

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125561Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

REVIEWER: Colleen Thomas, Ph.D.

ACTING BRANCH CHIEF: Patricia Hughes, Ph.D.

BLA: 125561
Applicant: Alexion Pharmaceuticals Inc.
US License Number: 1743
Submission Reviewed: Original BLA
Product: sebelipase alfa (recombinant human lysosomal acid lipase)
Indication: Treatment of lysosomal acid lipase deficiency
Dosage Form: Sterile, preservative-free liquid concentrate (2 mg/mL) supplied in single-use vials. The DP is administered by intravenous infusion after dilution.
DP Manufacturing Site: [REDACTED] (b) (4)
[REDACTED] (FEI: [REDACTED] (b) (4))
FDA Receipt Date: 21 November 2014
Action Date: 8 December 2015 (clock extension)

Conclusion and Approvability Recommendation

The amended application was reviewed from a product quality microbiology perspective and is recommended for approval. The post-marketing commitments are listed on the following page.

DP Quality Microbiology Post-marketing Commitments

1. Validate the [REDACTED] (b) (4) [REDACTED] [REDACTED] [REDACTED]. If the [REDACTED] (b) (4) is revised based on the validation study, update the BLA file accordingly.
2. Perform a microbial retention study to support the proposed [REDACTED] (b) (4) time limit for [REDACTED] (b) (4). Limit the validated time for [REDACTED] (b) (4) to [REDACTED] (b) (4) until the [REDACTED] (b) (4) time limit has been approved by the Agency.
3. Perform a study to confirm that the dye ingress test method used for drug product stability samples is capable of detecting small defects that could allow microbial ingress. The study should be performed with a range of small defect sizes [REDACTED] (b) (4). Revise the positive control defect size used for stability testing based on the results of the study and update the BLA file accordingly.
4. Conduct studies to understand the mechanism of endotoxin masking and/or interference in the drug product. Explore alternative test methods and develop a more suitable *in vitro* test method for the drug product.

Product Quality Microbiology Assessment: Drug Product

Drug Product Quality Microbiology Information Reviewed

Sequence	Supporting document	Submission date	
0092	93	14 October 2015	(b) (4) - process validation protocol
0093	94	30 October 2015	(b) (4) - sterility assurance package
0095	96	12 November 2015	(b) (4) - engineering lot release test data
0098	99	19 November 2015	Micro IR response
0099	100	25 November 2015	Module 3 update and micro IR response
0102	103	4 December 2015	Module 3 update and micro IR response
Not yet available*	Not yet available*	7 December 2015*	Module 3 update and micro IR response

* A PDF copy of the IR response was received by e-mail on 7 December 2015. To avoid delaying action on the application, the response was reviewed before it had been processed through the Gateway.

The BLA file was amended to change the DP manufacturing site from (b) (4) to (b) (4). The Agency agreed to a concurrent validation approach for transfer of the process to the (b) (4) site. The process validation protocol was provided in sequence 0092. Please refer to the review performed by OBP for process validation and product comparability information.

The product quality microbiology review covers the sterility assurance information provided to support sebelipase alfa DP manufacturing at the (b) (4) site. The sterility assurance information requested by the Agency was provided in Module 1 of sequence 0093. Module 3 of the BLA file was updated with the sterility assurance information on a rolling basis. Because these updates were not initiated until late November, this memo follows the question and response format from sequence 0093 instead of the eCTD format.

Sterility Assurance Information: (b) (4) **Site**

Information request Q1

1. Please provide the following information in sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate.



Response summary (0093, 0102)

Description of the Manufacturing Process and Controls



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/s/

COLLEEN THOMAS
12/07/2015

PATRICIA F HUGHES TROOST
12/07/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

REVIEWER: Colleen Thomas, Ph.D.
TEAM LEADER: Patricia Hughes, Ph.D.

