CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208114Orig1s000

CHEMISTRY REVIEW(S)

QUALITY ASSESSMENT

Recommendation: Approval

NDA 208114
Addendum to Review #1
Review Date: March 25, 2016

Drug Name/Dosage Form	Defibrotide Injection
Strength	200 mg/2.5 mL
Route of Administration	IV
Rx/OTC Dispensed	Rx
Applicant	Gentium S.p.A (a Jazz Pharmaceuticals company)
US agent, if applicable	Robin L. Hume

SUBMISSION(S) REVIEWED	DOCUMENT DATE
0001	3/30/2015
0002	7/31/2015
0004	08/28/2015
0007	09/24/2015
0011	10/19/2015
0015	11/10/2015
0016	11/16/2015
0022	12/04/2015

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Joseph Leginus	Branch II/New Drug API
Drug Product	Nina Ni	Branch II/DNDPI/ONDP
Process	Youmin Wang	Branch VII/OPF
Microbiology	Jessica Cole	
Facility	Robert Wittorf	
Biopharmaceutics	Gerlie Gieser	
Project/Business Process Manager	Rabiya Laiq	
Application Technical Lead	Anamitro Banerjee	Branch II/DNDPI/ONDP
Laboratory (OTR)		
ORA Lead		
Environmental Analysis (EA)	Raanan Bloom	ONDP/IO

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Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION:

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type III		(b) (4)	N/A	N/A	
	Type III			N/A	N/A	
	Type III			N/A	N/A	

[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	62118	Defibrotide Injection

3. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
OBP	Complete	Approval	14-Dec-15	Ennan Guan, Ph.D.

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Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant has provided adequate CMC information. No CMC deficiencies were identified. Facility review was pending at the time of Review 1. The facility review is now complete. ***All the facilities are now acceptable.*** This NDA is recommended for APPROVAL.

The executive summary from Review 1 is reproduced here for completeness.

Benefit/Risk Considerations: None

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

As per recommendation of the OBP reviewer Dr. Ennan Guan, the following Post marketing commitments were made by the applicant:

PMC# 3056-2: Develop a sensitive and specific anti-drug (defibrotide) binding and neutralizing assay. Submit validation reports on the assay in a final report to the NDA.

PMC Schedule Milestones:

Submission of Final Binding (total ADA) Assay Validation Report: 01/2017

Submission of NAb Assay Validation Report: 01/2021

PMC# 3056-3: Evaluate patients' sera for binding and neutralizing antibodies to defibrotide using the validated assay from PMC#2 and patient samples from a randomized, open-label multi-center clinical trial comparing defibrotide versus best supportive care in the prevention of hepatic veno-occlusive disease in adult and pediatric patients, and submit the data in a final immunogenicity study report.

PMC Schedule Milestones:

Final Protocol Submission: 04/2016

Final Trial Completion: 07/2021

Final Immunogenicity Report Submission: 01/2019

Other: Initial Protocol Submission: 01/2016

II. Summary of Quality Assessments

A. Drug Substance Defibrotide Quality Summary

1. Chemical Name or IUPAC Name/Structure

Chemical Name: Polydeoxyribonucleotide, sodium salt
USAN Name: Defibrotide sodium

2. Properties/CQAs Relevant to Drug Product Quality

Properties: Solubility of the API at pH range 6.8 7.8 in (b) (4) and stability in solution.
CQAs: Molecular weight distribution of the DNA fragments
Impurities related to the starting material and product
Viral load

3. List of starting materials

(b) (4)

4. Suppliers of starting materials (site)

(b) (4)

5 Summary of Synthesis

(b) (4)

6 Process

(b) (4)

(b) (4)

8. Retest Period & Storage Conditions

A retest period of (b) (4) months at (b) (4) is granted for the drug substance when stored in the proposed container closure.

B. Drug Product Defitelio (defibrotide) Injection Quality Summary

1. Strength

Sodium salt: 80 mg/mL sterile aqueous solution. (b) (4)

(b) (4)

2. Description/Commercial Image

The defibrotide drug product is a sterile aqueous solution for intravenous administration packaged in a 3.2 mL clear glass vial sealed with a (b) (4) stopper and (b) (4) (b) (4) flip off seal. Each carton contains 10 vials.

