CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761092Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

BLA/NDA Number: 761092
Review Number: 01
Review Date: 9/6/2018

Drug Name/Dosage Form	Revcovi (elapegademase) / Solution, Injection
Strength/Potency	2.4 mg/ 1.5 mL
Route of Administration	Intramuscular injection
Rx/OTC dispensed	Rx
Indication	Adenosine deaminase severe combined immune deficiency (ADA-SCID)
Applicant/Sponsor	Leadiant Biosciences Inc.
US agent, if applicable	n/a

Product Overview

Revcovi (elapegademase) is a pegylated recombinant bovine adenosine deaminase that catalyzes the irreversible hydrolytic deamination of adenosine or deoxyadenosine to inosine or deoxyinosine, respectively. The recombinant adenosine deaminase (rADA) (b) (4) is produced in E. coli (b) (4) (b) (4) (b) (4) Revcovi drug product is a sterile, clear, colorless solution supplied in a sterile, single-use vial containing 2.4 mg of elapegademase formulated in: sodium chloride (12.75 mg), sodium phosphate dibasic heptahydrate (12.70 mg), sodium phosphate monobasic monohydrate (3.81 mg), and Water for Injection, USP (b) (4) The Revcovi solution has a pH of 6.9.

Quality Review Team:

Discipline	Reviewer	Branch/Division
RBPM	Truong Quach	OPQ/OPRO
Drug Substance	Zhenzhen Liu	OBP/DBRRIII
Drug Product	Zhenzhen Liu	OBP/DBRRIII
Immunogenicity	Zhenzhen Liu	OBP/DBRRIII
Labeling	Vicky Hemphill-Borders	OBP
Facility	Ephrem Hunde/ Zhihao (Peter) Qiu	OPF/DIA
Microbiology – DS	Maria Jose Lopez-Barragan	OPF/DMA
Microbiology – DP	Lakshmi Narasimhan	OPF/DMA
QAL Microbiology - DP	Patricia Hughes	OPF/DMA
Application Team Lead	Steven Bowen	OBP/DBRRIII

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Jacquelyn Smith	DTOP
Cross-disciplinary Team Lead	Ozlem Belen	DTOP
Medical Officer	Marc Cavaille Coll	DTOP
Pharm/Tox	Maria Rivera/Lori Kotch	DTOP
Clinical Pharmacology	Abhay Joshi/ Phil Colangelo	OCP/DCPIV
Statistics	Hongling Zhou/ Yang Wang	OB/DBIV

1. **Names:**

a. Proprietary Name: Revcovi
b. Trade Name: Revcovi
c. Non-Proprietary Name/USAN: elapegademase
d. CAS Name: 1709806-75-6
e. Common Name: elapegademase
f. INN Name: elapegademase
g. Compendial Name: None
h. OBP systematic name: FUS: RPROTFRAG P56658 (ADA_BOVIN); SPROTFRAG PEG; [SC-PEG-rADA]
i. Other names: (Monomethoxypolyethylene glycol) recombinant adenosine deaminase, PEGylated Recombinant Adenosine Deaminase, EZN-2279, SC-PEG rADA

2. **Pharmacologic category:** recombinant bovine adenosine deaminase

Submissions Reviewed:

Submission:	Date Received:	Review Completed (yes or no)
STN 761092/SN0002 (b) (4) rADA	08/15/2017	Yes
STN 761092/SN0003 Drug Substance and Drug Product	09/15/2017	Yes
STN 761092/SN0006 Response to Product Quality IR	12/22/2017	Yes
STN 761092/SN0011 Response to Product Quality IR	04/13/2018	Yes
STN 761092/SN0014 Response to Product Quality IR	05/11/2018	Yes
STN 761092/SN0015 Response to Product Quality IR	05/30/2018	Yes
STN 761092/SN0018 Response to Product Quality IR	6/20/2018	Yes
STN 761092/SN0019 Response to Product Quality IR	06/21/2018	Yes
STN 761092/SN0020 Response to Product Quality IR	07/03/2018	Yes

STN 761092/SN0022 Response to Product Quality IR	07/13/2018	Yes
STN 761092/SN0025 Response to Product Quality IR	07/18/2018	Yes
STN 761092/SN0028/30 Response to Product Quality IR	07/27/2018	Yes
STN 761092/SN0031 Response to Product Quality IR	07/31/2018	Yes
STN 761092/SN0034 Response to Product Quality IR	08/09/2018	Yes
STN 761092/SN0037 Response to Product Quality IR	08/21/2018	Yes
STN 761092/SN0038 Response to Product Quality IR	08/21/2018	Yes
STN 761092/SN0039 Response to Product Quality IR	08/22/2018	Yes
STN 761092/SN0040 Response to Product Quality IR	08/23/2018	Yes
STN 761092/SN0028/42 Response to Product Quality IR	09/6/2018	Yes

Quality Review Data Sheet

1. **Legal Basis for Submission:** 351(a)

2. **Related/Supporting Documents:**

A. DMFs:

DMF#	DMF Holder	Item Referenced	Letter of Cross-Reference	Comments (status)
[redacted]	[redacted]	(b) (4)	Yes	No review was needed as all the relevant information related to quality of SC-PEG was in the BLA.
			Yes	No review was needed as all the relevant information related to compatibility with the product was in the BLA.
			Yes	No review was needed as all the relevant information related to compatibility with the product was in the BLA.

B. Other documents: IND, Referenced Listed Drug (RLD), or sister application.

- IND 100687 for the treatment of ADA-SCID
- NDA 19181 for Adagen® (pegademase bovine)
- BLA 103411 for Oncaspar® (pegaspargase) for PMC (b) (4) to conduct leachable testing on the container closure system. Leachable data from the Oncaspar drug product container closure is referenced to support the Revcovi container closure system. A letter of authorization was provided by Baxalta authorizing the reference of PMC (b) (4) and Seq 0008: Annual report, February 2, 2014- February 1, 2015 for BLA 103411 in support of BLA 761092.

