

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207953Orig1s000

CHEMISTRY REVIEW(S)

Expedited Review for NME

Recommendation: NDA: Approval

NDA 207953
Review #1
Review Date 12-Aug-15

Drug Name/Dosage Form	Trabectedin/ powder for reconstitution
Strength	1 mg
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Janssen Products, LP
US agent, if applicable	Janssen Research &Development, LLC

SUBMISSION(S) REVIEWED	DOCUMENT DATE
SN-000	11/24/14: new NDA
SN-002	12/16/14: proprietary name proposed
SN-006	01/23/15: quality response to IR P2, P3
SN-010	01/30/15: quality response to IR P26, micro
SN-013	02/27/15: labels, labeling
SN-014	03/05/15: quality response to IR P51, P52, P53
SN-016	03/19/15: quality response to IR EBR
SN-020	03/27/15: quality response to IR TS preparation
SN-022	04/21/15: quality response to IR P41, P51, P53

Quality Review Team

DISCIPLINE	REVIEWER
Drug Substance	Charles Jewell
Drug Product	William Adams
Process	Kumar Janoria
Microbiology	Erika Pfeiler
Facility	Robert Wittorf
Biopharmaceutics	Okpo Eradiri
Business Process Manager	Rabiya Laiq
Application Technical Lead	Olen Stephens
Laboratory (OTR)	
ORA Lead	Sharon Thoma
Environmental Assessment (EA)	Raanan Bloom

Table of Contents

Table of Contents	2
Quality Review Data Sheet.....	3
Executive Summary	4
Primary Quality Review.....	8
ASSESSMENT OF THE DRUG SUBSTANCE	8
2.3.S DRUG SUBSTANCE	8
ASSESSMENT OF THE DRUG PRODUCT	18
2.3.P DRUG PRODUCT	18
R.2 Comparability Protocols.....	59
ASSESSMENT OF THE PROCESS.....	59
2.3.P DRUG PRODUCT	60
ASSESSMENT OF THE FACILITIES.....	91
2.3.S DRUG SUBSTANCE	92
2.3.P DRUG PRODUCT	92
ASSESSMENT OF THE BIOPHARMACUETICS	94
ASSESSMENT OF MICROBIOLOGY	95
2.3.P.6 Reference Standards or Materials.....	96
A APPENDICES	96
A.2 Adventitious Agents Safety Evaluation	96
R.2 Comparability Protocols.....	97
I. Review of Common Technical Document-Quality (Ctd-Q) Module 1	97
Labeling & Package Insert.....	97
II. List of Deficiencies To Be Communicated.....	Error! Bookmark not defined.
III. Attachments	Error! Bookmark not defined.
IV. Administrative.....	Error! Bookmark not defined.

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS ¹	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II	(b) (4)	(b) (4)	Adequate	13-Feb-15	
	Type II			Adequate	13-Feb-15	
	Type III			Adequate		Sufficient information in the NDA
	Type V			Adequate	4-Dec-14	
	Type III			Adequate		Sufficient information in the NDA

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	050286	Trabectedin IND
IND	(b) (4)	Trabectedin IND

3. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
None				

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is recommended for approval from a CMC perspective pursuant the overall “approval” recommendation from the facilities reviewer. Sufficient stability data has been submitted to grant a 36 month shelf-life with storage conditions of 2-8 °C.

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 [Trabectedin] Quality Summary

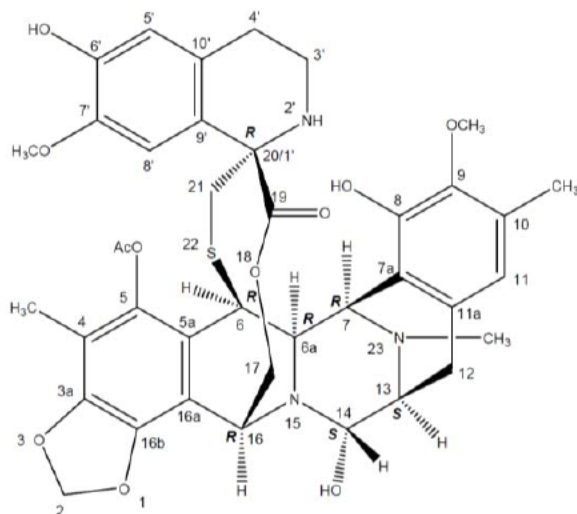
Trabectedin, (b) (4)

(b) (4)
is a white to off-white powder,
manufactured (b) (4) The

(b) (4)

The starting materials and their acceptance criteria, the manufacturing process, and control over reagents and solvents are described in the two DMFs. The retest date and container closure system for the drug substance is covered by DMF

(b) (4)



B. Drug Product [Yondelis] Quality Summary

Yondelis (trabectedin), for injection is a 1 mg lyophilized powder for infusion which is intended to be reconstituted with Water for Injection, USP (WFI) admixed with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP, then administered by IV infusion over 24 hours.

