mills

4. **MAJOR GRMP DEADLINES**

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Primary Review Due: August 8, 2015  
Late Cycle Meeting: September 2, 2015  
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5. **COMMUNICATIONS WITH SPONSOR AND OND:**

<b>Communication/Document</b>	<b>Date</b>
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Pre-BLA Meeting	7/8/2014
Information Request #2	11/26/2014
Information Request #3	1/27/2015

## Appendix B: Drug Product Quality Review: Office of Biotechnology Products

Team Meeting	2/19/2015
74-day Letter (Microbiology IR)	2/27/2015
T-con with Sponsor	3/5/2015
Information Request #4	3/6/2015
Team Meeting	3/11/2015
Information Request #5	4/17/2015
Information Request #6	4/20/2015
Team Meeting	4/21/2015
T-con with EMA	4/29/2015
Information Request #7	5/22/2015
Team Meeting	6/3/2015
Information Request #8	6/22/2015
Midcycle Meeting	6/24/2015
T-con with Sponsor	7/24/2015
Information Request #9	7/24/2015

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STN 125513/0004 (response to IR #1)	7/30/2014	Yes
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STN 125513/0014 (response to IR #3, IR#4, and 74-day Letter)	3/13/2015	Yes
STN 125513/0017 (response to 74-day letter)	3/30/2015	Yes
STN 125513/0025 (response to 74-day letter, IR #5, and IR#6)	4/30/2015	Yes
STN 125513/0029 (response to IR#3 and IR#7)	6/1/2015	Yes
STN 125513/0031 (response to IR#5, IR#6, and IR#8)	6/30/2015	Yes
STN 125513/0035 (response to 74-day Letter)	7/27/2015	Yes
STN 125513/0036 (response to IR#5)	7/31/2015	Yes

## Appendix B: Drug Product Quality Review: Office of Biotechnology Products

## 7. ADMINISTRATIVE

## A. Signature Block

Name and Title	Signature and Date
Michele Dougherty, Ph.D. Acting Review Chief Division of Biotechnology Review and Research IV	
Cris Ausin, Ph.D., Acting Team Leader Division of Biotechnology Review and Research IV	
Gunther Boekhoudt, Ph.D., Primary Reviewer Division of Biotechnology Review and Research IV	

## B. CC Block

Recipient	Date
Lisa Pitt	December 23, 2014
Division of Biotechnology Review and Research IV File/BLA STN 125513	December 23, 2014

## Appendix B: Drug Product Quality Review: Office of Biotechnology Products

**Table of Contents****P Drug Product**

3.2.P.1 Description and Composition of the Drug Product.....	175
3.2.P.2 Pharmaceutical Development .....	176
3.2.P.2.1 Components of the Drug Product .....	176
3.2.P.2.1.1 Drug Substance .....	177
3.2.P.2.1.2 Excipients.....	177
3.2.P.2.2 Drug Product .....	177
3.2.P.2.2.1 Formulation Development .....	177
3.2.P.2.2.2 Overages.....	177
3.2.P.2.2.3 Physicochemical and Biological Properties .....	178
3.2.P.2.3 Manufacturing Process Development.....	178
3.2.P.2.3.1 Overall Process Development Summary.....	178
3.2.P.2.3.2 Drug Product Critical Quality Attributes .....	178
3.2.P.2.3.3 Drug Product Manufacturing Process History .....	178
3.2.P.2.4 Container Closure System .....	179
3.2.P.2.4.1 Container Suitability.....	180
3.2.P.2.5 Microbiological Attributes [See DMPQ/BMAB's Review for details].....	183
3.2.P.2.6 Compatibility with administration materials .....	184
3.2.P.3 Manufacture .....	186
3.2.P.3.1 Manufacturer(s).....	186
3.2.P.3.2 Batch Formula .....	188
3.2.P.3.3 Description of Manufacturing Process and Process Controls.....	188
3.2.P.3.4 Controls of Critical Steps and Intermediates .....	190
3.2.P.3.5 Process Validation and/or Evaluation .....	191
3.2.P.4 Control of Excipients .....	202
3.2.P.4.1 Specifications .....	202
3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures .....	202
3.2.P.4.4 Justification of Specifications.....	202
3.2.P.4.5 Excipients of Human or Animal Origin .....	202
3.2.P.4.6 Novel Excipient.....	202
3.2.P.5 Control of Drug Product .....	203
3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s) .....	203
3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures .....	218
3.2.P.5.4 Batch Analyses.....	228
3.2.P.5.5 Characterization of Impurities.....	229
3.2.P.6 Reference Standards or Materials .....	229
3.2.P.7 Container Closure System .....	229
3.2.P.8 Stability.....	231
3.2.P.8.2 Post-Approval Stability Commitment .....	233
3.2.P.8.3 Stability Data.....	236
3.2.A Appendices Table of Contents .....	246
3.2.A.1 Facilities and Equipment .....	246
3.2.A.3 Novel Excipients.....	246
None .....	246
3.2.R Regional Information .....	246
3.2.R.1 Executed Batch Records .....	246
3.2.R.2 Method Validation Package.....	246
3.2.R.3 Comparability Protocols .....	246

Appendix B: Drug Product Quality Review: Office of Biotechnology Products

P DRUG PRODUCT

**3.2.P.1 Description and Composition of the Drug Product**

ALXN-1215 (asfotase alfa) is a recombinant human alkaline phosphatase intended to be used in an enzyme-replacement therapy for patients with hypophosphatasia (HPP). HPP is a rare, life-threatening, genetic metabolic disease with no approved treatment options.

**Description**

Asfotase alfa DP is supplied as a sterile, preservative-free aqueous solution for SC administration at two concentrations containing 40 mg/mL or 100 mg/mL asfotase alfa in (b) (4) sodium phosphate, (b) (4) sodium chloride at a pH between 7.2 and 7.6 in a 2 mL Type 1 glass vial. The vials are stoppered with a (b) (4) rubber stopper (b) (4) and sealed with aluminum seals with (b) (4) flip-off caps.

Asfotase alfa DP is supplied in single-use vials at different volumes ([Table 1](#)).

**Table 1 DP Dosage Strengths**

Asfotase alfa concentration	Extractable volume per vial	Amount of asfotase alfa per vial	Fill volume*
40 mg/mL	0.45 mL	18 mg	(b) (4)
	0.70 mL	28 mg	
	1.0 mL	40 mg	
100 mg/mL	0.80 mL	80 mg	

\* Fill volume as described in section [3.2.P.3.4 Control of critical steps and intermediates](#)

*Reviewer comment:* The fill volumes are within the USP <1151>. The (b) (4) excess volume is appropriate.

**Drug product composition and presentations**

The composition of both the 40 mg/mL and 100 mg/mL are shown in [Table 2](#) and [Table 3](#) respectively.

**Table 2: 40 mg/mL DP**

(Table 1 Section 3.2.P.1 in the BLA)

Appendix B: Drug Product Quality Review: Office of Biotechnology Products

Component (Formulation Concentration)	Quality Standard	Function	Available Quantity per Vial for Each Extractable Volume (b) (4)
asfotase alfa (40 mg/mL)	In-house	Active ingredient	(b) (4)
(b) (4) Sodium chloride (b) (4)	USP, Ph. Eur., JP	(b) (4)	
(b) (4) Dibasic sodium phosphate (b) (4)	USP, Ph. Eur.		
(b) (4) Monobasic sodium phosphate (b) (4)	USP, Ph. Eur.		
(b) (4)			

Table 3: 100 mg/mL DP

(Table 2 Section 3.2.P.1 in the BLA)

Component (Formulation Concentration)	Quality Standard	Function	Available Quantity per Vial for Each Extractable Volume (b) (4)
asfotase alfa (100 mg/mL)	In-house	(b) (4)	(b) (4)
(b) (4) Sodium chloride (b) (4)	USP, Ph. Eur., JP		
(b) (4) Dibasic sodium phosphate (b) (4)	USP, Ph. Eur.		
(b) (4) Monobasic sodium phosphate (b) (4)	USP, Ph. Eur.		
(b) (4)			

Asfotase alfa is indicated for (b) (4) (b) (4) for patients with perinatal, infantile, and juvenile-onset hypophosphatasia. The proposed dosage regimen is 6 mg/kg/week administered by SC injection. This is achieved by either 1 mg/kg six times per week or 2 mg/kg three times per week with a maximum injection volume of 1 mL/injection. Frequency of injection is left to the discretion of the patient or parent/guardian. Larger patients may necessitate multiple injections per dose and may wish to receive fewer injections more frequently.

*Reviewer comment:* Asfotase alfa comes in 2 mL vials for single use. Dosing is determined by patient weight but maximum administered volume per injection cannot exceed 1 mL. This implies that smaller patients (lighter patients) could receive one injection using one vial. In contrast, larger patients (heavier patients) could use multiple vials.

### 3.2.P.2 Pharmaceutical Development

#### 3.2.P.2.1 Components of the Drug Product

## Appendix B: Drug Product Quality Review: Office of Biotechnology Products

**3.2.P.2.1.1 Drug Substance**

Asfotase alfa is an IgG1 Fc fusion glycoprotein comprised of two identical polypeptide chains. Each chain consists of (b) (4) a soluble catalytic domain of human tissue non-specific alkaline phosphatase (sALP), a human IgG1 Fc domain, a deca-aspartate peptide (D<sub>10</sub>) used as a bone-targeting domain, and two amino acid long linkers between these domains. These chains are covalently linked by two disulfide bonds. The DS is formulated at 100 mg/mL, (b) (4) sodium phosphate, (b) (4) sodium chloride, (b) (4) (See [Table 2](#) and [Table 3](#) for DP composition). Asfotase alfa is compatible with all the excipients in the formulation.

There are no physicochemical characteristics or biological properties of the DS which influence the performance or manufacturability of the DP.

**3.2.P.2.1.2 Excipients**

DP excipients are all compendial grade ([Table 4](#))

**Table 4 DP Excipients**

Excipient	Grade	Concentration	Purpose
sodium chloride	USP, Ph. Eur., JP	(b) (4)	(b) (4)
sodium phosphate monobasic	USP, Ph. Eur.		
sodium phosphate dibasic	USP, Ph. Eur.		

*Reviewer comment: All excipients are standard pharmacopeial excipients.*

**3.2.P.2.2 Drug Product****3.2.P.2.2.1 Formulation Development**

Both the 40 mg/mL and the 100 mg/mL DP are formulated in the same formulation (b) (4) and it remained unchanged during non-clinical and clinical development. Formulation development of DS and DP are identical and is detailed in section 3.2.S.2.6.6 Drug Formulation Development (DS review by Joslyn Brunelle).

The formulation was designed based on (b) (4). Phosphate was chosen (b) (4). (b) (4). (b) (4). Sodium chloride was used (b) (4).

**3.2.P.2.2.2 Overages**

There are no overages in the amount of asfotase alfa added to the formulation (b) (4). The DP vials are filled with a (b) (4) overfill.

## Appendix B: Drug Product Quality Review: Office of Biotechnology Products

**Reviewer comment:** *The DP has no overages, but there is (b) (4) overfill in each vial to guarantee extraction of the desired volume. This overfill complies with the USP <1151> and is acceptable.*

**3.2.P.2.2.3 Physicochemical and Biological Properties**

The physicochemical and biological properties of the DP and DS are identical except for the concentration of asfotase alfa. DP is produced in two concentrations, 100 mg/mL and 40 mg/mL. (b) (4)  
(b) (4)

**3.2.P.2.3 Manufacturing Process Development****3.2.P.2.3.1 Overall Process Development Summary**

DP is manufactured (b) (4)  
(b) (4)

DP manufacturing process underwent two changes throughout clinical development,

(b) (4)

**3.2.P.2.3.2 Drug Product Critical Quality Attributes**

The DS critical quality attributes are similar to DP attributes except for those that are DP specific (see section 3.2.S.2.6 Manufacturing Process Development in [Appendix A](#)). DP specific critical quality attributes are sterility, particulate and extractable volume. Sterility testing is performed per USP <71> and Ph. Eur. 2.6.1, particulate testing is performed per USP <788> and Ph. Eur. 2.9.19, and extractable volume is performed per USP <1> and Ph. Eur. 2.9.17.

**Reviewer comment:** *Sterility, particulate, and extractable volume testing conform to USP and Ph. Eur. standards and are acceptable.*

**3.2.P.2.3.3 Drug Product Manufacturing Process History**

Manufacturing of DP was initially contracted to (b) (4) which in (b) (4) was transferred to (b) (4). At the same time, DS manufacturing was transferred to (b) (4). [Table 5](#) summarizes the differences between the (b) (4) processes.

**Table 5 Manufacturing changes in 2010**

	Drug Substance	Drug Product

## Appendix B: Drug Product Quality Review: Office of Biotechnology Products

(b) (4)

The validated commercial DP manufacturing process is described below in Section [3.2.P.3.3](#) (Description of Manufacturing Process and Process Controls) and the validation is described in Section [3.2.P.3.5](#) (Process Validation and/or Evaluation).

Studies supporting the comparability and consistency of the drug substance manufactured at the two clinical manufacturing scales are presented in Section 3.2.S.2.6.5.1 (Comparability between the (b) (4) and (b) (4) scale in Appendix A).

***Reviewer's comment:*** *The DP manufacturing process underwent minor changes during development. The sponsor did not provide a comparability assessment to evaluate potential effects of these manufacturing changes. Upon request from the Agency (3/6/2015), Alexion provided additional information to the BLA on 3/13/15 (SN0015).*

***Reviewer's Evaluation of Alexion Response 1 (SN0015 submitted on 3/13/15):***

*Alexion provided sufficient information to allow for a side-by-side comparison of the DPs manufactured (b) (4). Overall the data support that the DP produced (b) (4) is comparable (b) (4).*

*(b) (4) These statistical differences were all small and overall trending demonstrated a more pure and consistent manufacturing process. In addition, the differences observed should pose no safety risk to the patient. I agree with the sponsor that the DPs produced at both sites are comparable.*

### 3.2.P.2.4 Container Closure System

The DP container closure system for (40 mg/mL and 100 mg/mL) is a 2 mL USP/Ph. Eur. Type I glass vial, a (b) (4) rubber stopper (b) (4) and an aluminum seal with a (b) (4) flip-off cap. Packaging of DP consists of two configurations: 12 vials or a single vial in a (b) (4) carton. To differentiate between the two DP concentrations, (b) (4). The 40 mg/mL and the 100 mg/mL DP are sealed (b) (4), respectively.

## Appendix B: Drug Product Quality Review: Office of Biotechnology Products

**Reviewer comment:** *The commercial DP container closure system is the same one used throughout the clinical development. Therefore, no additional data are required.*

### 3.2.P.2.4.1 Container Suitability

#### Light Transmission

Asfotase alfa is light sensitive. Stability studies demonstrated that the DP was stable when using the [REDACTED] (b) (4) therefore the vial does not need to provide protection from light.

(b) (4)

**Reviewer comment:** *The photostability studies (See section 3.2.P.8.3 Stability Data for more detail) showed that the DP is sensitive to light [REDACTED] (b) (4). These changes were not observed when the DP was protected from light supporting the sponsor's claims that the [REDACTED] (b) (4) is sufficient to protect the DP from light. I agree with the sponsor's conclusions.*

Appendix B: Drug Product Quality Review: Office of Biotechnology Products



(b) (4)

**3.2.P.2.4.2 Container Closure System Integrity (CCSI)**

The CCSI study was used to confirm that the DP container is capable of preventing microbial contamination.

(b) (4)

[3.2.P.2.5](#) (Microbial Attributes) below.



(b) (4)

## Appendix B: Drug Product Quality Review: Office of Biotechnology Products

(b) (4)

**3.2.P.3 Manufacture****3.2.P.3.1 Manufacturer(s)**

DP manufacturing sites and responsibilities are as follows;

Facility	Responsibility
(b) (4)	

DP testing sites and responsibilities are as follows;

Facility	Responsibility
(b) (4)	

## Appendix B: Drug Product Quality Review: Office of Biotechnology Products

Alexion Pharmaceuticals Inc.  
Alexion Manufacturing Facility (ARIMF)  
100 Technology Way  
Smithfield, Rhode Island 02917  
US  
Food and Drug Administration Establishment  
Identifier: 3006568549  
Data Universal Numbering System(D.U.N.S):  
794325824

## Release Testing

(b) (4)

(b) (4)

Facility	Responsibility
<p>Alexion Pharmaceuticals Inc. Alexion Manufacturing Facility (ARIMF) 100 Technology Way Smithfield, Rhode Island 02917 US Food and Drug Administration Establishment Identifier: 3006568549 Data Universal Numbering System(D.U.N.S): 794325824</p>	<p>Stability Testing:</p> <p>(b) (4)</p>

(b) (4)

## Appendix B: Drug Product Quality Review: Office of Biotechnology Products

**Reviewer comment:** Multiple quality control labs were listed, Alexion Rhode Island site and (b) (4), as performing drug product release testing for asfotase alfa. A comment was sent to the sponsor on 4/17/15 for clarification for their strategy for drug product release testing, particularly the responsibility of the laboratories. Alexion provided a clarification on 4/30/15 (SN0026).

**Reviewer's Evaluation of Alexion Response 5 (SN0026 submitted on 4/30/15):**

The primary DP release testing site is the Alexion Rhode Island Manufacturing Facility (ARIMF). All DP release data submitted in the BLA were obtained from ARIMF. The secondary DP release testing site is (b) (4)

Alexion did clarify the primary and the secondary DP release testing sites. The response is adequate.

**3.2.P.3.2 Batch Formula**

The DS is formulated to a concentration of 100 mg/mL asfotase alfa and stored at (b) (4). The 100 mg/mL DP presentation is filled from the 100 mg/mL DS (b) (4). The 40 mg/mL DP is produced by (b) (4) at the DP manufacturing site (b) (4)

Each DP batch is manufactured from one DS batch while a single DS batch may be used to produce multiple DP batches.

**3.2.P.3.3 Description of Manufacturing Process and Process Controls**

(b) (4)

## Appendix B: Drug Product Quality Review: Office of Biotechnology Products



**Overall Reviewer comment:** *The data provided in this section show that the DP manufacturing process is validated and capable of performing within the pre-specified acceptance criteria. The quality attributes for all DP lots, including all microbial attributes were within specifications.*

**3.2.P.4 Control of Excipients****3.2.P.4.1 Specifications**

All excipients are added to the 100 mg/mL DP (b) (4) during DS manufacturing. For the 40 mg/mL DP, (b) (4). [Table 24](#) shows the quality control specifications for the DP excipients. A Certificate of Analysis is provided with each excipient.

**Table 24 Quality Control Specifications****(Table 1 Section 3.2.P.4.1 in the BLA)**

Excipient	Test
Sodium chloride	Complies with current USP and Ph. Eur., and JP monographs
Dibasic sodium phosphate, (b) (4)	Complies with current USP and Ph. Eur. monographs
Monobasic sodium phosphate, (b) (4)	Complies with current USP and Ph. Eur. monographs

**Reviewer comment:** *All excipients comply with compendial methods (USP, Ph. Eur., or JP). Formulation is performed at BDS stage and therefore no new excipients are added to DP. There are no human or novel excipients in drug product.*

**3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures**

Not applicable.

**3.2.P.4.4 Justification of Specifications**

Not applicable.

**3.2.P.4.5 Excipients of Human or Animal Origin**

Not applicable.

**3.2.P.4.6 Novel Excipient**

Not applicable.

## Appendix B: Drug Product Quality Review: Office of Biotechnology Products

**3.2.P.5 Control of Drug Product****3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)**The DP specifications and acceptance criteria are shown in the [Table 25](#):**Table 25 100 mg/mL and 40 mg/mL DP Specifications**

(b) (4)

(Table reproduced from Section 3.2.P.5.1, Tables 1 and 2 in the BLA)

	100 mg/mL Asfotase alfa	40 mg/mL Asfotase alfa
<b>Test</b>	<b>Acceptance criteria</b>	
Appearance (Visible Particles, Color, Clarity)	Few small translucent or white particles, may be present, Colorless to slightly yellow (b) (4) Clear, slightly opalescent or opalescent	
Osmolality	Osmolality (b) (4)	
pH	7.2 – 7.6	

(b) (4)

Appendix B: Drug Product Quality Review: Office of Biotechnology Products

(b) (4)		
Endotoxin (LAL)	(b) (4)	
Sterility	No growth	
Particulates	(b) (4)	(b) (4)
	(b) (4)	(b) (4)
Extractable Volume (Release test only)	80 mg/vial: Not Less Than 0.80 mL	(b) (4)
		18 mg/vial: Not Less Than 0.45 mL
		28 mg/vial: Not Less Than 0.70 mL
40 mg/vial: Not Less Than 1.0 mL		
Container Closure Integrity	N/A (Meets Requirements)	

**Reviewer comment:** *The DP specifications include three specifications that are unique to DP, namely; sterility, particulate analysis, and extractable volume. The particulate analysis and extractable volume are appropriate DP specific USP tests. Sterility testing is reviewed by DMA.*

*All other DP specifications are also DS specifications with the same acceptance criteria with two exceptions. DS has different acceptance criteria* (b) (4)

## Appendix B: Drug Product Quality Review: Office of Biotechnology Products

(b) (4)

*Overall the DP specifications test a wide variety of quality attributes with justifiable acceptance criteria and are therefore suitable to ensure product quality.*

**Table 26 Detail summary of DP specification, lot ranges, and justifications**

**(Table reproduced from Section 3.2.S.4.5 Table 1, 3.2.P.5.6 Table 1, and 3.2.P.5.4 Tables 3 - 12, in the BLA)**

Test	Requirements (Acceptance Criteria)	Range of Clinical Trial Material	Range of Process Validation/ Commercial lots	Justification of Specification and <i>Reviewer comments</i>
		<i>Information derived from the batch analyses provided by the Sponsor in the BLA.</i>		
Appearance (Visible Particles, Color, Clarity)	Few small translucent or white particles may be present, Colorless to slightly yellow (b) (4) Clear, slightly opalescent or opalescent	(b) (4)		
Osmolality	(b) (4)			



BLA 125513

Asfotase alfa



Appendix B: Drug Product Quality Review: Office of Biotechnology Products

		(b) (4)
pH	7.2 – 7.6	(b) (4)
(b) (4)		

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BLA 125513

Asfotase alfa



Appendix B: Drug Product Quality Review: Office of Biotechnology Products



(b) (4)

Endotoxin (LAL)	(b) (4)	(b) (4)	(b) (4)	<p>The DP endotoxin specification was established per Agency recommendation.</p> <p><i>This is acceptable. The specification for endotoxin is (b) (4) (b) (4). At the proposed maximum dose of 6 mg/kg/week, the endotoxin limit (b) (4) (b) (4) is below the Agency recommended amount (b) (4). All DP lots tested met specification</i></p>
Sterility	(b) (4)			The DP sterility specification was



BLA 125513

Asfotase alfa



## Appendix B: Drug Product Quality Review: Office of Biotechnology Products

				<p>established according to compendial requirements.</p> <p><i>The acceptability of the sterility specification is reviewed by DMA. All DP lots met sterility specification of no growth.</i></p>	
Particulates	(b) (4)			<p>(b) (4) The DP particulates specification was established according to compendial requirements.</p> <p><i>This is acceptable per USP &lt;788&gt; requirements. However, (b) (4)</i></p> <p>(b) (4) <i>were not characterized at release and on stability.</i></p>	
Extractable Volume <sup>1</sup>	80 mg/vial: Not Less Than 0.80 mL	<p>(b) (4)</p> <p>18 mg/vial: Not Less Than 0.45 mL</p> <p>28 mg/vial: Not Less Than 0.70 mL</p> <p>40 mg/vial: Not Less Than 1.0 mL</p>	(b) (4)		<p>The DP extractable volume specifications were established according to compendial requirements.</p> <p><i>This is acceptable. All DP lots met specifications.</i></p>

**Reviewer comment:** *The acceptance criterion for appearance is lacking a range for how many small translucent or white particles are acceptable. No justification was provided for the lack of upper limit in the color of the solution.* (b) (4)

*Comments were sent to the sponsor on 4/17/15 for additional information. Alexion provided the requested information on 4/30/15 (SN0026).*

**Reviewer's Evaluation of Alexion Response 6a (SN0026 submitted on 4/30/15):**

*Alexion claims that the quantitation of particles is difficult. Currently they are using a control standards (b) (4). Regarding color specification of DP, Alexion clarified that (b) (4) is the highest limit. The color (b) (4) stands for slightly yellow. The current DP color specification ranges from slightly yellow (b) (4) to colorless (b) (4). The sponsor responses are adequate.*

(b) (4)

Appendix B: Drug Product Quality Review: Office of Biotechnology Products

(b) (4)



**3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures**

A summary of the analytical methods were provided. For the DP analytical procedures that are identical to that of DS were described in Section 3.2.S.4.2 ([Appendix A](#)).