Executive Summary

I. Recommendations: Approval

A. Recommendation and Conclusion on Approvability:

Recommendation:
The Office of Biotechnology Products (OBP, OPQ, CDER), the Division of Microbiology Assessment (DMA, OPF, OPQ, CDER), and the Division of Inspectional Assessment (DIA, OPF, OPQ, CDER) recommend approval of STN 761092 for Revcovi manufactured by Leadiant Biosciences Inc. The manufacturing data and information provided in the submission are sufficient to support a conclusion that the manufacturing process of Revcovi is well controlled and leads to a product that is pure and potent for the duration of the product shelf life. OPQ recommends 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: Exelead, Inc., 6925 Guion Road, Indianapolis, IN 46268, USA Fill size and dosage form: 2.4 mg/1.5 mL in a single-dose vial
- Dating period:
  - Drug Product: 24 months at 2-8°C (b) (4)
  - Stability:
    - We have approved the stability protocols in your license application for the purpose of extending the expiration dating of your (b) (4) (b) (4) drug product under 21 CFR 601.12.
- Exempt from lot release
  - Revcovi is exempted from lot release per Docket No 95-29960 because Revcovi is a recombinant protein.

C. Benefit/Risk Considerations:

Revcovi is a pegylated recombinant bovine adenosine deaminase used for the treatment of the orphan disease, ADA-SCID. The currently available therapy for ADA-SCID is Adagen (NDA 19181), a pegylated bovine adenosine deaminase purified from bovine intestine. Adagen, also produced by Leadiant Biosciences Inc. (b) (4) (b) (4) Revcovi is a recombinant version of bovine ADA which has a favorable stability and impurity profile compared to Adagen. The succinimidyl carbonate (SC) PEG linker used for Revcovi is (b) (4) (b) (4) because Revcovi is recombinant, production is not dependent on the supply of primary bovine tissue as is the case with Adagen, and therefore is at a lower risk of drug shortage.

The Revcovi manufacturing processes are well-controlled and yield product that is safe, pure and potent. Five post-marketing commitments (PMCs) were agreed upon with the sponsor to improve the robustness of the (b) (4) DS manufacturing processes. Microbial stability (b) (4) is controlled through routine testing and validation studies with one batch. PMC-1, (b) (4) and PMC-3 are to conduct

hold time and method qualification studies with additional batches. Stability of end of production cells (EPCs) was supported by small-scale studies whereas absence of adventitious agents is controlled through routine testing. PMC-5 is to conduct a study to confirm that EPCs (b) (4) are stable and free from adventitious agents. (b) (4) PMC-4 is to conduct a study to investigate whether (b) (4) can be removed. (b) (4) (b) (4) (b) (4) These five PMCs will further support the robustness of the (b) (4) DS manufacturing process from microbial and product quality perspectives. The risk of leachables from the manufacturing processes and container closure systems assessed by risk assessments and individual studies is low. PMC-6 is to conduct leachable studies to confirm this assessment. Overall, these six PMCs will result in improvement and increased robustness of the manufacturing processes of Revcovi.

In conclusion, the data submitted in this application support the conclusion that the manufacture of Revcovi is well controlled and yields a product that is safe, pure and potent. From a product quality perspective, this product is approvable for human use.

D. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:

The following draft post marketing commitments have been proposed and accepted by the Sponsor:

Microbiology

PMC-1. Provide data from two additional rADA studies to support the (b) (4) hold times of the (b) (4) (b) (4) from a microbial control perspective.

(b) (4)

(b) (4)

Product Quality

PMC-4 Perform a study to evaluate the impact of the removal of (b) (4) If the data support removal of (b) (4) a plan for the removal of (b) (4) manufacturing process will be provided. The plan should include an evaluation of consistency of the (b) (4) and comparability of elapegademase manufactured with and without (b) (4)

PMC-5 To characterize the purity and stability of end of production cells at full commercial scale for the manufacturing of drug substance (b) (4) recombinant adenosine deaminase (rADA).

PMC-6 To perform a leachable study to evaluate leachables from the manufacturing process and the container closure system in Revcovi (elapegdemase, SC-PEG rADA) drug product and assess potential impact of leachables on product quality. The analysis will be performed using one drug product lot and/or a representative sample (e.g. (b) (4)) analyzed at the end of shelf life. Appropriate methods

will be used to detect, identify, and quantify organic non-volatile, volatile and semi-volatile species, and metals. Characterization of potential impact on product quality will be assessed using adequate analytical methods. Complete data and the risk evaluation for potential impact of leachables on product safety and quality will be provided in the final study report.

II. Summary of Quality Assessments:

Table 1 below is a summary of critical quality attributes and the associated control strategies for attributes that are intrinsic to the Drug Substance. Table 2 summarizes critical quality attributes that are relevant to the drug substance. For additional information, see the technical document on primary reviews of the Drug Substance Quality and Drug Product Quality by OBP/DBRR-III and the Drug Substance Microbiology and the Drug Product Microbiology by OPF/DMA.

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA (type)	Risk	Origin	Control Strategy
Enzymatic Activity	Efficacy	Intrinsic to the molecule, (b) (4) (b) (4)	(b) (4)
Enzyme Kinetics	Efficacy	Intrinsic to molecule	
Identity	Safety and Efficacy	Intrinsic to molecule	
Primary sequence	Efficacy	Intrinsic to molecule	
Higher Order Structure	Efficacy	Intrinsic to molecule	

		(b) (4)
High Molecular Weight (HMW) species/Aggregates	Efficacy, Pharmacokinetics, and Safety/Immunogenicity	
Fragmentation	Efficacy, Pharmacokinetics, and Immunogenicity	
(b) (4) species	Efficacy	
(b) (4) species	Efficacy and Safety	
(b) (4) species	Efficacy and Safety	
(b) (4) variants	Efficacy	
Modification with SC-PEG	Efficacy and Safety	
Molar ratio (b) (4) to SC-PEG rADA	Efficacy	

B. Drug Substance Elapegademase Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

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

CQA (type)	Risk	Origin	Control Strategy
Appearance	Safety	(b) (4)	
Host Cell Proteins (b) (4)	Safety and Immunogenicity		
Host Cell DNA (b) (4)	Safety		
Residual (b) (4)	Safety and Immunogenicity		
Residual (b) (4)	Safety		
Residual (b) (4)	Safety		
(b) (4) (contaminant)	Safety		
Leachables (b) (4)	Safety		
(b) (4)	Safety		
(b) (4) (b) (4) impurity	Safety		
Subvisible Particulates	Safety		