Compatibility studies have addressed interactions between the reconstituted solution in its packaging system, and the admixture solution in the containers and components for IV administration. Because the reconstituted solution is intended to be admixed with 5% Dextrose for Injection and the infusion will occur over 24 hours, microbial growth is a concern. Microbial challenge studies have demonstrated that this admixed drug product will support microbial growth. These concerns were discussed with the clinical division as well as potential risk mitigation approaches. Because of the way the clinical studies were conducted, (b) (4) was not a feasible risk mitigation option; (b) (4) were deemed unlikely to be successful due to developmental studies that did not yield sufficient control over microbial growth. In conjunction with the clinical division, the package insert was edited to direct the health care provider to use of an in-line filter during administration of the drug product to mitigate the risk of microbial growth. Compatibility studies have established material incompatibilities between the admixture solutions and (b) (4) polyethersulfone (PES) filters. The time from (b) (4) to end of infusion should be limited to 30 hours.

The drug product is formulated with sucrose and (b) (4). The manufacturing process (b) (4)

(b) (4) The procedure for manufacture is described in sufficient detail and the proposed process controls are appropriately justified.

An acceptable specification for batch release has been proposed. The tests are adequate to address appearance, identity, assay, purity, and USP <1> requirements for this dosage form. The analytical methods have been described in sufficient detail and validated for their intended use. The proposed criteria have been appropriately justified. Appropriate reference standards have been prepared.

Finished drug product is packaged in a type I USP glass vial, (b) (4) grey (b) (4) stopper (b) (4) and an aluminum crimp seal. The components have been described in sufficient detail and appropriate acceptance specifications are proposed.

Sufficient long-term stability data was submitted to support a 36 month shelf life at refrigerated conditions (2-8 °C) for the drug product.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Yondelis®
Non Proprietary Name of the Drug Product	Trabectedin, for Injection – for intravenous infusion only
Non Proprietary Name of the Drug Substance	trabectedin
Proposed Indication(s) including Intended Patient Population	(b) (4)
Duration of Treatment	Infusion for no longer than 24 hours every 3 weeks per treatment cycle
Maximum Daily Dose	1.5 mg/m ² body surface area
Alternative Methods of Administration	None

D. Biopharmaceutics Considerations

1. BCS Designation:
No BCS classification data for Trabectedin are provided in the NDA; the drug product is formulated for intravenous use.
2. Biowaivers/Biostudies
There is no biowaiver request for assessment in the Application. All clinical pharmacology studies have been assessed by the Office of Clinical Pharmacology.

- E. Novel Approaches:** The risk of microbial growth (as discussed in the executive summary) led to labeling in the package insert, instructing the healthcare provider to use an in-line filter during drug product administration. This is not a standard risk mitigation approach, but because the formulation supports microbial growth,

(b) (4)

the use of in-line filters was recommended to the clinical division.

- F. Any Special Product Quality Labeling Recommendations:** See above regarding the recommendation to use an in-line filter

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

- H. Life Cycle Knowledge Information (see Attachment B)**

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature: Based on the combined reviews of the OPQ team, I recommend NDA 207953 for approval.