3. Summary of Product Design

The injectable formulation for intravenous administration is the drug substance and a vehicle contained in an (b) (4) single use glass container. A citrate (b) (4) is used (b) (4) The applicant has provided comparability product profile and stability data for the current formulation (b) (4) No overage is used in the solution formulation. The batch size is approximately (b) (4) from a bulk solution of approximately (b) (4) L.

4. List of Excipients:

All the excipients are compendial: sodium citrate (b) (4) USP (b) (4) water for injection, USP (b) (4), sodium hydroxide (b) (4) NF (pH adjuster) or hydrochloric acid (b) (4) NF (pH adjuster). No novel or excipients from human or animal origin were used.

5. Process Selection (Unit Operations Summary)

The manufacturing process is (b) (4)

(b) (4)

(b) (4)

6. Container Closure

The drug product is packaged in 3.2 mL Type I neutral, clear (b) (4) glass vials with 13 mm (b) (4) stopper and a 13 mm (b) (4) flip-off cap. Container closure integrity test is performed on the vials (b) (4) The leachable/extractables study results provided by the applicant are acceptable. Based on the data provided by the applicant, lack of control for leachable and extractables in the final drug product specification is acceptable.

7. Expiration Date & Storage Conditions

The applicant provided primary and supporting stability data support the storage of the drug product under controlled room temperature 20 25°C (68 77°F) with the excursions permitted to 15 30°C (59 86°F). The proposed expiration dating period of 36 months for the drug product is supported by the real time (36 months) data from both primary stability batches and supporting stability batches, and thus granted.

8. List of co-packaged components

None

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Defitelio®
Non Proprietary Name of the Drug Product	Defibrotide injection
Non Proprietary Name of the Drug Substance	Defibrotide sodium
Proposed Indication(s) including Intended Patient Population	Treatment of patients with hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), (b) (4) following hematopoietic stem-cell transplantation (HSCT)
Duration of Treatment	A minimum of 21 days. If after 21 days signs and symptoms of VOD have not resolved, continue treatment until resolution
Maximum Daily Dose	6.25 mg/kg body weight given as a 2-hour intravenous infusion every 6 hours
Alternative Methods of Administration	N/A

D. Biopharmaceutics Considerations

1. BCS Classification: Not Applicable since the proposed drug product is not for oral administration
    - Drug Substance: N/A
    - Drug Product: N/A

2. Biowaivers/Biostudies
    - Biowaiver Requests– Not Applicable. The drug product is a solution intended for injection
    - PK studies Refer to the Clinical Pharmacology review
    - IVIVC- None

The NDA is recommended for approval from a Biopharmaceutics perspective. The bridging studies conducted for the two formulations used during the clinical development of defibrotide solution for injection are adequate.

E. Novel Approaches

None

F. Any Special Product Quality Labeling Recommendations

None

Primary Quality Review

ASSESSMENT OF THE DRUG SUBSTANCE

See Review 1 dated December 31, 2015 for the evaluation of the drug substance section.

ASSESSMENT OF THE DRUG PRODUCT

See Review 1 dated December 31, 2015 for the evaluation of the drug product section.

ASSESSMENT OF THE PROCESS

See Review 1 dated December 31, 2015 for the evaluation of the drug product process section.

ASSESSMENT OF THE FACILITIES

2.3.S DRUG SUBSTANCE

2.3.S.2 Manufacture

Manufacturer(s)

1. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Establishment name	FEI Number	Responsibilities and profile codes	Current status	Initial Risks Identified	Final Recommendation
Gentium S.p.A Piazza XX Settembre, 2 Villa Guardia, Italy	3003744181	DS manufacturing, QC release and stability testing. Also DP testing (release and stability)	Initial classification of PAI is NAI. Pending receipt of EIR	High risk due to lack of inspectional history.	Approve

(b) (4)

Reviewer's Assessment: Acceptable

The following table contains the Initial Facility Risk Assessment for the facilities involved in the drug substance manufacturing and testing for defibrotide:

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment	Recommendation
Gentium S.p.A	3003744181	CEX	Responsible for DS manufacturing, QC release and stability testing. Also DP testing (release and stability)	High	High	Med	High	PAI Requested. Scheduled for 11/30/2015

(b) (4)

Gentium S.p.A. (FEI 3003744181) located in Villa Guardia, Italy is the designated drug substance manufacturer for defibrotide. This facility's focus is on Research and Development activities and manufacturing of APIs. Release and stability testing of both the drug substance and drug product is also performed at this facility. The high risk identified in the Overall Initial Facility Risk Assessment is due to the fact that this firm has not previously been inspected by the USFDA. Also, this is a New Molecular Entity. As a result, a pre-approval inspection was requested.