(b) (4)



## Appendix B: Drug Product Quality Review: Office of Biotechnology Products

(b) (4)

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

Reviewer comment: *Review of this assay is deferred to the DMA reviewer.*

**Release and Stability Analytical Procedures**

**Sterility USP <71>, Ph. Eur. 2.6.1**

Reviewer comment: *Review of this assay is deferred to the DMA reviewer.*

**Particulates USP <788>, Ph. Eur. 2.9.19**

(b) (4) particles are measured (b) (4) by a compendial method, USP <788>.

Reviewer Comments: *This compendial method is acceptable.*

**Extractable Volume USP <1>, Ph. Eur. 2.9.17**

Extractable volume is measured through extraction by a compendial method, USP <1>.

Reviewer Comments: *This compendial method is acceptable.*

(b) (4)

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Appendix B: Drug Product Quality Review: Office of Biotechnology Products

(b) (4)



**3.2.P.5.4 Batch Analyses**

Batch analysis data were provided for all DP lots manufactured through the time of the BLA submission. Summary of the batches included in the batch analysis are shown below in Tables [27](#) and [28](#).

**Table 27 Summary of DP Commercial Process Batches (100 mg/mL)**

(Table 1 Section 3.2.P.4.1 in the BLA)

Drug Product Lot	Manufacturer	Date of Manufacture	Concentration	Drug Substance Batch	Intended Batch Use
3-FIN-1474	(b) (4)	25-Jul-2012	100 mg/mL	280897	Clinical, Stability, Process Validation, Commercial
3-FIN-1475	(b) (4)	15-Aug-2012	100 mg/mL	284989	Clinical, Stability, Process Validation, Commercial
3-FIN-1476	(b) (4)	08-May-2013	100 mg/mL	332604	Clinical, Stability, Process Validation, Commercial
3-FIN-1831	(b) (4)	22-Aug-2013	100 mg/mL	333366	Clinical, Stability, Process Validation, Commercial
3-FIN-1926	(b) (4)	05-Feb-2014	100 mg/mL	335332	Clinical, Commercial
3-FIN-2012	(b) (4)	12-Jun-2014	100 mg/mL	379564	Clinical, Commercial
140168	(b) (4)	21-Jul-2014	100 mg/mL	381604	Clinical, Stability, Commercial

## Appendix B: Drug Product Quality Review: Office of Biotechnology Products

Table 28 Summary of DP Commercial Process Batches (40 mg/mL)

(Table 2 Section 3.2.P.4.1 in the BLA)

Drug Product Lot	Manufacturer	Date of Manufacture	Concentration	Drug Substance Batch	Intended Batch Use
3-FIN-1485	(b) (4)	19-Sep-2012	40 mg/mL	259248	Clinical, Stability, Process Validation, Commercial
3-FIN-1483	(b) (4)	27-Sep-2012	40 mg/mL	259248	Clinical, Stability, Process Validation, Commercial
3-FIN-1747	(b) (4)	15-May-2013	40 mg/mL	338971	Stability, Process Validation
3-FIN-1729	(b) (4)	21-May-2013	40 mg/mL	338971	Stability, Process Validation
3-FIN-1484	(b) (4)	19-Jun-2013	40 mg/mL	335332	Clinical, Stability, Process Validation, Commercial
3-FIN-1730	(b) (4)	25-Jun-2013	40 mg/mL	335332	Clinical, Stability, Process Validation, Commercial
3-FIN-1927	(b) (4)	18-Feb-2014	40 mg/mL	341981	Clinical, Commercial
3-FIN-2013	(b) (4)	18-Jun-2014	40 mg/mL	381602	Clinical, Commercial
140165	(b) (4)	22-Jul-2014	40 mg/mL	381602	Clinical, Stability, Commercial
140167	(b) (4)	25-Jul-2014	40 mg/mL	381602	Clinical, Commercial
140169	(b) (4)	23-Jul-2014	40 mg/mL	381602	Clinical, Stability, Commercial

**Reviewer comment:** The release results for both the 40mg/mL and the 100mg/mL DP batches met the proposed commercial acceptance criteria. The data were reviewed and are sufficient to confirm the consistency of the manufacturing process.

### 3.2.P.5.5 Characterization of Impurities

The sponsor referred to the DS section 3.2.S.3.2, Impurities (refer to [Appendix A](#)), for information on impurities. The sponsor stated that no new impurities have been identified for the drug.

### 3.2.P.6 Reference Standards or Materials

The reference material for DP is identical to that of DS. Refer to Section 2.3.S.5 Reference Standards or Materials for more detail (refer to [Appendix A](#)).

### 3.2.P.7 Container Closure System

DP CCS consists of a 2 mL USP/Ph. Eur. Type I glass vial with a (b) (4) rubber stopper, (b) (4) with a (b) (4) flip-off cap. This CCS is used for both the 40 mg/mL and 100 mg/mL DP

## Appendix B: Drug Product Quality Review: Office of Biotechnology Products

**Vial:**

The vial is manufactured by

(b) (4)

(b) (4)

**Stopper:**

The stopper is manufactured and supplied

(b) (4)

(b) (4)

**Seal:**

The seal is manufactured and supplied (b) (4). The (b) (4) aluminum seals comes with a (b) (4) flip-off cap. The caps (b) (4) differentiate between the 40 mg/mL and the 100 mg/mL DP respectively. [Table 31](#) shows the seal specifications.

## Appendix B: Drug Product Quality Review: Office of Biotechnology Products

(b) (4)

***Reviewer comment:** Certificates of Analysis and technical drawings for the CCS components were provided. Each component must meet material specifications and incoming requirements at (b) (4). The container closure system is appropriate for long-term storage of the DP based on suitability studies and long-term stability data.*

### **3.2.P.8 Stability**

#### **3.2.P.8.1 Stability Summary and Conclusion**

The stability program for the DP consists of stress studies, long-term (2 - 8°C) and accelerated (23 - 27°C) storage. The stability-indicating methods used were potency methods, general property tests, and safety tests (sterility and endotoxin). All DP batches manufactured at (b) (4) scale are included to support the shelf-life. The data presented show that the DP is stable for up to (b) (4) months when stored at 2 - 8°C. The sponsor proposes a 24-month shelf-life for the 40 mg/mL and 100 mg/ml DP concentrations stored at 2 - 8 °C. [Table 32](#) and [Table 33](#) show the DP lots used in the long-term (2 - 8°C) stability studies.

Appendix B: Drug Product Quality Review: Office of Biotechnology Products

**Table 32 Long-Term Stability (2 – 8°C): 100 mg/mL DP Lots**

(Table 2 Section 3.2.P.8.1 in the BLA)

Asfotase Alfa Drug Product Lot	Date of Manufacture	Asfotase Alfa Drug Substance Batch	Strength (mg/vial), Target Fill Volume (mL)	Orientation	Time Points Completed (and pending)
FIL094H01	(b) (4)	PUR012H01	(b) (4)	Upright Inverted	(b) (4)
FIL130J01		169446		Upright Inverted	
3-FIN-1326		260464		Inverted	
3-FIN-1474 <sup>1</sup>		280897		Upright Inverted	
3-FIN-1475 <sup>1</sup>		284989		Upright Inverted	
3-FIN-1476 <sup>1</sup>		332604		Upright Inverted	
3-FIN-1831 <sup>1</sup>		333366		Upright Inverted	
140168		381604		Upright Inverted	

<sup>1</sup> Drug product process validation lot

**Table 33 Long-Term Stability (2 – 8°C): 40 mg/mL DP Lots**

(Table 4 Section 3.2.P.8.1 in the BLA)

Asfotase Alfa Drug Product Lot	Date of Manufacture	Asfotase Alfa Drug Substance Batch	Strength (mg/vial), Target Fill Volume (mL)	Orientation	Time Points Completed (and pending)
FIL094G01	(b) (4)	PUR012F01	(b) (4)	Upright Inverted	(b) (4)
FIL094G02		PUR012G01		Upright Inverted	
3-FIN-0976		169446		Inverted	
3-FIN-1348		260464		Inverted	
3-FIN-1486		280897		Upright Inverted	
3-FIN-1485 <sup>1</sup>		259248		Upright Inverted	
3-FIN-1483 <sup>1</sup>		259248		Upright Inverted	
3-FIN-1729 <sup>1</sup>		338971		Upright Inverted	
3-FIN-1747 <sup>1</sup>		338971		Upright Inverted	
3-FIN-1484 <sup>1</sup>		335332		Upright Inverted	
3-FIN-1730 <sup>1</sup>		335332		Upright Inverted	
140165		381602		Upright Inverted	

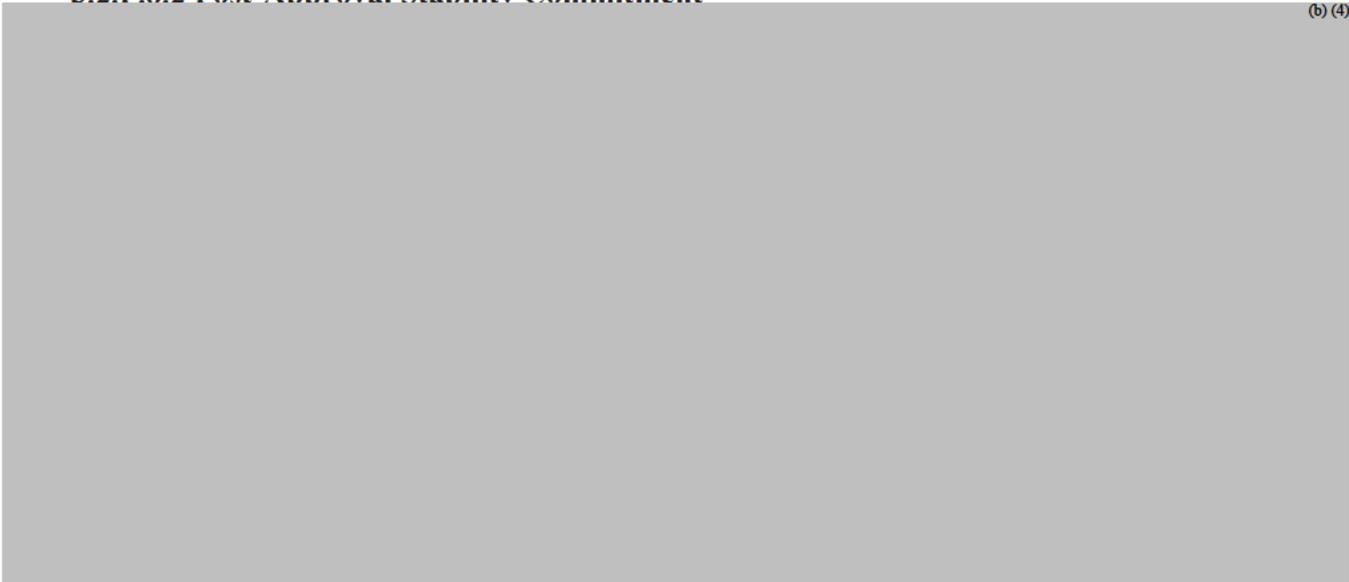
<sup>1</sup> Drug product process validation lot

**Reviewer comment:** The data provided support the DP 24-month shelf-life at 2 – 8°C. Determination of the shelf-life was done appropriately using assays and testing frequency which are consistent with ICH guidelines. The 24 month shelf-life at 2 – 8°C for Asfotase Alfa DP is acceptable. DP stability is also evaluated to support shipping validation (see Section 3.2.P.3.5.6 above and in the BLA).

Appendix B: Drug Product Quality Review: Office of Biotechnology Products

**3.2.P.8.2 Post-Approval Stability Commitment**

(b) (4)



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## Appendix B: Drug Product Quality Review: Office of Biotechnology Products

### **3.2.A Appendices Table of Contents**

#### **3.2.A.1 Facilities and Equipment**

*Reviewer comment: Review of the facilities and equipment are deferred to the OPF/DIA/IABI reviewer.*

#### **3.2.A.3 Novel Excipients**

None

### **3.2.R Regional Information (U.S.A.)**

#### **3.2.R.1 Executed Batch Records**

The submission included executed batch records corresponding to process validation lots 3-FIN-1476, 3-FIN-1747, 3-FIN-1485, 3-FIN-1484, and 3-FIN-1730.

#### **3.2.R.2 Method Validation Package**

Refer to section 3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures.

#### **3.2.R.3 Comparability Protocols**

None

**CMC Addendum  
BLA STN 125513**

**STRENSIQ (asfotase alfa)**

**Alexion**

**Reviewers: Joslyn Brunelle (DS) and Gunther Boekhoudt (DP)**

**TL Reviewer: Cris Ausin**

**Division of Biotechnology Review and Research IV**

## Appendix C: Drug Substance and Product Quality Review Addendum: Office of Biotechnology Products

## OBP CMC Review Data Sheet

## 7. COMMUNICATIONS WITH SPONSOR AND OND:

Communication/Document	Date
Information Request #8	6/22/2015
Midcycle Meeting	6/24/2015
T-con with Sponsor	7/24/2015
Information Request #9	7/24/2015
Information Request #10	8/11/2015
Information Request #11	8/18/2015
Pre-Late Cycle Meeting	8/19/2015
Late Cycle Meeting	9/2/2015

## 8. SUBMISSION(S) REVIEWED:

Submission	Date Received	Review Completed (Yes/No)
STN 125513/0038 (response to IR#9)	8/13/2015	Yes
STN 125513/0038 (response to labeling and PMCs/PMRs issues)	8/14/2015	Yes
STN 125513/0039 (response to IR #10)	8/18/2015	Yes
STN 125513/0039 (response to IR #11)	8/21/2015	Yes

## Appendix C: Drug Substance and Product Quality Review Addendum: Office of Biotechnology Products

**7. ADMINISTRATIVE****A. Signature Block**

Name and Title	Signature and Date
Michele Dougherty, Ph.D. Acting Review Chief Division of Biotechnology Review and Research IV	
Cris Ausin, Ph.D., Acting Team Leader Division of Biotechnology Review and Research IV	
Gunther Boekhoudt, Ph.D., Primary Reviewer (Drug Product) Division of Biotechnology Review and Research IV	
Joslyn Brunelle, Ph.D., Primary Reviewer (Drug Substance) Division of Biotechnology Review and Research IV	

**B. CC Block**

Recipient	Date
Lisa Pitt	December 23, 2014
Division of Biotechnology Review and Research IV File/BLA STN 125513	December 23, 2014

## SUMMARY OF QUALITY ASSESSMENTS

### I. Primary Reviewer Summary Recommendation

The Office of Biotechnology Products, OPQ, CDER, recommends approval of STN 125513 for Strensiq (asfotase alfa) manufactured by Alexion, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Strensiq is well controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert. The sponsor provided sufficient information to support a shelf life for Strensiq drug product of 24 months at 2-8°C.

### II. List of Deficiencies To Be Communicated

None

### III. List Of Post-Marketing Requirements

1. Develop an assay to directly compare the complement activating capacity of asfotase alfa to that of human IgG1. The assay should be set up under conditions to readily detect complement activation by IgG1. A dose response curve to demonstrate the sensitivity of the assay is recommended
2. Develop a validated cross-reactive immunologic material (CRIM) assay for patients with hypophosphatasia (HPP) and test patient samples in a cohort of untreated patients. Results should be correlated with antibody response (binding and neutralizing), genetic mutations, enzyme activity level and clinical outcome in patients who are receiving Asfotase alfa treatment. Patients with severe genetic mutations, such as complete deletions or large rearrangements, should be represented in the study.

### IV. List Of Post-Marketing Commitments

1. Evaluate the asfotase alfa manufacturing process and develop a control strategy (b) (4) (b) (4) (b) (4) that ensures consistent patient exposure. Provide detailed summaries of all data utilized to propose the revised control strategy (b) (4).

### V. Review Of Common Technical Document-Quality Module 1

- A. Environmental Assessment Or Claim Of Categorical Exclusion  
Alexion is claiming a categorical exclusion under 21 CFR 25.31(c) from the need to prepare an environmental assessment.

### VI. Primary Container Labeling Review

Primary review of the Container Labeling was performed by Jibril Abdus-Samad (OBP).

### VII. Review Of Common Technical Document-Quality Module 3.2

Primary reviews of the Quality Module 3.2 were performed by the OBP reviewers Joslyn Brunelle (Drug Substance) and Gunther Boekhoudt (Drug Product).

### VIII. Review Of Immunogenicity Assays – Module 3.2.1.4

Primary review of the Immunogenicity Assays was performed by Frederick Mills (OBP).

**Table of Contents**

S. DRUG SUBSTANCE.....	252
3.2.S.2 Manufacture.....	252
3.2.S.4 Control of Drug Substance.....	254
P DRUG PRODUCT.....	258
3.2.P.1 Description and Composition of the Drug Product.....	258
3.2.P.3. Manufacture.....	259
3.2.P.5 Control of Drug Product.....	263
3.2.P.8 Stability.....	264

**S. DRUG SUBSTANCE****3.2.S.2 Manufacture**

Information Request dated July 24, response received on August 13.



(b) (4)

Appendix C: Drug Substance and Product Quality Review Addendum: Office of Biotechnology Products



(b) (4)

**3.2.S.4 Control of Drug Substance**

Information Request dated July 24, response received on August 13.

The following comments were communicated to the sponsor:

## Appendix C: Drug Substance and Product Quality Review Addendum: Office of Biotechnology Products

**Question # 7**

Your proposed acceptance criterion, (b) (4) is (b) (4) for drug substance and drug product release testing. Based on the discussion during the July 24, 2015 teleconference, we recommend that you evaluate your (b) (4) acceptance criterion based on your current manufacturing capability. Please respond by August 7 with a revised acceptance criterion, (b) (4).

**Alexion Response:**

Alexion states that the manufacturing data to date does not support (b) (4) of the acceptance criteria based on the current manufacturing capability. The data (18 drug substance batches) were assessed using an evaluation including mean, 99%/95% tolerance interval, and PpK index (see Table below). Alexion states that the analysis does not support the (b) (4) of the specification at this time.

(b) (4)

Alexion commits to continuous monitoring (b) (4). It has been implemented as a long term process monitoring program to ensure the process is performing consistently. Alexion commits to reassess the specification by (b) (4) will provide an update to the Agency at that time. Alexion will continue to provide (b) (4) data assessments to the Agency until a total of 30 batches is available.

**Reviewer comment:**

## Appendix C: Drug Substance and Product Quality Review Addendum: Office of Biotechnology Products

*I agree that is not feasible to (b) (4) the specification at this time. The continuous process monitoring and updates to the Agency is adequate to support BLA approval. In addition, the sponsor has agreed to a post marketing commitment (PMC) to evaluate the asfotase alfa manufacturing process and develop a control strategy (b) (4) (b) (4) that ensures consistent patient exposure. The final report is expected by November 2016.*

Information Request dated August 11, response received on August 18.

The following comments were communicated to the sponsor:

**Question # 1**

(b) (4)  
(b) (4) *The data set included drug substance and drug product release and stability and two reference standards lots." However, you did not provide any data to support your revised specification. To confirm that the specification is adequate, provide a justification (b) (4) (b) (4) You should include drug substance and drug product release and stability data, as well as the reference standards used in your analysis.*

**Alexion Response:**

(b) (4)  
(b) (4) Alexion notes that (b) (4) (b) (4) some lots were not tested at release and some lots only have later stability time points.

## Appendix C: Drug Substance and Product Quality Review Addendum: Office of Biotechnology Products

(b) (4)

**Reviewer comment:**

The data provided on drug substance lots supports (b) (4) specification (b) (4)  
(b) (4)

(b) (4)

***Reviewer comment:****This is acceptable.***P DRUG PRODUCT****3.2.P.1 Description and Composition of the Drug Product**

Information Request dated August 18, response received on August 21.

(b) (4)

### 3.2.P.3. Manufacture

Information Request dated July 24, response received on August 13.

The following comments were communicated to the sponsor:

#### Question # 6

*The Code of Federal Regulation (21 CFR 610.14) requires that identity testing be performed on each filled lot of drug product after all labeling operations have been completed. The manufacturing step from which samples of asfotase alfa are obtained was not clearly identified in section 3.2.P.3.3, 3.2.P.3.4, or 3.2.A.1.4 [REDACTED] (b) (4) Clarify the process and revise the process if necessary to comply with the regulation.*

#### Alexion Response:

“Alexion confirms that identity testing in accordance with 21 CFR 610.14 will be implemented prior to the packaging of the first commercial batch. [REDACTED] (b) (4)

[REDACTED] (b) (4)  
[REDACTED] (b) (4), one vial is tested [REDACTED] (b) (4)  
[REDACTED] (b) (4) to confirm the identity of the labelled vials prior to release.

A revised CTD Section 3.2.P.3.3 Description of Manufacturing Process and Process Controls is provided.”

**Reviewer comment:**

The sponsor confirmed that identity testing is being performed per with 21 CFR 610.1. Section 3.2.P.3.3 was revised (b) (4). However, (b) (4) is not validated as an identity test and a comment was sent to the sponsor on August 18, 2015 to submit data supporting the use of this proposed identity test. Alexion submitted their response on August 21, 2015 (See Alexion Response dated August 21, 2015 Question # 1 below).

Information Request dated August 18, response received on August 21.

The following comments were communicated to the sponsor:

**Question # 1**

In your response submitted on August 13, 2015 to question 6, you confirm that drug product identity testing will be performed after all labeling operations have been completed in accordance with 21 CFR 610.14. In addition, you indicated that “one vial is tested by (b) (4). However, in the BLA submission the (b) (4) method is not validated as an identity test. You showed the specificity (b) (4). However, you did not demonstrate that this test method can discriminate asfotase alfa from other products. Provide additional data to support the validation (b) (4) method as an identity test. Alternatively, to comply with 21 CFR 610.14, select a different assay that is properly validated as an identity test.”

**Alexion Response:**

“Peptide Mapping will be used to confirm identity of asfotase alfa after all labeling operations have been completed in accordance to 21 CFR 610.14. Peptide Mapping had been validated as a drug product identity assay per CTD Section 3.2.P.5.3 Validation of Analytical Procedures.”

**Reviewer comment:**

Alexion clarified that Peptide mapping will be used as the identity test and not the initially proposed (b) (4) method. Peptide mapping is a validated method for the Identity test. The sponsor’s response is acceptable.

Information Request dated August 11, response received on August 18.

The following comments were communicated to the sponsor:

**Question # 3**

You have provided limited information regarding several drug product manufacturing steps. To ensure appropriate control of the drug product manufacturing process, revise Section 3.2.P.3.3

## Appendix C: Drug Substance and Product Quality Review Addendum: Office of Biotechnology Products

*Description of Manufacturing Process and Process Controls* [redacted] (b) (4)

[redacted] (b) (4) *In addition, revise Section 3.2.P.3.4*

*Control of Critical Steps and Intermediates* [redacted] (b) (4) :

[redacted] (b) (4)

**Alexion Response:**

“CTD Section 3.2.P.3.3 Description of Manufacturing Process and Process Controls has been revised [redacted] (b) (4)

[redacted] (b) (4) This section has also been revised to include the acceptable ranges for the key process parameters (KPP) outlined in Table 1 below. CTD Section 3.2.P.3.4 Control of Critical Steps and Intermediates has not been revised [redacted] (b) (4) .