Olen Stephens, PhD
Acting Branch Chief
Office of New Drug Products

Olen Stephens -S

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Primary Quality Review

ASSESSMENT OF THE DRUG SUBSTANCE

2.3.S DRUG SUBSTANCE

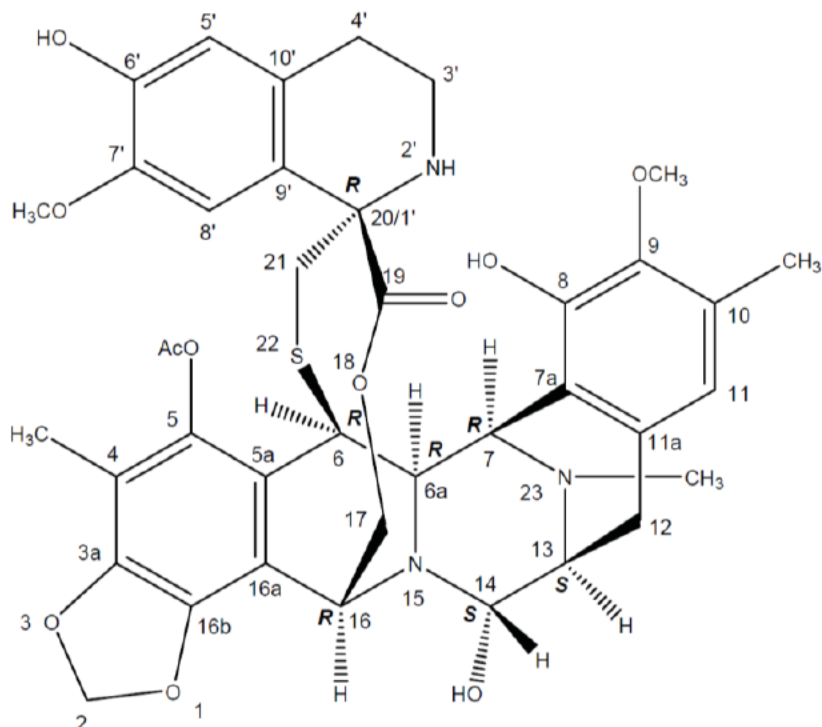
2.3.S.1 General Information

Applicant's Response:

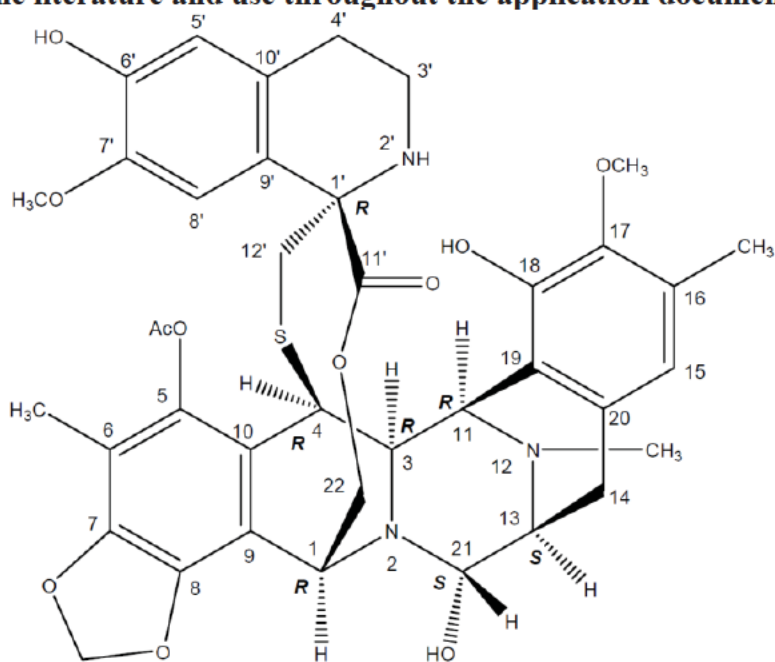
Nomenclature and Structural Representations

- **INN:** Trabectedin
- **USAN:** trabectedin
- **(Systematic numbering) IUPAC:** (b) (4)
[REDACTED]
- **CAS index name:** (1'R,6R,6aR,7R,13S,14S,16R)-5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethylspiro[6,16-(epithiopropoxymethano)-7-13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one
- **Company Code:** ET-743
- **Other Name:** Ecteinascidin 743
- **CAS Registry Number:** 114899-77-3

Structural Formula (using systematic numbering: this numbering was used in the IUPAC and CAS index names):



The following structure is the same but uses the atom numbering frequently used in the literature and use throughout the application document:



- **Molecular Formula:** C₃₉H₄₃N₃O₁₁S
- **Molecular Weight:** 761.84

General Properties:

- **Appearance:** white to off-white powder

Reviewer Assessment: : The general properties of trabectedin are well understood as evidenced by the pronouncements in this application, and supported by the DMFs covering its manufacturing method and characterization. These DMFs have been reviewed by this reviewer. Trabectedin is a well characterized molecule, meeting conventional standards for stereochemistry and purity. The manufacturing process covered in the DMFs is adequate to provide evidence for reproducibility for trabectedin drug substance manufacture.

Reviewer's Assessment: The full manufacturing process is referred to in DMF (b) (4) and DMF (b) (4) and those details have been reviewed and documented in DARRTS on 02/13/2015. Refer to these DMF reviews for further details. Among the details covered in the DMFs are:

- Starting materials and their control
- Control of solvents, reagents, and other materials
- In-process controls
- What impact the manufacturing process components have and what is critical to the final drug substance quality.

2. Is there any proposal for online/at line/in line monitoring technologies for routine commercial production that allows for real-time process monitoring and control? If so, is it acceptable?

Applicant's Response: None

Reviewer's Assessment: Not pertinent to this application. Standard technologies are used in the manufacturing process and standard analytical testing.