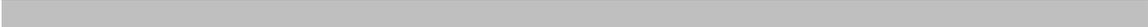
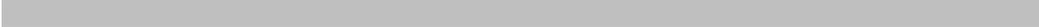
BLA: 125561
Applicant: Alexion Pharmaceuticals (transferred from Synageva BioPharma)
US License Number: 1743
Submission Reviewed: Original BLA
Product: sebelipase alfa (recombinant human lysosomal acid lipase)
Indication: Treatment of lysosomal acid lipase deficiency
Dosage Form: Sterile, preservative-free liquid concentrate (2 mg/ml) supplied in single-use vials. The DP is administered by intravenous infusion after dilution.
DP Manufacturing Site: (b) (4) (FEI: (b) (4))
FDA Receipt Date: 21 November 2014
Action Date: 8 September 2015

Conclusion and Approvability Recommendation

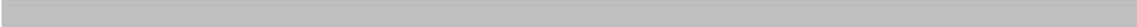
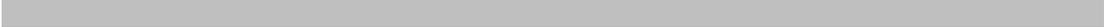
The BLA was reviewed for microbial control of the drug product manufacturing process and for assurance of drug product sterility and non-pyrogenicity. The BLA is recommended for approval. The post-marketing commitments are listed on the following page.

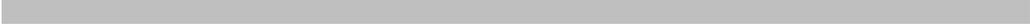
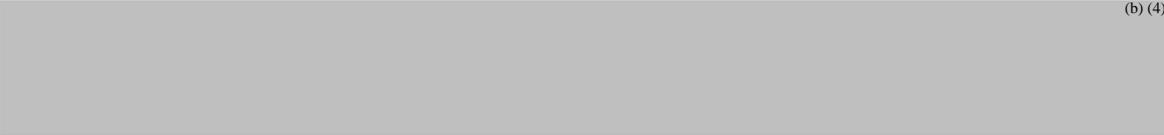
Post-marketing Commitments: Drug Product Quality Microbiology

Reviewer's comment: PMCs 1-4 were listed in the previous review memo.

1.  (b) (4)
2. Validate the  (b) (4)

. If the
 (b) (4) is revised based on the validation study, update the BLA file accordingly.
3. The microbial retention study  (b) (4)




4. Perform a study to confirm that the dye ingress test method used for drug product stability samples is capable of detecting small defects that could allow microbial ingress. The study should be performed with a range of small defect sizes  (b) (4). Revise the positive control defect size used for stability testing based on the results of the study and update the BLA file accordingly.
5.  (b) (4)
6. Conduct studies to understand the mechanism of endotoxin masking and/or interference in the drug product. Explore alternative test methods and develop a more suitable *in vitro* test method for the drug product.

Product Quality Microbiology Assessment: Drug Product

Drug product (DP) quality microbiology information in eCTD sequences up to and including 0056 was reviewed previously. The amendments reviewed in this memo addendum are listed in the table below.

Drug Product Quality Microbiology Information Reviewed

Sequence	Supporting document	Submission date	Description
0062	63	29 June 2015	Amendment
0064	65	14 July 2015	Amendment
0067	68	27 July 2015	Amendment
0073	74	5 August 2015	Response to LCM package

Module 3.2 - Drug Product

P.3 Manufacture

P.3.1 Manufacturers

Sequence 0073 added [REDACTED] (b) (4)
[REDACTED] as a rabbit pyrogen testing site for the DP.

P.3.3 Description of the Manufacturing Process and Process Controls

Reviewer's question: Some of the information provided in section 3.2.P.3.5 should also be provided in section 3.2.P.3.3 or 3.2.P.3.4. Please update the appropriate sections with the following information:

[REDACTED] (b) (4)

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SATISFACTORY

Conclusion

1. The BLA was reviewed for microbial control of the DP manufacturing process and for assurance of DP sterility and non-pyrogenicity. The BLA is recommended for approval. The post-marketing commitments are listed at the beginning of this memo.
2. Product quality aspects other than microbiology should be reviewed by OBP.
3. The DP manufacturing site was inspected by ORA from 11-19 May 2015. An FDA Form 483 form was issued with 11 observations.