- Description:
  Elapegademase is a recombinant bovine adenosine deaminase consisting of a 356 amino acid polypeptide chain covalently conjugated to 13 monomethoxypolyethylene glycol (mPEG)

molecules via a succinimidyl carbonate (SC) linker at lysine residues. (b) (4)

(b) (4)

- Mechanism of Action (MoA):
  ADA-deficiency results in severe combined immune deficiency (SCID). The mechanism of action of Revcovi is mediated by the enzyme activity of ADA involved in purine metabolism, catalyzing the irreversible hydrolytic deamination of adenosine or deoxyadenosine to inosine or deoxyinosine, respectively. In the absence of ADA, accumulation of cytotoxic amounts of adenosine, 2'-deoxyadenosine and dATP triggers irreversible inhibition of cellular transmethylation reactions, enhanced apoptosis, impaired cell division and DNA repair processes. ADA has also been shown to be essential for differentiation of lymphoid cells, particularly T lymphocytes, and maturation of monocytes to macrophages.

- Potency Assay:
  The enzyme activity assay for potency measures the conversion of adenosine to inosine by rADA. (b) (4)

  Enzyme kinetics are measured (b) (4)

  (b) (4)

- Reference Materials:
  (b) (4)

- (b) (4)

- Manufacturing process summary:
  (b) (4)

(b) (4)

C. Drug Product Elapegademase 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.

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

CQA (type)	Risk	Origin	Control Strategy
Color and Degree of Opalescence	Safety and Efficacy	Formulation, Contamination, or Degradation	(b) (4)
Osmolality	Safety	Formulation	
pH	Safety and Efficacy	Formulation	
Particulate Matter	Safety / Immunogenicity	Manufacturing process, container closure system, and on stability	
Extractable Volume	Efficacy / Dosing	Manufacturing process	
Leachables (b) (4)	Safety	Manufacturing equipment and CCS	
Bacterial endotoxin	Safety	Manufacturing process, contamination.	

Sterility	Safety	Manufacturing process, container closure system	(b) (4)

- Description and Strength:
  Revcovi (injection) is supplied in a single use 3.5mL vial containing 1.5 mL of Revcovi at a strength of 2.4 mg/ 1.5 mL (1.6 mg/mL) Potency of Revcovi is determined with an enzymatic activity assay measuring the conversion of adenosine to inosine measured (b) (4) The specific activity of the product is calculated (b) (4) (b) (4). The potency assay is the same as described in the drug substance section of this review.

- Summary of Product Design:
  Elapegademase is supplied as a sterile, single-use, ready-to-use, preservative-free solution for intramuscular injection in a vial. The drug product formulation consists of 1.6 mg/mL elapegademase, (b) (4)% sodium chloride and Water for Injection at pH 6.9. The extractable volume is 1.5 mL.

- List of Excipients:
  Excipients include sodium chloride, sodium phosphate dibasic heptahydrate, sodium phosphate monobasic monohydrate

- Reference Materials:
  A qualified elapegademase reference standard was derived from material representative of the pivotal clinical material. Adequate reference standard qualification system is in place to ensure that the elapegademase reference standard is suitable for use.

- Manufacturing process summary:
  Revcovi DP manufacturing, packaging, and labeling is performed at Exelead Inc. (Indianapolis, IN, USA). The manufacturing process for Revcovi DP is comprised of (b) (4) (b) (4)

  Vials are filled with 1.5 mL Revcovi bulk DP (1.6 mg/mL). All accepted vials are labeled and packaged at Exelead Inc. The vials are packaged in either a single unit carton (b) (4) (b) (4) The DP is stored at 2-8 ºC, protected from light.

  All drug product-contact equipment and components are (b) (4) (b) (4) Bioburden and endotoxin are tested during manufacture, and sterility and endotoxin are tested at DP lot release. Container closure integrity test using a validated method is included in the stability program.

- Container closure:
  The container closure system is a single-use, 3.5 mL (b) (4) glass vial with a 13mm gray rubber stopper composed of (b) (4) (b) (4)

- Dating period and storage conditions:
  The dating period for elapegademase drug product is 24 months at 2-8°C, protected from light.

D. Novel Approaches/Precedents:

A novel control strategy was implemented for the SC-PEG rADA DS (b) (4) (b) (4)

E. Any Special Product Quality Labeling Recommendations:

Store in a refrigerator at 2°C to 8°C (36°F to 46°F).
Store in product carton until time of use.
Protect from light.
Do not freeze.
Do not shake.

F. Establishment Information:

The Division of Inspectional Assessment recommends approval of the BLA. The manufacturing and testing facilities, their responsibilities in elapegademase production, and inspectional outcomes are summarized in the table below.

Overall Recommendation: APPROVE			
Drug Substance			
Responsibility	**Site Information**	**DUNS/FEI Number**	**Facility Status**
(b) (4)			Approve

(b) (4)	Approve
	Approve
	Approve
	Approve

Drug Product			
Responsibility	**Site Information**	**DUNS/FEI Number**	**Facility Status**
SC-PEG rADA (elapegademase) Drug product manufacture (b) (4) (b) (4) release, and stability quality control testing of drug product and raw materials. Packaging and labeling of drug product	Exelead, Inc. (formerly Sigma - Tau PharmaSource, Inc.) 6925 Guion Road, Indianapolis, IN 46268 (USA)	DUNS: 961822389 FEI: 1000517970	Approve
(b) (4)			Approve

G. Facilities:

(b) (4) A pre-license inspection (PLI) (b) (4) was conducted (b) (4) A Form 483 was issued with a recommendation of Voluntary Action Indicated (VAI).

Elapegademase (b) (4) DP manufacturing is performed at Exelead Inc., Indianapolis, Indiana, USA(FEIN: 1000517970). A PLI was performed at Exelead Inc. May 7-15, 2018. A 15-item Form FDA 483 was issued

with an initial recommendation of Withhold Approval. The Firm's responses to the FDA 483 observations were adequate and the status of the PLI was downgraded to Approve.

A surveillance inspection of Exelead Inc. was conducted by the Office of Regulatory Affairs (ORA) July 9-30, 2018. A 3-item Form FDA 483 was issued with a preliminary recommendation of Official Action Indicated (pOAI). On August 17, 2018 the firm responded to the Form FDA 483 and the responses were reviewed by the Office of Pharmaceutical Quality Operations and Office of Regulatory Affairs. The responses were deemed adequate to reclassify the inspection to Voluntary Action Indicated (VAI).