A PAI providing coverage of the drug substance, defibrotide, for this application (NDA 208114) was completed on 12/4/2015. This comprehensive inspection covered the Quality, Material, Facilities & Equipment, Production, and Laboratory Control systems. Based on preliminary information, all three objectives of the PAI program (readiness for commercial manufacturing, conformance to application, and acceptable data integrity) were met. Additionally, no FDA Form 483 was issued and the inspection was initially classified as NAI.

The draft version of the EIR was reviewed due to the finalized version being unavailable at the time of the final assessment for NDA 208114. Coverage included observing the manufacturing operations for NDA 208114 as well as the testing operations. A data integrity audit of the raw data did not reveal any significant deficiencies. Further the facility is manufacturing for other markets and was found in CGMP compliance on the inspection. DIA concurs with the assessment of the facility as NAI. No additional concerns were noted in the review. While the profile CSN was covered on the inspection, due to the operations in NDA 208114, the facility should be profiled CEX (animal-derived API extraction), (b) (4) and CSN (b) (4) (b) (4) FACTS will be finalized with these three profiles. Given the PDUFA date, CMS WA 114676 and FACTS will be finalized after the review recommendation. Gentium SPA is recommended for APPROVAL for NDA 208114.

Note: based on the API review and EIR, (b) (4)

(b) (4)

(b) (4)

2.3.P DRUG PRODUCT

2.3.P.3 Manufacture

Manufacturer(s)

2. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Establishment name	FEI Number	Responsibilities and profile codes	Current status	Initial Risks Identified	Final Recommendation
(b) (4)					

Reviewer's Assessment: Acceptable

(b) (4)

[redacted]

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(b) (4)

[redacted]

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature: Acceptable

A review of the testing capability and inspectional history of (b) (4) has been conducted. There are no significant outstanding facility risks and this facility is found acceptable to perform testing for NDA 208114.

The drug substance manufacturer (Gentium FEI 3003744181) had its first FDA inspection on (b) (4) while the drug product manufacturer (b) (4) was re-inspected (b) (4) Final assessment and recommendation for both of these facilities will be provided after receipt and review of these EIRs.

Quallyna Porte
Biologist, OPQ/OPF/DIA/BII
12/22/2015

A review of the manufacturing capability and inspectional documents of the manufacturing facilities listed above for NDA 208114 has been conducted. There are no significant, outstanding facility risks that prevent approval of this application. All of the noted facilities are found to be acceptable.

Quallyna Porte
Biologist, OPQ/OPF/DIA/BII
3/25/2016

Supervisor Comments and Concurrence:

Recommendation: APPROVE after removal of the pOAI alert in Panorama.

Derek S. Smith, Ph.D.
3/25/2016

ASSESSMENT OF THE BIOPHARMACEUTICS

See Review 1 dated December 31, 2015 for the biopharmaceutics evaluation.

ASSESSMENT OF MICROBIOLOGY

See Review 1 dated December 31, 2015 for the microbiology evaluation.

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

See Review 1 dated December 31, 2015 for the evaluation of the labeling section.

II. List of Deficiencies To Be Communicated

None

Anamitro Banerjee -S

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Anamitro Banerjee, Ph.D. (ATL)
Acting Branch Chief, ONDP, DNDP 1, Branch 2
March 30, 2016

Recommendation: Approval pending facility review

NDA 208114
Review #1
Review Date: December 31, 2015

Drug Name/Dosage Form	Defibrotide Injection
Strength	200 mg/2.5 mL
Route of Administration	IV
Rx/OTC Dispensed	Rx
Applicant	Gentium S.p.A (a Jazz Pharmaceuticals company)
US agent, if applicable	Robin L. Hume

SUBMISSION(S) REVIEWED	DOCUMENT DATE
0001	3/30/2015
0002	7/31/2015
0004	08/28/2015
0007	09/24/2015
0011	10/19/2015
0015	11/10/2015
0016	11/16/2015
0022	12/04/2015