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/s/

COLLEEN THOMAS
08/24/2015

PATRICIA F HUGHES TROOST
08/24/2015



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

Date: 8/14/2015
To: Administrative File, STN 125561/0
From: Bo Chi, Ph.D., CDER/OPQ/OPF/DMA/Branch IV
Endorsement: Patricia Hughes, Ph.D., Acting Branch Chief, CDER/OPQ/OPF/DMA/Branch IV
Subject: Addendum to review memo for New Biologic License Applications (BLA) STN 125561/0 dated 6/5/2015
Applicant: Alexion Pharmaceuticals Inc.
US License: 1743
Facility: (b) (4)
FEI: (b) (4)
Product: Kanuma (sebelipase alfa)
Dosage: 2 mg/mL, solution for injection, intravenous infusion
Indication: (b) (4) for patients with lysosomal acid lipase deficiency

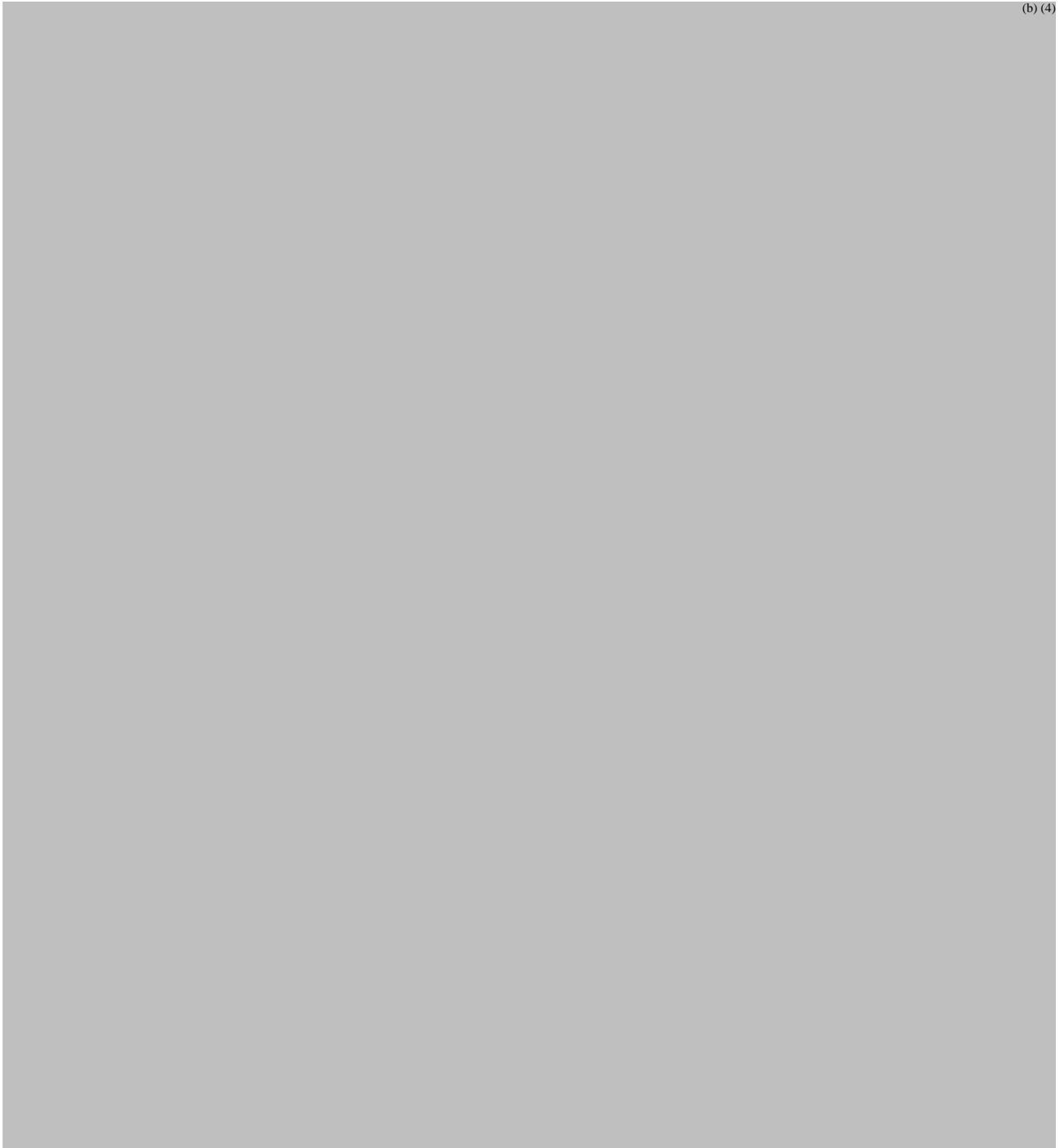
PDUFA date: September 8, 2015

Recommendation: The drug substance part of this BLA, as amended, is recommended for approval from product quality microbiology perspective with the following post-market commitments:

- Increase the bioburden test volume for (b) (4) samples to improve the sensitivity of the bioburden tests. In addition, provide bioburden qualification data for all in-process and drug substance samples from a total of three lots.
- Provide endotoxin qualification data for the in-process drug substance samples from a total of three lots.
- Improve the endotoxin method for the (b) (4) samples by optimizing the endotoxin test procedures.
- Develop and validate a reliable endotoxin test for the unformulated drug substance sample. In addition, validate the (b) (4) and drug substance endotoxin test using the modified endotoxin method involving the use of (b) (4) sample preparation system. Provide the validation information and data.

This review amends the drug substance microbiology product quality review memo for BLA STN125561/0 dated 6/5/2015 with new information and data submitted by the applicant [amendment dated 7/27/2015 (sequence 69), 7/29/2015 (Sequence 70), and 8/11/2015 (Sequence 76)] pertaining to:

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Conclusion

The drug substance part of this application, as amended, is recommended for approval from product quality microbiology perspective with the following post-market commitments:

- Increase the bioburden test volume for [redacted] (b) (4) samples to improve the sensitivity of the bioburden tests. In addition, provide bioburden qualification data for all in-process and drug substance samples from a total of three lots.

- Provide endotoxin qualification data for the in-process drug substance samples from a total of three lots.
- Improve the endotoxin method for the [REDACTED] ^{(b) (4)} samples by optimizing the endotoxin test procedures.
- Develop and validate a reliable endotoxin test for the unformulated drug substance sample. In addition, validate the [REDACTED] ^{(b) (4)} and drug substance endotoxin test using the modified endotoxin method involving the use of [REDACTED] ^{(b) (4)} sample preparation system. Provide the validation information and data.

Cc: Chi
Hughes
Bugin

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/s/

BO CHI
08/18/2015

PATRICIA F HUGHES TROOST
08/21/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

REVIEWER: Colleen Thomas, Ph.D.
TEAM LEADER: Patricia Hughes, Ph.D.

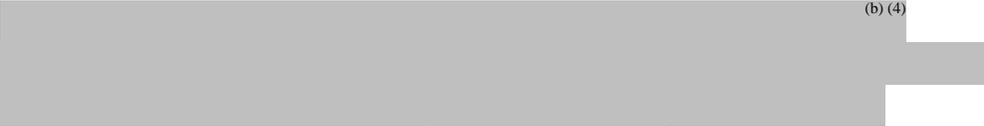
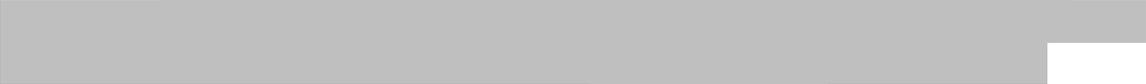
BLA: 125561
Applicant: Synageva BioPharma Corp.
US License Number: 2005
Submission Reviewed: Original BLA
Product: sebelipase alfa (recombinant human lysosomal acid lipase)
Indication: Treatment of lysosomal acid lipase deficiency
Dosage Form: Sterile, preservative-free liquid concentrate (2 mg/ml) supplied in single-use vials. The DP is administered by intravenous infusion after dilution.
DP Manufacturing Site: (b) (4) (FEI: (b) (4))
FDA Receipt Date: 21 November 2014
Action Date: 8 September 2015

Conclusion and Approvability Recommendation

The BLA was reviewed for microbial control of the DP manufacturing process and for assurance of DP sterility and non-pyrogenicity. Although no approvability issues have been identified thus far, additional data is needed in order to complete the review. An information request has been sent to the sponsor. In addition, new endotoxin method validation data will be performed by the end of June 2015. The new information will be reviewed in an addendum to this memo. The PMCs identified as of 8 June 2015 are listed below.