Control of Critical Steps and Intermediates

3. What are the critical steps which could significantly affect the structure of the drug substance and impurity profiles? If so, are the critical process parameters (CPPs) adequate to ensure the identity and purity of the drug substance?
4. Are intermediates controlled adequately to assure the structure and impurity profile of the final drug substance?

Applicant's Response:

Referenced to DMF (b) (4) and DMF (b) (4)

Reviewer's Assessment: Critical process parameters and in-process controls are discussed in the DMFs (b) (4). Specifications for all intermediates are discussed in the DMFs.

Process Validation and/or Evaluation

5. Is the proposed process validated adequately?

Manufacturing Process Development

6. What process development and scale up information supports the commercial process and proposed control strategy?

Applicant's Response:

Referenced to DMF (b) (4) and DMF (b) (4)

Reviewer's Assessment: Some of the data is captured and summarized in the batch analysis parts of answers to questions 9 and 10 below. The remainder is adequately covered under the two referenced DMFs. (b) (4)

The risk of concluding erroneous outcomes from testing of materials from the different sources in the studies is low.

2.3.S.3 Characterization

7. Do all the characterization data unequivocally support the proposed structure?
8. Are the potential impurities (e.g. related substances, degradants, inorganic impurities, residual solvents, reagents, and genotoxic impurities) well characterized and controlled in the drug substance?

Applicant's Response:

Referenced to DMF (b) (4) and DMF (b) (4)

Reviewer's Assessment: The characterization is adequately covered specifically for trabectedin in DMF (b) (4), but the information in DMF (b) (4) provides significant support.

2.3.S.4 Control of Drug Substance

9. Is the proposed specification adequate to assure the identity, strength, purity, and quality of the drug substance?
10. Are all the analytical procedures appropriately described and validated for their intended use?

Applicant's Response:

Table 4.1(1). Specification for trabectedin drug substance (b) (4)

(b) (4)

Trabectedin was originally isolated from the marine organism *Ecteinascidia turbinata* (b) (4)

atches produced by both methods have been characterized with respect to their structural, toxicological and in vitro pharmacological properties and these materials have been demonstrated equivalent in these respects. This was covered under DMF

(b) (4) Drug substance supplied by Janssen Pharmaceutica NV, Beerse, Belgium and

Reviewer's Assessment: The batch analysis data provided in the application and number of batches described support the ability of the manufacturer to reproducibly produce drug substance of similar quality. The limit setting for specification tests are adequately justified. Similarity of all batches used in clinical and non-clinical studies throughout development of this drug substance, whether by (b) (4) is justified. The (b) (4) proposed for use in marketing under this NDA. Risks of erroneous safety and efficacy evaluation due to quality issues surrounding material sourced from the above sites is therefore considered low.

11. Is the proposed control strategy for the drug substance manufactured at commercial stage acceptable? Is there any residual risk upon implementation of the control strategy at the commercial scale?

Applicant's Response:

Referenced to DMF (b) (4)

Reviewer's Assessment: Based on review of the DMFs and the data summarized above, the risk of using the described method is adequate. It has been demonstrated with at least 21 batches produced at commercial scale and using the commercial process at the commercial site.

2.3.S.5 Reference Standards or Materials

12. Are the drug substance reference standards satisfactory?

Applicant's Response:

Referenced to DMF (b) (4) and DMF (b) (4).

Reviewer's Assessment: Described and adequate in the referenced DMFs.

2.3.S.6 Container Closure System

13. Is the proposed container closure system(s) for commercial packaging of the drug substance adequate to protect the drug substance from the environment (oxygen, moisture, microorganism, etc.) during the storage?

Applicant's Response:

Referenced to DMF (b) (4)

Reviewer's Assessment: Described and adequate in referenced DMF (b) (4)

2.3.S.7 Stability

14. What is the proposed retest period for the drug substance? Do the drug substance stability data support the proposed retest period and storage conditions in the commercial container closure system? How does statistical evaluation of the stability data, if any and any observed trends support your proposed retest period?
15. Are the post-approval stability protocols and other stability commitments for the drug substance satisfactory?

Applicant's Response:

Referenced to DMF (b) (4)

Reviewer's Assessment: Described and adequate in referenced DMF (b) (4)**OVERALL ASSESSMENT AND SIGNATURES: DRUG SUBSTANCE**

Reviewer's Assessment and Signature: I recommend approval based on the drug substance information presented in this application and the two referenced DMFs: DMF (b) (4) and DMF (b) (4)

Charles F. Jewell Jr. 2/19/2015

Charles Jewell -S

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Supervisor Comments and Concurrence:

Kasturi Srinivasachar -A

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ASSESSMENT OF THE DRUG PRODUCT**2.3.P DRUG PRODUCT**

Yondelis (trabectedin) injection, 1mg is a sterile, lyophilized powder in a single-dose glass vial intended to be reconstituted with (b) (4) Water for Injection, USP to 50 ug/mL, then admixed with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to a concentration of (b) (4) ug/mL for IV infusion over 24 hours. Maximum hold time from reconstitution to end of administration is 30 hours.

