

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
12553Orig1s000

MICROBIOLOGY/VIROLOGY REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

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

Date: 01/30/2015
To: Administrative File, STN 125553
From: Steven Fong, Ph.D., Microbiologist, CDER/OPQ/OPF/DIA/Branch 1
Endorsement: Patricia Hughes, Ph.D., Quality Assessment Lead, CDER/OPQ/OPF/DMA/Branch IV
Subject: Original BLA
US License: 2003
Applicant: Sandoz, Inc.
Facility: GP Grenzach Produktions GmbH, Grenzach-Wyhlen, Germany
FEI 3006308309
Product: EP2006
Dosage: 10 mg/kg/day administered by IV infusion over 4 or 24 hours, or continuous subcutaneous infusion over 24 hours. Provided in prefilled syringes containing 300 mg/0.5 mL and 480 mg/0.8 mL sterile EP2006 DP solution.
Indication: All indications for which US-licensed Neupogen is currently licensed
Due date: BsUFA goal date: 03/08/2015

Recommendation on Approvability – The 351(k) BLA is recommended for approval from a product quality microbiology perspective. One PMC is listed at the end of the Review.

Drug Product Review: EP2006 DP Manufacture at GP Grenzach Produktions GmbH, Grenzach-Wyhlen, Germany

Summary:

The subject 351(k) BLA proposes marketing of EP2006 as a proposed biosimilar to US-licensed Neupogen for all indications for which US-licensed Neupogen is currently licensed. The EP2006 API is an *E. coli*-expressed, non-glycosylated, 175 amino acid biosimilar for recombinant human granulocyte colony stimulating factor (rh-GCSF) that contains two intramolecular disulfide bonds between Cys³⁷-Cys⁴³ and Cys⁶⁵-Cys⁷⁵. The reference product, US-licensed Neupogen, is licensed under BLA 103353 by Amgen, Inc.

EP2006 DP manufacture will be conducted at the GP Grenzach Produktions GmbH (b) (4) manufacturing facility in Grenzach-Wyhlen, Germany (Grenzach). (b) (4)

STN 125553 Sandoz EP2006

The current Review considers DP microbiology quality information provided in the submissions listed below in Table 1. The submissions included responses to four IRs. A LOA dated 10/01/2014 to review DMF [REDACTED] (b) (4), was provided in SDN 15. The IR questions and one PMC are presented at the end of the Review.

TABLE 1. Summary of Submissions reviewed in Current DP Microbiology Quality Review

eCTD Sequence Number	Support Document Number (SDN)	Receipt Date	IR Being Responded to	Comments
0000	1	05/08/2014	N/A	Original BLA
0008	9	07/01/2014	IR-1 submitted 06/25/2014	SDN 9 contained responses regarding [REDACTED] (b) (4) validation.
0013	14	09/30/2014	IR-2 submitted 09/17/2014	SDN 14 contained responses to IR-2 Questions 2b - 16.
0014	15	10/10/2014	IR-2 submitted 09/17/2014	SDN 15 contained responses to IR-2 Questions 1 – 2a.
0022	23	12/19/2014	IR-3 submitted 10/16/2014	Annex 02 of SDN 23 presented data demonstrating that CCIT is maintained following worst case shipping conditions.
0023	24	01/22/2015	IR-4 submitted 01/13/2015	SDN 24 presented data concerning sensitivity of the dye ingress CCIT assay, (b) (4) endotoxin testing, [REDACTED] (b) (4) and [REDACTED] (b) (4) validation.



(b) (4)

cGMP Status

Please see the TB-EER assessment.

Conclusion

- I. The BLA is recommended for approval from a sterility assurance and microbiology quality standpoint.
- II. Information and data in this submission not related to drug product sterility assurance was not evaluated and should be reviewed by an OBP reviewer.
- III. No inspectional follow-up items were identified.

Steven Fong -S

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ou=FDA, ou=People, cn=Steven Fong -S,
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**Patricia F.
Hughestroost
-S**

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6547, cn=Patricia F. Hughestroost -S
Date: 2015.02.02 07:41:55 -05'00'

Cc: Jessica Boehmer, Bo Chi, Maria Gutierrez-Lugo, Zhihao Qiu.
File Name: 125553.rev.mem.BLA.DP.01.30.2015.



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

Date: 1/22/2015
To: Administrative File, **STN 125553/0**
From: Bo Chi, Ph.D., CDER/OPQ/OPF/DMA
Endorsement: Patricia Hughes, Ph.D., Quality Assessment Lead, CDER/OPQ/OPF/DMA
Subject: New 351(k) Biologic License Applications (BLA)
Applicant: Sandoz Inc.
US License: 2003
Facility: Sandoz GmbH
Biochemiestrasse 10
A-6250 Kundl, Austria
FEI: 3002806523
Product: EP2006
Dosage: 300 mcg/0.5mL and 480 mcg/0.8 mL, Intravenous or subcutaneous, injection or infusion
Indication: Patients With Severe Chronic Neutropenia; Cancer Patients Receiving Myelosuppressive Chemotherapy; Cancer Patients Receiving Bone Marrow Transplant; Patients With Severe Chronic Neutropenia; Patients undergoing progenitor cell therapy
BsUFA date: March 8, 2015

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

Establish bioburden and endotoxin action limits [REDACTED] (b) (4) after data from more than 20 batches are available.

Conduct studies to support the worst-case hold times [REDACTED] (b) (4)
[REDACTED] (b) (4)
at scale from microbiology perspective.

Review Summary

Sandoz has submitted this Biologics License Application (BLA) under 351(k) of the Public Health Service Act for EP2006 to seek licensure for the same indications for which the reference product Neupogen is approved. The drug substance (DS) is manufactured at the Sandoz GmbH,

Kundl, Austria. The drug product (DP) is manufactured at GP Grenzach Produktions GmbH, Grenzach-Wyhlen, Germany. The application contains CMC information in an eCTD format.

This review contains the assessments of the manufacturing process of EP2006 drug substance from microbiology perspective.

(b) (4)



Primary reviewer signature

Bo Chi -A

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Chi -A,
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Secondary reviewer signature

**Patricia F.
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