Post-marketing Commitments

1.  (b) (4)

2. Validate the  (b) (4)

Provide the data in a PMC study report. If the  (b) (4) is revised based on the validation study, then update the BLA file accordingly.

3. The microbial retention study  (b) (4)

update the BLA file accordingly.

4. Perform a study to confirm that the dye ingress test method used for drug product stability samples is capable of detecting small defects that could allow microbial ingress. The study should be performed with a range of small defect sizes  (b) (4)). Provide the data in a PMC study report. Revise the positive control defect size used for stability testing based on the results of the study and update the BLA file accordingly.

Product Quality Microbiology Assessment: Drug Product

BLA 125561 was a rolling submission. The original BLA submission was complete when the quality information was provided in sequence 0003. Previous sequences did not contain product quality information. The submissions referenced in this review memo are listed in the table below. In addition, updates to the BLA file that were associated with amendments up to and including sequence 0056 were reviewed.

Drug Product Quality Microbiology Information Reviewed

Sequence	Supporting document	Submission date
0003	4	21 November 2014
0008	9	5 January 2015
0009	10	7 January 2015
0024	25	20 March 2015
0034	35	13 April 2015
0037	38	21 April 2015
0045	46	8 May 2015
0056	57	3 June 2015

Module 3.2 - Drug Product

P.1 Description and Composition of the Drug Product

The drug product (DP) is supplied as a sterile, preservative-free liquid concentrate (2mg/ml) for intravenous infusion supplied in single-use vials. The fill volume is (b) (4) ml to ensure that 10 ml can be withdrawn. The DP composition is described in the table below, which was provided in section P.1.

Table 1: Dosage Form Composition

Component	Quality Standard	Function	Quantity per vial	Amount per mL
Sebelipase alfa	In-house standard	Active Ingredient	(b) (4)	2 mg
Trisodium Citrate Dihydrate	USP, PhEur, JP	(b) (4)	(b) (4)	13.7 mg
Citric Acid Monohydrate	USP, PhEur, JP	(b) (4)	(b) (4)	1.57 mg
Human Serum Albumin	USP, PhEur, JP	(b) (4)	(b) (4)	10. mg
(b) (4)				

Reviewer's comment: The pH specification for the DP is (b) (4) (section P.5.1).

DESCRIPTION IS SATISFACTORY

P.2 Pharmaceutical Development

Post-Dilution Storage Time

The DP is diluted in 0.9% sodium chloride prior to administration. The labeling provided in the original BLA submission indicated that the diluted DP may be stored for up to 24 hours at 2-8°C (b)(4). At the request of the reviewer, the sponsor provided growth promotion study data in sequence 0034. The microorganisms listed in USP <51> and *Staphylococcus epidermidis* were used as challenge organism. The DP was diluted in the label-recommended diluent and inoculated with 10-100 CFU of the challenge organism. Growth was defined as an increase of ≥ 0.5 log between time points.

Two growth promotion studies were performed. The first study included all 6 challenge organisms. For storage at 2-8°C, duplicate samples were analyzed at 0, 8, 24, 32, 48, and 72 hours. (b)(4)

Four of the challenge organisms (*S. aureus*, *C. albicans*, *A. brasiliensis*, and *S. epidermidis*) did not exhibit growth at either temperature for the duration of the study. The diluted DP was growth-promoting for *P. aeruginosa* and *E. coli*. (b)(4)

The growth promotion testing results for *P. aeruginosa* and *E. coli* from the first and second studies are shown in the tables below, which were provided in the amendment. *P. aeruginosa* exhibited growth at 2-8°C by 32 hours (b)(4). *E. coli* did not exhibit growth at 2-8°C for the duration of the study, (b)(4). Growth continued to TNTC levels at later time points. As a result, the sponsor will remove the (b)(4) post-dilution storage recommendation from the proposed labeling. The revised label will indicate that diluted DP may be stored at 2-8°C for up to 24 hours.