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Joseph Leginus	Branch II/New Drug API
Drug Product	Nina Ni	Branch II/DNDPI/ONDP
Process	Youmin Wang	Branch VII/OPF
Microbiology	Jessica Cole	
Facility	Robert Wittorf	
Biopharmaceutics	Gerlie Gieser	
Project/Business Process Manager	Rabiya Laiq	
Application Technical Lead	Anamitro Banerjee	Branch II/DNDPI/ONDP
Laboratory (OTR)		
ORA Lead		
Environmental Analysis (EA)	Raanan Bloom	ONDP/IO

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Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION:

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type III		(b) (4)	N/A	N/A	
	Type III			N/A	N/A	
	Type III			N/A	N/A	

[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	62118	Defibrotide Injection

3. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics				
Pharmacology/Toxicology				
CDRH				
Clinical				
OBP	Complete	Approval	14-Dec-15	Ennan Guan, Ph.D.

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant has provided adequate CMC information. No CMC deficiencies were identified. The labeling should be revised to reflect the strength of the free acid rather than the sodium salt as per our current policy. Facility review is pending.

Benefit/Risk Considerations: None

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Quality Assessments

A. Drug Substance Defibrotide Quality Summary

1. Chemical Name or IUPAC Name/Structure

Chemical Name: Polydeoxyribonucleotide, sodium salt
USAN Name: Defibrotide

2. Properties/CQAs Relevant to Drug Product Quality

Properties: Solubility of the API at pH range 6.8 – 7.8 in (b) (4) and stability in solution.
CQAs: Molecular weight distribution of the DNA fragments
Impurities related to the starting material and product
Viral load

3. List of starting materials

(b) (4)

4. Suppliers of starting materials (site)

(b) (4)

5. Summary of Synthesis

(b) (4)

7. Container Closure

(b) (4)

8. Retest Period & Storage Conditions

A retest period of (b) (4) months at (b) (4) RH is granted for the drug substance when stored in the proposed container closure.

B. Drug Product Defitelio (defibrotide) Injection Quality Summary

1. Strength

Sodium salt: 80 mg/mL sterile aqueous solution. (b) (4)

(b) (4)

2. Description/Commercial Image

The defibrotide drug product is a sterile aqueous solution for intravenous administration packaged in a 3.2 mL clear glass vial sealed with a (b) (4) stopper and (b) (4) flip off seal. Each carton contains 10 vials.

3. Summary of Product Design

The injectable formulation for intravenous administration is the drug substance and a vehicle contained in an (b) (4) single use glass container. (b) (4) The applicant has provided comparability product profile and stability data for the current formulation (b) (4) (b) (4) No overage is used in the solution formulation. The batch size is approximately (b) (4) from a bulk solution of approximately (b) (4) L.

4. List of Excipients:

All the excipients are compendial: sodium citrate (b) (4) USP (b) (4) water for injection, USP (b) (4) sodium hydroxide (b) (4) NF (pH adjuster) or hydrochloric acid (b) (4) NF (pH adjuster). No novel or excipients from human or animal origin were used.

5. Process Selection (Unit Operations Summary)

The manufacturing process is (b) (4) (b) (4)

6. Container Closure

The drug product is packaged in 3.2 mL Type I neutral, clear (b) (4) glass vials with 13 mm (b) (4) stopper and a 13 mm (b) (4) flip-off cap. Container closure integrity test is performed on the vials (b) (4) The leachable/extractables study results provided by the applicant are acceptable. Based on the data provided by the applicant, lack of control for leachable and extractables in the final drug product specification is acceptable.

7. Expiration Date & Storage Conditions

The applicant provided primary and supporting stability data support the storage of the drug product under controlled room temperature 20 – 25°C (68 – 77°F) with the excursions permitted to 15 – 30°C (59 – 86°F). The proposed expiration dating period of 36 months for the drug product is supported by the real time (36 months) data from both primary stability batches and supporting stability batches, and thus granted.