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:
- annual stability protocol
- qualification of new working reference standard (b) (4)
- concurrent validation (b) (4)

ii. Outstanding review issues/residual risk:
-n/a

iii. Future inspection points to consider:
- Follow up on 483 observations and CAPAs

b. Drug Product

i. Protocols approved:
- annual stability protocol
- qualification of new working reference standard for elapegademase DP

ii. Outstanding review issues/residual risk:
See Post-Marketing Commitments in Section IB

iii. Future inspection points to consider:
- Follow up on 483 observations and CAPAs

Steven Bowen

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Maria Gutierrez Lugo

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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: September 6, 2018
To: Administrative File, STN 761092
From: Ephrem Hunde, Ph.D., Chemical Engineer, CDER/OPQ/OPF/DIA
Endorsement: Zhihao Peter Qiu, Ph.D., Branch 1 Chief, CDER/OPQ/OPF/DIA
Subject: New Biologic License Application (BLA)
US License: To be assigned
Applicant: Leadiant Biosciences, Inc.
Mfg Facility: Drug Substance: (b) (4)

Drug Product: Exelead, Inc., Indianapolis, IN (FEI 1000517970)
Product: SC-PEG rADA (elapegademase), solution for injection
Dosage: 1.6 mg/mL strength (1.5 mL solution in 3.5 mL vials)
Indication: For the treatment of adenosine deaminase severe combined immune deficiency (ADA-SCID).
Due Date: August 24, 2018.

RECOMMENDATION: This submission is recommended for approval from a facilities assessment perspective.

SUMMARY

BLA 761092 was submitted by Leadiant Biosciences, Inc., which provided information and data to support the manufacture of elapegademase, solution for injection. SC-PEG rADA (elapegademase) injection is a PEGylated recombinant Adenosine Deaminase (rADA) produced by E.coli covalently conjugated to monomethoxypolyethylene glycol (mPEG) using a succinimidyl carbonate (SC) linker.

(b) (4)

The SC-PEG rADA (elapegademase) Drug Product is formulated as a sterile, isotonic, (b) (4) (b) (4) solution for intramuscular administration. The solution is supplied as a preservative-free, clear, colorless liquid at a concentration of 1.6 mg/mL filled into vial. The container closure system for elapegademase is a 3.5 mL (b) (4) glass vial with a (b) (4) 13 mm gray rubber

stopper composed of [redacted] (b) (4)

ASSESSMENT

DRUG SUBSTANCE FACILITIES

3.2.S.2.1 DS Manufactures

The facilities proposed for SC-PEG rADA (elapegademase) DS manufacturing, and testing are provided in Table 1.

[redacted] (b) (4)

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(b) (4)

CONCLUSION

Adequate descriptions were provided for the facilities proposed for (b) (4) DS and DP manufacture and testing. The subject BLA is recommended for approval from a facilities assessment perspective.

Ephrem Hunde, Ph.D.
Chemical Engineer
OPF Division of Inspectional Assessment
Branch 1

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Zhihao (Peter) Qiu, Ph.D.
Supervisory Consumer Safety Officer
OPF Division of Inspectional Assessment
Branch 1 Chief

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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: July 25, 2018
To: Administrative File, STN 761092
From: Ephrem Hunde, Ph.D., Chemical Engineer, CDER/OPQ/OPF/DIA
Endorsement: Zhihao Peter Qiu, Ph.D., Branch 1 Chief, CDER/OPQ/OPF/DIA
Subject: New Biologic License Application (BLA)
US License: To be assigned
Applicant: Leadiant Biosciences, Inc.
Mfg Facility: Drug Substance: (b) (4)

Drug Product: Exelead, Inc., Indianapolis, IN (FEI 1000517970)
Product: SC-PEG rADA (elapegademase), solution for injection
Dosage: 1.6 mg/mL strength (1.5 mL solution in 3.5 mL vials)
Indication: For the treatment of adenosine deaminase severe combined immune deficiency (ADA-SCID).
Due Date: August 24, 2018.

RECOMMENDATION: This submission is not recommended for approval from a facilities assessment perspective.

SUMMARY

BLA 761092 was submitted by Leadiant Biosciences, Inc., which provided information and data to support the manufacture of elapegademase, solution for injection. SC-PEG rADA (elapegademase) injection is a PEGylated recombinant Adenosine Deaminase (rADA) produced by E.coli covalently conjugated to monomethoxypolyethylene glycol (mPEG) using a succinimidyl carbonate (SC) linker.

(b) (4)

The SC-PEG rADA (elapegademase) Drug Product is formulated as a sterile, isotonic, (b) (4) (b) (4) solution for intramuscular administration. The solution is supplied as a preservative-free, clear, colorless liquid at a concentration of 1.6 mg/mL filled into vial. The container closure system for elapegademase is a 3.5 mL (b) (4) glass vial with a (b) (4) 13 mm gray rubber

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stopper composed of [redacted] (b) (4)

ASSESSMENT

DRUG SUBSTANCE FACILITIES

3.2.S.2.1 DS Manufactures

The facilities proposed for SC-PEG rADA (elapegademase) DS manufacturing, and testing are provided in Table 1.

[redacted] (b) (4)

(b) (4)

CONCLUSION

Adequate descriptions were provided for the facilities proposed for (b) (4) DS and DP manufacture and testing. The subject BLA is not recommended for approval from a facilities assessment perspective due to the initial OAI classification of the recent surveillance inspection.