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

16. Are there any scientific or regulatory concerns about the proposed composition of the drug product?

3.2.P.1 Composition Statement

Component	Quality Reference	Function	Unit Quantity (per Vial) 1.0-mg Vial	Lyophilized Cake/Powder (% w/w)
Trabectedin ^a	DMF (b) (4)	Active ingredient	1.0 mg	(b) (4)
Sucrose	NF	(b) (4)	400 mg	
Potassium dihydrogen phosphate	NF		27.2 mg	
Phosphoric acid (b) (4)	NF	pH adjustment	q. s. to pH 3.6-4.2	
Potassium hydroxide (b) (4)	NF	pH adjustment (b) (4)	q. s. to pH 3.6-4.2	
(b) (4)	(b) (4)	(b) (4)	(b) (4)	
Total Weight		(b) (4)	(b) (4)	

Reviewer Assessment:

Acceptable in that the information is complete. Drug product is a lyophilized powder composed of (b) (4)

2.3.P.2 Pharmaceutical Development

17. Does the information described in the pharmaceutical development section support the proposed product design, commercial formulation, dosage form, compatibility, specification, and overall control strategy of the drug product?

3.2.P.2.4 Container Closure System*Primary Packaging*

Vial: (b) (4) glass

Closure: (b) (4)

Seal: aluminum crimpseal with uncolored flip-off cap

Protection

(b) (4)

P.8.3 Stability Data

Stability data presented in the application were in agreement with acceptance criteria.

Reviewer's Assessment:**ADEQUATE**

REVIEWER COMMENT – The stability information provided is adequate to ensure the microbiological quality of the drug product.

R REGIONAL INFORMATION**R.1 Executed Batch Record****2. REVIEW OF COMMON TECHNICAL DOCUMENT-
QUALITY (CTD-Q)
MODULE 1****A. PACKAGE INSERT**

Calculations to determine endotoxin load from the drug product are outlined in Table 7.

**Table 7. Endotoxin exposure from the maximum dose of the drug product.
Compiled from proposed package insert.**

Indication	Route of Administration	Maximum Product Dose	Endotoxin Specification	EU/maximum dose *
(b) (4)	Intravenous	1.5 mg/m ² , (b) (4) (Administered as a 24-hour infusion)	NMT 70 EU/mg of drug product	70 P

* Parenteral injection endotoxin limit:

The application contains studies to support a post-constitutional hold time for the drug product. Proposed product labeling states that the drug product should be reconstituted using 20 mL of WFI, and then added to 500 mL bags containing either 0.9% sodium chloride or 5% dextrose injection. The drug product is administered by infusion over a 24-hour period, and labeling states that the total elapsed time between initial reconstitution and completion of infusion should be not longer than 30 hours. (b) (4)

The applicant

presented data from studies to support the (b) (4) hold period necessary for product administration. For a full review of these studies and accompanying recommendations, see Section P.2.6 of this review.

Reviewer's Assessment:**ADEQUATE**

REVIEWER COMMENT – Endotoxin limits for the product are adequate to ensure that exposure limits are not exceeded. For more information on the microbiological considerations for product hold time, see Section P.2.6 of this review.

3. LIST OF MICROBIOLOGY COMMENTS:

N/A

R.2 Comparability Protocols

30. Is a Comparability Protocol included in the application for manufacturing process or manufacturing site post approval changes? If so, what post-approval changes are specified? What is the method of evaluation of the changes and the acceptance criteria for the change?? How will the changes be reported?

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

Reviewer's Assessment: Not Applicable.

No comparability protocol was identified or proposed within the submission.

OVERALL ASSESSMENT AND SIGNATURES: PROCESS**Reviewer's Assessment and Signature: Satisfactory KJanoria/03/23/2015**

Overall the application was found to be satisfactory from process development and manufacturing process perspective.

Kumar Janoria -S

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Supervisor Comments and Concurrence: LChristensen/03/23/2015

Edwin Jao -A

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ASSESSMENT OF THE FACILITIES

2.3.S DRUG SUBSTANCE

2.3.S.2 Manufacture

Manufacturer(s)

31. 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?