[redacted] (b) (4)

## Appendix C: Drug Substance and Product Quality Review Addendum: Office of Biotechnology Products

[Redacted] (b) (4)

In response to this question, Alexion commits to assessing [Redacted] (b) (4) and will implement [Redacted] (b) (4) through the batch record by Q1 2016.”

**Reviewer comment:**

*The sponsor has included sufficient information to our requested revisions in Section 3.2.P.3.4; this is acceptable.*

**Question # 4**

*To confirm the adequacy of the drug product shipping validation, provide a justification of the suitability of the shipping studies to confirm that the conditions used during the shipping studies (load, time elapsed, distance, etc.) represent a worst case scenario in terms of temperature control and physical impact to the product.*

**Alexion Response:**

“The drug product shipment validation (PQ-0106FR provided in CTD Section 3.2.R.4 Process Validation Scheme) [Redacted] (b) (4) (Souderton, PA) was completed [Redacted] (b) (4) [Redacted] (b) (4)

**Reviewer comment:**

*The sponsor provided clarification that the drug product shipment validation performed is considered worst case in term of distance and elapsed time.* (b) (4)

(b) (4)

(b) (4). *The information provided indicates that the shipping validation could be considered worst case scenario and the response is acceptable.*

**3.2.P.5 Control of Drug Product**

Information Request dated July 24, response received on August 13.

The following comments were communicated to the sponsor:

**Question # 1**

*In your Supporting Document received on 6-30-2015 you updated "Section 3.2.P.5.6 Justification of Specifications." We note that you removed most of the drug product justifications. Instead you are referencing "Section 3.2.S.4.5 Justification of Specification." However, section 3.2.S.4.5 does not include justifications for drug product specifications that are different than those of drug substance,* (b) (4)

(b) (4) *Revise section 3.2.P.5.6 to include all drug product justifications of specifications.*

**Alexion Response:** In amendment 39 (dated August 13, 2015) the sponsor submitted a revised CTD Section 3.2.P.5.6 Justification of Specification including the analysis and justification for the drug product specification. This detail was inadvertently removed during the response dated 30 June 2015 (Sequence 0031), there has been no change to the proposed specification, analysis or justification previously under review.

**Reviewer comment:**

*The sponsor, as requested, revised 3.2.P.5.6 to include all drug product justifications of specifications. The information provided is acceptable. In addition, refer to section [3.2.S.4](#) for additional information regarding the acceptance criteria* (b) (4).

**Question # 2**

*You provided accelerated stability data showing that drug product specific activity (pNPP) and purity* (b) (4) *change* (b) (4) *therefore, these assays are stability indicating. Draft Guidance for Industry, Analytical Procedures and Method*

## Appendix C: Drug Substance and Product Quality Review Addendum: Office of Biotechnology Products

*Validation for Drugs and Biologics, recommends that for stability indicating assays you should include “samples that have undergone various laboratory stress conditions; [REDACTED] (b) (4)*

*[REDACTED] As part of the validation of the transfer of analytical methods [REDACTED] (b) (4) you tested lots 3-FIN-1486, 3-FIN-1475, and 280897; however, you did not include any samples that show significant degradation. To demonstrate that specific activity, [REDACTED] (b) (4) are equally stability indicating at the receiving site, update the method transfers to include testing of samples that have undergone accelerated conditions. Alternatively, consider withdrawing the transfer of these assays from the application and re-submit the complete information post-approval.*

**Alexion Response:**

“Alexion agrees to complete a supplemental transfer of the specific activity (pNPP), [REDACTED] (b) (4) assays to include samples that demonstrate degradation and submit these transfer reports in a future supplement.

Alexion confirms that [REDACTED] (b) (4) will not be used for specific activity, [REDACTED] (b) (4) and [REDACTED] (b) (4) release testing until the subsequent submission and approval of the supplemental transfers. The transfers of these three assays are being withdrawn from the BLA.

A revised CTD Section 3.2.P.5.3 Validation of Analytical Procedures, Section 3.2.R.5 Documentation of Analytical Procedures [REDACTED] (b) (4) and Section 3.2.R.6.3 Method Transfer Qualification [REDACTED] (b) (4) are provided.”

**Reviewer comment:**

*The sponsor has agreed to our request to complete a supplemental transfer of the specific activity (pNPP), [REDACTED] (b) (4) assays to include samples that demonstrate degradation. The assay transfer report will be submitted post-approval. In addition, Alexion is withdrawing [REDACTED] (b) (4) as the testing site for specific activity, [REDACTED] (b) (4) [REDACTED] (b) (4). The information provided is adequate and acceptable.*

**3.2.P.8 Stability**

Information Request dated August 11, response received on August 18.

The following comments were communicated to the sponsor:

**Question # 5**

*In section 3.2.P.8.3 Stability Data you provided quantitative stability results. However, the submission did not include qualitative data. To confirm that drug product is stable during the*

Appendix C: Drug Substance and Product Quality Review Addendum: Office of Biotechnology Products

*proposed shelf life, provide representative raw stability data (gels and/or chromatographs) for your purity assays at time point 0 (initial) and at the last available time point.*

**Alexion Response:**

“Representative gels and chromatographs for the purity assays (b) (4)  
(b) (4)  
(b) (4) at time point  
(b) (4)

**Reviewer comment:**

*The sponsor, as requested, provided qualitative data. (b) (4)  
(b) (4). Time points provided were at  
time point (b) (4) data were reviewed and the  
results do appear to be in agreement with the quantitative data submitted to the BLA.*

**Late Cycle Meeting Information** communication dated September 2, response received on September 3.

The following comments were communicated to the sponsor by the Division of Inspectional Assessment:

*One facility has received a Form FDA 483 for pre-license inspection observations. These inspectional findings and any facility responses received within 15 days of the inspection will be reviewed. We will communicate any additional requests directly to this site. Please ensure that all facilities are ready for commercial CGMP manufacturing activities as described in the BLA. Satisfactory evaluation of all manufacturing facilities is required for BLA approval.*

**Alexion Response:**

Alexion agreed to withdraw the secondary testing site (b) (4)  
(b) (4) from the BLA.

**Reviewer comment:**

*The sponsor updated sections 3.2.P.3, 3.2.P.5, 3.2.A, 3.2.R.5, and 3.2.R.6 accordingly to reflect the withdrawal of the (b) (4) testing site. This is acceptable.*



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

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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 (b) (4) (b) (4) after data from thirty batches is available and (b) (4) the (b) (4) limits to reflect manufacturing process capability.

---

## **REVIEW SUMMARY**

Asfotase alfa is a soluble IgG<sub>1</sub> 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) is contracted by the sponsor for asfotase alfa drug substance manufacturing. (b) (4) (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, (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)	(b) (4)	Drug substance manufacture
(b) (4)		
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 inspection on (b) (4) and was NAI.

**S.2.2. Description of Manufacturing Process and Process Controls**

Asfotase alpha DS manufacturing process consists of

(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.



(b) (4)



**Reviewer Question:** (b) (4) limits for endotoxin are (b) (4) (b) (4) and appear to be high for these steps in the process. Provide justification for these limits or lower the limits in accordance with process capability.

**Sponsor Response:** The limits for the (b) (4) (b) (4) were determined based on available endotoxin data. The data did not fit a normal distribution therefore the data was fit to a log normal distribution. Table 1 from the response summarizes the results from the study and provided the 99<sup>th</sup>, 95<sup>th</sup>, and 90<sup>th</sup> percentile confidence intervals. The table is shown below.

The sponsor reported to make the following considerations when establishing the endotoxin limits for these process steps:

(b) (4)

*Reviewer's comments:* According to Table 1, the endotoxin results range from (b) (4) (b) (4). The (b) (4) limit (b) (4) still appears to be high.

With regard to (b) (4) the endotoxin data ranged from (b) (4) (b) (4). The results are (b) (4) and the limit of (b) (4) also appears to be high. Therefore, the sponsor has agreed to the following Post-Marketing agreement:

To re-evaluate the (b) (4) endotoxin limits (b) (4) (b) (4) and (b) (4) the (b) (4) limits to reflect manufacturing process capability.

(b) (4)

**Reviewer Question:** Specify in BLA section S.2.4 what quality assessments will be performed (b) (4)

(b) (4)

**Sponsor Response:** Section 3.2.S.2.4 Control of Critical Steps and Intermediates was revised to describe the quality assessment completed (b) (4)

(b) (4)

(b) (4) release testing  
results must meet (b) (4) limit and specifications. (b) (4)

(b) (4)

Hold times were validated (b) (4)

(b) (4)

### S.2.5 Process Validation and/or Evaluation

STN 125513/0 Alexion Pharmaceuticals, Inc. STRENSIQ™  
Appendix D: Microbiology Review: Division of Microbiology Assessment

Process validation studies were completed on four consecutive bulk drug substance (BDS) batches manufacturing between [REDACTED] (b) (4) (Batches 333101, 333103, 331539A, and 334487). The studies were performed at commercial scale [REDACTED] (b) (4) Normal operating ranges were used in the validation studies.

(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 (b) (4) (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 (b) (4) Limulus Amoebocyte Lysate (LAL) assay is used to measure endotoxin in (b) (4) (b) (4) samples. (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.4.2.2.22 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 sponsor states that the results for all samples types met acceptance criteria. However, (b) (4)  
(b) (4)

The sponsor will continue bioburden analysis on the sample for the detection of recoverable microorganism species.

##### S.4.3.1.6 Endotoxin

The bacterial endotoxin concentration in drug substance samples is determined by using the (b) (4)  
(b) (4) 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) and bulk drug substance samples. The sponsor provided the qualification report for endotoxin testing using the (b) (4) (b) (4). The limit of detection was (b) (4). The sponsor also conducted tests (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 using spiking studies. (b) (4)

(b) (4). Acceptance criteria are the same as what is used for the (b) (4) bioburden test validation studies (S.4.3.1.1 Bioburden). (b) (4)

#### S.4.3.2. Bioburden (ARIMF)

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

#### S.4.2.21 Endotoxin

##### S.4.2.21.1 (b) (4) Endotoxin (b) (4)

##### S.4.2.21.2 (b) (4) Endotoxin (ARIMF)

Both the 100 mg/mL and 40 mg/mL concentrations were tested for the absence or enhancement of the LAL reaction by completing spiking studies. 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 of (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 and (b) (4) where appropriate.

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) body weight at the maximum dose size. (b) (4). The (b) (4) endotoxin specification limits the endotoxin amount to (b) (4) which is lower than the FDA-recommended maximum limit of 350 EU/dose. Endotoxin data is reported (b) (4) (b) (4).

#### cGMP STATUS

The (b) (4) manufacturing facility (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) (b) (4) after data from thirty batches is available and (b) (4) (b) (4) to 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) 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) rubber stopper (b) (4) with (b) (4) flip-off cap for both presentations.

### P.2 Pharmaceutical Development

#### P.2.5 Microbiological Attributes

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

(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 (b) (4)

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

(b) (4)

(b) (4)

**P.3.3 Description of Manufacturing Process and Process Controls**

(b) (4)

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Immediately Following this Page

## 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 ( (b) (4) is used to measure bioburden (b) (4) (b) (4)

(b) (4)  
(b) (4) If no growth is observed, results are reported (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 <(b) (4)> and Ph.Eur. (b) (4). Results are reported as “No Growth” if 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 (b) (4)  
(b) (4)  
(b) (4) The acceptance criterion requires a sample spike recovery between (b) (4) of the spike control of each test organism. Results range from (b) (4) which meets acceptance criteria.

#### P.5.3.2.1 Endotoxin

(b) (4) Endotoxin (b) (4)

Spiking studies were completed to determine the absence of inhibition or enhancement of the LAL reaction. Samples were spiked with known quantities of endotoxin to determine acceptable endotoxin recoveries (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. The maximum valid dilution (MVD) for the 100 mg/mL concentration was determined to be (b) (4) for the 40 mg/mL. The absolute value of the correlation coefficient of the standard curve was (b) (4). Samples were spiked with known quantities of endotoxin. Results show that spike recovery ranged from (b) (4) which meets the acceptance criteria (b) (4)

(b) (4) Endotoxin (b) (4)

Spiking studies were completed to determine the suitability of the LAL method for endotoxin detection in asfotase alfa DP (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 from the spiking studies met acceptance criteria and are summarized in the table below.

(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) 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) rubber stopper, (b) (4) and aluminum seal with a (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 (b) (4)

### **P.8 Stability**

Stability protocols include long-term storage under the recommended storage conditions (2-8°C),

(b) (4) 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) (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 process validation batch 338971 which had a bioburden result of (b) (4). This result is more than (b) (4) (b) (4) the acceptance criteria of (b) (4).
4. Specify in BLA section S.2.4 what quality assessments will performed (b) (4) and specify (b) (4).

#### Section S.2.5 Process Validation and/or Evaluation

1. Will endotoxin samples be collected (b) (4) (b) (4) (b) (4). 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 "N/A (EU/mL)."
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) (b) (4) during process validation.

(b) (4)

With regard to the (b) (4) Hold Validation please provide the following:

- a. Please provide data from three runs to validate the hold time for the (b) (4) vessel which was not covered in the bracketing study. Include bioburden and endotoxin data (b) (4)  
(b) (4)
- b. The hold time study reports submitted (Sequence 0025) lists (b) (4) as the (b) (4) medium used in the hold time studies. However, the BLA section says that (b) (4) was used. Please amend the BLA to report the correct medium used in the studies.

#### Section P.2.5.1 Container Closure Integrity Study (CCIT)

Provide (b) (4) acceptance criteria for the microbial ingress test.

#### Section P.3.5 Process Validation and (or) Evaluation

Please provide a description (b) (4)  
(b) (4)

#### Section P.3.5.2 (b) (4) Process Validation

Provide action and alerts levels used for environmental monitoring during media fills.

Describe actions taken if media fills fail.

#### P.3.5.2 (b) (4) Process Validation

Your response submitted to the Agency on 30 April 2015 regarding (b) (4) was inadequate. Please clearly provide (b) (4) (b) (4). In addition, (b) (4) (b) (4) Please amend the BLA accordingly.

#### SIGNATURES



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) and (b) (4) the (b) (4) limits 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.

S.2.2.2 (b) (4)

(b) (4)

Results met all of the acceptance criteria.

(b) (4)

(b) (4)

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

**SATISFACTORY**

**SIGNATURES**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

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Food and Drug Administration  
Center for Drug Evaluation and Research  
WO Bldg. 51, 10903 New Hampshire Ave.  
Silver Spring, MD 20993

**Date:** 08/12/2015

**To:** Administrative File, STN 125513/0

**From:** Steven Fong, Ph.D., Quality Assessment Lead, CDER/OPQ/OPF/DIA

**Endorsement:** Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA

**Subject:** Original BLA

**US License:** Pending

**Applicant:** Alexion Pharmaceuticals

**Mfg Facility:** Drug Substance: [REDACTED] (b) (4)  
[REDACTED] (b) (4)

Drug Product: [REDACTED] (b) (4)  
[REDACTED] (b) (4)

**Product:** Strensiq (asphotase alfa) Injection

**Dosage:** 40 mg/mL and 100 mg/mL sterile aqueous solution for subcutaneous administration provided in single use glass vials

**Indication:** Therapy for Hypophosphatasia

**Due Date:** 11/23/2015

BLA 125513. Strensiq (Asfotase alfa) DS and DP Manufacture  
Appendix E: Facilities Review – Division of Inspectional Assessment

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**RECOMMENDATION:** As of the review submission date a final recommendation on the acceptability of the proposed manufacturing and testing facilities cannot be made. Compliance decisions are still pending for a (b) (4) inspection of the (b) (4) proposed for DS manufacture, and a (b) (4) inspection of (b) (4) (b) (4) proposed for DP release testing. An Amendment stating the final OPF-DIA decisions for these facilities will be submitted to the File once they are known. All other proposed manufacturing and testing sites are recommended for approval from a facilities assessment standpoint.

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## SUMMARY

The subject BLA proposes manufacture of Strensiq (asfotase alfa) DS and DP, respectively, at (b) (4) (b) (4) (b) (4) and Alexion Pharmaceuticals, Smithfield, RI.

Testing/packaging operations will occur at Alexion Pharma, Smithfield, RI (FEI 3006568549), (b) (4) (b) (4)

Asfotase alfa is a fusion protein expressed in CHO cells that is proposed as a treatment for hypophosphatasia. The protein is composed of the soluble catalytic domain of human tissue non-specific alkaline phosphatase (sALP), the Fc domain of human IgG1 Fc, and a deca-aspartate peptide (D10) used as a bone targeting domain. The DP is provided in two strengths, 40 mg/mL and 100 mg/mL, in a solution containing (b) (4) sodium chloride, (b) (4) dibasic sodium phosphate (b) (4) (b) (4) monobasic sodium phosphate (b) (4) (b) (4). The final dosage form is provided in 2 mL, single use glass vials filled with (b) (4) 0.45, 0.70, or 1.0 mL of 40 mg/mL asfotase alfa (b) (4) 18, 28, and 40 mg of DP), or 0.80 mL of 100 mg/mL asfotase alfa (80.0 mg of DP).

## ASSESSMENT

### DRUG SUBSTANCE FACILITIES

- **3.2.S.2.1 DS Manufacturers.**

The sites proposed for asfotase alfa DS manufacture, cell banking operations, and testing are presented below in Table 1.

BLA 125513. Strensiq (Asfotase alfa) DS and DP Manufacture  
 Appendix E: Facilities Review – Division of Inspectional Assessment

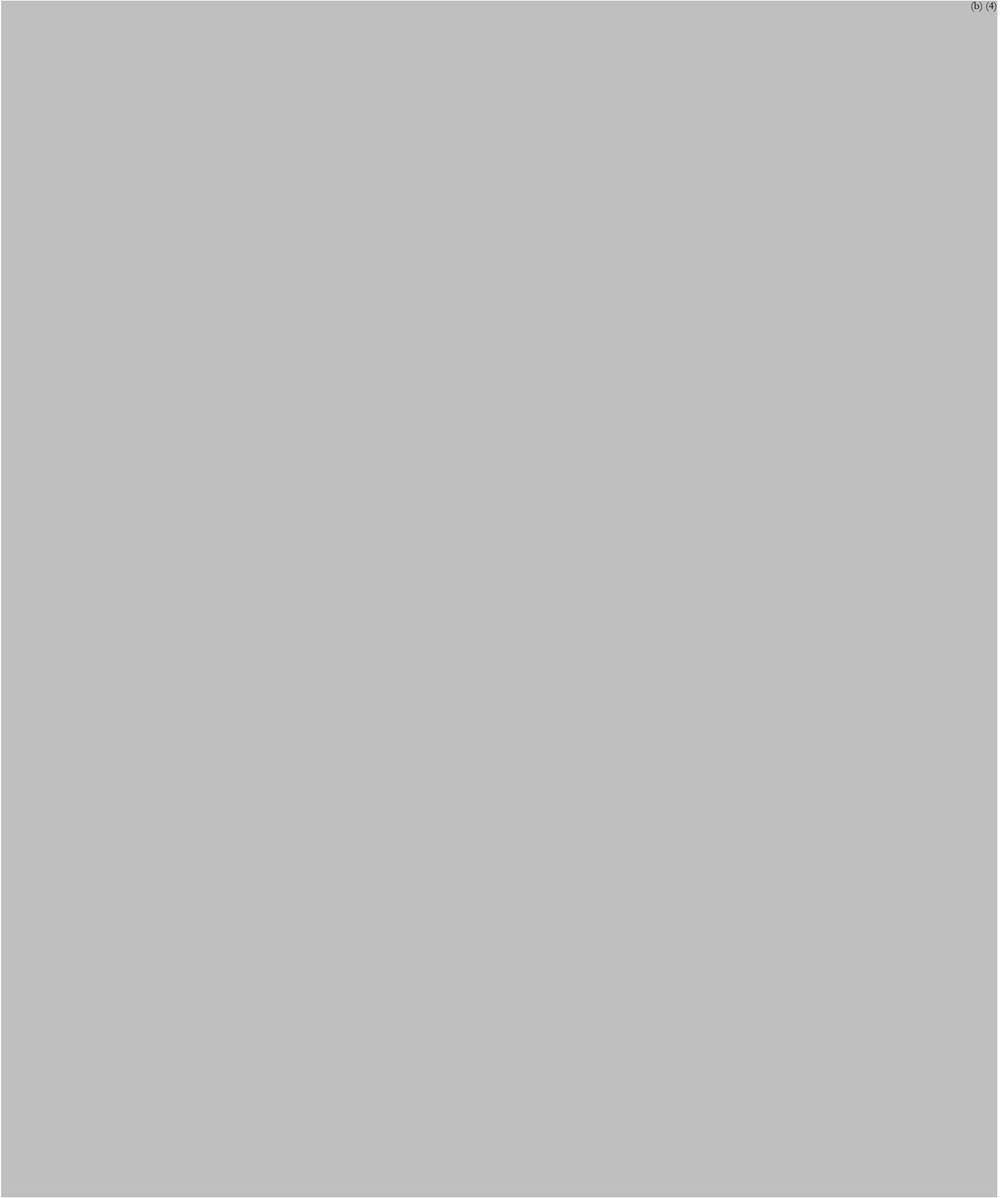
TABLE 1. Proposed Sites for Asfotase alfa DS Manufacture, Cell Banking and Testing Operations

Site Name	Address	FEI Number	Responsibilities
(b) (4)			
Alexion Pharmaceuticals Inc.	100 Technology Way Smithfield, RI 02917	3006568549	Storage of master and working cell bank.

**Reviewer Comment 1:** *The facilities for manufacture of Asfotase alfa DS are adequately described.*

- **Prior Inspection History for DS Manufacturing and Testing Sites**

(b) (4)
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BLA 125513. Strensiq (Asfotase alfa) DS and DP Manufacture  
Appendix E: Facilities Review – Division of Inspectional Assessment

(b) (4)

- Alexion Pharmaceuticals Inc. (FEI 3006568549). Master and Working Cell Bank Storage.  
As per ICH Q7A, the sites used for storage of cell banks used for biotechnology products do not pose a significant concern from a cGMP prospect. A facilities evaluation for this site is not required for cell banking. A facilities assessment for the firm for DP testing is presented below under *DRUG PRODUCT, Prior Inspection History for DP Manufacturing and Testing Sites*.

- **Current Prior Approval Inspection Decisions**

(b) (4)

*Reviewer Comment 2: A recommendation on the compliance status of the production and testing facilities associated with the manufacture of asfotase alfa DS cannot be made until a decision on the acceptability of the (b) (4) site is finalized by OPF-DIA. An Amendment stating the final decision for this facility will be submitted to the File once it is known.*

- **3.2.S.2.2. Overview of Asfotase alfa DS Manufacturing Operations Conducted**

(b) (4)

(b) (4)

BLA 125513. Strensiq (Asfotase alfa) DS and DP Manufacture  
 Appendix E: Facilities Review – Division of Inspectional Assessment

**DRUG PRODUCT FACILITIES**

• **3.2.P.3.1. DP Manufacturers.**

The sites proposed for asfotase alfa DP manufacture, testing, packaging, and labeling are presented below in Table 4.

TABLE 4. Sites Proposed for Strensiq DP Manufacture and Testing

Site Name	Address	FEI Number	Responsibilities
(b) (4)			
Alexion Pharmaceuticals, Inc.	100 Technology Way Smithfield, RI 02917	3006568549	DP release and stability testing (b) (4), (b) (4)
(b) (4)			

• **Prior Inspection History for DP Manufacturing and Testing Sites**

(b) (4)

BLA 125513. Strensiq (Asfotase alfa) DS and DP Manufacture  
Appendix E: Facilities Review – Division of Inspectional Assessment

(b) (4)

- Alexion Pharmaceuticals Inc. (FEI 3006568549). DP Release Testing Site.
  - Inspection Conducted 08/18-22/2014 by (b) (4) CPGM 7356.002- and CPGM 7356.002M-based inspection conducted as a follow-up to a 07/12/2012 – 08/06/2012 inspection that resulted in Warning Letter and an OAI classification (see below). This 2014 inspection determined that the deficiencies leading to the 2012 Warning Letter had been corrected. A 3-item FDA Form 483 was issued. The facility was reclassified to VAI.