Ephrem Hunde, Ph.D.
Chemical Engineer
OPF Division of Inspectional Assessment
Branch 1

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Zhihao (Peter) Qiu, Ph.D.
Supervisory Consumer Safety Officer
OPF Division of Inspectional Assessment
Branch 1 Chief

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Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELS AND LABELING REVIEW

Date of review:	August 9, 2018
Reviewer:	Vicky Borders-Hemphill, PharmD Labeling Review Specialist Office of Biotechnology Products (OBP)
Through:	Zhenzhen Liu, PhD, Product Quality Reviewer OBP/Division of Biotechnology Review and Research III
Application:	BLA 761092
Applicant:	Leadiant Biosciences, Inc.
Submission Date:	July 14, 2017
Product:	Proprietary Name (elapegademase-lvlr)
Dosage form(s):	Injection
Strength and Container-Closure:	2.4 mg/1.5 mL (1.6 mg/mL) single-dose vial
Indication, dose, route, and frequency of administration:	Indicated for the treatment of adenosine deaminase severe combined immune deficiency (ADA-SCID): • Patients receiving treatment with Adagen: the starting weekly intramuscular (IM) dose is 0.2 mg/kg and may be increased by increments of 0.033 mg/kg weekly • Adagen-naïve patients: the starting weekly IM dose is 0.4 mg/kg of ideal body weight (divided twice weekly) for a minimum of 12 to 24 weeks
Background and Summary Description:	The Applicant submitted an application for the treatment of adenosine deaminase severe combined immune deficiency
Recommendations:	The container labels and carton labeling (submitted on July 12, 2018) and prescribing information (submitted on August 1, 2018) are acceptable (see Appendix D) from an OBP labeling perspective.

Materials Considered for this Label and Labeling Review	
Materials Reviewed	**Appendix Section**
Proposed Labels and Labeling	A
Other	B (n/a)
Evaluation Tables	C
Acceptable Labels and Labeling	D

n/a = not applicable for this review

DISCUSSION and CONCLUSION

We evaluated the proposed labels and labeling for compliance to the applicable requirements in the Code of Federal Regulations, and United States Pharmacopeia (USP) standards (see Appendix C).

The prescribing information, medication guide, patient labeling, instructions for use, container labels, and carton labeling were reviewed and found to comply with relevant regulations (21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57; 21 CFR 201.100), and USP standards.

The container labels and carton labeling (submitted on July 12, 2018) and prescribing information (submitted on August 1, 2018) are acceptable (see Appendix D) from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

Prescribing Information (submitted on October 24, 2017
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Container Labels (submitted on October 24, 2017)

(b) (4)

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Appendix B: Other (n/a)
Appendix C: Evaluation Tables (Label[1,2] and Labeling[3] Standards)

Container[4] Label Evaluation

Regulations, Guidance and CDER Best Labeling Practices	Conforms
Proper Name (21 CFR 610.60, 21 CFR 201.50, 21 CFR 201.10) *for container of a product capable of bearing a full label* **Comment/Recommendation:** *considered a partial label*	☐ No ☐ Yes ☒ N/A
Manufacturer name, address, and license number (21 CFR 610.60) *for container of a product capable of bearing a full label* **Comment/Recommendation:** *considered a partial label*	☐ No ☐ Yes ☒ N/A
Lot number or other lot identification (21 CFR 610.60, 21 CFR 201.18, 21 CFR 201.100) **Comment/Recommendation:** *considered a partial label*	☐ No ☐ Yes ☒ N/A
Expiration date (21 CFR 610.60, 21 CFR 201.17) **Comment/Recommendation:** *considered a partial label*	☐ No ☐ Yes ☒ N/A
Multiple dose containers (recommended individual dose) 21 CFR 610.60	☐ No ☐ Yes ☒ N/A
Statement: "Rx only" 21 CFR 610.60 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
Medication Guide 21 CFR 610.60 21 CFR 208.24	☐ No ☐ Yes ☒ N/A
No Package for container 21 CFR 610.60	☐ No ☐ Yes ☒ N/A
Partial label 21 CFR 610.60 21 CFR 201.10	☒ No ☐ Yes ☐ N/A

[1] Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.
[2] Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.
[3] Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.
[4] Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

Comment/Recommendation:
Relocate the proprietary name, proper name, dosage form, strength, route of administration and package type term with associated discard statement to appear in the following order:
Revcovi
(elapegademase-lvlr)
Injection
2.4 mg/1.5 mL (1.6 mg/mL)
For Intramuscular Use Only
Single-Dose Vial. Discard unused portion.

The applicant revised as requested

Revise the manufacturer information to appear as the name of the manufacturer listed as the applicant on FDA form 356h. Since this is considered a partial label the words (b) (4) (b) (4) may be omitted. Relocate and revise the US license number to appear underneath the manufacturer name as follows:
Leadiant Biosciences
U.S. License No. xxxx
The applicant revised as requested

For partial labels (small container labels) per 21 CFR 610.60(c), only the applicant name is required. Although not required, OBP prefers to include the license number if there is enough space on the container label. Delete (b) (4) as it is not required information and deletion may permit space for other required information.
The applicant revised as requested

No container label 21 CFR 610.60	☐ No ☐ Yes ☒ N/A
Ferrule and cap overseal	☒ No ☐ Yes ☐ N/A

Comment/Recommendation:
FOR VIALS: Confirm there is no text on the ferrule and cap overseal of the vials to comply with a revised United States Pharmacopeia (USP), General Chapters: <7> Labeling (Ferrules and Cap Overseals).

Applicant's response: Leadiant confirms that the ferrule cap and cap overseal do not show any text in compliance with the revised United States Pharmacopeia (USP), General Chapters: <7> Labeling (Ferrules and Cap Overseals).

OBP labeling: we find this acceptable

Visual inspection 21 CFR 610.60	☒ No ☐ Yes ☐ N/A

Comment/Recommendation:
FOR VIALS: Confirm there is sufficient area on the container to allow for visual inspection when the label is affixed to the vial and indicate where the visual area of inspection is located per 21 CFR 610.60(e).