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment	Recommendation
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(b) (4)

Reviewer's Assessment:*Pre-Inspection Evaluation:*

There are two API manufacturers, based on the facility risk assessment evaluation, one facilit (b) (4)

(b) (4)

Inspectional results:

The inspection was performed (b) (4) At the close of inspection, a one item Form-483 was given to the firm stating that no written validation protocols or reports were available to verify the (b) (4) software. The firm's final analysis report with results is generated automatically in which calculation formulas are entered (b) (4) however no validation documentation or written protocol to support the validation of the calculation formulas. Raw data was reviewed by the investigator. No issues with data integrity was found or concerns with the raw data reviewed that correlates to the (b) (4) DIA spoke with the investigators and based on their findings and the promised corrective actions the investigators felt the (b) (4) site is acceptable with respect to NDA 207953. A review of the firm's response was also conducted and the corrective actions are acceptable. OPF/DIA considers the facility is acceptable with respect to NDA 207953.

2.3.P DRUG PRODUCT**2.3.P.3 Manufacture*****Manufacturer(s)***

32. 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?

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment	Recommendation
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(b) (4)

Reviewer's Assessment:***Pre-inspection evaluation:***

(b) (4)

Janssen facility inspection was waived due to the minimal risk of secondary packaging and labeling operations. The facility was inspected in (b) (4). Although a form 483 was issued to the firm, the observations were not related to the packaging and labeling operations that pertain to this product. The review team had no concerns with the waiving of this inspection.

(b) (4)

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature: The Office of Process and Facilities has determined that the facilities are acceptable as they pertain to this application.

Robert H. Wittorf, PharmD.
Quality Assessment Lead, DIA BRII

Supervisor Comments and Concurrence:

Mahesh R. Ramanadham -S
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Date: 2015.08.12 06:48:03 -04'00'

ASSESSMENT OF THE BIOPHARMACUETICS INFORMATION

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

Dissolution testing is not applicable to this drug product since the final dosage form is a solution that is administered intravenously.

(b) (4)

Reviewer's Assessment:

The NDA for Trabectedin Powder for Reconstitution (207953) does not contain any biopharmaceutics data for assessment.

**OVERALL ASSESSMENT AND SIGNATURES:
BIOPHARMACUTICS**

Reviewer's Assessment and Signature:

The Division of Biopharmaceutics defers final recommendation on the approvability of NDA 207953 to other reviewing disciplines within the Office of Pharmaceutical Quality as there was no substantial biopharmaceutics review activity in the assessment of the Application.

Okponanabofa Eradiri
-S

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Okpo Eradiri, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics/ONDP/OPQ

Supervisor Comments and Concurrence:

Angelica Dorantes
S

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Angelica Dorantes, Ph.D.
Acting Biopharmaceutics Branch Chief
Division of Biopharmaceutics/ONDP/OPQ

ASSESSMENT OF MICROBIOLOGY

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

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

Reviewer's Assessment: Refer above to the process review section where the microbiology issues are reviewed

2.3.P.6 Reference Standards or Materials

36. 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?

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

Reviewer's Assessment: Refer above to the process review section and drug product review for ingress studies.

A APPENDICES**A.2 Adventitious Agents Safety Evaluation**

37. 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: (b) (4)

38. 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: N/A

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:

Erika A. Pfeiler -S

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Date: 2015.08.12 07:12:57 -04'00'

Supervisor Comments and Concurrence:

Stephen E. Langille -A

Digitally signed by Stephen E. Langille -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300151320, cn=Stephen E. Langille -A
Date: 2015.08.12 07:48:16 -04'00'

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

Labeling & Package Insert

1. Package Insert (Amendment S-013)

(a) "Highlights" Section (21CFR 201.57(a))

Highlights of Prescribing Information

[REDACTED] (b) (4)

YONDELIS (trabectedin) **for** injection, for intravenous use
Initial U.S. Approval – 20yy

-----INDICATIONS AND USAGE-----

[REDACTED] (b) (4)

-----DOSAGE AND ADMINISTRATION-----

* Administer at 1.5 mg/m² body surface area as a 24-**hr** [REDACTED] (b) (4) intravenous infusion, every 3 weeks through a central venous line (2.1, 2.5)

* Premedicate (b) (4) dexamethasone 20 mg IV, 30 min before infusion (2.2)

-----DOSAGE FORMS AND STRENGTHS-----

For injection: 1 mg sterile lyophilized powder in a single-dose (b) (4) vial (3)

Item	Information Provided in NDA	Reviewer Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: Yondelis Established Name: trabectedin	Acceptable
Dosage form, route of administration	Dosage: 1 mg Route: powder for IV infusion	Acceptable
Controlled drug substance symbol (if applicable)	NA	N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	1 mg powder for IV infusion	Acceptable

Conclusion: Acceptable with editorial comment

(b) (4) Spell out as "hour".]

