CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761102Orig1s000

PRODUCT QUALITY REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Biotechnology Products

BLA 761102

Asparlas™ [Calaspargase Pegol]

Baxalta, Inc.

Xu Di, Ph.D., Chemist
Frances Namuswe, Ph.D., Team Leader

Division of Biotechnology Research and Review III
Office of Biotechnology Products (OBP)
Office of Pharmaceutical Quality (OPQ)
Center for Drug Evaluation and Research (CDER)

OBP CMC Review Data Sheet

1. BLA: 761102

2. Review Date: 4/9/2018, 5/7/2018, 6/18/2018, 7/26/2018, 8/13/2018, 9/10/2018

3. Primary Review Team:

a. Medical Officer: Patricia Dinndorf / Donna Przepiorka (Team Leader)
b. Pharm/Tox: Michael Manning/ Christopher Sheth (Team Leader)
c. Product Quality Team: OBP Xu Di / Frances Namuswe (Team Leader)
DMA Lakshmi Narasimhan (DS)/ Bo Chi (DP)/ Maria Jose Lopez-Barragan (Team Leader)
d. Facilities: Zhong Li/ Peter Qiu (Team Leader)
e. Clinical Pharmacology: Runyan Jin/ Xianhua Cao (Team Leader)
f. Statistics: Kunthel By/ Yuan Li Shen (Team Leader)
g. OBP Labeling: Scott Dallas
h. RBPM: Kelly Ballard

4. Major GRMP Deadlines:

a. Filing Meeting: February 9, 2018
b. Mid-cycle meeting: June 7, 2018
c. Wrap-up meeting: October 31, 2018
d. Primary review due: Original: August 22, 2018; New: November 28, 2018
e. Secondary review due: Original: August 27, 2018; New: November 28, 2018
f. PDUFA action date: December 22, 2018

5. Communications with Sponsor and OND:

Communication/Document:	Date:
Information Request #1	May 30, 2018
Information Request #2	July 17, 2018
Information Request #3	July 27, 2018
Information Request #4	July 27, 2018
Information Request #5	September 20, 2018
Information Request #6	November 1, 2018
Information Request #7	November 13, 2018
Information Request #8	November 20, 2018
Information Request #9	November 27, 2018

6. Submission Reviewed:

Submission:	Date Received:	Review Completed (yes or no)
STN 761102 / 18 (response to information request #1)	July 20, 2018	Yes

STN 761102 / 25 (response to information request #2)	July 27, 2018	Yes
STN 761102 / 26 (response to information request #3)	August 8, 2018	Yes
STN 761102 / 27 (response to information request #4)	August 8, 2018	Yes
STN 761102 / 32/34/35 (response to information request #5)	October 5, 2018 and October 19, 2018	Yes
STN 761102 / 37 (response to information request #6)	November 8, 2018	Yes
STN 761102 / 39 (response to information request #7)	November 16, 2018	Yes
STN 761102 / 42 (response to information request #8)	November 21, 2018	Yes
STN 761102 / 43 (response to information request #9)	November 28, 2018	Yes

7. Drug Product Name/Code/Type:

a. Proprietary Name: Asparlas™
b. Trade Name: Asparlas™
c. Non-Proprietary Name/USAN: Calaspargase Pegol
d. CAS Name: 941577-06-6
e. Common Name: Calaspargase Pegol
f. INN Name: Calaspargase Pegol
g. Compendial Name: Not assigned
h. OBP systematic name (refer to OPQ-SOP-OBP-3006):
CONJ: RPROT Q7L266 (ASGL1_HUMAN); PEG [EZN-2285]
i. Other names: EZN-2285, SC-PEG (succinimidyl carbonate-polyethylene glycol) *E. coli* L-asparaginase, SC-PEG L-asparaginase, PEG-L-ASNase

8. Pharmacological Category: Asparagine-specific enzyme

9. Dosage Form: Injection

10. Strength/Potency:

(i): 3750 IU/5 mL single use glass vial
(ii): Type of potency assay(s): RP-HPLC and Enzyme Kinetics

11. Route of Administration: Intravenous infusion

12. Referenced Drug Master Files (DMF):

DMF#	DMF Holder	Item Referenced	Letter of Cross-Reference	Comments (status)

DMF (b) (4) Type II	(b) (4)	Yes	DMF was reviewed by an ONDP reviewer and found adequate to support the BLA
DMF (b) (4) Type III		Yes	DMF was reviewed by an ONDP reviewer. The data in the DMF are adequate to support the BLA
DMF (b) (4) Type V		Yes	DMF review deferred to the DMA reviewer
DMF (b) (4)		Yes	DMF was reviewed by an ONDP reviewer and found adequate to support the BLA

Reviewer Comment:

(b) (4)

13. Inspectional Activities:

A pre-approval inspection (PAI) for the CalPEG DS and DP manufacturing site at (b) (4) was conducted on (b) (4) by DMA reviewers Bo Chi and Lakshmi Narasimhan, OBP reviewers Zhenzhen Liu and Steven Bowen, and ORA reviewer Jazmine Still. The site is responsible for manufacture of DS and DP, packaging and labeling, and DP release and stability testing. The inspection was system based and covered Quality, Facilities and Equipment, Production, Laboratory Control and Materials. Fifteen (15) 483 observations were issued at the end of the inspection. The inspection was classified as voluntary action indicated (VAI). The details of the inspection are covered in the EIR. Subsequent to the PAI, a FDA cGMP surveillance inspection of the (b) (4) site was performed by FDA ORA inspectors on (b) (4) Like the PAI, the surveillance inspection discovered several problems related to (b) (4) (b) (4). The FDA inspector recommended the inspection be classified as OAI, but subsequently downgraded to VAI due to appropriate responses from the Sponsor.

14. Consults Requested by OBP:

Since DMF (b) (4) for the (b) (4) had not been previously reviewed, OBP requested consult review of DMF (b) (4) by ONDP. ONDP reviewed the DMF and indicated that (b) (4) is of adequate quality to support the BLA.

15. Quality by Design Elements:

The following was submitted in the identification of QbD elements (check any that apply):

	Design Space
x	Design of Experiments
x	Formal Risk Assessment/Risk Management
x	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

16. Precedents:

Oncaspar is an asparagine specific enzyme approved by the FDA as a component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukemia. The same drug substance (b) (4) currently used in the manufacture of both Oncaspar and Calaspargase pegol is manufactured at the (b) (4)

17. Administrative:

Name and Title	Signature and Date
Xu Di, Ph.D. Product Quality and Immunogenicity Reviewer CDER/OPQ/OBP/DBRRIII	(at the end of the document)
Frances Namuswe, Ph.D. Team Leader, CDER/OPQ/OBP/DBRRIII Maria Gutierrez Lugo, Ph.D. Review Chief, CDER/OPQ/OBP/DBRRIII	(at the end of the document)

Summary of Quality Assessments

I. Primary Reviewer Summary Recommendation

We recommend approval of Calaspargase Pegol (CalPEG) BLA 761102 from an OBP product quality perspective. This review covers the information provided in sections 3.2.S Drug Substance, 3.2.P Drug Product, 3.2.A. Adventitious Agents Safety Evaluation and 3.2.R, Regional Information.

The CalPEG product quality information supports the approval of this BLA. The CalPEG drug substance (DS) and drug product (DP) is well characterized and free of adventitious infectious agents. The conditions used in the DS and DP manufacturing processes have been adequately validated. The process validation results demonstrate that the proposed commercial manufacturing process can consistently produce a pure and potent product. The Sponsor provided 36 months real time stability results for 3 PPQ lots and 4 clinical lots to support the

proposed 36 months expiry for CalPEG DP. No significant deficiencies have been identified during the review of BLA 761102 to date that preclude approval of this application from OBP's perspective. The adequacy of the immunogenicity assays and a risk assessment of the immunogenicity profile of CalPEG are covered in a separate review memo.

II. List of Deficiencies to be Communicated

None.

III. List of Post-Marketing Commitments/Requirements

1. *To perform a leachables study to evaluate leachables from the container closure system of Calapargase Pegol drug product and assess the potential impact of leachables on product quality at the end of the shelf-life. The analysis will be performed using one drug product lot and/or a representative sample (e.g. formulation buffer) 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 the potential impact on product quality will be assessed using adequate analytical methods. Complete data and the risk evaluation for the potential impact of leachables on product safety and quality will be submitted in accordance with 21 CFR 601.12.*

   PMC Milestone Date
   Final Report Submission: 6/30/2022

2. *To perform a shipping validation study under real time shipping conditions (i.e. temperature, mode of transport, shipping duration, and shipping containers and packing representative of the minimum and maximum load) using a representative commercial* (b) (4) (b) (4) *lot in the final commercial container closure and packaging systems to evaluate the ability of the shipping containers to maintain the recommended temperature and to evaluate the impact of shipping on the quality the of* (b) (4) *The shipping validation data will be submitted in accordance with 21 CFR 601.12.*

   PMC Milestone Date
   Final Report Submission: 7/31/2020

3. *To perform a shipping validation study under real time shipping conditions (i.e. temperature, mode of transport, shipping duration, and shipping containers and packing representative of the minimum and maximum load) using a representative commercial Calaspargase pegol drug product lot in the final commercial container closure and packaging systems to evaluate the ability of the shipping containers to maintain the recommended temperature and to evaluate the impact of shipping from the manufacturing site(s) to the distribution site(s) on the physical integrity and product quality of Calaspargase pegol drug product. The shipping validation data will be submitted in accordance with 21 CFR 601.12.*

PMC Milestone Date
Final Report Submission: 7/31/2020

IV. Review of Common Technical Document- Quality Module 1

A. Environmental Assessment or Claim of Categorical Exclusion

The sponsor requests a categorical exclusion from the requirement to prepare an environmental assessment in accordance with 21 CFR 25.31(c) and indicates that there are no extraordinary circumstances that may significantly affect the quality of the human environment. The claim of categorical exemption is acceptable because CalPEG is a protein product that occurs naturally and will be broken down in the environment. (b) (4) Therefore, it is not expected to significantly increase the amount of product entering the environment.

V. Primary Container Labeling Review

The CMC labeling review was conducted by OBP labeling officer: Scott Dallas, Pharma.D.

VI. Review of Common Technical Document- Quality Module 3.2

This document contains the review of the information provided for Calaspargase pegol drug substance (DS) (DS Section 3.2.S), and drug product (DP) (DP Section 3.2.P), the adventitious agents safety evaluation (3.2.A), and the batch records (3.2.R).

VII. Review of Immunogenicity Assays- Module 5.3.1.4

A review of the immunogenicity assays is provided in a separate review document.

Table of Contents

Description of Drug Substance and Drug Product

Background

The previous Sponsor for calaspagase pegol (EZN-2285, CalPEG), Sigma-Tau, (b) (4) The efficacy and safety data provided in current BLA761102 were derived from both AALL07P4 and DCFI 11-001 studies. In study DCFI 11-001, CalPEG was administrated to patients at a dose of 2500 IU/m2 at no more than every 21 days.

S. Drug Substance

(b) (4)

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Reviewer Comment:
Overall, the proposed shelf life of 36 months for CalPEG DP is supported by the following reasons:

(b) (4)

Therefore, the proposed 36-month shelf life at the long-term storage conditions of 5±3°C is acceptable for CalPEG DP.

3.2.A Appendices

3.2.A.2 Adventitious Agents Safety Evaluation

1. Viral Adventitious Agents/TSE
The Sponsor provided the following justification to demonstrate that the DP is free of viral adventitious agents and transmissible spongiform encephalopathy (TSE) agents.

1. The L-asparaginase is produced in *E.coli* and virus cannot replicate and survive in a bacterial cell host.
2. (b) (4)
3. The potential contamination (b) (4) is verified (b) (4)

2. No-Viral Adventitious Agents
1. Microbial Contamination
Microbial contamination is monitored and controlled by (b) (4) microbial control tests and a summary of various controls and operations, which contribute to the biological safety of the product is provided in Table 1 below.

(b) (4)

(b) (4)

Reviewer Comment:

(b) (4)

Therefore, the sponsor's viral evaluation is acceptable from OBP's perspective. For microbiology testing and controls, we defer to DMA.

3.2.R Regional Information

3.2. R1. Batch Records

The master batch records for DS and DP, and the batch records for DS and DP clinical lots 3058, 3059, and 4096 manufactured at the (b) (4) facility were provided in the BLA.

Reviewer Comments:
Both the master and executed batch records have been reviewed and considered to be acceptable.

Xu
Di

Digitally signed by Xu Di
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Maria
Gutierrez Lugo

Digitally signed by Maria Gutierrez Lugo
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Comments: Signing for Frances Namuswe