Applicant's response: Leadiant confirms that there is sufficient area on the container to allow for visual inspection per 21 CFR 610.60(e) when the label is affixed to the vial. The visual inspection can be performed on the full length of the vial since there is a 2.5 mm gap between the label's ends. In addition, the visual inspection can be performed on the circumference of the vial below the label that is positioned approximately 3 mm above the bottom of the vial

OBP labeling: we find this acceptable

NDC numbers 21 CFR 201.2 21 CFR 207.35	☐ No ☒ Yes ☐ N/A
Route of administration 21 CFR 201.5 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
Preparation instructions 21 CFR 201.5	☐ No ☐ Yes ☒ N/A
Package type term 21 CFR 201.5	☒ No ☐ Yes ☐ N/A

Comment/Recommendation: Revise to the appropriate package type term for this product. The appropriate package-type term for this product is "single-dose" vial. A single-dose container is a container of a sterile medication for parenteral administration (injection or infusion) that is not required to meet the antimicrobial effectiveness testing requirements. A single-dose container is designed for use with a single patient as a single injection/ infusion. Use of the term "single-dose" container does not imply the entire contents of the container constitute a single dose. In some instances, a single-dose container may contain more drug than is required for a single dose or multiple vials may be needed to obtain a single dose.
The applicant revised as requested

Drugs **Misleading statements** 21 CFR 201.6	☐ No ☐ Yes ☒ N/A
Strength 21 CFR 201.10 21CFR 201.100	☐ No ☐ Yes ☐ N/A

Comment/Recommendation: Per USP General Chapters: <7> Labeling for injectable products with containers that supply a volume of drug greater than 1 mL, the primary expression of strength is the strength per total volume followed in close proximity by a parenthetical that includes the strength/mL. Revise the strength presentation from (b) (4) to read "2.4 mg/1.5 mL (1.6 mg/mL)"
The applicant revised as requested

Drugs **Prominence of required label statements** 21 CFR 201.15	☐ No ☒ Yes ☐ N/A
Spanish-language (Drugs) 21 CFR 201.16	☐ No ☐ Yes ☒ N/A
FD&C Yellow No. 5 and/or FD&C Yellow No. 6 21 CFR 201.20	☐ No ☐ Yes ☒ N/A
Phenylalanine as a component of aspartame 21 CFR 201.21	☐ No ☐ Yes ☒ N/A
Sulfites; required warning statements 21 CFR 201.22	☐ No ☐ Yes ☒ N/A
Bar code label requirements 21 CFR 201.25 21CFR 610.67	☐ No ☒ Yes ☐ N/A
Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) 21 CFR 610.68 21 CFR 201.26	☐ No ☐ Yes ☒ N/A
Net quantity 21 CFR 201.51	☐ No ☒ Yes ☐ N/A
Usual dosage statement 21 CFR 201.55 21 CFR 201.100 **Comment/Recommendation:** *container label lacks space*	☐ No ☐ Yes ☒ N/A
Inactive ingredients 21 CFR 201.100 **Comment/Recommendation:** *container label lacks space*	☐ No ☐ Yes ☒ N/A
Storage requirements **Comment/Recommendation:** Ensure instructions for handling, "Do Not Shake", as appropriate based on the type of product when indicated by the character of the product, appear on the container label *The applicant revised as requested*	☒ No ☐ Yes ☐ N/A
Dispensing container 21 CFR 201.100	☐ No ☐ Yes ☒ N/A

Package Label[5] Evaluation

Regulations, Guidance, and USP	Conforms
Proper name (21 CFR 610.61, 21 CFR 201.50, 21 CFR 201.10)	☐ No ☒ Yes ☐ N/A
Comment/Recommendation: Relocate the proprietary name, proper name, dosage form, strength, route of administration and package type term with associated discard statement to appear on the principal display panel in the following order: Revcovi (elapegademase-lvlr) Injection 2.4 mg/1.5 mL (1.6 mg/mL) For Intramuscular Use Only Single-Dose Vial. Discard unused portion. *The applicant revised as requested*	
Manufacturer name, address, and license number 21 CFR 610.61	☒ No ☐ Yes ☐ N/A
Comment/Recommendation: To comply with 21 CFR 610.61(b), revise the manufacturer information to appear as the name and address of the manufacturer listed as the applicant on FDA form 356h. Relocate the US license number to appear underneath the manufacturer name and address. The drug manufacturing site (Exelead Inc. Indianapolis, IN) may be included if the requirements for 21 CFR 610.61(b) are met. Revise the drug manufacturing site statement to read "at Exelead Inc. Indianapolis, IN 46268" as follows: Manufactured by: Leadiant Biosciences Gaithersburg, MD 20878 U.S. License No. xxxx at Exelead Inc. Indianapolis, IN 46268 *The applicant revised as requested*	
Lot number or other lot identification 21 CFR 610.61	☒ No ☐ Yes ☐ N/A
Comment/Recommendation: Ensure lot number appears on the label per 21 CFR 610.61 (c). *The applicant indicated an area for the lot number*	
Expiration date 21 CFR 610.61 21 CFR 201.17	☒ No ☐ Yes ☐ N/A

[5] Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus, this includes the carton, prescribing information, and patient labeling.

Comment/Recommendation: Ensure the expiration date appears on the label per 21 CFR 610.61 (d).
The applicant indicated an area for the expiration date

Preservative 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
Number of containers 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
Strength/volume 21 CFR 610.61 21 CFR 201.10 21 CFR 201.100	☒ No ☐ Yes ☐ N/A

Comment/Recommendation: Per USP General Chapters: <7> Labeling for injectable products with a container that supply a volume of drug greater than 1 mL, the primary expression of strength is the strength per total volume followed in close proximity by a parenthetical that includes the strength/mL. Revise the strength presentation on all panels from (b) (4) to read "2.4 mg/1.5 mL (1.6 mg/mL)".
The applicant revised as requested

Storage temperature/requirements 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
Handling: "Do Not Shake", "Do not Freeze" or equivalent (21 CFR 610.61)	☒ No ☐ Yes ☐ N/A

Comment/Recommendation: Ensure instructions for handling, "Do Not Shake", as appropriate based on the type of product when indicated by the character of the product, appear on the carton labeling per 21 CFR 610.61 (i).
The applicant revised as requested

Multiple dose containers (recommended individual dose) 21 CFR 610.61	☐ No ☐ Yes ☒ N/A
Route of administration 21CFR 610.61 21 CFR 201.5 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
Known sensitizing substances 21 CFR 610.61	☐ No ☐ Yes ☒ N/A
Inactive ingredients 21 CFR 610.61 21 CFR 201.100	☒ No ☐ Yes ☐ N/A

Comment/Recommendation: Revise the ingredient list from (b) (4) (b) (4) to read as follows: "Each 1.5 mL of solution contains 2.4 mg elapegademase-lvlr, sodium chloride (12.75 mg), sodium phosphate dibasic heptahydrate (12.7 mg), sodium phosphate monobasic monohydrate (3.81 mg), and Water for