8. List of co-packaged components

None

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Defitelio®
Non Proprietary Name of the Drug Product	Defibrotide injection
Non Proprietary Name of the Drug Substance	Defibrotide
Proposed Indication(s) including Intended Patient Population	Treatment of patients with hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), with (b) (4) dysfunction following hematopoietic stem-cell transplantation (HSCT)
Duration of Treatment	A minimum of 21 days. If after 21 days signs and symptoms of VOD have not resolved, continue treatment until resolution
Maximum Daily Dose	6.25 mg/kg body weight given as a 2-hour intravenous infusion every 6 hours
Alternative Methods of Administration	N/A

D. Biopharmaceutics Considerations

1. BCS Classification: Not Applicable since the proposed drug product is not for oral administration
   - Drug Substance: N/A
   - Drug Product: N/A

2. Biowaivers/Biostudies
   - Biowaiver Requests– Not Applicable. The drug product is a solution intended for injection
   - PK studies– Refer to the Clinical Pharmacology review
   - IVIVC- None

The NDA is recommended for approval from a Biopharmaceutics perspective. The bridging studies conducted for the two formulations used during the clinical development of defibrotide solution for injection are adequate.

E. Novel Approaches

None

F. Any Special Product Quality Labeling Recommendations

None

G. Process/Facility Quality Summary (see Attachment A)

H. Life Cycle Knowledge Information (see Attachment B)

Anamitro Banerjee -S

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Anamitro Banerjee
(ATL)

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34. Are the in-vitro dissolution test and acceptance criteria adequate for assuring consistent bioavailability of the drug product?

Not Applicable. The proposed drug product is a sterile aqueous solution intended for intravenous infusion.

35. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

Yes.

The proposed commercial drug product is a sterile, *preservative-free* aqueous solution containing 200 mg/2.5 mL (80 mg/mL) defibrotide in sodium citrate (b) (4) (b) (4) adjusted to a final pH of 6.8 to 7.8, and packaged in single-use glass *vials*; the proposed commercial manufacturer is (b) (4) The to-be-marketed drug product was evaluated (b) (4) in the Phase 3 expanded access safety/efficacy trial (Study 2006-005), and is currently marketed (as Defitelio®) in Europe and Israel. Per FDA recommendation, the use of the preservative-free drug product in single-use vials manufactured by (b) (4) was introduced via Protocol Amendment 3 (dated 11 August 2010).

The initial formulation (b) (4) used in the pivotal Phase 3 clinical trial (Study 2005-01) (b) (4) and was manufactured by (b) (4) Table 34-1 provides the comparison of the (b) (4) (initial) and the vial (proposed commercial) drug products.

Table 34-1. Comparison of Initial ((b) (4) Drug Product and Proposed Commercial (Vial) Drug Product [200 mg/2.5 mL = 80 mg/mL; with versus without (b) (4)]

Component	(b) (4) Drug Product (Studies R09-1425 and 99-118)	Commercial Drug Product (Study DF VOD-2012-03-PKRen)
Defibrotide concentration [mg/mL]	80	80
Defibrotide content [mg/vial]	200	200
Sodium Citrate (b) (4) (b) (4)	(b) (4)	(b) (4)
Water-for-injection	q.s. to 2.5 mL	q.s. to 2.5 mL
Container Closure System	(b) (4)	
Manufacturer		

Source: Table 1, Module 3.2.P.2.2

In pivotal Phase 3 Study 2005-01, the lot numbers of the (b) (4) used were DVD006, DVD008, 2060020004, 2070010001, 2070030003 and 2070040004; the last three (b) (4) lots were also used in Phase 3 Study 2006-05, along with (b) (4) lots 2080020004, and 2080030006, and starting in 2009, vial lots 09G01, 10G03, 11G03, 11G05, 12G01, 12G04, 12G07, 13G01, and 13G02.

The Applicant states that based on the results of comparability studies, the two pivotal Phase 3 trial drug products (200 mg/2.5 mL = 80 mg/mL, [redacted] are similar in terms of manufacturing process [redacted]. Additionally, based on the overall results of various comparability studies including those conducted with R&D vial batches [redacted] 80 mg/mL, [redacted] manufactured for these studies by [redacted] [Table 34-2], the initial and the final (proposed commercial) Phase 3 drug products are not appreciably different in terms of label assay potency, purity, osmolality/osmolarity, [redacted] etc. [Tables 34-3 and 34-4]. Based on the results of Extractable studies, [redacted] stopper [redacted]) will be used for the commercial product. Stability studies showed that the [redacted] closure system used in the two developmental vial batches were compatible with the drug product solution.