(b) "Full Prescribing Information" Section

2 DOSAGE AND ADMINISTRATION

2.4 Preparation for Administration

* Using aseptic technique, inject 20 mL of Sterile Water for Injection, USP into the vial. Shake the vial until complete dissolution. The reconstituted solution is clear, colorless to pale brownish yellow- (b) (4)

(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))	Information is present	Acceptable
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Information is present	Acceptable
Net contents (21 CFR 201.51(a))	Information is present	Acceptable
Lot number per 21 CFR 201.18	Information is present	Acceptable
Expiration date per 21 CFR 201.17	Information is present	Acceptable
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]	Information is present	Acceptable
Sterility Information (if applicable)	Information is present	Acceptable
“Rx only” statement per 21 CFR 201.100(b)(1)	Information is present	Acceptable
Storage Conditions	Information is present	Acceptable
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Information is present	Acceptable
Bar Code per 21 CFR 201.25(c)(2)**	Information is present	Acceptable
Name of manufacturer/distributor	Information is present	Acceptable
“See package insert for dosage information” (21 CFR 201.55)	Information is present	Acceptable
“Keep out of reach of children” (optional for Rx, required for OTC)	Information is present	Acceptable
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	Information is present	Acceptable

Conclusion: Acceptable

Environmental Assessment Or Claim Of Categorical Exclusion

Janssen Products, LP has submitted a claim for categorical exclusion. The applicant cites the exclusion listed at 21 CFR 25.31(b) and provides a statement of “no extraordinary circumstances.” The applicant provide (b) (4)

Available data do not establish that, at the expected level of exposure, there is the potential for serious harm to the environment.

In addition, trabectedin is prepared by total synthesis and not derived from either plant or animal sources.

Reviewer Assessment:

The requested categorical exclusion is granted based on the MEI calculation.

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FILING REVIEW

Application #: 207953 Submission Type:

Established/Proper Name:
trabectedin

Applicant: Janssen Letter Date: 11-24-14

Dosage Form: Powder for
reconstitution

Chemical Type: Stamp Date: 11-24-14

Strength: 1mg

A. FILING CONCLUSION				
	Parameter	Yes	No	Comment
1.	DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?	x		This is an NME indicated for the treatment of patients with (b) (4)
2.	If the application is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			NA
3.	Are there any potential review issues to be forwarded to the Applicant, not including any filing comments stated above?	x		1. The DMF holders will be asked to provide shipping studies for the drug substance intermediates to demonstrate adequate stability in the bulk hold containers under their specified storage conditions.

B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
Product Type				
1.	New Molecular Entity ¹	☒	☐	
2.	Botanical ¹	☐	☒	
3.	Naturally-derived Product	☒	☐	(b) (4)
4.	Narrow Therapeutic Index Drug	☐	☒	
5.	PET Drug	☐	☒	
6.	PEPFAR Drug	☐	☒	
7.	Sterile Drug Product	☒	☐	
8.	Transdermal ¹	☐	☒	
9.	Pediatric form/dose ¹	☐	☒	
10.	Locally acting drug ¹	☐	☒	
11.	Lyophilized product ¹	☒	☐	
12.	First generic ¹	☐	☒	
13.	Solid dispersion product ¹	☐	☒	
14.	Oral disintegrating tablet ¹	☐	☒	
15.	Modified release product ¹	☐	☒	
16.	Liposome product ¹	☐	☒	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
17.	Biosimilar product ¹	☐	☒	
18.	Combination Product _____	☐	☒	
19.	Other _____	☐	☒	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Regulatory Considerations				
20.	USAN Name Assigned	☒	☐	Trabectedin
21.	End of Phase II/Pre-NDA Agreements	☐	☒	Note the documents under section 1.6.3 that outline deficiencies identified with the initial (but withdrawn) NDA submission for Yondelis (Apr through Oct 2009). These issues may have been resolved by changing drug substance manufacturers and improvements in the microbiological controls.
22.	SPOTS (Special Products On-line Tracking System)	☒	☐	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application	☐	☒	
24.	Comparability Protocol(s) ²	☐	☒	None noted in 3.2.R
25.	Other	☐	☒	
Quality Considerations				
26.	Drug Substance Overage	☐	☒	
27.	Design Space	Formulation	☐	☒
28.		Process	☐	☒
29.		Analytical Methods	☐	☒
30.		Other	☐	☒
31.	Real Time Release Testing (RTRT)	☐	☒	
32.	Parametric Release in lieu of Sterility Testing	☐	☒	
33.	Alternative Microbiological Test Methods	☐	☒	
34.	Process Analytical Technology ¹	☐	☒	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	☒	☐
36.		Excipients	☐	☒
37.		Microbial	☐	☒
38.	Unique analytical methodology ¹	☐	☒	
39.	Excipients of Human or Animal Origin	☐	☒	
40.	Novel Excipients	☐	☒	
41.	Nanomaterials ¹	☐	☒	
42.	Hold Times Exceeding 30 Days	☐	☒	
43.	Genotoxic Impurities or Structural Alerts	☐	☐	This information is contained in the referenced DMFs
44.	Continuous Manufacturing	☐	☒	
45.	Other unique manufacturing process ¹	☐	☒	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).	☐	☒	
47.	New delivery system or dosage form ¹	☐	☒	
48.	Novel BE study designs	☐	☒	
49.	New product design ¹	☐	☒	
50.	Other	☐	☒	