Injection, USP" *The applicant revised as requested*	
Source of the product 21 CFR 610.61 **Comment/Recommendation:** Remove the statement (b) (4) (b) (4) as it is not required information for the carton labeling and this information is provided in the prescribing information *The applicant revised as requested*	☐ No ☐ Yes ☐ N/A
Minimum potency of product 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
Rx only 21CFR 610.61 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
Divided manufacturing 21 CFR 610.63	☐ No ☐ Yes ☐ N/A
Distributor 21 CFR 610.64	☐ No ☐ Yes ☒ N/A
Bar code 21 CFR 610.67 21 CFR 201.25	☐ No ☒ Yes ☐ N/A
Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) 21 CFR 610.68 21 CFR 201.26	☐ No ☐ Yes ☒ N/A
NDC numbers 21 CFR 201.2 21 CFR 207.35	☐ No ☒ Yes ☐ N/A
Preparation instructions 21 CFR 201.5	☐ No ☒ Yes ☐ N/A
Package type term 21 CFR 201.5 **Comment/Recommendation:** Revise to the appropriate package type term for this product, single-dose vial. *The applicant revised as requested*	☒ No ☐ Yes ☐ N/A
Drugs **Misleading statements** 21 CFR 201.6	☐ No ☐ Yes ☒ N/A
Drugs **Prominence of required label statements** 21 CFR 201.15	☐ No ☒ Yes ☐ N/A

Spanish-language (Drugs) 21 CFR 201.16	☐ No ☐ Yes ☒ N/A
FD&C Yellow No. 5 and/or FD&C Yellow No. 6 21 CFR 201.20	☐ No ☐ Yes ☒ N/A
Phenylalanine as a component of aspartame 21 CFR 201.21	☐ No ☐ Yes ☒ N/A
Sulfites; required warning statements 21 CFR 201.22	☐ No ☐ Yes ☒ N/A
Net quantity 21 CFR 201.51	☐ No ☒ Yes ☐ N/A
Usual dosage statement 21 CFR 201.55 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
Dispensing container 21 CFR 201.100	☐ No ☐ Yes ☒ N/A
Medication Guide 21 CFR 610.60 21 CFR 208.24	☐ No ☐ Yes ☒ N/A

Prescribing Information and Patient Labeling Evaluation

Regulations	Conforms
PRESCRIBING INFORMATION	
Highlights of prescribing information	
PRODUCT TITLE 21 CFR 201.57(a)(2)	☒ No ☐ Yes ☐ N/A
Comment/Recommendation: Revise the route of administration in the product title to "for intramuscular use" per FDA Guidance https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm592850.pdf *The applicant revised as requested*	
DOSAGE AND ADMINISTRATION 21 CFR 201.57(a)(7)	☐ No ☒ Yes ☐ N/A
DOSAGE FORMS AND STRENGTHS 21 CFR 201.57(a)(8)	☒ No ☐ Yes ☐ N/A
Comment/Recommendation: We added the dosage form per 21 CFR 201.57(a)(8) The appropriate package-type term for this product is "single-dose". A single-dose container is a	

container of a sterile medication for parenteral administration (injection or infusion) that is not required to meet the antimicrobial effectiveness testing requirements. A single-dose container is designed for use with a single patient as a single injection/ infusion. Use of the term "single-dose" container does not imply the entire contents of the container constitute a single dose. In some instances, a single-dose container may contain more drug than is required for a single dose or multiple vials may be needed to obtain a single dose.

The applicant revised as requested

Per USP General Chapters: <7> Labeling, for injectable products with containers that supply a volume of drug greater than 1 mL, the primary expression of strength is the strength per total volume followed in close proximity by a parenthetical that includes the strength/mL. We revised the strength presentation to read "2.4 mg/1.5 mL (1.6 mg/mL)"
The applicant revised as requested

Full Prescribing Information

2 DOSAGE AND ADMINISTRATION
21 CFR 201.57(c)(3)

☒ No ☐ Yes ☐ N/A

Comment/Recommendation: We added "Visually inspect TRADE NAME for particulate matter and discoloration prior to administration. TRADE NAME is a clear colorless solution, discard if solution is discolored or cloudy."
The applicant revised as requested

3 DOSAGE FORMS AND STRENGTHS
21 CFR 201.57(c)(4)

☒ No ☐ Yes ☐ N/A

Comment/Recommendation: We added the dosage form per 21 CFR 201.57(c)(4)
The applicant revised as requested
We added the identifying characteristics per 21 CFR 201.57(c)(4).
The applicant revised as requested
We revised to the appropriate package type term
The applicant revised as requested

6.2 IMMUNOGENICITY
Draft Guidance for Industry: Labeling for Biosimilar Products

☐ No ☒ Yes ☐ N/A

11 DESCRIPTION
(21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q))

☒ No ☐ Yes ☐ N/A

Comment/Recommendation: We deleted the proprietary name from this first paragraph since it discusses the drug substance.
The applicant revised as requested

We added the dosage form per 21 CFR 201.57(c)(12)
The applicant revised as requested
We added the route of administration per 21 CFR 201.57(c)(12)
The applicant revised as requested
We added the list of all inactive ingredients per 21 CFR 201.57(c)(12) and listed them in alphabetical order per USP General Chapters <1091> Labeling of inactive ingredients
The applicant revised as requested

16 HOW SUPPLIED/ STORAGE AND HANDLING
21 CFR 201.57(c)(17)

☒ No
☐ Yes
☐ N/A

Comment/Recommendation: We added the dosage from and identifying characteristics per 21 CFR 201.57(c)(17)
The applicant revised as requested
We ask that the applicant add the NDC # per 21 CFR 201.57(c)(17)
The applicant revised as requested
We relocated discard instructions to section 2.2
The applicant revised as requested
We deleted the statement (b) (4) The instructions to store in the refrigerator may be sufficient.
The applicant revised as requested

MANUFACTURER INFORMATION
21 CFR 610.61, 21 CFR 610.64

☒ No
☐ Yes
☐ N/A

Comment/Recommendation: To comply with 21 CFR 610.61(b), we revised the manufacturer information to appear as the name and address of the manufacturer listed as the applicant on FDA form 356h. We added the US license number to appear after the manufacturer name and address. The drug manufacturing site (Exelead Inc. Indianapolis, IN) may be included if the requirements for 21 CFR 610.61(b) are met. We revised the drug manufacturing site statement to read "at Exelead Inc. Indianapolis, IN 46268"
The applicant revised as requested

