CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208114Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

Product Quality Microbiology Review

16 DEC 2015

NDA: 208-114

Drug Product Name
Proprietary: Defitelio
Non-proprietary: Defibrotide

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
30 MAR 2015	30 MAR 2015	15 DEC 2014	22 DEC 2014
28 AUG 2015	28 AUG 2015	N/A	N/A
04 DEC 2015	04 DEC 2015	N/A	N/A

Applicant/Sponsor
Name: Gentium S.p.A. (a Jazz Pharmaceuticals company)
Address: Piazza XX, Settembre 2
Villa Guardia, Italy
Representative: Robin L. Hume
Telephone: 650-496-2903

Name of Reviewer: Jessica G. Cole, PhD

Conclusion: Recommended for Approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original 505(b)(1) NDA with a rolling submission

2. SUBMISSION PROVIDES FOR: A new drug product

3. MANUFACTURING SITE:
(b) (4)

FDA Registration number: 3004110157

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

- 200 mg in a (b) (4) mL glass vial with 13 mm rubber stopper
- 80 mg/mL solution for IV infusion

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Indicated for the treatment of (b) (4) hepatic vena-occlusive disease following hematopoietic stem cell transplant (HSCT)

B. SUPPORTING/RELATED DOCUMENTS: The 04 December 2014 microbiology review of DMF (b) (4) found (b) (4) be adequate.

C. REMARKS: This submission is in the eCTD format. An information request was sent on 21 July 2015 and 06 November 2015 and the responses are incorporated into the text of this review.

filename: N208114R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability - Recommended for Approval

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – Not applicable

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The product is (b) (4) [redacted] he final product is diluted prior to administration.

B. Brief Description of Microbiology Deficiencies – Not applicable.

C. Contains Potential Precedent Decision(s)- ☐ **Yes** ☒ **No**

III. Product Quality Microbiology Risk Assessment

A. Initial Product Quality Microbiology Risk Assessment

CQA	Risk Factor	Prob. of Occ. (O)	Modifier for O[3, 4, 5]	Severity of Effect (S)	Detect. (D)	Risk Priority Number[6] (RPN)	Additional Review Emphasis based on Risk (in addition to normal review process)
Ster.	(b) (4) [redacted]	10	+2 (4 and 5)	5	5	300	(b) (4) [redacted]
Endo		2		4	4	32	

(b) (4) [redacted]

B. Final Risk Assessment – The (b) (4) [redacted] and (b) (4) [redacted] validation studies were provided and support the proposed manufacturing process. The post-dilution hold times are limited and the release specifications are appropriate. The information provided demonstrates that the manufacturing process is controlled and will minimize patient risk due to sterility and endotoxin issues. The viral clearance data for the drug substance was reviewed by OBP.

IV. Administrative

A. Reviewer's Signature _____
Jessica G. Cole, PhD

B. Endorsement Block _____
Stephen E. Langille, PhD

Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q)
MODULE 3.2: BODY OF DATA

S DRUG SUBSTANCE The drug substance is tested according to USP<61> and <62> with ≤ (b) (4) EU/mg. The drug substance is (b) (4) from porcine intestines. See the Office of Biological Product review for more information on the viral clearance information for the drug substance.

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- **Description of drug product** – Sterile, single dose solution in a (b) (4) mL glass vial.
- **Drug product composition** –

Table 1- Drug product composition (Applicant Table 1 Module 3.2.P.1.2)

Component	Reference to Standard Quality	Function	80 mg/mL for Infusion	Concentration per mL
Defibrotide	In-house standard	Drug Substance	200.0 mg	80.0 mg
Sodium Citrate (b) (4)	USP – Ph. Eur.	(b) (4)	(b) (4)	10.0 mg
Water-for-injection	USP – Ph. Eur.	(b) (4)	q.s. to 2.5 mL[a]	(b) (4)
Sodium hydroxide (b) (4) hydrochloric acid	NF – Ph. Eur. NF – Ph. Eur.	pH adjustment	As required for pH 6.8–7.8	As required for pH 6.8–7.8

(b) (4)

(b) (4)

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Jessica Cole -S

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Date: 2015.12.16 11:23:57 -05'00'

Stephen E. Langille -S

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Date: 2015.12.17 10:40:49 -05'00'