¹Contact Office of Testing and Research for review team considerations

²Contact Post Marketing Assessment staff for review team considerations

C. FILING CONSIDERATIONS					
	Parameter	Yes	No	N/A	Comment
GENERAL/ADMINISTRATIVE					

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FILING REVIEW

C. FILING CONSIDERATIONS					
1.	Has an environmental assessment report or categorical exclusion been provided?	☒	☐	☐	Categorical exclusion claimed as per 21 CFR 25.31(b)
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ☐ Drug Substance ☐ Drug Product ☐ Appendices ☐ Facilities and Equipment ☐ Adventitious Agents Safety Evaluation ☐ Novel Excipients ☐ Regional Information ☐ Executed Batch Records ☐ Method Validation Package ☐ Comparability Protocols	☐	☐	☒	Not required for NDA's; however all sections are complete, appear uncorrupted and the NDA appears ready for review.
FACILITY INFORMATION					
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: ☐ Name of facility, ☐ Full address of facility including street, city, state, country ☐ FEI number for facility (if previously registered with FDA) ☐ Full name and title, telephone, fax number and email for on-site contact person. ☐ Is the manufacturing responsibility and function identified for each facility, and ☐ DMF number (if applicable)	☒	☐	☐	
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ☐ Is a manufacturing schedule provided? ☐ Is the schedule feasible to conduct an inspection within the review cycle?	☒	☐	☐	
DRUG SUBSTANCE INFORMATION					
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	☒	☐	☐	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ☐ general information ☐ manufacture - Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) - Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only - Includes complete description of product lots and their uses during development – BLA only ☐ characterization of drug substance ☐ control of drug substance - Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) - Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only ☐ reference standards or materials ☐ container closure system ☐ stability - Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment	☒	☐	☐	The application relies on DMFs (b) (4) (b) (4) (b) (4) (b) (4)
DRUG PRODUCT INFORMATION					
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ☐ Description and Composition of the Drug Product ☐ Pharmaceutical Development - Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots - Includes complete description of product lots and their uses during development ☐ Manufacture	☒	☐	☐	The drug product is a (b) (4) lyophilized powder of drug substance, sucrose, potassium dihydrogen phosphate, phosphoric acid, and potassium hydroxide. The manufacturing process (b) (4) (b) (4) The product does not require protection from light. The product is intended for reconstitution and dilution into 0.9% sodium chloride injection, USP or 5% Dextrose injection, USP. Two degradation products (b) (4) and (b) (4) are monitored on stability

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FILING REVIEW

C. FILING CONSIDERATIONS					
	○ If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? ☐ Control of Excipients ☐ Control of Drug Product ○ Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Analytical validation package for release test procedures, including dissolution ☐ Reference Standards or Materials ☐ Container Closure System ○ Include data outlined in container closure guidance document ☐ Stability ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment ☐ APPENDICES ☐ REGIONAL INFORMATION				and are controlled as per ICH Q3B.
BIOPHARMACEUTICS					
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?	☐	☐	☒	In-vivo exposure data will be assessed by the Clinical Pharmacology Reviewer.
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? <i>(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)</i>	☐	☐	☒	The dosage form is a solution for intravenous infusion.
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type	☐	☒	☐	The final dosage form for administration is an intravenous solution.

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS				
	of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.			
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	☐	☐	☒
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	☐	☐	☒
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	☐	☒	☐
REGIONAL INFORMATION AND APPENDICES				
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	☐	☒	☐
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	☒	☐	☐
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? ☐ facilities and equipment ○ manufacturing flow; adjacent areas ○ other products in facility ○ equipment dedication, preparation, sterilization and storage ○ procedures and design features to prevent contamination and cross-contamination ☐ adventitious agents safety evaluation (viral and non-viral) e.g.: ○ avoidance and control procedures ○ cell line qualification ○ other materials of biological origin ○ viral testing of unprocessed bulk ○ viral clearance studies ○ testing at appropriate stages of production ☐ novel excipients	☐	☐	☒
17.	Are the following information available for Biotech Products: ☐ Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: ○ LAL instead of rabbit pyrogen ○ Mycoplasma Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples			

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