Table 3: Growth of *P. aeruginosa* at 2-8°C and (b)(4)°C in Diluted sebelipase alfa

Sampling Point (h)	<i>P. aeruginosa</i> (b)(4)							
	2-8°C							
	Study 1				Study 2			
	Set 1		Set 2		Set 1		Set 2	
	CFU ^a	Log increase	CFU	Log increase	CFU	Log increase	CFU	Log increase
0	67	-	44	-	43	-	43	-
2								
4								
6					37	0	40	0
8	63	0	29	0				
12					33	0	35	0
16								
18					31	0	28	0
24	54	0	27	0	28	0	27	0
32	455	0.9	310	0.8	270	0.8	300	0.9
48	TNTC	>0.5	TNTC	>0.5				
72	TNTC	>0.5	TNTC	>0.5				

^a - CFU = Average number of colony forming units per 10 mL
 TNTC - Too numerous to count

Table 4: Growth of *E. coli* at 2-8°C and (b) (4) °C in Diluted sebelipase alfa

Sampling Point (h)	2-8°C				<i>E. coli</i> (b) (4)
	Study 1				
	Set 1		Set 2		
	CFU ^a	Log increase	CFU	Log increase	
0	58	-	61	-	
2					
4					
6					
8	63	0	63	0	
12					
16					
24	68	0	65	0	
32	75	0.1	69	0	
48	77	0.1	71	0.1	
72	83	0.1	74	0.1	

^a - CFU = Average number of colony forming units per 10 mL
 TNTC - Too numerous to count

Reviewer’s comment: The growth promotion studies were done with a variety of organisms. The inoculum levels were acceptable. The studies support post-dilution storage at 2-8°C for up to 24 hours. Therefore, the revision to the proposed labeling is acceptable.

SATISFACTORY

P.3 Manufacture

P.3.1 Manufacturers

A list of sites involved in DP manufacturing, testing, packaging, and labeling is provided in Table 1. The DP is manufactured at the following site:

- (b) (4)
 FEI: (b) (4)

P.3.2 Batch Formula

(b) (4) The DP is manufactured by (b) (4). The target fill volume is (b) (4) ml. The declared maximum batch size for the DP is approximately (b) (4) L. The batch size is based on the capacity of the (b) (4). A (b) (4) L batch would yield approximately (b) (4) vials of DP.

Reviewer’s comment: All of the DP process validation lots are smaller than the (b) (4) L maximum batch size. The largest process validation batch yielded only (b) (4) vials. However, approximately (b) (4) vials were filled during the (b) (4). During process validation, maximum hold times were simulated from (b) (4). The microbial retention study for the (b) (4) was designed based on a (b) (4) L batch size.

SATISFACTORY

P.3.3 Description of the Manufacturing Process and Process Controls

(b) (4)



SATISFACTORY

Conclusion

1. The BLA was reviewed for microbial control of the DP manufacturing process and for assurance of DP sterility and non-pyrogenicity. Although no approvability issues have been identified thus far, additional data is needed in order to complete the review. An information request has been sent to the sponsor. In addition, new endotoxin method validation data will be performed by the end of June 2015. The new information will be reviewed in an addendum to this memo. The PMCs identified as of 8 June 2015 are listed on the front page of this memo.
2. Product quality aspects other than microbiology should be reviewed by OBP.
3. The DP manufacturing site was inspected by ORA from [REDACTED] (b) (4). A 483 form was issued with 11 observations.

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/s/

COLLEEN THOMAS
06/10/2015

PATRICIA F HUGHES TROOST
06/12/2015



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

Date: 6/5/2015
To: Administrative File, STN 125561/0
From: Bo Chi, Ph.D., CDER/OPQ/OPF/DMA/Branch IV
Endorsement: Patricia Hughes, Ph.D., Acting Branch Chief, CDER/OPQ/OPF/DMA/Branch IV
Subject: New Biologic License Applications (BLA)
Applicant: Synageva BioPharma Corp.
US License: 2005
Facility: (b) (4)
FEI: (b) (4)
Product: sebelipase alfa
Dosage: 2 mg/mL, solution for injection, intravenous infusion
Indication: (b) (4) for patients with lysosomal acid lipase deficiency
PDUFA date: September 8, 2015

Recommendation: The recommendation for approval of the drug substance part of this BLA from product quality microbiology perspective is pending until the following information and data have been submitted and reviewed:

- Endotoxin recovery data from (b) (4) samples
- Feasibility and qualification data for (b) (4)
- Bioburden qualification data of (b) (4)
- Feasibility study data for (b) (4)
- Feasibility study data for (b) (4)
- Endotoxin spike and hold study for (b) (4)
- Validation of the (b) (4) and drug substance endotoxin samples using the modified endotoxin method involving the use of (b) (4) sample preparation system
- Feasibility study data evaluating (b) (4) sample preparation system in endotoxin spiking and hold study with two additional drug substance lots
- Qualification of the in-process and drug substance samples for the bioburden test using samples from three lots
- Qualification of the in-process and unformulated drug substance samples for the endotoxin test using samples from three lots

The pending data will be reviewed in an addendum to this review memo.

Review Summary

Synageva submitted this Biologics License Application (BLA) for sebelipase alfa for enzyme replacement therapy for patients with lysosomal acid lipase (LAL) deficiency. The drug substance (DS) is manufactured at (b) (4)

The drug product (DP) is manufactured at (b) (4). The application contains CMC information in an eCTD format.

This review contains the assessments of the manufacturing process of sebelipase alfa drug substance from microbiology perspective.

Assessment

Drug Substance (3.2.S)

General Information (3.2.S.1)

Sebelipase alfa is purified from egg white of transgenic *Gallus*. The recombinant human LAL has the same amino acid sequence as the native human enzyme. LAL deficiency leads to the lysosomal accumulation of cholesteryl esters and triglycerides in various tissues and cell types throughout the body. Sebelipase alfa catalyzes the hydrolysis of cholesteryl esters and triglycerides to free cholesterol, glycerol and free fatty acids in the lysosomes of target cells. The sebelipase alfa drug substance contains 2 mg/mL sebelipase alfa, 13.7 mg/mL Sodium Citrate Dihydrate, 1.57 mg/mL Citric Acid Monohydrate, 10 mg/mL Human Serum Albumin, pH 5.9.

Manufacture (3.2.S.2)

Manufacturer(s) (3.2.S.2.1)

Egg white harvest and testing

Synageva BioPharma Corp.,
150 Ben Burton Road (BBR)
Bogart, GA 30622
FEI: 3009804853

Egg white harvest and testing

Synageva BioPharma Corp., Holden Production Facility (HPF)
100 Industrial Drive,
Holden, MA 01520
FEI: 3011161897

Drug substance manufacture and testing

(b) (4)

FEI: (b) (4)

Description of Manufacturing Process and Process Controls (3.2.S.2.2) and Controls of Critical Steps and Intermediates (3.2.S.2.4)

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Reviewer comment: The bioburden test schedule on the stability program is acceptable. The stability program and data should be further reviewed by the DTP reviewer.

Satisfactory

Conclusion

I. The recommendation for approval of the drug substance part of this BLA from product quality microbiology perspective is pending until the following information and data have been submitted and reviewed:

- Endotoxin recovery data from (b) (4)
- Feasibility and qualification data for (b) (4)
- Bioburden qualification data of egg (b) (4)
- Feasibility study data for (b) (4)
- Feasibility study data for (b) (4)
- Endotoxin spike and hold study for unformulated drug substance sample
- Validation of the (b) (4) and drug substance endotoxin samples using the modified endotoxin method involving the use of (b) (4) sample preparation system
- Feasibility study data evaluating (b) (4) sample preparation system in endotoxin spiking and hold study with two additional drug substance lots
- Qualification of the in-process and drug substance samples for the bioburden test using samples from three lots
- Qualification of the in-process and unformulated drug substance samples for the endotoxin test using samples from three lots

The pending data will be reviewed in an addendum to this review memo.

II. Information and data in this submission not related to microbial control of the drug substance should be reviewed by the OBP reviewer.

III. See panorama for GMP status of the relevant facilities.

Cc: Chi
Hughes
Bugin

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/s/

BO CHI
06/10/2015

PATRICIA F HUGHES TROOST
06/10/2015