Table 34-2. Composition of Development Vial Batches manufactured by [redacted] versus Proposed Commerical Batch manufactured by [redacted] [200 mg/2.5 mL = 80 mg/mL]

Component	DVD005[a]	DVD007[b]	Proposed Commercial Formulation[b]
Defibrotide content [mg/mL]	80	80	80
Defibrotide content [mg/vial]	500	500	200
Sodium Citrate, [redacted] mg/mL]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
WFI	[redacted]	[redacted]	q.s. to 2.5 mL

(a) Batch size: [redacted] vials of [redacted]
(b) Batch size [redacted] vials of 2.5 mL each

Source: Module 3.2.P.2.2, Table 2

(b) (4)

(b) (4)

Per the Applicant, only defibrotide drug substance extracted from porcine mucosa had been used for the manufacture of investigational products evaluated in the clinical trials supporting this NDA (b) (4)

Reviewer's Assessment:

A biowaiver request was not submitted for defibrotide solution for intravenous infusion. *In vivo* BA and/or BE are generally self-evident for drugs in solution and intended for parenteral administration [21 CFR 473 320.22(b)(3)]. Additionally, defibrotide PK was determined following intravenous infusion of the to-be-marketed drug product to humans in Study DF VOD-2012-03-PKRen.

Two formulations were used during the clinical development of defibrotide solution for injection; the Biopharmaceutics reviewer considers the bridging studies conducted by the Applicant to be adequate. Per the Applicant, evidence of efficacy and safety was provided for both the initial drug product (b) (4) and the proposed commercial drug product (single-use vial (b) (4), i.e., via the pivotal Phase 3 clinical trial (Study 2005-01) and/or the ongoing Phase 3 US Expanded Access trial (Study 2006-005). [Refer to the Medical review for the assessment of the clinical efficacy of defibrotide solution for intravenous injection in these Phase 3 trials.] Secondly, based on cross-study comparison of the clinical PK data of defibrotide following intravenous infusions of the formulation (b) (4) (Studies R09-1425 and 99-118), and the final, (b) (4) formulation (Study DF VOD-2012-03-PKRen), it appears that the drug product changes during development did not significantly impact the disposition of defibrotide particularly in healthy subjects who received 6.25 mg/kg Q6h via IV infusion, when considering the potential impact of factors including PK covariates (e.g., age) and the different PK assay methods used. [Refer to the Clinical Pharmacology review for the assessment of the defibrotide PK data and the associated bioanalytical methods.]

Provided the Drug Product Reviewer considers the proposed specifications used by the Applicant in the comparability studies to be acceptable, (b) (4) the change (b) (4) did not also negatively impact the overall quality of defibrotide solution for injection.

The acceptability of the proposed Finished Drug Product specification for the biological (plasmin) assay will be determined by the Drug Product reviewer.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Assessment and Signature:
From a Biopharmaceutics perspective, NDA 208-114 Defibrotide solution for injection is recommended for APPROVAL.

11/9/2015
Gerlie Gieser, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics/OPQ

Supervisor Comments and Concurrence:

I concur with Dr. Gieser's review and approval recommendation for NDA 208114.

11/9/2015
Okpo Eradiri, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics/OPQ

ASSESSMENT OF MICROBIOLOGY

36. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Yes. See the response to Question 29 above for more details.

2.3.P.6 Reference Standards or Materials

37. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Yes. See the response to Question 29 above for more details.

A.2 Adventitious Agents Safety Evaluation

38. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment: TSE is not associated with products derived from porcine sources. Personal communication with the OBP team lead, Howard Anderson, Ph.D. The risk for TSE in this product is low. Refer also to the OBP consult review in Panorama dated 11-Dec-15 for viral contamination evaluation.

39. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment: This risk factor was addressed by Dr. Ennan Guan and Dr. Howard Anderson within OBP. Please refer to their consult review dated 11-Dec-15, which recommend the NDA may be approved from the perspective of the viral clearance studies and the potency bioassays release and stability methods to quantify Defibrotide anticoagulant activity.

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: The information summarized under Question 29 was provided by this reviewer and is adequate to support the manufacture of this sterile drug product.