BLA 125513. Strensiq (Asfotase alfa) DS and DP Manufacture  
Appendix E: Facilities Review – Division of Inspectional Assessment

- Inspection Conducted 07/12/2012 – 08/06/2012 by (b) (4). CPGM 7356.002- and CPGM 7356.002M-based cGMP surveillance inspection covering PAC codes 56002 and 56002M that resulted in a Warning Letter and an OAI classification. The classification was based on adulteration of records.
- Inspection Conducted 01/20/2011 – 02/18/2011 by (b) (4). CPGM 7356.002- and 7356.002M-based cGMP surveillance inspection covering PAC codes 56002 and 56002M. The inspection resulted in issuance of a 7-item FDA Form 483. The inspection was classified VAI.

(b) (4)



BLA 125513. Strensiq (Asfotase alfa) DS and DP Manufacture  
Appendix E: Facilities Review – Division of Inspectional Assessment

- **Current Prior Approval Inspection Decisions**

(b) (4)

- Alexion Pharmaceuticals Inc. (FEI 3006568549). DP Release Testing Site. Facility approved based on file review.

(b) (4)

**Reviewer Comment 12.** A recommendation on the compliance status of the production and testing facilities associated with the manufacture of Asfotase alfa DP cannot be made until a decision on the acceptability of the (b) (4) site proposed for DP release testing is finalized by OPF-DIA. An Amendment stating the final decision for this facility will be submitted to the File once it is known.

- **3.2.P.3. Overview of Asfotase alfa DP Manufacturing Operations Conducted** (b) (4).

(b) (4)

## CONCLUSION

Adequate descriptions were provided for the (b) (4) (b) (4) facilities proposed for Asfotase alfa DS and DP manufacture. All proposed manufacturing and testing sites except (b) (4) (b) (4) are recommended for approval from a facilities assessment standpoint. However, a final facilities recommendation for the BLA cannot be made until compliance decisions have been rendered for a (b) (4) PAI of (b) (4) and a (b) (4) inspection of (b) (4). An Amendment stating the final OPF/DIA decisions for these sites and the final facilities recommendation will be submitted to the File once they are known.

---

Steven E. Fong, M.S., Ph.D.

Acting Quality Assessment Lead

OPF Division of Inspectional Assessment

Branch 1

---

Zhihao Peter Qiu, Ph.D.

Branch Chief

OPF Division of Inspectional Assessment

Branch 1



Food and Drug Administration  
Center for Drug Evaluation and Research  
WO Bldg. 51,10903 New Hampshire Ave.  
Silver Spring, MD 20993

**Date:** 09/23/2015  
**To:** Administrative File, STN 125513/0  
**From:** Steven Fong, Ph.D., Acting Quality Assessment Lead, CDER/OPQ/OPF/DIA  
**Endorsement:** Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA  
**Subject:** Original BLA  
**US License:** Pending  
**Applicant:** Alexion Pharmaceuticals  
**Mfg Facility:** Drug Substance (b) (4)  
(b) (4)  
Drug Product: (b) (4)  
(b) (4)  
**Product:** Strensiq (asphotase alfa) Injection  
**Dosage:** 40 mg/mL and 100 mg/mL sterile aqueous solution for subcutaneous administration provided in single use glass vials  
**Indication:** Therapy for Hypophosphatasia  
**Due Date:** 11/23/2015

**RECOMMENDATION:** The application is recommended for approval from a facilities assessment standpoint.

### SUMMARY

This assessment is an addendum for an 08/12/2015 facilities Review of BLA 125513. In the 08/12/2015 Review a final facilities recommendation was not made because compliance decisions were still pending for the (b) (4) proposed for DS manufacture, and the (b) (4) (b) (4), proposed for DP release testing. A Compliance decision of Approve has now been rendered for the (b) (4) DS site, and the Sponsor has withdrawn (b) (4) (b) (4) as a testing facility. DP release testing will be conducted at one site only: (b) (4) (b) (4). All listed facilities are now currently in a state of compliance and the application is recommended for approval from a facilities assessment standpoint.

BLA 125513. Strensiq (Asfotase alfa) DS and DP Manufacture  
Appendix E-2: Facilities Review – Division of Inspectional Assessment

## ASSESSMENT

An assessment of the proposed DS and DP manufacturing and testing sites for the subject BLA was presented in the 08/12/2015 facilities Review. A final facilities recommendation was not rendered in that Review because of uncertainties regarding the compliance statuses of the proposed DS manufacturing site, (b) (4) and one of two proposed DP release testing sites, (b) (4). The statuses of these two facilities with respect to this application are now known and are summarized below:

(b) (4)

## CONCLUSION

As amended, all manufacturing, packaging and testing sites listed in the submission are recommended for approval from a facilities assessment standpoint.

---

Steven E. Fong, M.S., Ph.D.  
Microbiologist and Acting Quality Assessment Lead  
OPF Division of Inspectional Assessment  
Branch 1

---

Zhihao Peter Qiu, Ph.D.  
Branch Chief  
OPF Division of Inspectional Assessment  
Branch 1

**From:** Frederick C. Mills, PhD., Staff Scientist, Division 4, OBP, OPS

**To:** Gerald Feldman, Ph.D., Lab Chief, Division 4, OBP, OPS

**Subject:** Review of Immunogenicity data and Assay Validation for BLA 125513

Asfotase alfa (alkaline phosphatase) for treatment of Hypophosphatasia (HPP)

**Sponsor:** Alexion

**Date of review:** March 11, 2015

**Revised** August 3, 2015 to incorporate Sponsor's IR responses

### **Comments to the File**

Immunogenicity assays for anti-product antibodies to asfotase alfa are appropriately validated with adequate sensitivity. The Sponsor has responded satisfactorily to IRs regarding drug tolerance, assay sensitivity, and the Nab assay positive control. Approximately 80 % of patients became binding Ab positive. This high incidence is expected, since asfotase is not a native protein, but a fusion of TNSALP domain with an IgG1 Fc and a D10 bone targeting peptide, together with two amino acid linker segments. Approximately 50 % of binding antibody positive samples are neutralizing. Although there is a correlation of infusion reaction with antibody responses, they do not appear to affect clinical course. Therefore, I find no immunogenicity issue that would prevent approval.

The Sponsor is being asked to provide a PMR to formalize a pre-BLA commitment to develop an assay for Cross Reactive Immunological Material (CRIM), which in this case is endogenous TNSAP (Tissue Non-Specific Alkaline Phosphatase). This assay will help identify patients without endogenous TNSALP, who are most at risk for producing antibodies that may result in loss of asfotase efficacy.

## Table of Contents

<b>Section</b>	<b>page number</b>
Heading	1
Comments to the File	1
Table of Contents	2
Executive Summary	4
Hyphosphatasia and Asofotase treatment	4
Summary of Immunogenicity Sampling in Clinical Trials	4
Immunogenicity Analysis Pathway	4
Immunogenicity Methodology	5
Binding antibody assay	5
Second Tier Assays	6
Confirmatory Assay	6
Titer Determination	6
Characterization of Reactive Domains	7
Neutralizing Antibody Assay	7
Summary of patient results	8
Background	9
Asfotase alfa	9
Hypophosphatasia	9
Clinical Immunogenicity Data	11
Hypersensitivity	11
Antibody Sampling Schedules	11
Binding Antibody Correlation with Safety	11
Safety Analysis of Neutralizing Antibody Positive Patients	13
Evaluation of Effect of Immunogenicity on Pharmacokinetics	15
Immunogenicity Analysis Pathway	16
ECL antibody binding assay	16
Assay Overview	16
Sensitivity	16
Screening Cutpoint	17
Specificity (Confirmatory) Cutpoint	17
Positive Controls	18
Intra-Assay Precision	18
Inter-Assay Precision	19
Relative Assay Sensitivity	20

Appendix F: Immunogenicity Review: Office of Biotechnology Products  
BLA 125513 Asfotase Alfa Immunogenicity Review

Selectivity	20
Drug Interference	20
Specificity of the Immune Response	21
Stability of anti-ENB0040 antibodies in Human Serum	21
Confirmatory Assay	22
Titration Assay	22
Characterization Assay	24
Neutralizing Antibody Assay	24
Assay Description	24
Negative Control	24
Positive Controls	25
Nab assay cutpoint	25
Precision	26
Intra-Assay Precision	26
Inter-Assay Precision	26
Sensitivity	27
Prozone or Hook Effect	28
Recovery	29
Stability of Positive Controls (PC)	29
Drug Tolerance	30

### Executive Summary

#### Summary of Hypophosphatasia and Asfotase Alfa Treatment

Hypophosphatasia (HPP) is a rare, inherited metabolic life-threatening disease that manifests with bone mineralization defects as well as other systemic effects. This disease results from mutations in Tissue Non-Specific Alkaline Phosphatase (TNSALP), leading to deficiencies in TNSALP enzymatic activity. For treatment of HPP, Alexion has developed an enzyme replacement therapy using Asfotase alfa (Strensiq), which is a soluble IgG<sub>1</sub> Fc fusion glycoprotein comprised of two identical polypeptide chains, (b) (4)

Each polypeptide chain is comprised of a soluble catalytic domain of human tissue-nonspecific alkaline phosphatase (TNSALP) (Millan, 2006), a human immunoglobulin IgG<sub>1</sub> Fc domain, a deca-aspartate peptide (D<sub>10</sub>) used as a bone-targeting domain.

#### Summary of Immunogenicity Sampling in Clinical Trials

The Sponsor has provided antibody sampling schedules for the 7 clinical trials supporting the BLA. These include studies on infantile, (b) (4) and juvenile patients.

##### Reviewer comments

*The antibody sampling times are appropriate because at a minimum they all capture baseline, the initial strong (secondary) antibody responses, and the long term-natural history of patient immunogenicity.*

(b) (4)

*neutralizing antibody assay is adequate for its intended purpose, even in the absence of a high affinity positive control.*

**Summary of patient results.**

(b) (4)



The Sponsor evaluated the relation between immunogenicity and pharmaco-kinetics using Population-PK (Pop-PK) modeling. The Sponsor states that this model predicts some effect of binding and neutralizing antibodies, but that the Asfotase concentration is expected to stay within the therapeutic range.

Reviewer comments

*Visual inspection supports the Sponsor's contention that the impact of immunogenicity on PK is low, but I defer to the Clinical Pharmacology reviewer regarding the accuracy of the Sponsor's statements.*

**Background**Asfotase alfa

Asfotase alfa is a soluble IgG<sub>1</sub> Fc fusion glycoprotein comprised of two identical polypeptide chains, (b) (4). Each polypeptide chain is comprised of a soluble catalytic domain of human tissue-nonspecific alkaline phosphatase (TNSALP) (Millan, 2006), a human immunoglobulin IgG<sub>1</sub> Fc domain, a deca-aspartate peptide (D<sub>10</sub>) used as a bone-targeting domain (Millan, 2008), and two amino acid long linkers between these domains. Each polypeptide chain (b) (4). The two polypeptides are covalently linked together by (b) (4) disulfide bonds.

Hypophosphatasia

Hypophosphatasia (HPP) is a rare, inherited metabolic life-threatening disease that manifests with bone mineralization defects as well as other systemic effects including inadequate respiratory function, seizures, muscle weakness and nephrocalcinosis (see Wythe 2010 Ann. NY Acad Sci. 1192 pp 190-200). HPP is caused by inactivating mutations in the gene encoding TNSALP. The TNSALP gene, localized on chromosome 1p36-34, consists of 12 exons distributed over 50 kb (Weiss et al. 1988) and is subject to very strong allelic heterogeneity. To date, at least 268 distinct mutations and 16 polymorphisms are known, (for a list of mutations see [http://www.sesep.uvsq.fr/03\\_hypo\\_mutations.php](http://www.sesep.uvsq.fr/03_hypo_mutations.php)). These genetic mutations lead to the primary biochemical defect in HPP, which is a deficiency of TNSALP enzymatic activity. The loss of alkaline phosphatase activity leads to elevated circulating levels of the known substrates, inorganic pyrophosphate (PPi), pyridoxal-5'-phosphate (PLP), and phosphoethanolamine (PEA)

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Center for Drug Evaluation and Research  
WO Bldg. 51, 10903 New Hampshire Ave.  
Silver Spring, MD 20993

**Date:** 09/23/2015  
**To:** Administrative File, STN 125513/0  
**From:** Steven Fong, Ph.D., Acting Quality Assessment Lead, CDER/OPQ/OPF/DIA  
**Endorsement:** Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA  
**Subject:** Original BLA  
**US License:** Pending  
**Applicant:** Alexion Pharmaceuticals  
**Mfg Facility:** Drug Substance: (b) (4)  
(b) (4)  
Drug Product: (b) (4)  
(b) (4)  
**Product:** Strensiq (asphotase alfa) Injection  
**Dosage:** 40 mg/mL and 100 mg/mL sterile aqueous solution for subcutaneous administration provided in single use glass vials  
**Indication:** Therapy for Hypophosphatasia  
**Due Date:** 11/23/2015

---

**RECOMMENDATION:** The application is recommended for approval from a facilities assessment standpoint.

---

## SUMMARY

This assessment is an addendum for an 08/12/2015 facilities Review of BLA 125513. In the 08/12/2015 Review a final facilities recommendation was not made because compliance decisions were still pending for the (b) (4) proposed for DS manufacture, and the (b) (4) proposed for DP release testing. A Compliance decision of Approve has now been rendered for the (b) (4) DS site, and the Sponsor has withdrawn (b) (4) as a testing facility. DP release testing will be conducted at one site only: (b) (4). All listed facilities are now currently in a state of compliance and the application is recommended for approval from a facilities assessment standpoint.

## ASSESSMENT

An assessment of the proposed DS and DP manufacturing and testing sites for the subject BLA was presented in the 08/12/2015 facilities Review. A final facilities recommendation was not rendered in that Review because of uncertainties regarding the compliance statuses of the proposed DS manufacturing site, (b) (4) and one of two proposed DP release testing sites, (b) (4). The statuses of these two facilities with respect to this application are now known and are summarized below:

- (b) (4)  
On 09/22/2015, CDER/OPF/DIA rendered an approve decision for a PAI conducted (b) (4) to assess Asfotase alfa DS manufacture at this facility. This was a CPGM 7356/002M-, ICH Q7A- and CPGM 7346.832-based inspection that covered PAC code 46832M. Quality, Materials, Production, Laboratory Controls, Facilities, and Equipment Systems were assessed (b) (4) for Asfotase alfa DS manufacture.
- (b) (4)  
This site currently has an OAI status. On 09/03/2015 the Sponsor submitted an Amendment, SDN 44 (sequence 0043), stating that the facility was being withdrawn as a DP release testing site. DP release testing will only be conducted at (b) (4). As noted in the 08/12/2015 Review, the (b) (4) site is currently approved for DP release testing operations for this BLA.

## CONCLUSION

As amended, all manufacturing, packaging and testing sites listed in the submission are recommended for approval from a facilities assessment standpoint.

**Steven Fong -S**

Digitally signed by Steven Fong -S  
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ou=People, cn=Steven Fong -S,  
0.9.2342.19200300.100.1.1=2000287433  
Date: 2015.09.23 08:55:25 -0400

Steven E. Fong, M.S., Ph.D.  
Microbiologist and Acting Quality Assessment Lead  
OPF Division of Inspectional Assessment  
Branch 1

**Zhihao Qiu -S**

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ou=FDA, ou=People, cn=Zhihao Qiu -S,  
0.9.2342.19200300.100.1.1=2000438274  
Date: 2015.09.23 20:02:07 -0400

Zhihao Peter Qiu, Ph.D.  
Branch Chief  
OPF Division of Inspectional Assessment  
Branch 1

**CMC Addendum  
BLA STN 125513**

**STRENSIQ (asfotase alfa)**

**Alexion**

**Reviewers: Joslyn Brunelle (DS) and Gunther Boekhoudt (DP)  
TL Reviewer: Cris Ausin  
Division of Biotechnology Review and Research IV**

### OBP CMC Review Data Sheet

1. **COMMUNICATIONS WITH SPONSOR AND OND:**

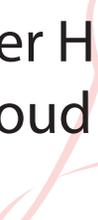
<b>Communication/Document</b>	<b>Date</b>
Information Request #8	6/22/2015
Midcycle Meeting	6/24/2015
T-con with Sponsor	7/24/2015
Information Request #9	7/24/2015
Information Request #10	8/11/2015
Information Request #11	8/18/2015
Pre-Late Cycle Meeting	8/19/2015
Late Cycle Meeting	9/2/2015

2. **SUBMISSION(S) REVIEWED:**

<b>Submission</b>	<b>Date Received</b>	<b>Review Completed (Yes/No)</b>
STN 125513/0038 (response to IR#9)	8/13/2015	Yes
STN 125513/0038 (response to labeling and PMCs/PMRs issues)	8/14/2015	Yes
STN 125513/0039 (response to IR #10)	8/18/2015	Yes
STN 125513/0040 (response to IR #11)	8/21/2015	Yes
STN 125513/0043 (response to Late Cycle Meeting issues)	9/3/2015	Yes

**7. ADMINISTRATIVE**

**A. Signature Block**

Name and Title	Signature and Date
<p>Michele Dougherty, Ph.D. Acting Review Chief Division of Biotechnology Review and Research IV</p>	<p><b>Michele Dougherty -S</b>                        Digitally signed by Michele Dougherty -S                      DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0010556865, cn=Michele Dougherty -S                      Date: 2015.09.04 13:22:06 -04'00'</p>
<p>Cris Ausin, Ph.D., Acting Team Leader Division of Biotechnology Review and Research IV</p>	<p><b>Cristina Ausin-moreno -S</b>                        Digitally signed by Cristina Ausin-moreno -S                      DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011707091, cn=Cristina Ausin-moreno -S                      Date: 2015.09.03 16:32:05 -04'00'</p>
<p>Gunther Boekhoudt, Ph.D., Primary Reviewer (Drug Product) Division of Biotechnology Review and Research IV</p>	<p><b>Gunther H. Boekhoudt -S</b>                        Digitally signed by Gunther H. Boekhoudt -S                      DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000605472, cn=Gunther H. Boekhoudt -S                      Date: 2015.09.03 16:21:14 -04'00'</p>
<p>Joslyn Brunelle, Ph.D., Primary Reviewer (Drug Substance) Division of Biotechnology Review and Research IV</p>	<p><b>Joslyn K. Brunelle -S</b>                        Digitally signed by Joslyn K. Brunelle -S                      DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000396541, cn=Joslyn K. Brunelle -S                      Date: 2015.09.03 16:28:57 -04'00'</p>

**B. CC Block**

Recipient	Date
Lisa Pitt	December 23, 2014
Division of Biotechnology Review and Research IV File/BLA STN 125513	December 23, 2014

## SUMMARY OF QUALITY ASSESSMENTS

### I. Primary Reviewer Summary Recommendation

The Office of Biotechnology Products, OPQ, CDER, recommends approval of STN 125513 for Strensiq (asfotase alfa) manufactured by Alexion, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Strensiq is well controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert. The sponsor provided sufficient information to support a shelf life for Strensiq drug product of 24 months at 2-8°C.

### II. List of Deficiencies To Be Communicated

None

### III. List Of Post-Marketing Requirements

1. Develop an assay to directly compare the complement activating capacity of asfotase alfa to that of human IgG1. The assay should be set up under conditions to readily detect complement activation by IgG1. A dose response curve to demonstrate the sensitivity of the assay is recommended
2. Develop a validated cross-reactive immunologic material (CRIM) assay for patients with hypophosphatasia (HPP) and test patient samples in a cohort of untreated patients. Results should be correlated with antibody response (binding and neutralizing), genetic mutations, enzyme activity level and clinical outcome in patients who are receiving Asfotase alfa treatment. (b) (4)

(b) (4)

### IV. List Of Post-Marketing Commitments

1. Evaluate the asfotase alfa manufacturing process and develop a control strategy (b) (4)  
(b) (4) that ensures consistent patient exposure. Provide detailed summaries of all data utilized to propose the revised control strategy (b) (4)  
(b) (4)

### V. Review Of Common Technical Document-Quality Module 1

#### A. Environmental Assessment Or Claim Of Categorical Exclusion

Alexion is claiming a categorical exclusion under 21 CFR 25.31(c) from the need to prepare an environmental assessment.

### VI. Primary Container Labeling Review

Primary review of the Container Labeling was performed by Jibril Abdus-Samad (OBP).

### VII. Review Of Common Technical Document-Quality Module 3.2

Primary reviews of the Quality Module 3.2 were performed by the OBP reviewers Joslyn Brunelle (Drug Substance) and Gunther Boekhoudt (Drug Product).

#### VIII. Review Of Immunogenicity Assays – Module 3.2.1.4

Primary review of the Immunogenicity Assays was performed by Frederick Mills (OBP).

## Table of Contents

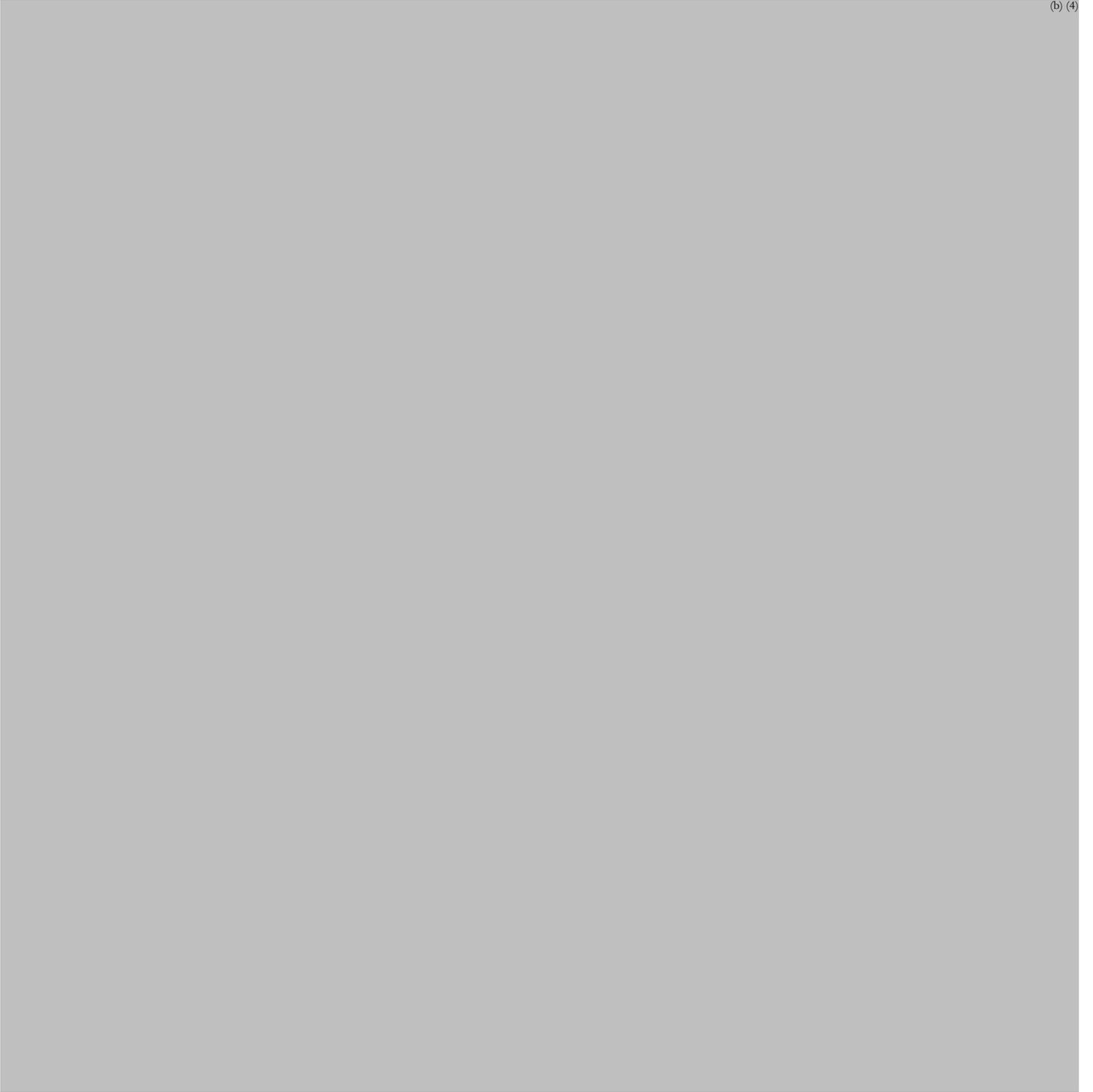
S. DRUG SUBSTANCE.....	7
3.2.S.2 Manufacture.....	7
3.2.S.4 Control of Drug Substance .....	9
P DRUG PRODUCT .....	12
3.2.P.1 Description and Composition of the Drug Product .....	12
3.2.P.3. Manufacture.....	13
3.2.P.5 Control of Drug Product .....	17
3.2.P.8 Stability.....	18

## **S. DRUG SUBSTANCE**

### **3.2.S.2 Manufacture**

Information Request dated July 24, response received on August 13.

(b) (4)



***Reviewer comment:***  
*This is acceptable.*

**3.2.S.4 Control of Drug Substance**

Information Request dated July 24, response received on August 13.

The following comments were communicated to the sponsor:

**Question # 7**

(b) (4)

(b) (4) *Based on the discussion during the July 24, 2015 teleconference, we recommend that you evaluate your ability to raise the lower value of your acceptance criterion based on your current manufacturing capability. Please respond by August 7 with a revised acceptance criterion.* (b) (4)

**Alexion Response:**

Alexion states that the manufacturing data to date does not support raising the lower value of the acceptance criteria based on the current manufacturing capability. (b) (4)

(b) (4) Alexion states that the analysis does not support the (b) (4) of the specification at this time.



Alexion commits to continuous monitoring of sialic acid. It has been implemented as a long term process monitoring program to ensure the process is performing consistently. Alexion commits to reassess the specification by Q4 2015 and will provide an update to the Agency at that time. Alexion will continue to provide biannual data assessments to the Agency until a total of 30 batches is available.

**Reviewer comment:**

*I agree that is not feasible to (b) (4) the specification at this time. The continuous process monitoring and updates to the Agency is adequate to support BLA approval. In addition, the sponsor has agreed to a post marketing commitment (PMC) to evaluate the asfotase alfa manufacturing process and develop a control strategy (b) (4)*

*(b) (4) that ensures consistent patient exposure. The final report is expected by November 2016.*

Information Request dated August 11, response received on August 18.

The following comments were communicated to the sponsor:

**Question # 1**

In the (b) (4) specification revision submitted on June 30, 2015, you stated that “a limit (b) (4) (b) (4) was determined (b) (4) The data set included drug substance and drug product release and stability and two reference standards lots.” However, you did not provide any data to support your revised specification. To confirm that the specification is adequate, provide a justification for defining the (b) (4) specification (b) (4) (b) (4) You should include drug substance and drug product release and stability data, as well as the reference standards used in your analysis.

**Alexion Response:**

The data used to set the (b) (4) specification to 5-9 integrated peaks within pI range of 6.45-6.95 is in the tables below. The reference standards used were QC-2178 (DS lot 169466) and current reference standard RS12150413 (DS lot 338971). In addition, Alexion notes that (b) (4) was implemented at a later date than other test methods. Therefore, some lots were not tested at release and some lots only have later stability time points.

**Table 1: Asfotase Alfa Drug Substance Release and Stability Data for (b) (4)**

Drug Substance Batch	Release Data		Stability Data at 2-8°C	
	Peak Number	PI Range	Peak Number	PI Range
280897	NR	NR	(b) (4)	(b) (4)
284989	NR	NR		
332604	(b) (4)	(b) (4)		
335332				
333366				
338971				
341981				
379564				

**Reviewer comment:**

The data provided on drug substance lots supports the (b) (4) specification (b) (4) (b) (4).

**Question # 2**

The Agency notes that you are using (b) (4) (b) (4)

(b) (4) Clarify whether you have obtained a sufficient number of kits (from a single lot number) that will be used for release testing over a specified period of time. Please be aware that, prior to their use, you should qualify new lots of kit to confirm that the antibody coverage is comparable.

**Alexion Response:**

Alexion has enough kits to cover the next two manufacturing campaigns. “Alexion commits to qualify new lots of kits, when a critical reagent has been changed, to confirm the antibody coverage is comparable.”

**Reviewer comment:**

This is acceptable.

**P DRUG PRODUCT**

**3.2.P.1 Description and Composition of the Drug Product**

Information Request dated August 18, response received on August 21.

### **3.2.P.3. Manufacture**

Information Request dated July 24, response received on August 13.

The following comments were communicated to the sponsor:

#### **Question # 6**

*The Code of Federal Regulation (21 CFR 610.14) requires that identity testing be performed on each filled lot of drug product after all labeling operations have been completed. The manufacturing step from which samples of asfotase alfa are obtained was not clearly identified in section 3.2.P.3.3, 3.2.P.3.4, or 3.2.A.1.4 (b) (4). Clarify the process and revise the process if necessary to comply with the regulation.*

#### **Alexion Response:**

“Alexion confirms that identity testing in accordance with 21 CFR 610.14 will be implemented prior to the packaging of the first commercial batch. (b) (4)

(b) (4)

labeling. Following packaging and labeling operations, one vial is tested (b) (4) (b) (4) to confirm the identity of the labelled vials prior to release.

A revised CTD Section 3.2.P.3.3 Description of Manufacturing Process and Process Controls is provided.”

**Reviewer comment:**

The sponsor confirmed that identity testing is being performed per with 21 CFR 610.1. Section 3.2.P.3.3 was revised to include that a vial is tested (b) (4). However, (b) (4) is not validated as an identity test and a comment was sent to the sponsor on August 18, 2015 to submit data supporting the use of this proposed identity test. Alexion submitted their response on August 21, 2015 (See Alexion Response dated August 21, 2015 Question # 1 below).

Information Request dated August 18, response received on August 21.

The following comments were communicated to the sponsor:

**Question # 1**

In your response submitted on August 13, 2015 to question 6, you confirm that drug product identity testing will be performed after all labeling operations have been completed in accordance with 21 CFR 610.14. In addition, you indicated that “one vial is tested (b) (4) (b) (4). However, in the BLA submission the (b) (4) (b) (4) method is not validated as an identity test. You showed the specificity (b) (4). However, you did not demonstrate that this test method can discriminate asfotase alfa from other products. Provide additional data to support the validation of the (b) (4) method as an identity test. Alternatively, to comply with 21 CFR 610.14, select a different assay that is properly validated as an identity test.

**Alexion Response:**

“Peptide Mapping will be used to confirm identity of asfotase alfa after all labeling operations have been completed in accordance to 21 CFR 610.14. Peptide Mapping had been validated as a drug product identity assay per CTD Section 3.2.P.5.3 Validation of Analytical Procedures.”

**Reviewer comment:**

Alexion clarified that Peptide mapping will be used as the identity test and not the initially proposed (b) (4) method. Peptide mapping is a validated method for the Identity test. The sponsor’s response is acceptable.

Information Request dated August 11, response received on August 18.

The following comments were communicated to the sponsor:

**Question # 3**

You have provided limited information regarding several drug product manufacturing steps. To ensure appropriate control of the drug product manufacturing process, revise Section 3.2.P.3.3 Description of Manufacturing Process and Process Controls (b) (4)

(b) (4)

*In addition, revise Section 3.2.P.3.4 Control of Critical Steps and Intermediates to include appropriate limits for the following:*

(b) (4)

**Alexion Response:**

“CTD Section 3.2.P.3.3 Description of Manufacturing Process and Process Controls has been revised (b) (4)

(b) (4) This section has also been revised to include the acceptable ranges for the key process parameters (KPP) outlined in Table 1 below. CTD Section 3.2.P.3.4 Control of Critical Steps and Intermediates has not been revised since it only includes critical process parameters.

(b) (4)

**Reviewer comment:**

*The sponsor has included sufficient information to our requested revisions in Section 3.2.P.3.4; this is acceptable.*

**Question # 4**

*To confirm the adequacy of the drug product shipping validation, provide a justification of the suitability of the shipping studies to confirm that the conditions used during the shipping studies (load, time elapsed, distance, etc.) represent a worst case scenario in terms of temperature control and physical impact to the product.*

**Alexion Response:**

“The drug product shipment validation (PQ-0106FR provided in CTD Section 3.2.R.4 Process Validation Scheme) (b) (4)

(b) (4) was completed (b) (4)

(b) (4)

(b) (4) therefore, the shipping validation represents worst case (b) (4)  
(b) (4)

**Reviewer comment:**

*The sponsor provided clarification that the drug product shipment validation performed is considered worst case (b) (4)*

(b) (4)

(b) (4) *The information provided indicates that the shipping validation could be considered worst case scenario and the response is acceptable.*

### 3.2.P.5 Control of Drug Product

Information Request dated July 24, response received on August 13.

The following comments were communicated to the sponsor:

#### Question # 1

*In your Supporting Document received on 6-30-2015 you updated “Section 3.2.P.5.6 Justification of Specifications.” We note that you removed most of the drug product justifications. Instead you are referencing “Section 3.2.S.4.5 Justification of Specification.” However, section 3.2.S.4.5 does not include justifications for drug product specifications that are different than those of drug substance, (b) (4). Revise section 3.2.P.5.6 to include all drug product justifications of specifications.*

**Alexion Response:** In amendment 39 (dated August 13, 2015) the sponsor submitted a revised CTD Section 3.2.P.5.6 Justification of Specification including the analysis and justification for the drug product specification. This detail was inadvertently removed during the response dated 30 June 2015 (Sequence 0031), there has been no change to the proposed specification, analysis or justification previously under review.

#### Reviewer comment:

*The sponsor, as requested, revised 3.2.P.5.6 to include all drug product justifications of specifications. The information provided is acceptable. In addition, refer to section 3.2.S.4 for additional information regarding the acceptance criteria (b) (4)*

#### Question # 2

*You provided accelerated stability data showing that drug product specific activity (pNPP) and purity (b) (4) (b) (4) therefore, these assays are stability indicating. Draft Guidance for Industry, Analytical Procedures and Method Validation for Drugs and Biologics, recommends that for stability indicating assays you should include “samples that have undergone various laboratory stress conditions; and actual product samples (produced by the final manufacturing process) that are either aged or have been stored under accelerated temperature and humidity conditions”. As part of the validation of the transfer of analytical methods to (b) (4) you tested lots 3-FIN-1486, 3-FIN-1475, and 280897; however, you did not include any samples that show significant degradation. To demonstrate that specific activity, (b) (4) are equally stability indicating at the receiving site, update the method transfers to include testing of samples that have undergone accelerated conditions. Alternatively, consider withdrawing the transfer of these assays from the application and re-submit the complete information post-approval.*

#### Alexion Response:

“Alexion agrees to complete a supplemental transfer of the specific activity (pNPP), (b) (4) (b) (4) assays to include samples that demonstrate degradation and submit these transfer reports in a future supplement.

Alexion confirms that (b) (4) will not be used for specific activity, (b) (4) (b) (4) release testing until the subsequent submission and approval of the supplemental transfers. The transfers of these three assays are being withdrawn from the BLA.

A revised CTD Section 3.2.P.5.3 Validation of Analytical Procedures, Section 3.2.R.5 Documentation of Analytical Procedures (b) (4) and Section 3.2.R.6.3 Method Transfer Qualification (b) (4) are provided.”

**Reviewer comment:**

*The sponsor has agreed to our request to complete a supplemental transfer of the specific activity (pNPP), (b) (4) assays to include samples that demonstrate degradation. The assay transfer report will be submitted post-approval. In addition, Alexion is withdrawing the (b) (4) as the testing site for specific activity, (b) (4) (b) (4) The information provided is adequate and acceptable.*

**3.2.P.8 Stability**

Information Request dated August 11, response received on August 18.

The following comments were communicated to the sponsor:

**Question # 5**

*In section 3.2.P.8.3 Stability Data you provided quantitative stability results. However, the submission did not include qualitative data. To confirm that drug product is stable during the proposed shelf life, provide representative raw stability data (gels and/or chromatographs) for your purity assays at time point 0 (initial) and at the last available time point.*

**Alexion Response:**

“Representative gels and chromatographs for the purity assays (b) (4) (b) (4) (b) (4) at time point 0 as well as long-term storage (2-8°C) at 24 months and (b) (4) storage (b) (4) at (b) (4) months are provided with this response.”

**Reviewer comment:**

*The sponsor, as requested, provided qualitative data. The data included representative (b) (4) (b) (4) (b) (4) chromatographs. Time points provided were at time point (b) (4) 24 months at 2-8°C, and (b) (4) months at (b) (4) The data were reviewed and the results do appear to be in agreement with the quantitative data submitted to the BLA.*

**Late Cycle Meeting Information** communication dated September 2, response received on September 3.

The following comments were communicated to the sponsor by the Division of Inspectional Assessment:

*One facility has received a Form FDA 483 for pre-license inspection observations. These inspectional findings and any facility responses received within 15 days of the inspection will be reviewed. We will communicate any additional requests directly to this site. Please ensure that all facilities are ready for commercial CGMP manufacturing activities as described in the BLA. Satisfactory evaluation of all manufacturing facilities is required for BLA approval.*

**Alexion Response:**

Alexion agreed to withdraw the secondary testing site [REDACTED] (b) (4) [REDACTED] (b) (4) from the BLA.

**Reviewer comment:**

*The sponsor updated sections 3.2.P.3, 3.2.P.5, 3.2.A, 3.2.R.5, and 3.2.R.6 accordingly to reflect the withdrawal of the [REDACTED] (b) (4) testing site. This is acceptable.*



Food and Drug Administration  
Center for Drug Evaluation and Research  
WO Bldg. 51, 10903 New Hampshire Ave.  
Silver Spring, MD 20993

**Date:** 08/12/2015  
**To:** Administrative File, STN 125513/0  
**From:** Steven Fong, Ph.D., Quality Assessment Lead, CDER/OPQ/OPF/DIA  
**Endorsement:** Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA  
**Subject:** Original BLA  
**US License:** Pending  
**Applicant:** Alexion Pharmaceuticals  
**Mfg Facility:** Drug Substance: (b) (4)  
(b) (4)  
Drug Product: (b) (4)  
(b) (4)  
**Product:** Strensiq (asphotase alfa) Injection  
**Dosage:** 40 mg/mL and 100 mg/mL sterile aqueous solution for subcutaneous administration provided in single use glass vials  
**Indication:** Therapy for Hypophosphatasia  
**Due Date:** 11/23/2015

**RECOMMENDATION:** As of the review submission date a final recommendation on the acceptability of the proposed manufacturing and testing facilities cannot be made. Compliance decisions are still pending for a (b) (4) inspection of (b) (4) (b) (4) proposed for DS manufacture, and a (b) (4) inspection of (b) (4) (b) (4) proposed for DP release testing. An Amendment stating the final OPF-DIA decisions for these facilities will be submitted to the File once they are known. All other proposed manufacturing and testing sites are recommended for approval from a facilities assessment standpoint.

**SUMMARY**

The subject BLA proposes manufacture of Strensiq (asfotase alfa) DS and DP, respectively, at (b) (4) (b) (4) and Alexion Pharmaceuticals, Smithfield, RI. Testing/packaging operations will occur at Alexion Pharma, Smithfield, RI (FEI 3006568549) (b) (4), (b) (4)

(b) (4)

Asfotase alfa is a fusion protein expressed in CHO cells that is proposed as a treatment for hypophosphatasia. The protein is composed of the soluble catalytic domain of human tissue non-specific alkaline phosphatase (sALP), the Fc domain of human IgG1 Fc, and a deca-aspartate peptide (D10) used as a bone targeting domain. The DP is provided in two strengths, 40 mg/mL and 100 mg/mL, in a solution containing (b) (4) sodium chloride, (b) (4) dibasic sodium phosphate (b) (4) (b) (4) monobasic sodium phosphate (b) (4) (b) (4). The final dosage form is provided in 2 mL, single use glass vials filled with (b) (4) 0.45, 0.70, or 1.0 mL of 40 mg/mL asfotase alfa (b) (4) 18, 28, and 40 mg of DP), or 0.80 mL of 100 mg/mL asfotase alfa (80.0 mg of DP).

## ASSESSMENT

### DRUG SUBSTANCE FACILITIES

- **3.2.S.2.1 DS Manufacturers.**

The sites proposed for asfotase alfa DS manufacture, cell banking operations, and testing are presented below in Table 1.

TABLE 1. Proposed Sites for Asfotase alfa DS Manufacture, Cell Banking and Testing Operations

Site Name	Address	FEI Number	Responsibilities
(b) (4)			
Alexion Pharmaceuticals Inc.	100 Technology Way Smithfield, RI 02917	3006568549	Storage of master and working cell bank.

**Reviewer Comment 1:** *The facilities for manufacture of Asfotase alfa DS are adequately described.*

- **Prior Inspection History for DS Manufacturing and Testing Sites**

(b) (4)



- Alexion Pharmaceuticals Inc. (FEI 3006568549). Master and Working Cell Bank Storage. As per ICH Q7A, the sites used for storage of cell banks used for biotechnology products do not pose a significant concern from a cGMP prospect. A facilities evaluation for this site is not required for cell banking. A facilities assessment for the firm for DP testing is presented below under *DRUG PRODUCT, Prior Inspection History for DP Manufacturing and Testing Sites.*

- **Current Prior Approval Inspection Decisions**

(b) (4)

**Reviewer Comment 2:** A recommendation on the compliance status of the production and testing facilities associated with the manufacture of asfotase alfa DS cannot be made until a decision on the acceptability of the (b) (4) site is finalized by OPF-DIA. An Amendment stating the final decision for this facility will be submitted to the File once it is known.

- **3.2.S.2.2. Overview of Asfotase alfa DS Manufacturing Operations Conducted**

(b) (4)

(b) (4)

(b) (4)



**DRUG PRODUCT FACILITIES**

- **3.2.P.3.1. DP Manufacturers.**

The sites proposed for asfotase alfa DP manufacture, testing, packaging, and labeling are presented below in Table 4.

TABLE 4. Sites Proposed for Strensiq DP Manufacture and Testing

Site Name	Address	FEI Number	Responsibilities
(b) (4)			
Alexion Pharmaceuticals, Inc.	100 Technology Way Smithfield, RI 02917	3006568549	DP release and stability testing (b) (4), (b) (4)
(b) (4)			

- **Prior Inspection History for DP Manufacturing and Testing Sites**





- Alexion Pharmaceuticals Inc. (FEI 3006568549). DP Release Testing Site.
  - Inspection Conducted 08/18-22/2014 by (b) (4). CPGM 7356.002- and CPGM 7356.002M-based inspection conducted as a follow-up to a 07/12/2012 – 08/06/2012 inspection that resulted in Warning Letter and an OAI classification (see below). This 2014 inspection determined that the deficiencies leading to the 2012 Warning Letter had been corrected. A 3-item FDA Form 483 was issued. The facility was reclassified to VAI.
  - Inspection Conducted 07/12/2012 – 08/06/2012 by (b) (4) CPGM 7356.002- and CPGM 7356.002M-based cGMP surveillance inspection covering PAC codes 56002 and 56002M that resulted in a Warning Letter and an OAI classification. The classification was based on adulteration of records.
  - Inspection Conducted 01/20/2011 – 02/18/2011 by (b) (4). CPGM 7356.002- and 7356.002M-based cGMP surveillance inspection covering PAC codes 56002 and 56002M. The inspection resulted in issuance of a 7-item FDA Form 483. The inspection was classified VAI.





(b) (4)



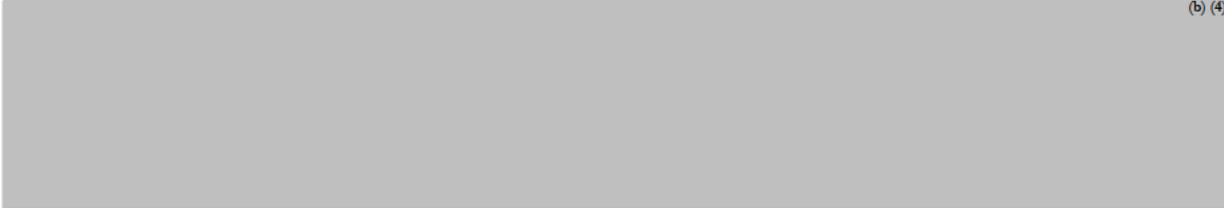
• **Current Prior Approval Inspection Decisions**

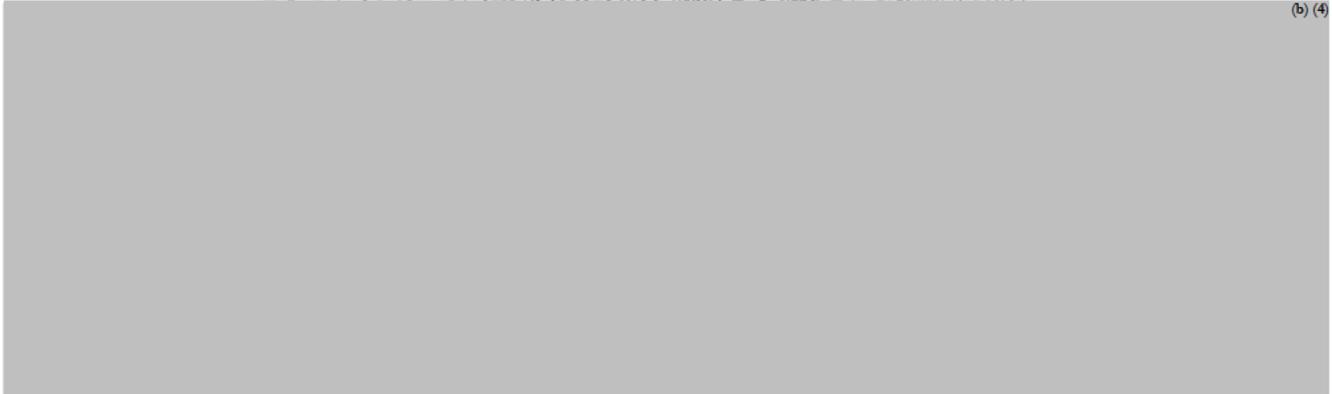
(b) (4)



- Alexion Pharmaceuticals Inc. (FEI 3006568549). DP Release Testing Site. Facility approved based on file review.

(b) (4)





*Reviewer Comment 12. A recommendation on the compliance status of the production and testing facilities associated with the manufacture of Asfotase alfa DP cannot be made until a decision on the acceptability of the (b) (4) site proposed for DP release testing is finalized by OPF-DIA. An Amendment stating the final decision for this facility will be submitted to the File once it is known.*



## CONCLUSION

Adequate descriptions were provided for the (b) (4) (b) (4) facilities proposed for Asfotase alfa DS and DP manufacture. All proposed manufacturing and testing sites except for (b) (4) (b) (4) are recommended for approval from a facilities assessment standpoint. However, a final facilities recommendation for the BLA cannot be made until compliance decisions have been rendered for a (b) (4) PAI o (b) (4) and a (b) (4) inspection (b) (4). An Amendment stating the final OPF/DIA decisions for these sites and the final facilities recommendation will be submitted to the File once they are known.

Steven Fong -S

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OPF Division of Inspectional Assessment  
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# **BLA STN 125513**

## **STRENSIQ (asfotase alfa) Drug Product**

**Alexion**

**Reviewer: Gunther Boekhoudt  
LC/TL Reviewer: Cris Ausin  
Division of Biotechnology Review and Research IV**

**OBP CMC Review Data Sheet**

1. **BLA#: STN 125513**

2. **REVIEW DATE: August 5, 2015**

3. **PRIMARY REVIEW TEAM:**

Clinical TL: Anil Rajpal  
 Clinical Reviewer: Carla Epps  
 Clinical Pharmacology TL: Yow-Ming Wang  
 Clinical Pharmacology: Christine Hon  
 Clinical Pharmacometrics: Justin Earp  
 Product Quality TL: Cris Ausin  
 Product Quality Reviewer (Drug Substance): Joslyn Brunelle, Mate Tolnay  
 Product Quality Reviewer (Drug Product): Gunther Boekhoudt  
 Product Quality Reviewer (Immunogenicity): Fred Mills  
 Product Quality Labeling Reviewer: Jibril Abdus-Samad  
 Micro TL: Patricia Hughes  
 Micro Reviewer: Candace Gomez-Broughton  
 Facilities Reviewer: Steven Fong  
 Immunogenicity: Fred Mills

4. **MAJOR GRMP DEADLINES**

Received: December 23, 2014  
 Filing Meeting: January 21, 2015  
 Mid-Cycle Meeting: June 24, 2015  
 Primary Review Due: August 8, 2015  
 Late Cycle Meeting: September 2, 2015  
 Wrap-Up Meeting: September 29, 2015  
 CDTL Memo Due: September 25, 2015  
 PDUFA Action Date: November 23, 2015

5. **COMMUNICATIONS WITH SPONSOR AND OND:**

<b>Communication/Document</b>	<b>Date</b>
CMC Pre-BLA Meeting	11/26/2013
T-con with EMA	12/3/2014
Immunogenicity Pre-BLA Meeting	1/14/2014
Information Request #1	5/15/2014
Pre-BLA Meeting	7/8/2014
Information Request #2	11/26/2014
Information Request #3	1/27/2015
Team Meeting	2/19/2015
74-day Letter (Microbiology IR)	2/27/2015
T-con with Sponsor	3/5/2015
Information Request #4	3/6/2015

Team Meeting	3/11/2015
Information Request #5	4/17/2015
Information Request #6	4/20/2015
Team Meeting	4/21/2015
T-con with EMA	4/29/2015
Information Request #7	5/22/2015
Team Meeting	6/3/2015
Information Request #8	6/22/2015
Midcycle Meeting	6/24/2015
T-con with Sponsor	7/24/2015
Information Request #9	7/24/2015

6. **SUBMISSION(S) REVIEWED:**

Submission	Date Received	Review Completed (Yes/No)
STN 125513/0	3/31/2014	Yes
STN 125513/0002 (response to IR #1)	5/15/2014	Yes
STN 125513/0004 (response to IR #1)	7/30/2014	Yes
STN 125513/0005 (response to IR #2)	12/19/2014	Yes
STN 125513/0006 (final rolling submission)	12/23/2014	Yes
STN 125513/0011 (response to IR #3)	2/12/2015	Yes
STN 125513/0014 (response to IR #3, IR#4, and 74-day Letter)	3/13/2015	Yes
STN 125513/0017 (response to 74-day letter)	3/30/2015	Yes
STN 125513/0025 (response to 74-day letter, IR #5, and IR#6)	4/30/2015	Yes
STN 125513/0029 (response to IR#3 and IR#7)	6/1/2015	Yes
STN 125513/0031 (response to IR#5, IR#6, and IR#8)	6/30/2015	Yes
STN 125513/0035 (response to 74-day Letter)	7/27/2015	Yes
STN 125513/0036 (response to IR#5)	7/31/2015	Yes

7. **ADMINISTRATIVE**

A. Signature Block

Name and Title	Signature and Date
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<p>Cris Ausin, Ph.D., Acting Team Leader Division of Biotechnology Review and Research IV</p>	<p><b>Cristina Ausin- moreno -S</b></p> <p>Digitally signed by Cristina Ausin-moreno -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011707091, cn=Cristina Ausin-moreno -S Date: 2015.08.07 10:07:53 -04'00'</p>
<p>Gunther Boekhoudt, Ph.D., Primary Reviewer Division of Biotechnology Review and Research IV</p>	<p><b>Gunther H. Boekhoud t -S</b></p> <p>Digitally signed by Gunther H. Boekhoudt -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000605472, cn=Gunther H. Boekhoudt -S Date: 2015.08.07 09:51:59 -04'00'</p>

## B. CC Block

Recipient	Date
Lisa Pitt	December 23, 2014
Division of Biotechnology Review and Research IV File/BLA STN 125513	December 23, 2014

## Table of Contents

<a href="#">P DRUG PRODUCT [21 CFR 312.23 (a)(7)(iv)(b)]</a> .....	1
<a href="#">3.2.P.1 Description and Composition of the Drug Product</a> .....	6
<a href="#">3.2.P.2 Pharmaceutical Development</a> .....	7
<a href="#">3.2.P.2.1 Components of the Drug Product</a> .....	7
<a href="#">3.2.P.2.2 Drug Product</a> .....	8
<a href="#">3.2.P.2.3 Manufacturing Process Development</a> .....	8
<a href="#">3.2.P.2.4 Container Closure System</a> .....	10
<a href="#">3.2.P.2.5 Microbiological Attributes</a> .....	14
<a href="#">3.2.P.2.6 Compatibility</a> .....	14
<a href="#">3.2.P.3 Manufacture</a> .....	16
<a href="#">3.2.P.3.1 Manufacturer(s)</a> .....	16
<a href="#">3.2.P.3.2 Batch Formula</a> .....	18
<a href="#">3.2.P.3.3 Description of Manufacturing Process and Process Controls</a> .....	18
<a href="#">3.2.P.3.4 Controls of Critical Steps and Intermediates</a> .....	20
<a href="#">3.2.P.3.5 Process Validation and/or Evaluation</a> .....	21
<a href="#">3.2.P.4 Control of Excipients</a> .....	30
<a href="#">3.2.P.4.1 Specifications</a> .....	30
<a href="#">3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures</a> .....	31
<a href="#">3.2.P.4.4 Justification of Specifications</a> .....	31
<a href="#">3.2.P.4.5 Excipients of Human or Animal Origin</a> .....	31
<a href="#">3.2.P.4.6 Novel Excipient</a> .....	31
<a href="#">3.2.P.5 Control of Drug Product</a> .....	31
<a href="#">3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)</a> .....	31
<a href="#">3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures</a> .....	44
<a href="#">3.2.P.5.4 Batch Analyses</a> .....	53
<a href="#">3.2.P.5.5 Characterization of Impurities</a> .....	54
<a href="#">3.2.P.6 Reference Standards or Materials</a> .....	54
<a href="#">3.2.P.7 Container Closure System</a> .....	54
<a href="#">3.2.P.8 Stability</a> .....	56
<a href="#">3.2.P.8.1 Stability Summary and Conclusion</a> .....	56
<a href="#">3.2.P.8.2 Post-Approval Stability Commitment</a> .....	57
<a href="#">3.2.P.8.3 Stability Data</a> .....	59
<a href="#">3.2.A Appendices Table of Contents</a> .....	67
<a href="#">3.2.A.1 Facilities and Equipment</a> .....	67
<a href="#">3.2.A.3 Novel Excipients</a> .....	67
<a href="#">3.2.R Regional Information (U.S.A.)</a> .....	67
<a href="#">3.2.R.1 Executed Batch Records</a> .....	67
<a href="#">3.2.R.2 Method Validation Package</a> .....	68
<a href="#">3.2.R.3 Comparability Protocols</a> .....	68

P DRUG PRODUCT

**3.2.P.1 Description and Composition of the Drug Product**

ALXN-1215 (asfotase alfa) is a recombinant human alkaline phosphatase intended to be used in an enzyme-replacement therapy for patients with hypophosphatasia (HPP). HPP is a rare, life-threatening, genetic metabolic disease with no approved treatment options.

**Description**

Asfotase alfa DP is supplied as a sterile, preservative-free aqueous solution for SC administration at two concentrations containing 40 mg/mL or 100 mg/mL asfotase alfa in (b) (4) sodium phosphate, (b) (4) sodium chloride at a pH between 7.2 and 7.6 in a 2 mL Type 1 glass vial. The vials are stoppered with a (b) (4) rubber stopper (b) (4), (b) (4) and sealed with aluminum seals with (b) (4), flip-off caps.

Asfotase alfa DP is supplied in single-use vials at different volumes ([Table 1](#)).

**Table 1 DP Dosage Strengths**

Asfotase alfa concentration	Extractable volume per vial	Amount of asfotase alfa per vial	Fill volume*
40 mg/mL	0.45 mL	18 mg	(b) (4)
	0.70 mL	28 mg	(b) (4)
	1.0 mL	40 mg	(b) (4)
100 mg/mL	0.80 mL	80 mg	(b) (4)

\* Fill volume as described in section [3.2.P.3.4 Control of critical steps and intermediates](#)

***Reviewer comment:** The fill volumes are within the USP <1151>. The (b) (4) excess volume is appropriate.*

**Drug product composition and presentations**

The composition of both the 40 mg/mL and 100 mg/mL are shown in [Table 2](#) and [Table 3](#) respectively.

**Table 2: 40 mg/mL DP**  
(Table 1 Section 3.2.P.1 in the BLA)

Component (Formulation Concentration)	Quality Standard	Function	Available Quantity per Vial for Each Extractable Volume		
			(b) (4) 0.45 mL	0.70 mL	1.0 mL
asfotase alfa (40 mg/mL)	In-house	Active ingredient	18 mg	28 mg	40 mg
(b) (4) Sodium chloride (b) (4)	USP, Ph. Eur., JP				(b) (4)
(b) (4) Dibasic sodium phosphate (b) (4)	USP, Ph. Eur.				(b) (4)
(b) (4) Monobasic sodium phosphate (b) (4)	USP, Ph. Eur.				(b) (4)

**Table 3: 100 mg/mL DP**  
(Table 2 Section 3.2.P.1 in the BLA)

Component (Formulation Concentration)	Quality Standard	Function	Available Quantity per Vial for Each Extractable Volume
			0.80 mL
asfotase alfa (100 mg/mL)	In-house	Active ingredient	80 mg
(b) (4) Sodium chloride (b) (4)	USP, Ph. Eur., JP	(b) (4)	(b) (4)
(b) (4) Dibasic sodium phosphate (b) (4)	USP, Ph. Eur.		
(b) (4) Monobasic sodium phosphate (b) (4)	USP, Ph. Eur.		
(b) (4)	USP, Ph. Eur., JP		

Asfotase alfa is indicated for (b) (4) therapy for patients with perinatal, infantile, and juvenile-onset hypophosphatasia. The proposed dosage regimen is 6 mg/kg/week administered by SC injection. This is achieved by either 1 mg/kg six times per week or 2 mg/kg three times per week with a maximum injection volume of 1 mL/injection. Frequency of injection is left to the discretion of the patient or parent/guardian. Larger patients may necessitate multiple injections per dose and may wish to receive fewer injections more frequently.

*Reviewer comment:* Asfotase alfa comes in 2 mL vials for single use. Dosing is determined by patient weight but maximum administered volume per injection cannot exceed 1 mL. This implies that smaller patients (lighter patients) could receive one injection using one vial. In contrast, larger patients (heavier patients) could use multiple vials.

**3.2.P.2 Pharmaceutical Development**

**3.2.P.2.1 Components of the Drug Product**

**3.2.P.2.1.1 Drug Substance**

Asfotase alfa is an IgG1 Fc fusion glycoprotein comprised of two identical polypeptide chains. Each chain consists of (b) (4), a soluble catalytic domain of human tissue non-specific alkaline phosphatase (sALP), a human IgG1 Fc domain, a deca-aspartate peptide (D<sub>10</sub>) used as a bone-targeting domain, and two amino acid long linkers between these domains. These chains are covalently linked by two disulfide bonds. The DS is formulated at 100 mg/mL, (b) (4) sodium phosphate, (b) (4) sodium chloride, pH (b) (4) (b) (4) (b) (4) (u) (4). (See Table 2 and Table 3 for DP composition). Asfotase alfa is compatible with all the excipients in the formulation.

There are no physicochemical characteristics or biological properties of the DS which influence the performance or manufacturability of the DP.

**3.2.P.2.1.2 Excipients**

DP excipients are all compendial grade ([Table 4](#))

**Table 4 DP Excipients**

Excipient	Grade	Concentration	Purpose
sodium chloride	USP, Ph. Eur., JP		(b) (4)
sodium phosphate monobasic	USP, Ph. Eur.		
sodium phosphate dibasic	USP, Ph. Eur.		

*Reviewer comment: All excipients are standard pharmacopeial excipients.*

**3.2.P.2.2 Drug Product**

**3.2.P.2.2.1 Formulation Development**

Both the 40 mg/mL and the 100 mg/mL DP are formulated in the same formulation (b) (4) and it remained unchanged during non-clinical and clinical development. Formulation development of DS and DP are identical and is detailed in section 3.2.S.2.6.6 Drug Formulation Development (DS review by Joslyn Brunelle).

The formulation was designed based on the (b) (4) Phosphate was chosen (b) (4) (b) (4) (b) (4). Sodium chloride was used (b) (4) (b) (4).

**3.2.P.2.2.2 Overages**

There are no overages in the amount of asfotase alfa added to the formulation in excess of the label claim. The DP vials are filled with a (b) (4) overfill.

*Reviewer comment: The DP has no overages, but there is (b) (4) overfill in each vial to guarantee extraction of the desired volume. This overfill complies with the USP <1151> and is acceptable.*

**3.2.P.2.2.3 Physicochemical and Biological Properties**

The physicochemical and biological properties of the DP and DS are identical except for the concentration of asfotase alfa. DP is produced in two concentrations, 100 mg/mL and 40 mg/mL. (b) (4) (b) (4).

**3.2.P.2.3 Manufacturing Process Development**

**3.2.P.2.3.1 Overall Process Development Summary**

DP is manufactured by (b) (4) (b) (4)

(b) (4)

(b) (4)

### 3.2.P.2.3.2 Drug Product Critical Quality Attributes

The DS critical quality attributes are similar to DP attributes except for those that are DP specific (see section 3.2.S.2.6 Manufacturing Process Development in the DS review by Joslyn Brunelle). DP specific critical quality attributes are sterility, particulate and extractable volume. Sterility testing is performed per USP <71> and Ph. Eur. 2.6.1, particulate testing is performed per USP <788> and Ph. Eur. 2.9.19, and extractable volume is performed per USP <1> and Ph. Eur. 2.9.17.

*Reviewer comment:* Sterility, particulate, and extractable volume testing conform to USP and Ph. Eur. standards and are acceptable.

### 3.2.P.2.3.3 Drug Product Manufacturing Process History

Manufacturing of DP was initially contracted (b) (4) which in (b) (4) was transferred (b) (4). At the same time, DS manufacturing was transferred to (b) (4). [Table 5](#) summarizes the differences between the (b) (4) processes.

**Table 5 Manufacturing changes in 2010**

	Drug Substance	Drug Product
Prior to 2010	(b) (4)	
After 2010		

The validated commercial DP manufacturing process is described below in Section [3.2.P.3.3](#) (Description of Manufacturing Process and Process Controls) and the validation is described in Section [3.2.P.3.5](#) (Process Validation and/or Evaluation).

Studies supporting the comparability and consistency of the drug substance manufactured at the two clinical manufacturing scales are presented in Section 3.2.S.2.6.5.1 (Comparability between the (b) (4) and (b) (4) scale in the DS review by Joslyn Brunelle).

*Reviewer's comment:* The DP manufacturing process underwent minor changes during development. The sponsor did not provide a comparability assessment to evaluate potential

effects of these manufacturing changes. Upon request from the Agency (3/6/2015), Alexion provided additional information to the BLA on 3/13/15 (SN0015).

**Reviewer's Evaluation of Alexion Response 1 (SN0015 submitted on 3/13/15):**

Alexion provided sufficient information to allow for a side-by-side comparison of the DPs manufactured at the (b) (4) sites. Overall the data support that the DP produced at (b) (4) (post-change) is comparable to that from the (b) (4) site (pre-change). For the most part the data show no statistical differences between the two sites (b) (4). There were statistical differences (b) (4). These statistical differences were all small and overall trending demonstrated a more pure and consistent manufacturing process. In addition, the differences observed should pose no safety risk to the patient. I agree with the sponsor that the DPs produced at both sites are comparable.

**3.2.P.2.4 Container Closure System**

The DP container closure system for (40 mg/mL and 100 mg/mL) is a 2 mL USP/Ph. Eur. Type I glass vial, a (b) (4) rubber stopper (b) (4) and an aluminum seal with a (b) (4) flip-off cap. Packaging of DP consists of two configurations: 12 vials or a single vial in a (b) (4) carton. To differentiate between the two DP concentrations, the sponsor uses different colored (b) (4). The 40 mg/mL and the 100 mg/mL DP are sealed with a (b) (4) cap, respectively.

**Reviewer comment:** The commercial DP container closure system is the same one used throughout the clinical development. Therefore, no additional data are required.

**3.2.P.2.4.1 Container Suitability**

**Light Transmission**

Asfotase alfa is light sensitive. Stability studies demonstrated that the DP was stable when using the (b) (4), therefore the vial does not need to provide protection from light.

**Representative study results** (for more details see Section [3.2.P.8.3](#) Stability Data):

Control samples were stored wrapped in foil. Direct exposure samples were stored exposed to light. Indirect exposure samples were packaged in secondary packaging (carton) and exposed to light. [Table 6](#) shows representative study results for the 100 mg/mL DP lot 3-FIN-1475 where observed differences are boxed in.

**Reviewer comment:** The photostability studies (See section 3.2.P.8.3 Stability Data for more detail) showed that the DP is sensitive to light and changes in color, clarity, and purity (b) (4) - (b) (4) were observed. These changes were not observed when the DP was protected from light supporting the sponsor's claims that the (b) (4) packaging is sufficient to protect the DP from light. I agree with the sponsor's conclusions.

(b) (4)

**Reviewer comment:** The chemical resistance test was performed by the vial manufacturer; therefore, no data was provided by the Sponsor.

#### 3.2.P.2.4.2 Container Closure System Integrity (CCSI)

The CCSI study was used to confirm that the DP container is capable of preventing microbial contamination. Two main tests were used, (b) (4). See Section 3.2.P.2.5 (Microbial Attributes) below.

#### 3.2.P.2.4.3 Closure Suitability

The CCS for asfotase alfa drug product uses a (b) (4) 13 mm stopper (b) (4) (b) (4)

#### Physiochemical Testing

Rubber stoppers comply with USP<381> and Ph.Eur. 3.2.9. The manufacturer, (b) (4) (b) (4) tested the stoppers (b) (4) (b) (4)

(b) (4) All results met acceptance criteria.

**Reviewer comment:** *The tests were performed by the stopper manufacturer; therefore, no data was provided by the Sponsor.*

### **Extractable Evaluation**



**Reviewer comments:** *The sponsor used the results from the extractables studies to identify as the primary potential leachable compound and concluded that the remaining extracted compounds did not constitute a safety concern and did not need to be evaluated further.* (b) (4)



(b) (4)

(b) (4) *The evaluation of extractables on the stopper was performed appropriately. However, no information was provided regarding the extractable and leachable studies for the DP vials. Upon request from the Agency (3/6/2015), Alexion provided additional information to the BLA on 3/13/15 (SN0015).*

**Reviewer's Evaluation of Alexion Response 2a (SN0015 submitted on 3/13/15):**

*Alexion provided information regarding the extractable evaluation performed on the stopper in the form of chromatogram and tabular data.*

(b) (4)

(b) (4)

(b) (4) *The information provided is sufficient and is adequate.*

**Reviewer's Evaluation of Alexion Response 2b (SN0015 submitted on 3/13/15):**

*Alexion provided information regarding the extractable evaluation performed on the stopper and the 2 mL DP vial in the form of chromatogram and tabular. The data were similar to those of the stopper extractable studies with no new extractable compounds observed. The information provided in this response is sufficient and adequate and supports the sponsor's decision to select only (b) (4) as the compound to be controlled during the leachable studies.*

**Leachable Evaluation**

A 36 months leachable study is being conducted to evaluate the stopper used for the asfotase alfa container closure. Six DP batches (three each of 40 mg/mL and 100 mg/mL DP) were stored inverted at 2 – 8°C and tested at 0, 6, 12, 24, and 36 months and tested for (b) (4). The results (Table 8) of the 0, 6, and 12 months time interval show no detection of (b) (4) (b) (4)). Alexion commits to notify the Agency if any results at the subsequent time points are greater than the limit of quantitation (LOQ = 1.0 µg/mL).

**Table 8 Stopper Leachable Data**  
(Table 2 Section 3.2.P.2.4.3.3 in the BLA)

Concentration	Asfotase Alfa Drug Product Batches	Time Interval
100 mg/mL	3-FIN-1474	T=0, 6 M, 12 M
	3-FIN-1475	T=0, 6 M, 12 M
	3-FIN-1476	T=0
40 mg/mL	3-FIN-1482	T=0, 6 M, 12 M
	3-FIN-1483	T=0, 6 M, 12 M
	3-FIN-1730	T=0

(b) (4)

**Reviewer comments:** *Leachable evaluation looking only at (b) (4) is ongoing. The data presented showed that the level of (b) (4) is (b) (4) which is the LOD of the assay. The sponsor commits to notify the agency of any result that is greater than the limit of quantitation (b) (4). The ADI (b) (4) is (b) (4)). At the maximum dose of 6 mg/week for a 70 kg patient (maximum volume is 1 mL/injection), the highest level of (b) (4) would be (b) (4). This (b) (4) level is below the ADI and is acceptable.*

### 3.2.P.2.5 Microbiological Attributes [See DMPQ/BMAB's Review for details]

Asfotase alfa DP does not contain antimicrobial preservatives and it is manufactured to meet sterility requirements per USP (b) (4) and Ph. Eur. < (b) (4)

*The following is a summary of the information provided in the BLA. The microbiology reviewer (DMA) will perform a detailed review.*

#### Container Closure Integrity Study (CCIT)

CCIT was performed using vials identical to the commercial vial, stopper, and seal. Two tests were used: (b) (4)

(b) (4) In addition, following visual inspection (b) (4)  
18 vials (2 per test organism and 4 negative controls) were inoculated with (b) (4)  
(b) (4) of the following ATCC organisms

(b) (4)

(b) (4)

***Reviewer comments:** The CCIT was evaluated and the DMA microbiology reviewer will determine the acceptability of the analysis. The sponsor claims that all acceptance criteria of the study were met.*

#### 3.2.P.2.6 Compatibility with administration materials

The compatibility of the DP with administration materials was assessed using three types of needle and syringe systems (Table 9) used for SC administration. (b) (4)

**Reviewer comments:** *The results of the compatibility with administration materials assessment showed, for the most part (see exception below), no adverse impact in the concentration, purity, or enzymatic activity of the DP after being in contact with the product for up to 24 hours at 2 – 8 °C or (b) (4). The use of (b) (4) as a measure of purity is acceptable (b) (4)*

*(b) (4) During the compatibility assessment the sponsor saw one “outlier” result for the potency assay at t=8 hours for Lot 3-FIN-1747 at (b) (4). The potency result, (b) (4) was outside of the DP potency specification (b) (4). A laboratory investigation determined that this out of specification result was not due to the interaction with administration materials. An IR was sent on 3/6/15 requesting addition information regarding the out of specification result. Alexion*

*provided the information on 3/13/15 (SN0015). I agree that this result was an outlier based on the totality of the all the results presented. At 24 hours, the potency was back within DP specification and all the other potency results were within specification.*

*These studies are sufficient to support the package insert's information that once withdrawn from the vial, STRENSIQ should be administered within 1 hour.*

**Reviewer's Evaluation of Alexion Response 3 (SN0015 submitted on 3/13/15):**

*Alexion provided the memorandum of the laboratory investigation which looked at reagents, equipment, calculations, assay performance, training and documentation. The cause of the outlier was not determined but the investigation suggests that it might be an error during sample preparation. The sponsor's response is adequate.*

**3.2.P.3 Manufacture**

**3.2.P.3.1 Manufacturer(s)**

DP manufacturing sites and responsibilities are as follows;



DP testing sites and responsibilities are as follows;



Alexion Pharmaceuticals Inc.  
 Alexion Manufacturing Facility (ARIMF)  
 100 Technology Way  
 Smithfield, Rhode Island 02917  
 US  
 Food and Drug Administration Establishment  
 Identifier: 3006568549  
 Data Universal Numbering System(D.U.N.S):  
 794325824

Or

(b) (4)

Release Testing

(b) (4)

**Facility**

Alexion Pharmaceuticals Inc.  
 Alexion Manufacturing Facility (ARIMF)  
 100 Technology Way  
 Smithfield, Rhode Island 02917  
 US  
 Food and Drug Administration Establishment  
 Identifier: 3006568549  
 Data Universal Numbering System(D.U.N.S):  
 794325824

And

(b) (4)

**Responsibility**

Stability Testing:

(b) (4)

**Reviewer comment:** Multiple quality control labs were listed, Alexion Rhode Island site and 2 (b) (4) sites (b) (4) as performing drug product release testing for asfotase alfa. A comment

was sent to the sponsor on 4/17/15 for clarification for their strategy for drug product release testing, particularly the responsibility of the laboratories. Alexion provided a clarification on 4/30/15 (SN0026).

**Reviewer's Evaluation of Alexion Response 5 (SN0026 submitted on 4/30/15):**

The primary DP release testing site is the Alexion Rhode Island Manufacturing Facility (ARIMF). All DP release data submitted in the BLA were obtained from ARIMF. The secondary DP release testing site



Alexion did clarify the primary and the secondary DP release testing sites. The response is adequate.

**3.2.P.3.2 Batch Formula**

The DS is formulated to a concentration of 100 mg/mL asfotase alfa and stored at (b) (4). The 100 mg/mL DP presentation is filled from the 100 mg/mL DS (b) (4). The 40 mg/mL DP is produced by (b) (4) with formulation (b) (4) sodium phosphate, (b) (4) sodium chloride, (b) (4) at the DP manufacturing site (b) (4).

Each DP batch is manufactured from one DS batch while a single DS batch may be used to produce multiple DP batches.

**3.2.P.3.3 Description of Manufacturing Process and Process Controls**

The DP manufacturing process is shown in [Figure 1](#).

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***Overall Reviewer comment:** The data provided in this section show that the DP manufacturing process is validated and capable of performing within the pre-specified acceptance criteria. The quality attributes for all DP lots, including all microbial attributes were within specifications.*

(b) (4)

### **3.2.P.4 Control of Excipients**

#### **3.2.P.4.1 Specifications**

All excipients are added to the 100 mg/mL DP (b) (4) during DS manufacturing. For the 40 mg/mL DP, the 100 mg/mL DS is diluted using the same formulation (b) (4) during the drug substance manufacturing process. [Table 24](#) shows the quality control specifications for the DP excipients. A Certificate of Analysis is provided with each excipient.

**Table 24 Quality Control Specifications**  
(Table 1 Section 3.2.P.4.1 in the BLA)

Excipient	Test
Sodium chloride	Complies with current USP and Ph. Eur., and JP monographs
Dibasic sodium phosphate, (b) (4)	Complies with current USP and Ph. Eur. monographs
Monobasic sodium phosphate, (b) (4)	Complies with current USP and Ph. Eur. monographs

*Reviewer comment: All excipients comply with compendial methods (USP, Ph. Eur., or JP). Formulation is performed at BDS stage and therefore no new excipients are added to DP. There are no human or novel excipients in drug product.*

**3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures**

Not applicable.

**3.2.P.4.4 Justification of Specifications**

Not applicable.

**3.2.P.4.5 Excipients of Human or Animal Origin**

Not applicable.

**3.2.P.4.6 Novel Excipient**

Not applicable.

**3.2.P.5 Control of Drug Product**

**3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)**

The DP specifications and acceptance criteria are shown in the [Table 25](#):

**Table 25 100 mg/mL and 40 mg/mL DP Specifications**

(Table reproduced from Section 3.2.P.5.1, Tables 1 and 2 in the BLA)

	100 mg/mL Asfotase alfa	40 mg/mL Asfotase alfa
<b>Test</b>	<b>Acceptance criteria</b>	
Appearance (Visible Particles, Color, Clarity)	Few small translucent or white particles, may be present, Colorless to slightly yellow (b) (4) Clear, slightly opalescent or opalescent	
Osmolality	Osmolality (b) (4)	
pH	7.2 – 7.6	



(b) (4)

Endotoxin (LAL)			(b) (4)
Sterility			
Particulates			
Extractable Volume (Release test only)	80 mg/vial: Not Less Than 0.80 mL	12 mg/vial: Not Less Than 0.30 mL 18 mg/vial: Not Less Than 0.45 mL 28 mg/vial: Not Less Than 0.70 mL 40 mg/vial: Not Less Than 1.0 mL	
Container Closure Integrity	N/A (Meets Requirements)		

**Reviewer comment:** *The DP specifications include three specifications that are unique to DP, namely; sterility, particulate analysis, and extractable volume. The particulate analysis and extractable volume are appropriate DP specific USP tests. Sterility testing is reviewed by DMA. All other DP specifications are also DS specifications with the same acceptance criteria with two exceptions. DS has different acceptance criteria*

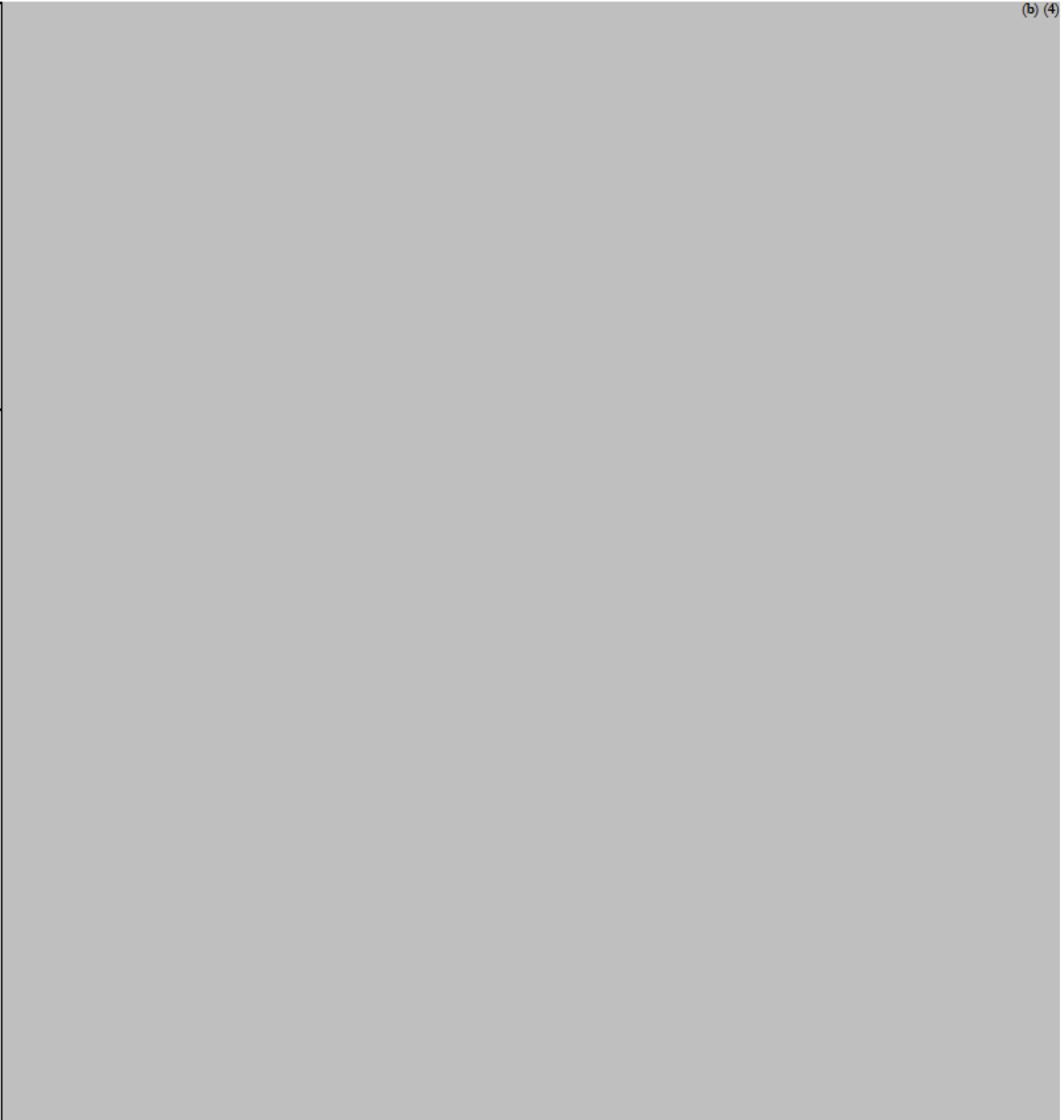
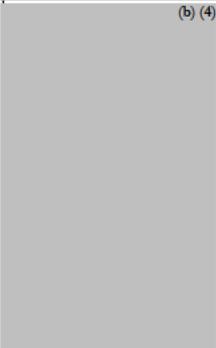
(b) (4)

(b) (4)



*Overall the DP specifications test a wide variety of quality attributes with justifiable acceptance criteria and are therefore suitable to ensure product quality.*

**Table 26 Detail summary of DP specification, lot ranges, and justifications**  
(Table reproduced from Section 3.2.S.4.5 Table 1, 3.2.P.5.6 Table 1, and 3.2.P.5.4 Tables 3 - 12, in the  
BLA)

Test	Requirements (Acceptance Criteria)	Range of Clinical Trial Material	Range of Process Validation/ Commercial lots	Justification of Specification and <i>Reviewer comments</i>
		<i>Information derived from the batch analyses provided by the Sponsor in the BLA.</i>		
Appearance (Visible Particles, Color, Clarity)	Few small translucent or white particles may be present, Colorless to slightly yellow Clear, slightly opalescent or opalescent			
Osmolality	 (b) (4)			
pH	7.2 – 7.6			

(b) (4)

				<p>(b) (4)</p>
<p>Sterility</p>				<p>The DP sterility specification was established according to compendial requirements.</p> <p><i>The acceptability of the sterility specification is reviewed by DMA. All DP lots met sterility specification of no growth.</i></p>
<p>Particulates</p>				<p>The DP particulates specification was established according to compendial requirements.</p> <p><i>This is acceptable per USP &lt;788&gt; requirements. However, (b) (4) (b) (4) were not characterized at release and on stability.</i></p>
<p>Extractable Volume<sup>1</sup> <sup>1</sup> Release test only</p>	<p>80 mg/vial: Not Less Than 0.80 mL</p>	<p>(b) (4)</p> <p>18 mg/vial: Not Less Than 0.45 mL 28 mg/vial: Not Less Than 0.70 mL 40 mg/vial: Not Less Than 1.0 mL</p>		<p>The DP extractable volume specifications were established according to compendial requirements.</p> <p><i>This is acceptable. All DP lots met specifications.</i></p>

**Reviewer comment:** *The acceptance criterion for appearance is lacking a range for how many small translucent or white particles are acceptable. No justification was provided for the lack of upper limit in the color of the solution.* (b) (4)

*Comments were sent to the sponsor on 4/17/15 for additional information. Alexion provided the requested information on 4/30/15 (SN0026).*

**Reviewer's Evaluation of Alexion Response 6a (SN0026 submitted on 4/30/15):**

*Alexion claims that the quantitation of particles is difficult. Currently they are using a control standards (b) (4). Regarding color specification of DP, Alexion clarified (b) (4). The current DP color specification ranges from slightly yellow (b) (4) to colorless (b) (4). The sponsor responses are adequate.*

(b) (4)



### **3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures**

A summary of the analytical methods were provided. For the DP analytical procedures that are identical to that of DS were described in Section 3.2.S.4.2 (DS review by Joslyn Brunelle).



(b) (4)

(b) (4) **Bioburden USP** (b) (4) **Ph. Eur.** (b) (4)

**Reviewer comment:** *Review of this assay is deferred to the DMA reviewer.*

#### **Release and Stability Analytical Procedures**

**Sterility USP** < (b) (4) **Ph. Eur.** (b) (4)

**Reviewer comment:** *Review of this assay is deferred to the DMA reviewer.*

**Particulates USP** < (b) (4) **Ph. Eur.** (b) (4)

(b) (4) particles are measured (b) (4) by a compendial method, USP <788>.

**Reviewer Comments:** *This compendial method is acceptable.*

**Extractable Volume USP <1>, Ph. Eur. 2.9.17**

Extractable volume is measured through extraction by a compendial method, USP <1>.

**Reviewer Comments:** *This compendial method is acceptable.*

The validated product-specific methods have been transferred from the ARIMF quality control laboratories to the (b) (4) quality control laboratories (b) (4), (b) (4). Appropriate transfer criteria were specified in transfer protocols where multiple DP batches were compared to results from the ARIMF Quality Control laboratories. Compendial methods were not formally transferred to the (b) (4) laboratories but were qualified for their intended use.

(b) (4)

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**3.2.P.5.4 Batch Analyses**

Batch analysis data were provided for all DP lots manufactured through the time of the BLA submission. Summary of the batches included in the batch analysis are shown below in Tables [27](#) and [28](#).

**Table 27 Summary of DP Commercial Process Batches (100 mg/mL)**  
**(Table 1 Section 3.2.P.4.1 in the BLA)**

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 28 Summary of DP Commercial Process Batches (40 mg/mL)**  
 (Table 2 Section 3.2.P.4.1 in the BLA)

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

***Reviewer comment:** The release results for both the 40mg/mL and the 100mg/mL DP batches met the proposed commercial acceptance criteria. The data were reviewed and are sufficient to confirm the consistency of the manufacturing process.*

**3.2.P.5.5 Characterization of Impurities**

The sponsor referred to the DS section 3.2.S.3.2, Impurities (refer to DS review by Joslyn Brunelle), for information on impurities. The sponsor stated that no new impurities have been identified for the drug.

**3.2.P.6 Reference Standards or Materials**

The reference material for DP is identical to that of DS. Refer to Section 2.3.S.5 Reference Standards or Materials for more detail (refer to DS review by Joslyn Brunelle).

**3.2.P.7 Container Closure System**

DP CCS consists of a 2 mL USP/Ph. Eur. Type I glass vial with a (b) (4) rubber stopper, (b) (4) and aluminum seal (b) (4) flip-off cap. This CCS is used for both the 40 mg/mL and 100 mg/mL DP

**Vial:**

The vial is manufactured (b) (4). They are constructed of Type I (b) (4) glass (USP/Ph. Eur.) with 13 mm neck diameter. (b) (4)

(b) (4)

**Stopper:**

The stopper is manufactured and supplied (b) (4). It is constructed with

(b) (4) rubber,

(b) (4)

(b) (4)

**Seal:**

The seal is manufactured and supplied (b) (4). The (b) (4) aluminum seals comes with a (b) (4) flip-off cap.

(b) (4)

(b) (4)

(b) (4)

See Section [3.2.P.2.4 Container Closure System](#) for container suitability, and extractables and leachables studies.

**Reviewer comment:** *Certificates of Analysis and technical drawings for the CCS components were provided. Each component must meet material specifications and incoming requirements (b) (4). The container closure system is appropriate for long-term storage of the DP based on suitability studies and long-term stability data.*

**3.2.P.8 Stability**

**3.2.P.8.1 Stability Summary and Conclusion**

The stability program for the DP consists of stress studies, long-term (2 - 8°C) and accelerated (b) (4) storage. The stability-indicating methods used were potency methods, general property tests, and safety tests (sterility and endotoxin). All DP batches manufactured at (b) (4) scale are included to support the shelf-life. The data presented show that the DP is stable for up to (b) (4) months when stored at 2 - 8°C. The sponsor proposes a 24-month shelf-life for the 40 mg/mL and 100 mg/ml DP concentrations stored at 2 – 8 °C. [Table 32](#) and [Table 33](#) show the DP lots used in the long-term (2 – 8°C) stability studies.

**Table 32 Long-Term Stability (2 – 8°C): 100 mg/mL DP Lots**  
(Table 2 Section 3.2.P.8.1 in the BLA)

Asfotase Alfa Drug Product Lot	Date of Manufacture	Asfotase Alfa Drug Substance Batch	Strength (mg/vial), Target Fill Volume (mL)	Orientation	Time Points Completed (and pending)
FIL094H01	(b) (4)	PUR012H01	(b) (4)	Upright Inverted	(b) (4)
FIL130J01		169446		Upright Inverted	
3-FIN-1326		260464		Inverted	
3-FIN-1474 <sup>1</sup>		280897		Upright Inverted	
3-FIN-1475 <sup>1</sup>		284989		Upright Inverted	
3-FIN-1476 <sup>1</sup>		332604		Upright Inverted	
3-FIN-1831 <sup>1</sup>		333366		Upright Inverted	
140168		381604		Upright Inverted	

<sup>1</sup> Drug product process validation lot

**Table 33 Long-Term Stability (2 – 8°C): 40 mg/mL DP Lots**  
**(Table 4 Section 3.2.P.8.1 in the BLA)**

Asfotase Alfa Drug Product Lot	Date of Manufacture	Asfotase Alfa Drug Substance Batch	Strength (mg/vial), Target Fill Volume (mL)	Orientation	Time Points Completed (and pending)
FIL094G01	(b) (4)	PUR012F01	(b) (4)	Upright Inverted	(b) (4)
FIL094G02		PUR012G01		Upright Inverted	
3-FIN-0976		169446		Inverted	
3-FIN-1348		260464		Inverted	
3-FIN-1486		280897		Upright Inverted	
3-FIN-1485 <sup>1</sup>		259248		Upright Inverted	
3-FIN-1483 <sup>1</sup>		259248		Upright Inverted	
3-FIN-1729 <sup>1</sup>		338971		Upright Inverted	
3-FIN-1747 <sup>1</sup>		338971		Upright Inverted	
3-FIN-1484 <sup>1</sup>		335332		Upright Inverted	
3-FIN-1730 <sup>1</sup>		335332		Upright Inverted	
140165		381602		Upright Inverted	

<sup>1</sup> Drug product process validation lot

**Reviewer comment:** *The data provided support the DP 24-month shelf-life at 2 – 8°C. Determination of the shelf-life was done appropriately using assays and testing frequency which are consistent with ICH guidelines. The 24 month shelf-life at 2 – 8°C for Asfotase Alfa DP is acceptable. DP stability is also evaluated to support shipping validation (see Section 3.2.P.3.5.6 above and in the BLA).*

**3.2.P.8.2 Post-Approval Stability Commitment**

The post approval stability commitment consists of storing DP vials in (b) (4) light-protecting cartons, both upright and inverted positions. The stability protocol requires storing of DP at long-term (2 – 8°C) and accelerated (b) (4) conditions and testing adhering to DP specifications (Section 3.2.P.5.1 Specification). Alexion commits to the following:

- “The first three commercial lots at each drug product concentration shall be placed on stability to confirm expiry.”
- “No less than one lot of commercial product per year at each drug product concentration and worst case fill volume configuration for which product is manufactured in a given year.”
- “Results of post-approval stability studies will be reported in periodic updates requested by regulatory authorities.”
- “Any confirmed stability result outside of the approved drug substance specification will be thoroughly investigated for impact to drug substance and drug product lots.”

The proposed post approval stability commitment protocols for the long-term (2 – 8°C) and the accelerated (b) (4) conditions are provided in Table 34 and Table 35, respectively.

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### **3.2.A Appendices Table of Contents**

#### **3.2.A.1 Facilities and Equipment**

*Reviewer comment: Review of the facilities and equipment are deferred to the OPF/DIA/IABI reviewer.*

#### **3.2.A.3 Novel Excipients**

None

### **3.2.R Regional Information** (U.S.A.)

#### **3.2.R.1 Executed Batch Records**

The submission included executed batch records corresponding to process validation lots 3-FIN-1476, 3-FIN-1747, 3-FIN-1485, 3-FIN-1484, and 3-FIN-1730.

### **3.2.R.2 Method Validation Package**

Refer to section 3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures.

### **3.2.R.3 Comparability Protocols**

None

**BLA STN 125513**

**Product USAN name  
Asfotase alfa**

**Manufacturer  
Alexion**

**Joslyn Brunelle -DS  
Gunther Boekhoudt -DP  
Cris Ausin - TL  
Michele Dougherty - RC**

**OBP CMC Review Data Sheet**

1. **BLA#:** STN 125513
2. **REVIEW DATE:** August 5, 2015
3. **PRIMARY REVIEW TEAM:**  
**Medical Officer:** Carla Epps  
**Pharm/Tox:** Dinesh Gautam  
**Product Quality Team:** Joslyn Brunelle (DS), Gunther Boekhoudt (DP), Mate Tolnay (Fc portion only), Fred Mills (Immunogenicity)  
**BMT or Facilities:** Candace Gomez-Broughton and Steven Fong  
**Clinical Pharmacology:** Christine Hon, Justin Earp  
**Statistics:** Ben Vali  
**OBP Labeling:** Jibril Abdus-Samad  
**RPM:** Lisa Pitt and Kevin Bugin
4. **MAJOR GRMP DEADLINES**  
**Received:** December 23, 2014  
**Filing Meeting:** January 21, 2015  
**Mid-Cycle Meeting:** June 24, 2015  
**Primary Review Due:** August 8, 2015  
**Late Cycle Meeting:** September 2, 2015  
**Wrap-Up Meeting:** September 29, 2015  
**CDTL Memo Due:** September 25, 2015  
**PDUFA Action Date:** November 23, 2015
5. **COMMUNICATIONS WITH SPONSOR AND OND:**

<b>Communication/Document</b>	<b>Date</b>
CMC Pre-BLA Meeting	11/26/2013
T-con with EMA	12/3/2014
Immunogenicity Pre-BLA Meeting	1/14/2014
Information Request #1	5/15/2014
Pre-BLA Meeting	7/8/2014
Information Request #2	11/26/2014
Information Request #3	1/27/2015
Team Meeting	2/19/2015
74-day Letter (Microbiology IR)	2/27/2015
T-con with Sponsor	3/5/2015
Information Request #4	3/6/2015
Team Meeting	3/11/2015
Information Request #5	4/17/2015
Information Request #6	4/20/2015

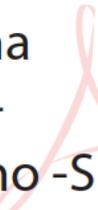
Team Meeting	4/21/2015
T-con with EMA	4/29/2015
Information Request #7	5/22/2015
Team Meeting	6/3/2015
Information Request #8	6/22/2015
Midcycle Meeting	6/24/2015
T-con with Sponsor	7/24/2015
Information Request #9	7/24/2015

6. **SUBMISSION(S) REVIEWED:**

Submission	Date Received	Review Completed (Yes/No)
STN 125513/0	3/31/2014	Yes
STN 125513/0002 (response to IR #1)	5/15/2014	Yes
STN 125513/0004 (response to IR #1)	7/30/2014	Yes
STN 125513/0005 (response to IR #2)	12/19/2014	Yes
STN 125513/0006 (final rolling submission)	12/23/2014	Yes
STN 125513/0011 (response to IR #3)	2/12/2015	Yes
STN 125513/0014 (response to IR #3, IR#4, and 74-day Letter)	3/13/2015	Yes
STN 125513/0017 (response to 74-day letter)	3/30/2015	Yes
STN 125513/0025 (response to 74-day letter, IR #5, and IR#6)	4/30/2015	Yes
STN 125513/0029 (response to IR#3 and IR#7)	6/1/2015	Yes
STN 125513/0031 (response to IR#5, IR#6, and IR#8)	6/30/2015	Yes
STN 125513/0035 (response to 74-day Letter)	7/27/2015	Yes
STN 125513/0036 (response to IR#5)	7/31/2015	Yes

**7.ADMINISTRATIVE**

Signature Block

Name and Title	Signature and Date
<p>Michele Dougherty, Ph.D. Acting Review Chief Office of Biotechnology Products Division of Biotechnology Review and Research IV</p>	<p><b>Michele Dougherty -S</b>             Digitally signed by Michele Dougherty -S            DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0010556865, cn=Michele Dougherty -S            Date: 2015.08.06 14:34:25 -04'00'</p>
<p>Cristina Ausin-Moreno, Ph.D. Acting Team Leader Office of Biotechnology Products Division of Biotechnology Review and Research IV</p>	<p><b>Cristina Ausin-moreno -S</b>             Digitally signed by Cristina Ausin-moreno -S            DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011707091, cn=Cristina Ausin-moreno -S            Date: 2015.08.06 12:56:47 -04'00'</p>
<p>Joslyn Brunelle, Ph.D. Drug Substance Primary Reviewer Office of Biotechnology Products Division of Biotechnology Review and Research IV</p>	<p><b>Joslyn K. Brunelle -S</b>             Digitally signed by Joslyn K. Brunelle -S            DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000396541, cn=Joslyn K. Brunelle -S            Date: 2015.08.06 11:34:08 -04'00'</p>

**TABLE OF CONTENTS**

3.2.S.1.2 Structure .....	6
3.2.S.1.3 General Properties .....	8
3.2.S.2 Manufacture.....	8
3.2.S.2.1 Manufacturer(s).....	8
3.2.S.2.2 Description of Manufacturing Process and Process Controls .....	8
3.2.S.2.2.1 Batch and Scale Definition.....	8
3.2.S.2.2.2 Cell Culture and (b) (4).....	10
3.2.S.2.2.3 Purification and Modification Reactions .....	15
3.2.S.2.2.4 Filling, Storage, and Transportation.....	24
3.2.S.2.3 Control of Materials .....	25
3.2.S.2.3.3 Source, History, and Generation of the Cell Substrate .....	25
3.2.S.2.3.4 Cell Banking System, Characterization, and Testing .....	26
3.2.S.2.4 Controls of Critical Steps and Intermediates .....	32
3.2.S.2.5 Process Validation and/or Evaluation .....	43
3.2.S.2.6 Manufacturing Process Development .....	45
3.2.S.3 Characterization .....	48
3.2.S.3.1 Elucidation of Structure and Other Characteristics .....	48
3.2.S.4 Control of Drug Substance .....	66
3.2.S.4.1 Specification and 3.2.S.4.5 Justification of Specification.....	66
3.2.S.4.2 Analytical methods and 3.2.S.4.3 Validation of methods.....	73
3.2.S.4.4 Batch Analysis .....	107
3.2.S.5 Reference Standard .....	108
3.2.S.6 Container Closure .....	115
3.2.S.7 Stability.....	116
3.2.S.7.1 Stability summary and conclusions .....	116
3.2.S.7.2 Post approval stability protocol and stability commitment.....	117
3.2.A.2 Appendix Adventitious Agents Safety Evaluation.....	121

## DESCRIPTION OF DRUG SUBSTANCE

### S. DRUG SUBSTANCE

#### 3.2.S.1.2 Structure

Asfotase alfa is a soluble IgG1 Fc fusion glycoprotein composed of 2 identical polypeptide chains. Each polypeptide chain has 3 components: human tissue non-specific alkaline phosphatase (TNSALP), human immunoglobulin IgG1 Fc domain, and a deca-aspartate peptide (D10) used as a bone targeting domain. There are 2 disulfide bonds that link the polypeptide chains. In addition, each polypeptide chain contains (b) (4)

(b) (4) The amino acid sequence and graphic representation of the asfotase alfa structure is below in Figure 1.

(b) (4)



**Figure 1: Asfotase Alfa Amino Acid Sequence**



(b) (4)

(b) (4)

### 3.2.S.1.3 General Properties

**Table 1: General Properties of Asfotase Alfa**

Property	Result
Number of Amino Acids <sup>1</sup>	(b) (4)
Theoretical Molecular Weight <sup>2</sup>	(b) (4)
Chemical Formula	(b) (4)
Isoelectric (pI) range	(b) (4)
Extinction Coefficient at	(b) (4)

The biological function is due to the tissue non-specific alkaline phosphatase (TNSALP) portion of the protein. TNSALP is an enzyme that catalyzes the hydrolysis of phosphomonoesters with release of inorganic phosphate and alcohol. Enzymatic activity is determined using a synthetic substrate (nitrophenyl phosphate - pNPP) and a natural substrate (pyrophosphate - PPi).

**Table 2: Specific Activity and Kinetic Data for Asfotase Alfa Drug Substance**

Property	Result
Specific Activity	(b) (4)
Alkaline Phosphatase Enzyme Kinetic Parameters	(b) (4)
Hydroxyapatite (HA) Binding	(b) (4)

### 3.2.S.2 Manufacture

#### 3.2.S.2.1 Manufacturer(s)

Manufacture of Drug Substance, Raw material testing, (b) (4) testing:

(b) (4)

Storage of Cell Banks, Release and Stability Testing:

Alexion Pharmaceuticals Inc.

Alexion Manufacturing Facility (ARIMF)

100 Technology Way

Smithfield, RI 02917

FEI #3006568549

#### 3.2.S.2.2 Description of Manufacturing Process and Process Controls

##### 3.2.S.2.2.1 Batch and Scale Definition

Each Drug Substance (DS) batch is manufactured

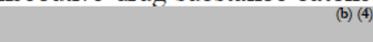
(b) (4)

(b) (4)

(b) (4)



### 3.2.S.2.5 Process Validation and/or Evaluation

Process validation was performed on four consecutive drug substance batches manufactured between 2012-2013. The manufacturing process was <sup>(b) (4)</sup> as outlined above in Section 3.2.S.2.2.

(b) (4)



(b) (4)

**Reviewer comment:**

*The sponsor provided the data for all process parameters for all four process validation batches (332604, 333366, 335332, 338971). Overall, the data is within the acceptable ranges for each process parameter.*

(b) (4)



(b) (4)

Overall, the manufacturing history at the (b) (4) scale includes approximately 19 DS lots. This is significantly more experience than the Agency would expect a sponsor of an Orphan Drug (with a small patient population) to have at the BLA stage. This demonstrates that the drug substance manufacturing process (b) (4) can consistently produce asfotase alfa drug substance. In summary, I conclude that process validation is acceptable.

**3.2.S.2.6 Manufacturing Process Development**



(b) (4)

**Table 11: Batch Summary for Comparability Evaluation of (b) (4) Asfotase Alfa Drug Substance**

Manufacturing Scale	Process	Batch	Date of Manufacture
(b) (4)	(b) (4)	PUR018H04	(b) (4)
(b) (4)	(b) (4)	PUR018J02	(b) (4)
(b) (4)	(b) (4)	PUR018J05	(b) (4)
(b) (4)	(b) (4)	169466	(b) (4)
(b) (4)	(b) (4)	229329	(b) (4)
(b) (4)	(b) (4)	260464	(b) (4)

After further manufacturing experience had been obtained with the (b) (4) process, additional pre-process validation lots were evaluated. In total, data on five (b) (4) process lots and seven (b) (4) process lots was submitted to the IND 100619, amendment 107.

**Reviewer comment:**

The information was reviewed at the IND stage and the overall conclusion was that the (b) (4) and (b) (4) processes were comparable.

(b) (4) The comparability data is also found in Section 3.2.S.2.6 of this BLA. As noted below in Table 4, both the (b) (4) processes were used in the clinical studies.

A list of drug substance lots used in non-clinical studies can be found in Table 3 and a list of drug substance batches used in clinical trials can be found in Table 4.

**Table 3: Asfotase Alfa Drug Substance Lot Usage for Non-Clinical Studies**

Lot	Study	Study Type
259248 <sup>1</sup>	902237, 902231, 902238	Reproductive and Developmental Toxicology Studies
169466 <sup>1</sup>	902230, 902233, 902234, 902480, 902235, 902236	
PUR012G01 <sup>2</sup> , FIL094G02 <sup>2</sup> , PUR012G02 <sup>2</sup>	670315	GLP Safety and Toxicology Studies
PUR012F01 <sup>2</sup>	1007-2491, 670388, 1007-2501	
PUREA2 No. 3 (b) (4) <sup>3</sup> , PUR012F01 <sup>2</sup>	70552	
PUREA2 No. (1+2) (b) (4)	670314, 1007-1503	
080229 <sup>3</sup>	PK2008021951	Non-GLP Safety Studies
070629 <sup>3</sup>	70385, 2007-0693, ALP-PT-10	

<sup>3</sup> Development Scale Material

**Table 4: Asfotase Alfa Drug Substance Lot Usage for Clinical Studies**

Drug Substance Batch Number	Drug Substance Date of Manufacture	Drug Substance Manufacturer & Cell Culture Scale	Drug Product Batch Number	Drug Product Date of Manufacture	Drug Product Manufacturer	Clinical Study
PUR012F01	(b) (4)	(b) (4)	FIL094G01	(b) (4)	(b) (4)	ENB-001-08, ENB-002-08
PUR012G01			FIL094G02			ENB-001-08, ENB-002-08, ENB-003-08
PUR012H01			FIL094H01			ENB-006-09
PUR018H01			FIL110H01			ENB-006-09, ENB-008-10
PUR018H02			FIL110H02			ENB-006-09, ENB-008-10, ENB-009-10
PUR012H03			FIL094H03			ENB-002-08, ENB-003-08
PUR018H04			FIL110J01			ENB-008-10, ENB-010-10
PUR018J01			FIL110J02			ENB-008-10, ENB-009-10
PUR018J02			FIL110J03			ENB-008-10, ENB-009-10
PUR018J04			FIL110J04			ENB-008-10, ENB-009-10
PUR018J05			FIL094J01			ENB-003-10, ENB-008-10, ENB-010-10
PUR018K01			3-FIN-1177			ENB-008-10, ENB-009-10
169466			FIL130J01			ENB-008-10, ENB-009-10
			3-FIN-0975			ENB-008-10, ENB-009-10
			3-FIN-0976			ENB-003-08, ENB-008-10, ENB-009-10
229329			3-FIN-1176			ENB-008-10, ENB-009-10
259248			3-FIN-1485			ENB-003-10, ENB-010-10
			3-FIN-1483			ENB-003-10, ENB-010-10
260464			3-FIN-1348			ENB-003-08, ENB-008-10, ENB-009-10, ENB-010-10
			3-FIN-1326			ENB-008-10, ENB-009-10
			3-FIN-1398			ENB-003-10, ENB-010-10

Drug Substance Batch Number	Drug Substance Date of Manufacture	Drug Substance Manufacturer & Cell Culture Scale	Drug Product Batch Number	Drug Product Date of Manufacture	Drug Product Manufacturer	Clinical Study
280897	(b) (4)	(b) (4)	3-FIN-1486	(b) (4)	(b) (4)	ENB-003-08, ENB-008-10, ENB-009-10, ENB-010-10
			3-FIN-1474			ENB-003-08, ENB-008-10, ENB-009-10, ENB-010-10
284989			3-FIN-1475			ENB-003-08, ENB-008-10, ENB-009-10, ENB-010-10
332604			3-FIN-1476			ENB-003-08, ENB-008-10, ENB-009-10, ENB-010-10
335332			3-FIN-1484			ENB-003-08, ENB-008-10, ENB-009-10, ENB-010-10
			3-FIN-1730			ENB-003-08, ENB-008-10, ENB-009-10, ENB-010-10
333366			3-FIN-1831			ENB-003-08, ENB-008-10, ENB-009-10, ENB-010-10

(b) (4)

**Reviewer comment:**

Note that both the (b) (4) lots were used in the clinical studies.

The formulation (b) (4) composition has remained unchanged during development and clinical manufacturing. The formulation (b) (4) is (b) (4) sodium phosphate, (b) (4) sodium chloride, (b) (4). The bulk drug substance is 100mg/mL protein concentration. The formulation was designed based on (b) (4). (b) (4) (b) (4) the sponsor wanted to avoid any excipient related issues with a drug meant for subcutaneous injection. Sodium chloride was used to (b) (4). Drug substance stability was evaluated (b) (4).

**Reviewer comment:**

The stability data (reviewed in section 3.2.S.7) indicates that the product is stable for up to 24 months when stored at 2-8 °C. Therefore, there are no issues with the formulation (b) (4).

### 3.2.S.3 Characterization

#### 3.2.S.3.1 Elucidation of Structure and Other Characteristics

Characterization studies used batch 260464 (b) (4) to evaluate asfotase alfa (b) (4)

**Reviewer comment:**

The BLA provides complete characterization for only one lot (260464) of the (b) (4) scale. However, the comparability study between the (b) (4) scales submitted under the IND 100619 was very extensive. Overall, the comparability study included release testing, the majority of the extended characterization assays summarized in this review, and forced degradation studies (b) (4). The study included 5 lots from the (b) (4) process and 5 lots from the (b) (4) process. The data can be found in the manufacturing process development section 3.2.S.2.6.

The Fc portion will be reviewed by Mate Tolnay. One of the concerns with an Fc region is that it could activate the complement system. The FDA requested that Alexion develop an (b) (4) assay to assess the potential for complement activation; this will be a postmarketing requirement. See Mate's Review in Panorama.

The identity of asfotase alfa was analyzed using 5 different analytical methods. (b) (4)

**Reviewer comment:**

(b) (4)

(b) (4) Overall, Alexion followed the Agency's recommendations and the assays appear adequate to analyze biological activity of asfotase alfa. More detailed information on the assay validation for release and stability testing can be found in Section 3.2.S.4.2.

*Of note, the number of lots tested using the physiologically relevant substrate is limited. Therefore, the data with which to set the specification for this assay is limited. The Agency acknowledged this during the CMC meeting in November 2013.*

*In summary, the characterization of asfotase alfa is adequate. Where appropriate, orthogonal methods were used to evaluate asfotase alfa characteristics.*

### 3.2.S.3.2 Impurities

The following product related impurities have been observed as summarized below in Table 45.

**Table 45: Summary of Asfotase Alfa Product Related Impurities**

Impurity	Analytical Method
(b) (4)	

**Reviewer comment:**

Product related impurities are monitored at release and stability. (b) (4)

(b) (4)

Eleven potential (b) (4) impurities were identified in the asfotase alfa manufacturing process.

(b) (4)

(b) (4) Based on an impurity clearance assessment using drug substance batches 280897 and 284989, Alexion concluded that the impurities pose minimal risk to patient safety and no routine testing is necessary. This assessment was based on the impurity safety factor (ISF) method. It is based on worst case assumptions ( (b) (4)

(b) (4)

(b) (4)

**Reviewer comment:**

*Alexion has demonstrated that either very low levels of impurities are present*

(b) (4)

(b) (4)

(b) (4)



(b) (4)

*Overall, I agree with the sponsor's assessment that no further (b) (4) analysis or acceptance criteria (b) (4) are necessary*

(b) (4)

### 3.2.S.4 Control of Drug Substance

#### 3.2.S.4.1 Specification and 3.2.S.4.5 Justification of Specification

**Table 1: Asfotase Alfa Drug Substance Clinical and Proposed Commercial Specifications**

Test	Clinical Acceptance Criteria	Proposed Commercial Acceptance Criteria Presented in Original BLA	Updated Proposed Commercial Acceptance Criteria
Appearance (Visible Particles, Color, Clarity)	(b) (4) Clear, slightly opalescent or opalescent	Few small translucent or white particles, Colorless to slightly yellow (b) (4) Clear, slightly opalescent or opalescent	Few small translucent or white particles may be present, Colorless to slightly yellow (b) (4) Clear, slightly opalescent or opalescent
Osmolality	(b) (4)		
pH	7.2 – 7.6	7.2 – 7.6	7.2 – 7.6

(b) (4)

(Continued)



(b) (4)

**Reviewer comments:**

*This section includes my analysis of Alexion's proposed specifications. I included control charts/graphs that Alexion provided in their submission in order to illustrate the ranges used in clinical studies, where appropriate.*

1.



(b) (4)

(b) (4) *The sponsor states that "trending of release results is reviewed on an annual basis. Alexion commits that the drug substance specification will be reevaluated after data from 30 batches using the (b) (4) process is available and will be (b) (4) further if appropriate." This is acceptable.*

2. *March 13, 2015 amendment, Alexion agreed to revise the peptide mapping specification as below. This is acceptable.*



(b) (4)

(b) (4)

#### 3.2.S.4.4 Batch Analysis

There are 12 drug substance lots from the (b) (4) scale and 11 drug substance lots from the (b) (4) scale used in clinical studies. Overall, there is release data from 16 lots of the (b) (4) (commercial) scale.

***Reviewer comment:***

*This is covered under Section 3.2.S.4.1 where the specifications are evaluated.*

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**Reviewer comment:**

The sponsor provided stability data for its previously used reference standards (b) (4), (b) (4). The data support an initial 2 year expiry, (b) (4). This is acceptable.

### 3.2.S.6 Container Closure

The drug substance container closure is

(b) (4)

(b) (4)

**Reviewer comment:**

*I agree with the sponsor's assessment; the leachable data indicates the risk to the patient is low. The drug substance container closure is acceptable. (b) (4) containers are commonly used in manufacturing of biologics.*

### 3.2.S.7 Stability

#### 3.2.S.7.1 Stability summary and conclusions

Stability studies for drug substance include long term storage at (b) (4) and accelerated conditions (b) (4)

(b) (4) Table 2 and 3 summarize the batches of DS placed on stability. In summary, the evaluation includes 10 drug substance batches (b) (4) scale) (b) (4) (5 of these batches have been evaluated (b) (4)). The sponsor is requesting a (b) (4) shelf-life for drug substance.

**Table 2: Long-Term Stability (b) (4) Batches Asfotase Alfa Drug Substance**

Asfotase Alfa Drug Substance Batch	Date of Manufacture	Scale	Container/Orientation	Time Points Completed (and pending)
PUR018H04 <sup>1</sup>	(b) (4)	(b) (4)	(b) (4)	(b) (4)
169466	(b) (4)	(b) (4)	(b) (4)	(b) (4)
259248	(b) (4)	(b) (4)	(b) (4)	(b) (4)
260464	(b) (4)	(b) (4)	(b) (4)	(b) (4)
280897	(b) (4)	(b) (4)	(b) (4)	(b) (4)
284989	(b) (4)	(b) (4)	(b) (4)	(b) (4)
332604 <sup>2</sup>	(b) (4)	(b) (4)	(b) (4)	(b) (4)
333366 <sup>2</sup>	(b) (4)	(b) (4)	(b) (4)	(b) (4)
335332 <sup>2</sup>	(b) (4)	(b) (4)	(b) (4)	(b) (4)
338971 <sup>2</sup>	(b) (4)	(b) (4)	(b) (4)	(b) (4)
341981	(b) (4)	(b) (4)	(b) (4)	(b) (4)
379564	(b) (4)	(b) (4)	(b) (4)	(b) (4)
381602	(b) (4)	(b) (4)	(b) (4)	(b) (4)
381604	(b) (4)	(b) (4)	(b) (4)	(b) (4)

<sup>1</sup> (b) (4) drug substance data presented in Section 3.2.S.7.3 Drug Substance Stability Data but not included in evaluation of shelf-life.

<sup>2</sup> Drug substance process validation batch

**Table 3: Accelerated Stability (b) (4) Batches Asfotase Alfa Drug Substance**

Asfotase Alfa Drug Substance Batch	Date of Manufacture	Scale	Container/Orientation	Time Points Completed (and pending)
PUR018H04 <sup>1</sup>	(b) (4)	(b) (4)	(b) (4)	(b) (4)
169466	(b) (4)	(b) (4)	(b) (4)	(b) (4)
259248	(b) (4)	(b) (4)	(b) (4)	(b) (4)
260464	(b) (4)	(b) (4)	(b) (4)	(b) (4)
280897	(b) (4)	(b) (4)	(b) (4)	(b) (4)
284989	(b) (4)	(b) (4)	(b) (4)	(b) (4)
332604 <sup>2</sup>	(b) (4)	(b) (4)	(b) (4)	(b) (4)
333366 <sup>2</sup>	(b) (4)	(b) (4)	(b) (4)	(b) (4)
335332 <sup>2</sup>	(b) (4)	(b) (4)	(b) (4)	(b) (4)
379564	(b) (4)	(b) (4)	(b) (4)	(b) (4)
381602	(b) (4)	(b) (4)	(b) (4)	(b) (4)
381604	(b) (4)	(b) (4)	(b) (4)	(b) (4)
411607	(b) (4)	(b) (4)	(b) (4)	(b) (4)

<sup>1</sup> (b) (4) drug substance data presented in Section 3.2.S.7.3 Drug Substance Stability Data but not included in evaluation of shelf-life.

<sup>2</sup> Drug substance process validation batch

Drug substance stability program test methods include appearance, osmolality, pH, (b) (4)

(b) (4)

(b) (4) bioburden, endotoxin.

(b) (4)

**Reviewer comment:**

The data supporting real time stability is very extensive. I conclude the data support a (b) (4) shelf-life for drug substance stored at (b) (4)

Note that forced degradation studies were performed on 100mg/mL drug product batches. The DS and DP are both at the same 100mg/mL concentration and formulation. DP manufacturing consists of a (b) (4), so this is acceptable. See section 3.2.P.8 for more information on the forced degradation studies.

**3.2.S.7.2 Post approval stability protocol and stability commitment**

The following is copied directly from the submission:

The following commitments for post approval stability testing are given:

- The first three commercial batches shall be placed on stability to confirm expiry.
- No less than one batch of commercial product per year per manufacturing facility in which product is manufactured will be tested according to the post approval stability protocol.
- Results of post-approval stability studies will be reported in the Annual Report (US) or in periodic updates requested by regulatory authorities.
- Any confirmed stability result outside of the approved drug substance specification will be thoroughly investigated for impact to drug substance and drug product lots.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Center for Drug Evaluation and Research – Food and Drug Administration  
Office of Biotechnology Products / Office of Pharmaceutical Quality

BLA: 125513  
DATE: July 10, 2015  
FROM: Mate Tolnay, Ph.D. LIB/OBP/DBRR IV  
THROUGH: Gerald Feldman, Ph.D. Chief, LIB, OBP/DBRR IV  
PRODUCT: STRENSIQ™ (Asfotase alfa)

**Summary and recommendation**

Asfotase alfa contains a functional IgG1 Fc region which can potentially engage and activate the complement system. The complement activation assay used by Alexion, considered insensitive by FDA, detected no complement activation. Alexion was advised to directly compare the complement activating capacity of asfotase alfa to that of human IgG1. FDA noted a specific assay format that could be used. Alexion stated the feasibility of such an assay will be assessed and committed to provide an update by end of 3Q of 2015. A PMC to compare the complement activating capacity of asfotase alfa to that of human IgG1 is recommended. If asfotase alfa binds complement more strongly than human IgG1, further studies might be necessary.

*The following review consists of selected text edited from the original IND submission. All Tables and Figures are copied from the submission, and then edited. Reviewer’s comments are distinguished by use of italic font.*

**3.2.S.3.1 Elucidation of Structure and Other Characteristics**

**1.3. Immunochemical Properties**

Asfotase alfa contains an intact Fc region and can potentially bind to Fc receptors and thereby activate the complement system. The potential of asfotase alfa to activate complement in serum samples was evaluated using an (b) (4) which determined the (b) (4)

[Redacted text block]

The serum from 11 normal volunteers along with one batch of (b) (4) (b) (4) were then analyzed for TCC, which are the end product of the activation of the complement. (b) (4)

[Redacted text block]

[Redacted text block]