APPENDIX D. Acceptable Labels and Labeling

Prescribing Information (submitted on August 1, 2018 **\\cdsesub1\evsprod\bla761092\0032\m1\us\114-labeling\114a-draft-label\draft-labeling-text.pdf**)

Container Labels (submitted on July 12, 2018)

(b) (4)

Carton Labeling (submitted on July 12, 2018)

Note per cover letter dated July 12, 2018: Leadiant has decided to launch Revcovi in the single vial per carton presentation and therefore only the single vial carton label has been revised at this time. (b) (4)

(b) (4)

(b) (4)

Zhenzhen Liu

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Vicky Borders-Hemphill

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Center for Drug Evaluation and Research
WO Bldg. 22
10903 New Hampshire Ave
Silver Spring, MD 20993

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

Reviewer: Maria Jose Lopez-Barragan, Ph.D.
Branch Chief: Patricia Hughes, Ph.D.

BLA:	761092/0
Applicant:	Leadiant Biosciences, Inc.
US License:	2073
Subject:	Original Biologic License Application
Facilities:	(b) (4)
Product:	REVCOVI® (elapegademase; SC-PEG rADA; Monomethoxypolytheylene glycol) recombinant adenosine deaminase; internal company name: EZ-002
Dosage:	Sterile solution (1.6 mg/mL) in single use vials for intramuscular injection
Indication:	Treatment of adenosine deaminase severe combined immunodeficiency (ADA-SCID)
Goal date:	8/24/2018

Recommendation for approvability: The (b) (4) drug substance sections of BLA 761092, as amended, are recommended for approval from a microbial control and microbiology product quality perspective with the following post-marketing commitments:

1. Provide data from two additional rADA studies to support the (b) (4) hold times of the (b) (4) (b) (4) from a microbial control perspective.
2. (b) (4)
3. Conduct bioburden and endotoxin method qualifications using two additional batches of the SC-PEG rADA (b) (4) bulk drug substance.

SUMMARY

Leadiant Biosciences, Inc. has submitted BLA 761092 to obtain approval of REVCOVI® (elapegademase). Elapegademase (SC-PEG rADA) is a PEGylated recombinant (b) (4) bovine ADA. (b) (4) (b) (4)

BLA 761092 was submitted as a rolling BLA with the first rolling component submitted on 7/14/2018 and the final (fourth) rolling component submitted on 10/24/2018. CMC components (Module 3) were submitted in amendments 0002 and 0003.

This review contains the assessment of elapegademase dug substance (DS) (b) (4) (b) (4) from a microbiology product quality perspective. Microbiology product quality and sterility assurance of REVCOVI® drug product were reviewed by Dr. Lakshmi Narasimhan.

DS (b) (4) Microbiology Quality Information Reviewed

Description	eCTD Sequence	Date
Original BLA (rolling)	0002	8/15/2017
Original BLA (rolling)	0003	9/15/2017
Amendment (response to Information Request)	0006	12/22/2017
Amendment (response to Information Request)	0014	5/11/2018
Amendment (response to Information Request/Q3)	0025	7/18/2018
Amendment (response to Information Request)	0031	7/31/2018

(b) (4)

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Patricia Hughes Troost

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U.S. FOOD & DRUG ADMINISTRATION

Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue,
Building 22,
Silver Spring, MD 20993

Date: July 31, 2018
To: Administrative File, BLA 761092\0
From: Lakshmi Rani Narasimhan, Ph.D., CDER/OPQ/OPF/DMA
Endorsement: Patricia F. Hughes, Ph.D., Acting Branch Chief, CDER/ OPQ/OPF/DMA
Subject: Biological License Application (BLA)
US License: 2073
Applicant: Leadiant Biosciences, Inc.
Facility: Exelead, Inc. (Formerly Sigma-Tau PharmaSource, Inc.), 6925 Guion Road, Indianapolis, IN 46268 (FEI #1835063)
Product: Revcovi (Elapegademase) SC-PEG rADA
Dosage: Sterile, solution for intramuscular injection in a single use vial (1.6 mg/mL)
Indication: For the treatment of adenosine deaminase severe combined immune deficiency (ADA-SCID)
Due Date: August 24, 2018

Recommendation for Approvability: The drug product section of this BLA, as amended, is recommended for approval from a product quality microbiology perspective.

SUMMARY: Leadiant Biosciences Inc. has submitted a new biologics license application, BLA 761092 to license the use of Elapegademase (SC-PEG rADA). SC-PEG rADA drug product is PEGylated recombinant adenosine deaminase. The drug substance (b) (4) is manufactured by (b) (4) (b) (4)

The application was submitted in eCTD format and included Module 1.1.2 - FDA form 356h, Module 1.2 - Cover letter, and 1.14 – Labeling, Module 2 and Module 3.
Letter of authorization (LOA) for (b) (4) Type V DMF (b) (4) (b) (4) are provided.

INTRODUCTION:
Elapegademase (SC-PEG rADA) drug product (DP) is manufactured by (b) (4) (b) (4) Exelead, Inc., Indianapolis, IN.

This review covers the evaluation of the drug product aspects of the application from a product quality microbiology perspective.

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0003	September 15, 2017	Original
0006	December 22, 2017	IR response
0010	April 06, 2018	IR response
0014	May 11, 2018	IR response
0018	June 20, 2018	IR response
0019	June 21, 2018	IR response
0022	July 13, 2018	IR response
0025	July 18, 2018	IR response
0028	July 27, 2018	IR response
0030	July 27, 2018	IR response

ASSESSMENTS:

3.2. P DRUG PRODUCT

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

DP is a preservative-free, sterile, and clear, colorless liquid presented in a single-use vial for intramuscular administration. Each vial contains 1.5 mL of 1.6 mg/mL DP in (b) (4) saline ((b) (4) pH 6.9, (b) (4)% sodium chloride). The composition of DP provided in Table 1 is reproduced below.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

[a] Sodium p
monograph

(b) (4)

(b) (4)

(b) (4)

Satisfactory

3.2. P.2 PHARMACEUTICAL DEVELOPMENT

Microbiological Attributes

The DP solution is (b) (4)

(b) (4)

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Patricia Hughes Troost

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