Jessica Cole, PhD – 12/16/15

Supervisor Comments and Concurrence:

Stephen Langille, PhD- 12/16/15

Note: additional reviewers can be added, as appropriate

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))
DEFITELIO (defibrotide) injection, for intravenous use
Initial U.S. Approval: 20XX

DEFITELIO injection is supplied as 200 mg/ 2.5 mL [redacted] 80 mg/mL) in a single-use clear glass vial.

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: DEFITELIO Established Name: defibrotide	Adequate
Dosage form, route of administration	Dosage: injection Route: for intravenous use	Adequate
Controlled drug substance symbol (if applicable)	N/A	Adequate
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	DEFITELIO injection is supplied as 200 mg/ 2.5 mL [redacted] of 80 mg/mL)	Inadequate. 80 mg/mL is based on sodium salt [redacted] of defibrotide.

Conclusion: Inadequate.

(b) "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

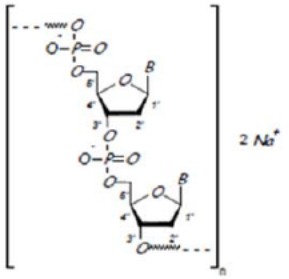
DEFITELIO (defibrotide) injection is a clear, light yellow to brown [redacted] solution [redacted] 200 mg/2.5 mL (concentration of 80 mg/mL) in a single-use [redacted] glass vial.

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Injection	Adequate
Strengths: in metric system	200 mg/2.5 mL (concentration of 80 mg/mL)	Inadequate. Strength should be expressed as [redacted] sodium salt of defibrotide
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	a clear, light yellow to brown solution	Adequate

Conclusion: Inadequate.

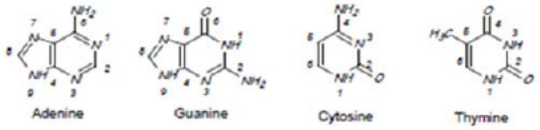
#11: Description (21CFR 201.57(c)(12))

Defibrotide is the sodium salt of a polydisperse mixture of predominantly single-stranded (ss) polydeoxyribonucleotides derived from porcine intestinal tissue and having a mean weighted molecular weight (MW) of 13-20 kDa, and a potency of about 27-39 biological units per mg [redacted] (b) (4) The chemical name of defibrotide is polydeoxyribonucleotide, sodium salt. The primary structure is shown below.



n = from about 2 to 50

B =



DEFITELIO (defibrotide) injection is a clear, light yellow to brown, sterile, preservative-free [redacted] (b) (4) solution for intravenous use. Each milliliter of the injection contains 80 mg of defibrotide and 10 mg of sodium citrate, USP in Water for Injection, USP. Hydrochloric acid and/or sodium hydroxide may have been used to adjust pH to 6.8-7.8.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	DEFITELIO (defibrotide) injection	Adequate
Dosage form and route of administration	Solution for intravenous infusion	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	80 mg/mL as sodium salt	Inadequate. It should be expressed as free acid form of defibrotide not sodium salt form
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Provided.	Adequate
Statement of being sterile (if applicable)	Provided.	Adequate
Pharmacological/therapeutic class	Not provided. Pharmacological class is not defined as per Pharm Tox reviewer.	Adequate
Chemical name, structural formula, molecular weight	Provided.	Adequate
If radioactive, statement of important nuclear characteristics.	NA	Adequate

Other important chemical or physical properties (such as pKa, solubility, or pH)	Provided.	Adequate

Conclusion: Inadequate.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

DEFITELIO (defibrotide) injection is supplied in a single-use, clear glass vial as a clear, light yellow to brown, sterile, preservative-free [(b) (4)] solution for intravenous infusion. Each [(b) (4)] vial (NDC 68727-800-01) contains 200 mg/2.5 mL (concentration of 80 mg/mL) of defibrotide injection.
Each carton of DEFITELIO (NDC 68727-800-02) contains 10 vials.
DEFITELIO (defibrotide) injection [(b) (4)] at 20 - 25°C (68 - 77°F); excursions permitted to 15° to 30°C (59° to 86°F) (see USP controlled room temperature).

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	200 mg/2.5 mL (80 mg/mL)	Inadequate. It should be expressed as [(b) (4)] sodium salt form
Available units (e.g., bottles of 100 tablets)	Each carton contains 10 vials	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	NDC numbers for both carton and single vial are provided.	Adequate
Special handling (e.g., protect from light, do not freeze)	Provided.	Adequate
Storage conditions	DEFITELIO (defibrotide) injection [(b) (4)] stored at 20 - 25°C (68 - 77°F); excursions permitted to 15° to 30°C (59° to 86°F) (see USP controlled room temperature).	Adequate

Manufacturer/distributor name listed at the end of PI, following Section #17

Distributed by:
Jazz Pharmaceuticals, Inc.
Palo Alto, CA 94304

TRADENAME is owned by Gentium S.p.A. and is used under license by Jazz Pharmaceuticals, Inc.

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Provided.	Adequate

Conclusion: Inadequate.

2. Labels

1) Immediate Container Label

2 [redacted]

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	DEFITELIO (defibrotide)	Inadequate. Injection needs to be added.
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	200 mg/2.5 mL (80 mg/mL)	Inadequate. It should be expressed as [redacted] sodium salt form
Net contents (21 CFR 201.51(a))	Single-use vial is missing	Inadequate. Single-use vial is missing.
Lot number per 21 CFR 201.18	Space is allocated.	Adequate
Expiration date per 21 CFR 201.17	Space is allocated.	Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)	Missing.	Inadequate
Storage (not required)	N/A	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided.	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	Provided.	Adequate
Name of manufacturer/distributor	Provided.	Adequate
Others	For intravenous use only. Must be diluted prior to administration.	Adequate

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.

**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: Inadequate.

3) Cartons

(b) (4)

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	DEFITELIO (defibrotide) For intravenous use	Inadequate. Injection is missing.
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	200 mg/2.5 mL (80 mg/mL)	Inadequate. It should be expressed as (b) (4) sodium salt form.
Net contents (21 CFR 201.51(a))	Contains 10 single use vials	Adequate
Lot number per 21 CFR 201.18	Space is allocated.	Adequate
Expiration date per 21 CFR 201.17	Space is allocated.	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]	Each 2.5 mL vial contains 200 mg defibrotide and 25 mg sodium citrate (b) (4) USP in water for injection, USP. Hydrochloric acid, NF or sodium hydroxide, NF to adjust pH to 6.8 – 7.8.	Adequate
Sterility Information (if applicable)	Not provided.	Inadequate. Sterile is missing.
"Rx only" statement per 21 CFR 201.100(b)(1)	Provided.	Adequate
Storage Conditions	Stored at 20 - 25°C (68 - 77°F); excursions permitted to 15° to 30°C (59° to 86°F) (see USP controlled room temperature).	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided.	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	Provided.	Adequate
Name of manufacturer/distributor	Provided.	Adequate
"See package insert for dosage information" (21 CFR 201.55)	Provided.	Adequate
"Keep out of reach of children" (optional for Rx, required for OTC)	N/A	Adequate
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	For intravenous use only. Must be diluted prior to administration.	Adequate

Conclusion: Inadequate.

II. List of Deficiencies To Be Communicated

A. Drug Substance
B. Drug Product
C. Process/Facility
D. Biopharmaceutics
E. Microbiology
F. Label/Labeling

III. Attachments

A. Facility

OVERALL RECOMMENDATION:				
DRUG SUBSTANCE				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION
DRUG PRODUCT				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION

B. Lifecycle Knowledge Management

a) Drug Substance

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Initial Risk Ranking*	Justification	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations / Comments**
	H, M, or L			Acceptable or Not Acceptable	

b) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking*	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments**
Sterility	• Formulation • Container closure • Process parameters • Scale/equipment • Site	H	Sterile (b) (4)	L	
Endotoxin Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipment • Site	M	Water for injection used and BET is controlled for drug substance	L	

Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L		L	
Uniformity of Dose (Fill Volume/ Deliverable volume)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L		L	
Osmolality	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L		L	
pH-(High)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L		L	
pH-(Low)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L		L	
Particulate matter (non-aggregate for solution only)	• Formulation • Container closure • Process parameters	M	Controlled in the drug product specification	L	

	• Scale/equipment • Site				
Leachable Extractables	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L		L	
Appearance (color/turbidity)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L		L	

*Risk ranking applies to product attribute/CQA
**For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval, etc.

IV. Administrative

A. Reviewer's Signature

B. Endorsement Block

Reviewer Name/Date: [*Same date as draft review*]
Secondary Reviewer Name/Date:
Project Manager Name/Date: