

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206473Orig1s000

CHEMISTRY REVIEW(S)

NDA 206473

**Linezolid Injection
600 mg/300 mL**

Hospira, Inc.

Dorota Matecka, Ph.D.

**Office of New Drug Product
Division of New Drug Product I
Branch III**

For Division of Anti-Infective Products

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2. REVIEW #: 3
3. REVIEW DATE: June 15, 2015
4. REVIEWER: Dorota Matecka, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original Submission, SDN-01	26-Nov-2013

6. SUBMISSION(S) BEING REVIEWED:

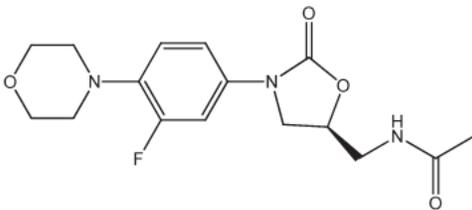
<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Resubmission	19-Dec-2014

7. NAME & ADDRESS OF APPLICANT:

Name: Hospira Inc.
 Address: 275 North Field Drive
 Lake Forest, IL 60045-5046
 Representative: Neda Yaleh
 Manager, Global Regulatory Affairs
 Telephone: 224-212-6163
 Fax: 224-212-5401
 Email: neda.yaleh@hospira.com

8. DRUG PRODUCT NAME/CODE/TYPE:

Chemistry Review Data Sheet

- a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Linezolid
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 5 (New formulation)
 - Submission Priority: Standard
9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)
10. PHARMACOL. CATEGORY: oxazolidinone antibacterial
11. DOSAGE FORM: injection
12. STRENGTH/POTENCY: 600 mg/300 mL
13. ROUTE OF ADMINISTRATION: intravenous
14. Rx/OTC DISPENSED: Y Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
- SPOTS product – Form Completed
- Y Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
- (S)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide
- 
- CAS No [165800-03-3]
Molecular Formula: C₁₆H₂₀FN₃O₄
Molecular Weight: 337.35
17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	adequate	5/19/2015	By S. Kelly
	III			1	adequate	5/27/2014	By J. Chang
	III			4	N/A	N/A	The information provided in the NDA was reviewed by Microbiology Reviewer, Dr. Jessica Cole.

*The DMF is titled

(b) (4)

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	110122	Linezolid Injection in 0.9% Sodium Chloride

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	01/30/2014	By C. Capacci-Daniel
Facilities	Acceptable	06/10/2015	OPF

Executive Summary Section

Chemistry Review

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The NDA provides sufficient information to assure the identity, strength, purity, and quality of the drug product. All label/labeling have required information. The Office of Process and Facilities has made an overall "Acceptable" recommendation for the facilities involved in this NDA. Therefore, from the OPQ perspective, this NDA is recommended for "Approval".

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

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

(1) Drug Product

Linezolid Injection, 600 mg/300 mL, is a sterile aqueous solution for intravenous infusion. The drug product is comprised of a clear, colorless to slightly yellow solution with a pH range of 4.4 to 5.2. It is a (b) (4) sterilized product containing no antimicrobial preservatives. Linezolid Injection is presented in a (b) (4) mL VisIV flexible container with a 300 mL fill in a foil laminate overwrap. The flex bag will be closed with administration and additive port assemblies.

The manufacture of Linezolid Injection involves the following units of operation:

(b) (4)

No novel excipients are used. Inactive ingredients include: citric acid anhydrous USP 1.92 mg/mL, sodium chloride USP 9 mg/mL, and sodium hydroxide NF 0.76

Executive Summary Section

mg/mL, and water for injection USP. Sodium hydroxide NF and/or hydrochloric acid NF are used to adjust the pH.

The proposed specification (see page 10) for Linezolid Injection is acceptable. The specification include clarity, volume, color (visual and instrumental), particulate matter, bacterial endotoxins, sterility, assay, pH, related substances, total sodium, osmolality, and identification (UV and HPLC). The analytical procedures and their method validations were reviewed and found to be adequate to support their intended purpose.

The manufacturing process that relates to product quality microbiology and the analytical procedures and acceptance criteria for sterility and endotoxins were reviewed by Product Quality Microbiology Reviewer, Dr. Jessica Cole, and found to be acceptable.

Per Biopharmaceutics Review dated 7/15/2014 by Dr. Elsbeth G Chikhale, the applicant's request for a biowaiver was granted.

The stability data support the proposed expiration dating period of 24 months when stored at 20° – 25°C (68° – 77°F), excursions permitted to 15° – 30°C (59° – 86°F).

The request for a categorical exclusion from the preparation of an environmental assessment (EA) under 21 CFR 25.31(a) is acceptable.

Quality risk assessment for Linezolid Injection summarized in the first cycle CMC review by Jane Chang remains unchanged.

(2) Drug Substance

The drug substance is linezolid, which is manufactured by (b) (4). CMC information for linezolid is referenced to (b) (4) DMF (b) (4) and a letter of authorization has been provided. DMF (b) (4) had been previously reviewed and found to be adequate in support of the original NDA. In addition, in support of the NDA resubmission, a recent amendment to DMF (b) (4) was reviewed and found to be adequate (refer to DMF review by S. Kelly dated 5/19/2015 in DARRTS).

Linezolid exhibits multiple (b) (4). Linezolid (b) (4) is used for the manufacture of Linezolid Injection. The proposed linezolid specification includes testing for appearance, color, identification (IR and HPLC), (b) (4) loss on drying, heavy metals, residue on ignition, (b) (4), assay, related substances, residual solvents (GC), particle size distribution, and bacterial endotoxins. The analytical procedures and their validations were reviewed and found to be adequate to support their intended purpose. A retest date of (b) (4) months has been established by (b) (4).

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B. Description of How the Drug Product Is Intended to Be Used

Linezolid Injection should be administered by intravenous infusion over a period of 30 to 120 minutes. This intravenous container should not be used in series connections. Additives should not be introduced into this solution. If Linezolid Injection is to be given concomitantly with another drug, each drug should be given separately in accordance with the recommended dosage and route of administration for each product.

C. Basis for Approval Recommendation

The applicant has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA has also provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period of 24 months.

All facilities have acceptable site recommendations. All labels have the required information.

III. Administrative**A. Reviewer's Signature**

See appended electronic signature page

B. Endorsement Block

See appended electronic signature page

C. CC Block

Entered electronically in Panorama.

Executive Summary Section

Chemistry Assessment

The NDA was tentatively approved on 9/26/2014 because the listed drug was subject to a period of patent and/or exclusivity protection and therefore final approval of the NDA was not possible be made effective until the aforesaid protection has expired. All CMC issues were resolved during the first review cycle and the NDA was recommended for approval from the product quality perspective. The only change in the current NDA resubmission includes an update to DMF (b)(4) referenced for linezolid drug substance. In addition, facilities involved in the manufacture, testing and packaging of the proposed drug substance and the drug product were re-evaluated by the Office of Process and Facilities and found to be acceptable in support of this NDA (Attachment I, below).

**I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2:
Body of Data****S DRUG SUBSTANCE**

The CMC information for linezolid drug substance is referenced to DMF (b)(4) Type II held by (b)(4). DMF (b)(4) had been previously reviewed and found to be adequate in support of the original NDA. In addition, in support of the current NDA resubmission, a recent amendment to DMF (b)(4) was reviewed and found to be adequate (refer to DMF review by S. Kelly dated 5/19/2015, in DARRTS).

P DRUG PRODUCT*Drug Product Specification*

The regulatory specification is presented in the following table.

Executive Summary Section

Table P.5.2: Linezolid Injection Specification (per the 6/27/2014 amendment)

Test	Acceptance Criteria	Regulatory Analytical Procedure	Alternate Analytical Procedure
Clarity	Solution must be clear. Solution must be free of visible particles.	Visual	N/A
Volume	(b) (4) mL*	USP<1>*	N/A
Color, Visual	Colorless to slightly yellow	Visual	N/A
Color, Instrumental	NMT (b) (4) APHA	In-house	N/A
Particulate Matter ≥ 10 µm	NMT (b) (4) per mL	USP <788>	N/A
≥ 25 µm	NMT (b) (4) per mL		
Bacterial Endotoxins	NMT (b) (4) EU/mL (NMT (b) (4) EU/mg)	USP <85> Gel Clot	N/A**
Sterility	Meets Test Requirements	USP<71>	N/A
Linezolid assay	(b) (4) %	In-house	N/A
pH	4.4 - 5.2***	USP <791>	N/A
Related Substances: (b) (4)	NMT (b) (4) % ----- NMT % ----- NMT % ----- NMT % ----- Individual Unspecified Degradation Product NMT % ----- Total NMT %	In-house	N/A
Total Sodium	(b) (4) %		
Osmolality	(b) (4) mOsmol/kg		
Identification (HPLC)	The average retention time of Linezolid in the sample preparation is within 2.0% of the average retention time of Linezolid in the Working Standard preparation of that Sample's bracket.		
Identification (UV)	The sample spectrum exhibits maximum and minimum absorptions at the same wavelengths as the standard spectrum.		

*Revised in the 6/16/2014 amendment. In the 4/18/2014 amendment, the acceptance criterion was (b) (4) mL by USP <1151>.

**Revised in the 6/27/2014 amendment. In the 6/16/2014 amendment, an in-house procedure was stated to be an alternate procedure.

***Revised in the 4/18/2014 amendment.

Executive Summary Section

Table P.8.2: Linezolid Injection Stability Specification

Test	Acceptance Criteria	Analytical Procedure
Clarity	Solution must be clear. Solution must be free of visible particles.	Visual
Color, Visual	Colorless to slightly yellow	Visual
Color, Instrumental	NMT (b) (4) APHA	In-house
Particulate Matter ≥ 10 μm	NMT (b) (4)	USP <788>
≥ 25 μm	NMT (b) (4)	
Bacterial Endotoxin	NMT (b) (4) EU/mL (NMT (b) (4) EU/mg)	USP <85> Gel Clot, In-house
Sterility	Meets Test Requirements	USP<71>
Linezolid assay	(b) (4) %	In-house
pH	(b) (4)	USP <791>
Related Substances:		In-house
(b) (4)	NMT (b) (4) %	
	NMT %	
	NMT %	
	NMT %	
	NMT %	
Individual Unspecified	NMT %	
Total	NMT %	
Total Sodium	(b) (4) %	In-house
Osmolality	(b) (4) mOsmol/kg	USP <785>, C-1191

*All samples tested prior to the 3-month interval were tested using the previous procedure. All samples tested at or after the 3-month interval were tested using the procedure described in Section P.5.2.

Executive Summary Section

Table P.8.4: Linezolid Injection Stability Specification (per the 4/18/2014 amendment)

Test	Acceptance Criteria	Analytical Procedure
Clarity	Solution must be clear. Solution must be free of visible particles.	Visual
Color, Visual	Colorless to slightly yellow	Visual
Color, Instrumental	NMT (b) (4) APHA	In-house
Particulate Matter ≥ 10 μm	NMT (b) (4)/mL	USP <788>
≥ 25 μm	NMT (b) (4)/mL	
Bacterial Endotoxin	NMT (b) (4) EU/mL (NMT (b) (4) EU/mg)	USP <85> Gel Clot, In-house
Sterility	Meets Test Requirements	USP<71>
Linezolid assay	(b) (4) %	In-house
pH	4.4 to 5.2	USP <791>
Related Substances:		In-house
(b) (4)	NMT (b) (4) %	
	NMT %	
	NMT %	
	NMT %	
	NMT %	
Individual Unspecified	NMT %	
Total	NMT %	
Total Sodium	(b) (4) %	In-house
Osmolality	(b) (4) mOsmol/kg	USP <785>, C-1191

Chemistry Assessment Section

Attachment I

Facility Re-Evaluation Report
 Provides the Office of Process and Facilities (OPF) Reviewer and District Office Pre-Approval Manager (DO PAM) a list of facilities that require re-evaluation based on the last inspection date.
 Title: n/a; 01/10/2015 11:37:34 AM

Application Type	Application Number	Submission Type	Submission Number	Sponsor Name	Application Goal Date	Target Action Date	Application Status	Drug Name	OPF Overall Application Recommendation	OPF Overall Application Re-Evaluation Date	Overall Manufacturing Inspection Recommendation Task Completion Date	OPF Overall Application Recommender
NDA	206473	Original	1	HOSPRA INC				LINEZOLID	Approve	5/30/2015	6/10/2015	

Facility Name	FEI	DUNS	Profile	OPF Facility Recommendation	OPF Facility Re-Evaluation Date	OPF Facility Recommendation Task Completion Date	Application Type	Application Number	Submission Type	Submission Number	Product Name	First Name	Last Name
HOSPRA INC	300491926	027721038	CTL CONTROL TESTING LABORATORY	Approve Facility	12/9/2017	4/20/2018	NDA	206473	Original	1	LINEZOLID	FRANK	WACHED
(b) (4)													
HOSPRA INC	1021343	037605671	OVP SMALL VOLUME PARACETAMOLS (INCLUDES STERILE POWDERS)	Approve Facility	6/13/2015	4/20/2016	NDA	206473	Original	1	LINEZOLID	FRANK	WACHED
HOSPRA INC	1021343	037605671	CTL CONTROL TESTING LABORATORY	Approve Facility	6/13/2017	6/17/2015	NDA	206473	Original	1	LINEZOLID		
(b) (4)													

Data refreshed on: 06/11/15 07:31:27 AM

Dorota M. Matecka -S
 Digitally signed by Dorota M. Matecka -S
 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300123291, cn=Dorota M. Matecka -S
 Date: 2015.06.16 22:02:41 -0400

Balajee Shanmugam -S
 Digitally signed by Balajee Shanmugam -S
 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300217143, cn=Balajee Shanmugam -S
 Date: 2015.06.16 22:22:31 -0400

NDA 206473

**Linezolid Injection
600 mg/300 mL**

Hospira, Inc.

Jane L. Chang, Ph.D.

Review Chemist

**Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch V**

For Division of Anti-Infective Products

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Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 206473
2. REVIEW #: 2
3. REVIEW DATE: 18-Sep-2014
4. REVIEWER: Jane L. Chang, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
12/13/2010 Pre-IND Meeting Minutes	07-Jan-2011
Original Submission, SDN-01	26-Nov-2013
Amendment, SDN-02	01-Apr-2014
Amendment, SDN-03	18-Apr-2014
Amendment, SDN-04	16-Jun-2014
Amendment, SDN-05	27-Jun-2014
Amendment, SDN-06	21-Jul-2014
Amendment, SDN-08	04-Aug-2014
Amendment, SDN-09	07-Aug-2014
CMC review #1	21-Aug-2014

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment, SDN-10	04-Sep-2014

7. NAME & ADDRESS OF APPLICANT:

Name: Hospira Inc.
Address: 275 North Field Drive
Lake Forest, IL 60045-5046
Representative: Neda Yaleh
Manager, Global Regulatory Affairs
Telephone: 224-212-6163
Fax: 224-212-5401

Chemistry Review Data Sheet

Email: neda.yaleh@hospira.com

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Linezolid
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 5 (New formulation)
 - Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: oxazolidinone antibacterial

11. DOSAGE FORM: injection

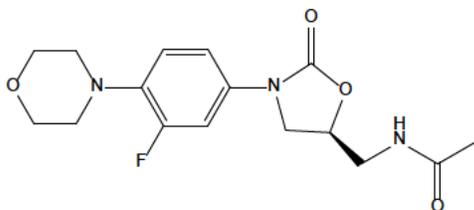
12. STRENGTH/POTENCY: 600 mg/300 mL

13. ROUTE OF ADMINISTRATION: intravenous

14. Rx/OTC DISPENSED: Y Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): SPOTS product – Form Completed Y Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(S)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide



CAS No [165800-03-3]

Molecular Formula: C₁₆H₂₀FN₃O₄

Molecular Weight: 337.35

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	adequate	8/8/2014	By J. Chang
	III			1	adequate	5/27/2014	By J. Chang
	III			4	N/A	N/A	The information provided in the NDA was reviewed by Microbiology Reviewer, Dr. Jessica Cole. See page 38.

*The DMF is titled (b) (4)

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

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7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	110122	Linezolid Injection in 0.9% Sodium Chloride

Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	01/30/2014	By C. Capacci-Daniel
Pharm/Tox	The proposed limits for the 3 ^{(b) (4)} [redacted] are considered qualified.*	04/15/2014	By Wendelyn Schmidt
Biopharm	Recommended for approval	7/15/2014	By Elsbeth Chikhale
Methods Validation	N/A, according to the current ONDQA IQP 5105		
Office of Drug Safety	No proprietary name was proposed. Labeling revisions were recommended.	07/03/2014	Aleksander P Winiarski
EA	Categorical exclusion (see this review)	07/07/2014	Jane Chang
Microbiology	Recommended for approval	7/11/2014	By Jessica Cole

* ^{(b) (4)} [redacted] are also known as ^{(b) (4)} [redacted], respectively. See page 63.

Executive Summary Section

Chemistry Review

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant of this NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product. All label/labeling have required information. The Office of Compliance has made an overall "Acceptable" recommendation for the facilities involved in this NDA. Therefore, from the ONDQA perspective, this NDA is recommended for "Approval".

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

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

(1) Drug Product

Linezolid Injection, 600 mg/300 mL, is a sterile aqueous solution for intravenous infusion. The drug product is comprised of a clear, colorless to slightly yellow solution with a pH range of 4.4 to 5.2. It is a (b) (4) sterilized product containing no antimicrobial preservatives. Linezolid Injection is presented in a (b) (4) mL VisIV flexible container with a 300 mL fill in a foil laminate overwrap. The flex bag will be closed with administration and additive port assemblies.

The manufacture of Linezolid Injection involves the following units of operation:

(b) (4)

No novel excipients are used. Inactive ingredients include: citric acid anhydrous USP 1.92 mg/mL, sodium chloride USP 9 mg/mL, and sodium hydroxide NF 0.76

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mg/mL, and water for injection USP. Sodium hydroxide NF and/or hydrochloric acid NF are used to adjust the pH.

The proposed specification (see page 55) for Linezolid Injection is acceptable. The specification include clarity, volume, color (visual and instrumental), particulate matter, bacterial endotoxins, sterility, assay, pH, related substances, total sodium, osmolality, and identification (UV and HPLC). The analytical procedures and their method validations were reviewed and found to be adequate to support their intended purpose.

The manufacturing process that relates to product quality microbiology and the analytical procedures and acceptance criteria for sterility and endotoxins were reviewed by Product Quality Microbiology Reviewer, Dr. Jessica Cole, and found to be acceptable.

Per Biopharmaceutics Review dated 7/15/2014 by Dr. Elsbeth G Chikhale, the applicant's request for a biowaiver is granted.

The stability data support the proposed expiration dating period of 24 months when stored at 20° – 25°C (68° – 77°F), excursions permitted to 15° – 30°C (59° – 86°F).

The request for a categorical exclusion from the preparation of an environmental assessment (EA) under 21 CFR 25.31(a) is acceptable.

Quality risk assessment for Linezolid Injection is summarized in the following table.

Executive Summary Section

From Initial Quality Assessment ¹			Review Assessment		
Product Attribute/ CQA	Factors that can impact the CQA	Risk Ranking ²	Risk Mitigation Approach	Risk Evaluation	Lifecycle Considerations/ Comments ³
Sterility	Formulation Raw materials Container closure Process parameters Scale/Equipment/Site	H	Environmental monitoring including product bioburden (b) (4) as well as adequate safety margin for the proposed lower limit of (b) (4)	Acceptable	(b) (4) control and evaluation is critical for this (b) (4) sterilization process.
Endotoxin	See Sterility	M	Environmental monitoring and control of endotoxin for API, citric acid, sodium chloride, and water for injection.	Acceptable	
Particulate matter	See Sterility	M	Environmental monitoring and (b) (4)	Acceptable	
Related substances	See Sterility	L	The limits for specified impurities (b) (4) have been qualified. Establishment of an upper limit of (b) (4) minimizes formation of degradation products.	Acceptable	See page 66
Assay	See Sterility	L	Control of (b) (4) to facilitate dissolution of linezolid	Acceptable	
Appearance	See Sterility	L	-	Acceptable	
Leachable/ extractable	See Sterility	L	Acceptable leachable/extractable data for (b) (4). Acceptable product specific extractable/leachable data for the container closure system.	Acceptable	See page 36 for (b) (4)
Osmolality	Formulation Raw materials Process Parameters	L	-	Acceptable	
pH	See Osmolality	L	The product solution contains (b) (4) to maintain pH of the formulation.	Acceptable	
Deliverable volume	Container closure Process parameter Equipment	M	The acceptance criterion of deliverable volume, (b) (4), has been revised to (b) (4) mL.	Acceptable	

¹ See Attachment 1, page 103.

² Risk ranking applies to product attribute/CQA.

³ For example, post marketing commitment, knowledge management post approval, etc.

⁴ Information from Microbiology Review #1 was summarized by this reviewer.

⁵ The comment was provided by Microbiology Reviewer, Dr. Jessica Cole, through email. See Attachment 2.

Executive Summary Section

(2) Drug Substance

The drug substance is linezolid, which is manufactured by (b) (4). CMC information for linezolid is referenced to (b) (4) DMF (b) (4) and a letter of authorization has been provided. DMF (b) (4) has been reviewed by this reviewer and found to be adequate.

Linezolid exhibits multiple (b) (4). Linezolid (b) (4) is used for the manufacture of Linezolid Injection. The proposed linezolid specification (see page 16) includes testing for appearance, color, identification (IR and HPLC), (b) (4) loss on drying, heavy metals, residue on ignition, (b) (4), assay, related substances, residual solvents (GC), particle size distribution, and bacterial endotoxins. The analytical procedures and their validations were reviewed and found to be adequate to support their intended purpose. A retest date of (b) (4) months has been established by (b) (4).

B. Description of How the Drug Product Is Intended to Be Used

Infection*	Dosage and Route, and Frequency of Administration		Recommended Duration of Treatment (consecutive days)
	Pediatric Patients† (b) (4)	Adults and Adolescents (12 Years and Older)	
Nosocomial pneumonia Community-acquired pneumonia, including concurrent bacteremia Complicated skin and skin structure infections	10 mg/kg intravenous infusion every 8 hours	600 mg intravenous infusion every 12 hours	10 to 14
Vancomycin-resistant <i>Enterococcus faecium</i> infections, including concurrent bacteremia	10 mg/kg intravenous infusion every 8 hours	600 mg intravenous infusion every 12 hours	14 to 28

* Due to the designated pathogens [see *Indications and Usage (1)*]

† (b) (4)

Linezolid Injection should be administered by intravenous infusion over a period of 30 to 120 minutes. This intravenous container should not be used in series connections. Additives should not be introduced into this solution. If Linezolid Injection is to be given concomitantly with another drug, each drug should be given separately in accordance with the recommended dosage and route of administration for each product.

C. Basis for Approval Recommendation

Executive Summary Section

The applicant has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA has also provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period of 24 months.

All facilities have acceptable site recommendations.
All labels have the required information.

III. Administrative

A. Reviewer's Signature

See appended electronic signature page

B. Endorsement Block

See appended electronic signature page

C. CC Block

Entered electronically in DARRTS

Chemistry Assessment Section

Chemistry Assessment

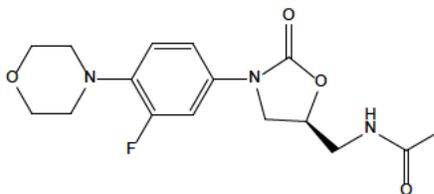
Reviewer's Comments: A Complete Response recommendation was made in the CMC Review #1 dated 21-Aug-2014 due to lack of extractable/leachable data for the container closure system and labeling issues. Subsequently, the applicant submitted an amendment dated 04-Sep-2014 and revised labeling via an email dated 12-Sep-2014, which are the subjects of this review. For convenience, information presented in Review #1 is also included in this review.

**I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2:
Body of Data****S DRUG SUBSTANCE****S.1 General Information****S.1.1 Nomenclature**

INN: Linezolid
USAN: Linezolid
Chemical name: (S)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide

Or

(b) (4)

S.1.2 Structure

CAS No [165800-03-3]

Molecular formula: C₁₆H₂₀FN₃O₄

Molecular weight: 337.35

S 1.3 General Properties

General description: (b) (4) powder
Melting point: 178 - 182°C
pKa: 1.7
Chirality: one chiral center as S-isomer

(b) (4)

Chemistry Assessment Section

Solubility: Slightly soluble in methanol¹ and soluble in chloroform
 Hygroscopicity: Non-hygroscopic
 Partition Coefficient: 0.55
 Particle Size: D (v, 0.5) ≤ (b) (4) μm
 D (v, 0.9) ≤ (b) (4) μm
 D (v, 0.99) ≤ (b) (4) μm

S.2 Manufacture

S.2.1 Manufacturers

Name and Address	Responsibility	Reference
(b) (4)	Drug Substance manufacture; release testing; stability testing	(b) (4)
Hospira, Inc. Highway 301 North Rocky Mount, NC 27801	Drug substance acceptance testing	FEI No: 1021343 DUNS No: 093132819

The responsibility was added in the 7/21/2014 amendment.

Reviewer's Assessment: Establishment evaluation was requested for each site listed above. The Office of Compliance has issued an "acceptable" recommendation for each site used in the manufacture and control of the drug substance (see page 105).

S.2.2 Description of Manufacturing Process and Process Controls

See DMF (b) (4)

S.2.3 Control of Materials

See DMF (b) (4)

S.2.4 Controls of Critical Steps and Intermediates

See DMF (b) (4)

¹ Reviewer's Comment: (b) (4)

Chemistry Assessment Section

A.3 Novel Excipients
N/A

R REGIONAL INFORMATION

R.1 Executed Batch Records
Representative executed batch records were provided for the registration batches (Batch Numbers: 12-094-SB, 12-095-SB, and 12-096-SB).

R.2 Comparability Protocols
N/A

R.3 Methods Validation Package
See section I.P.5.2 on page 55 of this review for the analytical procedures. The analytical procedures and their validation were reviewed and found to be adequate. Methods validation packages will not be sent to FDA laboratories because the methods do not meet the “method validation request criteria” according to the current ONDQA IQP 5105 effective 3/31/2012.

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. LABELING & PACKAGE INSERT

Labeling information provided in the original submission is summarized below.

1. Physician’s Labeling Rule Prescription Drug Labeling

1) “Highlights” Section

Linezolid Injection

Initial U.S. Approval: 2000

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

Injection: 600 mg (b) (4)

Reviewer's Assessment:

Item	Comments	Conclusions
Proprietary name and established name	Proprietary name is not required for NDA approval. Because there is no proprietary name, the established name should be presented in all capital letters.	Unsatisfactory
Dosage forms and strengths	(b) (4) the strength should be expressed as “600 mg in 300 mL” per USP <1>.	Unsatisfactory

Chemistry Assessment Section

Route of administration	“for intravenous use” was not provided.	Unsatisfactory
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Conclusion: The “Highlights” section is unsatisfactory.

In July 2014, this reviewer provided the following edits for the labeling in the Division’s share drive:

~~Linezolid Injection~~ **LINEZOLID INJECTION, for intravenous use**

Initial U.S. Approval: 2000

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

Injection: 600 mg (b) (4) in 300 mL

Based on the revised labeling provided to the Chief Project Manager Ms. Frances LeSane on 12-Sep-2014 via email, the applicant accepted all of the above recommendations.

2) “Full Prescribing Information” Section

a. Section 2.3 Compatibilities

Compatible intravenous solutions include 0.9% Sodium Chloride Injection, USP, 5% Dextrose Injection, USP, and Lactated Ringer’s Injection, USP.

Conclusion: This section is satisfactory. The data provided in Section P.2.6 support the labeling statement.

b. Section 3 Dosage Forms and Strengths

Linezolid Injection: (b) (4) single-use, ready-to-use flexible plastic VisIV™ containers in a foil laminate overwrap. (b) (4)

Reviewer's Assessment:

Item	Comments	Conclusions
Dosage form and strength	The correct dosage form, i.e. injection, is provided. Per USP <1151>, solutions administered by injection are officially titled injections. This reviewer recommend revising expression of strength to “600 mg linezolid in 300 mL” per USP <1>.	Unsatisfactory
Others	The statement of (b) (4) should be deleted because (b) (4)	Unsatisfactory

Chemistry Assessment Section

Conclusion: *This section is unsatisfactory.*

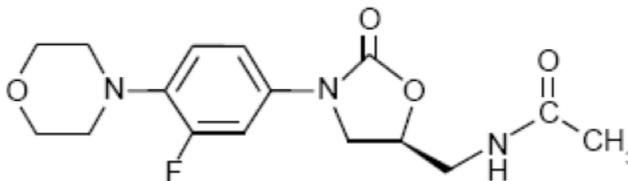
In July 2014, this reviewer provided the following edits for the labeling in the Division's share drive:

Linezolid Injection: (b) (4) in 300 mL in a single-use, ready-to-use flexible plastic VisIV containers in a foil laminate overwrap. (b) (4)

Based on the revised labeling provided to the Chief Project Manager Ms. Frances LeSane on 12-Sep-2014 via email, the applicant accepted all of the above recommendations.

c. Section 11 Description

Linezolid Injection, contains linezolid, which is a synthetic antibacterial agent of the oxazolidinone class. The chemical name for linezolid is (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl] methyl]-acetamide. The empirical formula is C₁₆H₂₀FN₃O₄. Its molecular weight is 337.35, and its chemical structure is represented below:



Linezolid Injection is supplied as a ready-to-use sterile isotonic solution for intravenous infusion. Each (b) (4) contains (b) (4) mg of linezolid. Inactive ingredients (b) (4)

The sodium (Na) content is 3.98 mg/mL (52 mEq/300-mL container).

Reviewer's Assessment:

Chemistry Assessment Section

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name and established name*	Established name "Linezolid Injection" is provided. Proprietary name is not provided. Proprietary name is not a requirement for NDA approval.	Satisfactory
Dosage form and route of administration	The correct dosage form, injection, and route of administration, intravenous, are provided.	Satisfactory
Active moiety expression of strength	This reviewer recommend revising expression of strength to "600 mg of linezolid in 300 mL" per USP <1>.	Unsatisfactory
Inactive ingredient information (quantitative, if injectables per 21 CFR 201.100(b)(5)(iii))	(b) (4) inactive ingredients are: citric acid, sodium chloride, sodium hydroxide and hydrochloric acid (for pH adjustment), and water for injection. Furthermore, quantitative information for inactive ingredients (except that ingredients added to adjust the pH (b) (4) may be declared by name and a statement of their effect) must be provided per 21 CFR 201.100(b)(5)(iii).	Unsatisfactory
Statement of being sterile	The sterile statement is provided.	Satisfactory
Pharmacological/therapeutic class	The pharmacological class, oxazolidinone antibacterial, is provided.	Satisfactory
Chemical name, structural formula, molecular weight	Chemical name, molecular formula, structural formula and molecular weight are correctly described in this section.	Satisfactory
Other important chemical or physical properties (such as pKa or pH)	The sodium (Na ⁺) content is 3.98 mg/mL (52 mEq/300-mL container).	Satisfactory

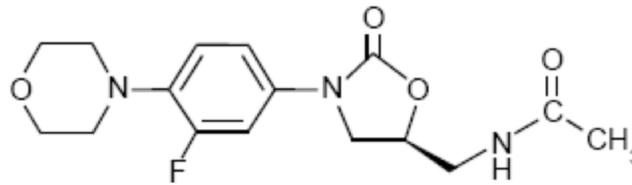
Conclusion: The "Description" section is unsatisfactory.

In July 2014, this reviewer provided the following edits for the labeling in the Division's share drive:

Linezolid Injection₇ contains linezolid, which is a synthetic antibacterial agent of the oxazolidinone class. The chemical name for linezolid is (*S*)-*N*-[[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl] methyl]-acetamide.

The empirical formula is C₁₆H₂₀FN₃O₄. Its molecular weight is 337.35, and its chemical structure is represented below:

Chemistry Assessment Section



Linezolid Injection is supplied as a ready-to-use sterile isotonic solution for intravenous infusion. Each (b) (4) container contains (b) (4) 600 mg of linezolid in 300 mL of a clear, colorless to slightly yellow aqueous solution. Inactive ingredients include: (b) (4) citric acid anhydrous USP 1.92 mg/mL, sodium chloride USP 9 mg/mL, (b) (4) sodium hydroxide NF 0.76 mg/mL, and water for injection USP (b) (4) Sodium hydroxide NF and/or hydrochloric acid NF are used to adjust the pH. The sodium (Na⁺) content is 3.98 mg/mL (52 mEq/300-mL container).

Based on the revised labeling provided to the Chief Project Manager Ms. Frances LeSane on 12-Sep-2014 via email, the applicant accepted all of the above recommendations.

d. Section 16 How Supplied/Storage and Handling

(b) (4)
Linezolid Injection is available in single-use, ready-to-use flexible plastic container (VisIV™ Container) in a foil laminate overwrap. (b) (4)
The container (b) (4) available in the following package size (b) (4)
(b) (4) NDC 0409-4883-01

(b) (4)
Store at 20 to 25°C (68 to 77°F) [see USP Controlled Room Temperature]. Protect from light. It is recommended that the containers be kept in the overwrap until ready to use. Protect containers from freezing.

Reviewer's Assessment:

Chemistry Assessment Section

Item	Comments on the Information Provided in NDA	Conclusions
Strength of dosage form in metric system	This reviewer recommend revising expression of strength to "600 mg in 300 mL" per USP <1>.	Unsatisfactory
Units of dosage form	Available unit is correctly described as 300 mL.	Satisfactory
Identification of dosage forms, NDC number	The dosage form injection is correctly described. NDC Number is stated:	Satisfactory
Special handling (e.g., protect from light)	The statements that the containers be kept in the overwrap until ready to use and be protected from freezing are provided.	Satisfactory
Storage condition	Inclusion of permitted excursion temperature is recommended.	Unsatisfactory
Others	The statement of (b) (4) should be deleted.	Unsatisfactory

Conclusion: The "How Supplied/Storage and Handling" section is unsatisfactory.

In July 2014, this reviewer provided the following edits for the labeling in the Division's share drive:

(b) (4)
 Linezolid Injection is available in a single-use, ready-to-use flexible plastic container (VisIV™ Container) in a foil laminate overwrap. (b) (4)
 (b) (4) The container (b) (4) is available in the following package size (b) (4)
600 mg in 300 mL (b) (4) NDC 0409-4883-01

(b) (4)
 Store at 20 to 25°C (68 to 77°F), **excursion permitted to 15 – 30°C (59-86°F)** [see USP Controlled Room Temperature]. Protect from light. It is recommended that the containers be kept in the overwrap until ready to use. Protect containers from freezing.

Based on the revised labeling provided to the Chief Project Manager Ms. Frances LeSane on 12-Sep-2014 via email, the applicant accepted all of the above recommendations.

e. Manufacturer's or Distributor's name

Hospira, Inc., Lake Forest, IL 60045 USA

Reviewer's Assessment: The information was provided at the end of labeling.
Conclusion: **Satisfactory**

2. Labels

1) Immediate Container Label

Chemistry Assessment Section



Reviewer's Assessment:

Chemistry Assessment Section

Item	Comments	Conclusions
Proprietary name, established name	The applicant did not propose a proprietary name. (b) (4) The established name should be "Linezolid Injection".	Unsatisfactory
Route of administration	The route of administration, intravenous, is correctly described. However, it should be placed in a prominent place, i.e. under the strength.	Unsatisfactory
Strength	Strength (600 mg/300 mL) is correctly expressed. However, the statement "(2 mg/mL)" should be deleted.	Unsatisfactory
Net contents	The net content 300 mL is correctly described	Satisfactory
Lot number per 21 CFR 201.18	A space for this information is not indicated.	Unsatisfactory
Expiration date per 21 CFR 201.17	A space for this information is not indicated.	Unsatisfactory
"Rx only" statement	The statement is displayed.	Satisfactory
Storage	Storage condition should include permitted excursion temperature.	Unsatisfactory
Name of all inactive ingredients and quantitative ingredient information	Quantitative information for inactive ingredients, including citric acid anhydrous, sodium chloride, and sodium hydroxide, is provided. Quantitative information is not required for water as vehicle and for inactive ingredients used for pH adjustment.	Satisfactory
NDC number	NDC number is indicated.	Satisfactory
Bar Code	Barcode is indicated.	Satisfactory
Name of manufacturer/distributor	The name of manufacturer is correctly described.	Satisfactory
Others	(b) (4)	Unsatisfactory

Conclusion: The immediate container was unsatisfactory. See the comments on pages 94 and 96.

2) Overwrap

Front:

Chemistry Assessment Section

(b) (4)



Reviewer's Assessment:

Chemistry Assessment Section

Item	Comments	Conclusions
Proprietary name, established name	The applicant did not propose a proprietary name. (b) (4) The established name should be "Linezolid Injection".	Unsatisfactory
Strength	Strength, 600 mg/300 mL, is correctly expressed. However, the statement "(2mg/mL)" should be deleted.	Unsatisfactory
Net contents	The net content 300 mL is correctly described	Satisfactory
Lot number per 21 CFR 201.18	A space for this information is not indicated.	Unsatisfactory
Expiration date per 21 CFR 201.17	A space for this information is not indicated.	Unsatisfactory
Name of all inactive ingredients and quantitative ingredient information	Quantitative information for inactive ingredients, including citric acid anhydrous, sodium chloride, and sodium hydroxide, is provided. Quantitative information is not required for water as vehicle and for inactive ingredients used for pH adjustment.	Satisfactory
"Rx only" statement	The statement is displayed on the main panel.	Satisfactory
Storage Conditions	Inclusion of permitted excursion temperature is recommended.	Unsatisfactory
NDC number	NDC number is indicated.	Satisfactory
Bar Code	Bar code is indicated.	Satisfactory
Name of manufacturer/distributor	The name of manufacturer is correctly described.	Satisfactory
(b) (4)	The statement is present.	Satisfactory
Route of Administration	The route of administration, intravenous, is correctly described. However, it should be placed in a prominent place, i.e. under the strength.	Unsatisfactory
Others	(b) (4)	Unsatisfactory

Conclusion: The overwrap labeling was unsatisfactory.

The following comments were conveyed to the applicant on 5/27/2014.

Regarding the container label and overwrap labeling:

- Revise the established name to "Linezolid Injection". The established name should be displayed in the same line with the same font size. The statement (b) (4)
- Indicate the locations where lot number and expiration date will be placed.
- Include permitted excursion temperature "excursions permitted to 15-30°C (59-86°F).

In the 6/16/2014 amendment, revised container label and overwrap labeling, together with the following information, were provided.

Chemistry Assessment Section

- The established name has been revised to “Linezolid Injection” (b) (4)

- Hospira prints the product expiration date and lot number on the primary container and the foil overwrap during batch manufacture. The location for the information on lot number and expiration date is indicated with a red box.
- The statement “excursions permitted to 15 to 30°C (59 to 86°F)” has been added.

Revised container label:**Revised overwrap labeling:**(b) (4)


The response is acceptable.

Chemistry Assessment Section

The issue regarding the location for the route of administration has also been identified by DMEPA reviewer, Aleksander P Winiarski, dated 03-Jul-2014.

The container label and the overwrap labeling contain

(b) (4)

(b) (4)

Furthermore, the pH range should be changed from (b) (4) to "4.4 – 5.2" (see page 55).

The following comments were conveyed to the applicant on 7/18/2014:

1. Regarding the container label and overwrap labeling:
 - a) Place the route of administration "for intravenous infusion" under the strength to ensure appropriate prominence.
 - b) Express the strength only by 600 mg/300 mL. Delete "(2 mg/mL)".
 - c) (b) (4)
 - d) Change pH range from (b) (4) to "4.4 – 5.2".
2. (b) (4)

In the 8/7/2014 amendment, the applicant provided updated container label and carton labeling, which have incorporated all of the above recommendations except for Item 1b). The strength "(2 mg/mL)" is expressed using a smaller font size.

The response is acceptable. Inclusion of "(2 mg/mL)" at a smaller font size (less prominent) is acceptable per USP <1>. The strength per mL is used for calculation of the dose for pediatric patients based on body weight.

Chemistry Assessment Section

Final revised container label:**Final revised overwrap labeling:**

(b) (4)

**3. Product Data Elements in Structured Product Labeling**

Chemistry Assessment Section

Item		Information Provided in NDA		
Trade name	None			
Established name	Linezolid Injection			
Product Code	NDC:0409-4883			
Route of Administration	INTRAVENOUS			
DEA Schedule	None			
Active Ingredient/Active Moiety	Ingredient Name	Basis of Strength	Strength	
	LINEZOLID (LINEZOLID)	LINEZOLID	2 mg in 1 mL	
Inactive Ingredients	Ingredient Name	Strength		
	SODIUM HYDROXIDE			
	ANHYDROUS CITRIC ACID			
	SODIUM CHLORIDE			
	WATER			
	HYDROCHLORIC ACID			
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0409-4883-01	10 in 1 CASE		
1		1 in 1 POUCH		
1		300 mL in 1 BAG		
Marketing Information				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	
NDA	NDA206473			

Labeler - Hospira, Inc. (141588017)		
Establishment		
Name	ID/FEI	Business Operations
	(b) (4)	api manufacture(0409-4883)
Hospira, Inc.	093132819	analysis(0409-4883), manufacture(0409-4883)
Hospira, Inc.	827731089	analysis(0409-4883)
	(b) (4)	analysis(0409-4883)
		analysis(0409-4883)

Reviewer's Assessment: The labeling information in drug listing data elements is unsatisfactory. Quantitative information for excipients should be provided. The following comment was conveyed to the applicant on 5/27/2014:

Provide the strength of inactive ingredients, including anhydrous citric acid, sodium chloride, and sodium hydroxide in Product Data Elements in Structured Product Labeling.

In the 6/16/2014 amendment, the Product Data Elements in Structured Product Labeling has been revised to include strength of inactive ingredients, including anhydrous citric

Chemistry Assessment Section

acid (1.92 mg in 1 mL), sodium chloride (9 mg in 1 mL), and sodium hydroxide (0.76 mg in 1 mL). *The response is acceptable.*

B. ENVIRONMENTAL ASSESSMENT OR CLAIM OF CATEGORICAL EXCLUSION

A categorical exclusion from the preparation of an environmental assessment (EA) was requested under 21 CFR 25.31. The basis of this exclusion is the fact that Linezolid Injection will not be indicated for administration at a higher dose level, nor for a longer duration, or for different indications than those that are in effect.

Reviewer's Assessment: The (b) (4) for Linezolid Injection (in 0.9% sodium chloride) is (b) (4) Zyvox (linezolid) injection with the same dosage and route of administration. Hospira's formulation does not contain dextrose, but contains higher amount of sodium. It is expected that action on the NDA will not increase the use of the active moiety. Thus, the claim of categorical exclusion is acceptable per 21 CFR 25.31 (a).

III. List Of Deficiencies

All deficiencies have been addressed adequately. There are no outstanding deficiencies.

The following information was requested from the applicant in the 3/27/2014 FDA information request letter. The applicant has responded adequately in the 4/18/2014 amendment for all items except for Items 4, 5, 7, and 15a). The response for Item 4 was provided in the 6/16/2014 amendment.

1. Provide the analytical procedure for instrumental color testing for the drug substance. Provide information on the standards as to whether they are (b) (4). If they are (b) (4), please provide the (b) (4).
2. Regarding linezolid drug substance specification, tighten the acceptance criterion for each unspecified impurity to NMT (b) (4)%, which corresponds to (b) (4) mg per day, per ICH Q3A.
3. Regarding the drug substance container closure system, clarify whether the silica (b) (4). The information appears to be inconsistent with the description in DMF (b) (4).
4. Provide linezolid (b) (4) solubility data in the formulation vehicle, i.e. (b) (4). The solubility of the (b) (4) should be characterized because your formulation uses (b) (4).
5. Provide data on extractables/leachables for (b) (4) as well as (b) (4) that are in direct contact with the product. The data should be obtained using Linezolid Injection or the vehicle solution.
6. To support the proposed hold time of (b) (4) hours for the bulk solution, provide data to demonstrate its quality is not adversely affected. In the absence of such data, limit the hold time to (b) (4) hours, which was used for the registration stability batches.
7. Your proposed acceptance criterion of (b) (4) mL to (b) (4) mL (target (b) (4) mL), which corresponds to (b) (4)% to (b) (4)% of the label claim, for fill volume is not acceptable. Please

Chemistry Assessment Section

- tighten the acceptance criterion to comply with the USP <1151> recommendation of 2% excess for injectable drug products of 50.0 mL or more.
8. Regarding the non-compendial analytical procedures for testing of the drug product:
 - a) Provide the analytical procedures and the respective method validation data for total sodium.
 - b) Provide the analytical procedures for color by instrumental, identification by UV, and identification by HPLC.
 - c) Clarify the analytical procedure for osmolality. The following analytical procedures are listed: "in house" in Section 3.2.P.5.1; "USP <785>, C-1191" in Sections 3.2.P.8.1 and 3.2.P.8.2. If non-compendial analytical procedure is used, please provide the procedure.
 9. Please clarify the amount of (b) (4) impurity for the three registration batches of the drug product. The amount reported in the certificate of analysis for each registration batch is (b) (4). However, the amount reported in the summary table (Table 2 of Section 3.2.P.5.4) is (b) (4) %.
 10. Please provide a summary in Section 3.2.P.5.5 for the analytical techniques used in structural characterization of potential impurities, including Impurities (b) (4).
 11. Address the following items regarding the drug product specification:
 - a) Provide specific acceptance criterion for identification by HPLC and by UV. The proposed acceptance criterion of "Meets test requirements" is not acceptable because the test requirements are not provided.
 - b) Revise the acceptance criterion for fill volume from "NLT labeled volume" to "(b) (4) mL - (b) (4) mL".
 - c) Revise the acceptance criteria for particulate matter from "NMT (b) (4)" to "NMT (b) (4) per mL" for particles $\geq 10 \mu\text{m}$ and from "NMT (b) (4)" to "NMT (b) (4) per mL" for particles $\geq 25 \mu\text{m}$.
 - d) Delete testing for (b) (4). The specification should reflect actual testing performed for release and stability study.
 - e) Revise the acceptance criterion for pH for release and stability from "(b) (4)" to "4.4 to 5.2". Please note that your proposed release acceptance criterion in Section 2.3 ((b) (4)) is inconsistent with that in Section 3.2.P.5.1 (4.3 – 5.3).
 - f) Tighten the acceptance criterion for total impurities from (b) (4) % to (b) (4) %.
 - g) Tighten the acceptance criterion for color APHA from NMT (b) (4) to NMT (b) (4). This limit is supported by the regression analysis of the long-term stability data of the registration batches.
 12. Please provide the source, batch number, and the amount of total impurities of the reference standards for Impurities (b) (4) for testing of the drug substance and/or drug product.
 13. Please specify the (b) (4) to be used for Linezolid Injection container. In Section 3.2.P.7, you state that (b) (4) may be used in addition to (b) (4).
(b) (4)
 14. Please include testing for (b) (4) in the drug product stability protocol as per ICH Q1A(R2). The drug product is packaged in a (b) (4).
(b) (4)
 15. Please address the following issues regarding extractables/leachables for Linezolid Injection:

Chemistry Assessment Section

- a) Provide product specific extractable data, i.e. extractable study using Linezolid Injection or the vehicle solution, for all components of the container closure system that are in direct contact with the product.
- b) Provide the quantitation limits for all known leachables.
- c) Clarify whether the (b) (4) administration port, and additive port are in contact with the product solution for stability samples of the three registration batches stored in the (b) (4) orientation. Provide the orientation of the (b) (4) administration port and additive port in the (b) (4) orientation.
- d) Provide the chromatographic overlay of samples stored at 40°C for 6 months.
- e) As a postapproval stability commitment, please commit to a one-time leachable study for three batches of Linezolid Injection under long-term for the proposed expiration dating period and under accelerated condition for 6 months. The samples should be stored under the worst case scenario, i.e. the product solution in contact with all components of the container closure system that are in direct contact with the product.

To address Item 4 from above, additional comment was conveyed to the applicant on 7/11/2014 (see page 102). To address Items 5, 7, and 15a) from above, additional comments were conveyed to the applicant on 5/27/2014.

The following information was requested from the applicant in the 5/27/2014 FDA information request letter. The applicant has responded adequately in the 6/16/2014 amendment for all items except for Items 3.

1. Your response on the extractable/leachable study for (b) (4) in the April 18, 2014 amendment is not acceptable because (b) (4).
(b) (4)
Until this issue is addressed, commit to use (b) (4), instead of (b) (4) for the manufacture of Linezolid Injection.
2. Revise the upper limit of fill volume from (b) (4) mL to (b) (4) mL for the drug product specification based on the variability observed for the three registration batches. Furthermore, revise the analytical procedure for volume determination from USP <1151> to USP <1> because USP <1151> does not contain analytical procedure for volume determination.
3. Your response on the extractable/leachable study for the container closure system for the drug product (Item 15a of the 3/27/2014 FDA Letter) in the April 18, 2014 amendment is not acceptable because (b) (4).
(b) (4). The extractable data from an aqueous solution of a pH similar (or a lower pH as the worst case scenario) to the drug product solution should be provided since different pH solutions may result in different extractable profiles.

If the data have been submitted, please provide the exact location (e.g. date of submission, Section, DMF, etc.) where the information is presented.

4. Regarding the container label and overwrap labeling:

Chemistry Assessment Section

- a. Revise the established name to “Linezolid Injection”. The established name should be displayed in the same line with the same font size. (b) (4)
 - b. Indicate the locations where lot number and expiration date will be placed.
 - c. Include permitted excursion temperature “excursions permitted to 15-30°C (59-86°F).
5. Provide the strength of inactive ingredients, including anhydrous citric acid, sodium chloride, and sodium hydroxide in Product Data Elements in Structured Product Labeling.

The following information was requested from the applicant in the 7/11/2014 FDA information request letter. The applicant has responded adequately in the 7/21/2014 and 8/4/2014 amendments.

Revise the drug substance specification to include testing for (b) (4). Your solubility data as provided in the 6/16/2014 amendment show that both quality attributes affect the dissolution rate of linezolid in the formulation vehicle.

The following information was requested from the applicant in the 7/18/2014 FDA information request letter. The applicant has responded adequately in the 8/7/2014 amendment.

1. Regarding the container label and overwrap labeling:
 - a. Place the route of administration “for intravenous infusion” under the strength to ensure appropriate prominence.
 - b. Express the strength only by 600 mg/300 mL. Delete “(2 mg/mL)”.
 - c. (b) (4)
 - d. Change pH range from (b) (4) to “4.4 – 5.2”
2. (b) (4)

Refer to pertinent sections of this review for the evaluation of the applicant’s response.

Chemistry Assessment Section

IV. Attachments

1. Initial Quality Risk Assessment

The following is initial quality risk assessment for Linezolid Injection 600 mg/300 mL, jointly conducted by CMC Lead Dr. Dorota Matecka and this reviewer.

Product attribute/CQA	Factors that can impact the CQA	Probability of Occurrence (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number*	Comment, if any
Sterility	Formulation Raw materials Container closure Process parameters Scale/Equipment/Site	4	5	5	100	(b) (4) sterilization: (b) (4)
Endotoxin	See Sterility	2	4	4	32	
Particulate matter	See Sterility	3	5	3	45	
Related substances	See Sterility	3	2	1	6	(b) (4) sterilization (b) (4)
Assay	See Sterility	2	3	1	6	Assign independent RPN numbers for assay and related substances.
Appearance	See Sterility	3	3	1	9	
Leachable/extractable	See Sterility	2	4	3	24	
Osmolality	Formulation Raw materials Process Parameters	2	5	2	20	
pH	See Osmolality	2	2	1	4	Target pH 4.8. Use (O)(S)(D) values of low pH.
Deliverable volume	Container closure Process parameter Equipment	5	2	5	50	Target fill volume: (b) (4) mL. Only the lower limit was proposed per USP <1>.

*Risk Ranking:

Low (L): 25 ≤ RPN

Medium (M): 26 ≤ RPN ≤ 60

High (H): RPN > 60

CMC REVIEW NDA 206473

Chemistry Assessment Section

2. Email Communication with Microbiology Reviewer

Chang, Jane

From: Cole, Jessica
Sent: Wednesday, July 16, 2014 8:48 AM
To: Chang, Jane
Subject: RE: Micro Risk Assessment for NDA 206473

One comment below regarding the life cycle management.

Jessica Cole, PhD
 301-796-5148

From: Chang, Jane
Sent: Tuesday, July 15, 2014 11:41 AM
To: Cole, Jessica
Subject: Micro Risk Assessment for NDA 206473

Hi Jessica,

As you may be aware that ONDQA reviewers are required to include a risk assessment for NDAs with GRMP dates after August 1, 2014. Because your review does not include a formal risk assessment template (see below), I would like to seek your input on this subject for microbiological quality attributes for NDA 206473. Below is a template that ONDQA use. Please let me know if you have any comments on Risk Mitigation Approach and Lifecycle Considerations/Comments.

From Initial Quality Assessment		Review Assessment			
Product attribute/ CQA	Factors that can impact the CQA	Risk Ranking*	Risk Mitigation approach	Risk Evaluation	Lifecycle Considerations/ Comments**
Sterility	Formulation Raw materials Container closure Process parameters Scale/Equipment/Site	H	Environmental monitoring including product bioburden (b) (4) (b) (4) as well as adequate safety margin for the proposed lower limit of (b) (4)	Acceptable	(b) (4) control and evaluation is critical for this (b) (4) finalization process.
Endotoxin	See Sterility	M	Environmental monitoring and control of endotoxin for API, citric acid, sodium chloride, and water for injection.	Acceptable	

*Risk ranking applies to product attribute/CQA

**For example, post marketing commitment, knowledge management post approval, etc.

***Information from Microbiology Review #1 was summarized by this reviewer.

Please Note that The Initial Quality Assessment Section has yet to be generated by Dorota and filed in DARRTS.
 Thanks.

Jane

Chemistry Assessment Section

3. EES Report

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 206473/000	Sponsor:	HOSPIRA INC
Org. Code:	520		275 NORTH FIELD DR DEPT 0389 BLDG H2 2
Priority:			LAKE FOREST, IL 60045
Stamp Date:	26-NOV-2013	Brand Name:	LINEZOLID IN 0.9% SODIUM CHLORIDE
PDUFA Date:	26-SEP-2014	Estab. Name:	
Action Goal:		Generic Name:	LINEZOLID IN 0.9% SODIUM CHLORIDE
District Goal:	27-MAR-2014	Product Number; Dosage Form; Ingredient; Strengths	001: INJECTABLE; LINEZOLID; 2MG

FDA Contacts:	J. CHANG	Prod Qual Reviewer	3017961973
	N. BHANDARI	Product Quality PM	2404023815
	S. SAMANTA	Regulatory Project Mgr	(HFD-520) 3017960803

Overall Recommendation: ACCEPTABLE on 30-JAN-2014 by C. CAPACCI-DANIEL () 3017963532

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER
FINISHED DOSAGE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 23-DEC-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 23-DEC-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE



Chemistry Assessment Section

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: CFN: 1021343 FEI: 1021343
HOSPIRA WORLDWIDE, INC

DMF No: ROCKY MOUNT, , UNITED STATES 27804 **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER
FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE OTHER TESTER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STERILITY TESTER

Profile: LARGE VOLUME PARENTERALS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 30-JAN-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: FEI: 3004591926
HOSPIRA WORLDWIDE, INC

DMF No: LAKE FOREST, , UNITED STATES 60045 **AADA:**

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 23-DEC-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 23-DEC-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Chemistry Assessment Section

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER
FINISHED DOSAGE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 23-DEC-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JANE L CHANG
09/18/2014

DOROTA M MATECKA
09/18/2014

RAPTI D MADURawe
09/19/2014

NDA 206473

**Linezolid Injection
600 mg/300 mL**

Hospira, Inc.

Jane L. Chang, Ph.D.

Review Chemist

**Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch V**

For Division of Anti-Infective Products

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Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 206473
2. REVIEW #: 1
3. REVIEW DATE: 20-Aug-2014
4. REVIEWER: Jane L. Chang, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
12/13/2010 Pre-IND Meeting Minutes	07-Jan-2011

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission, SDN-01	26-Nov-2013
Amendment, SDN-02	01-Apr-2014
Amendment, SDN-03	18-Apr-2014
Amendment, SDN-04	16-Jun-2014
Amendment, SDN-05	27-Jun-2014
Amendment, SDN-06	21-Jul-2014
Amendment, SDN-08	04-Aug-2014
Amendment, SDN-09	07-Aug-2014

7. NAME & ADDRESS OF APPLICANT:

Name: Hospira Inc.
Address: 275 North Field Drive
Lake Forest, IL 60045-5046
Representative: Neda Yaleh
Manager, Global Regulatory Affairs
Telephone: 224-212-6163
Fax: 224-212-5401
Email: neda.yaleh@hospira.com

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Linezolid
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 5 (New formulation)
 - Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: oxazolidinone antibacterial

11. DOSAGE FORM: injection

12. STRENGTH/POTENCY: 600 mg/300 mL

13. ROUTE OF ADMINISTRATION: intravenous

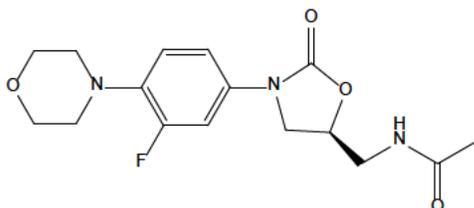
14. Rx/OTC DISPENSED: Y Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

 SPOTS product – Form Completed

Y Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(S)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide



CAS No [165800-03-3]

Molecular Formula: C₁₆H₂₀FN₃O₄

Molecular Weight: 337.35

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	adequate	8/8/2014	By J. Chang
	III			1	adequate	5/27/2014	By J. Chang
	III			4	N/A	N/A	The information provided in the NDA was reviewed by Microbiology Reviewer, Dr. Jessica Cole. See page 38.

*The DMF is titled (b) (4)

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	110122	Linezolid Injection in 0.9% Sodium Chloride

Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	01/30/2014	By C. Capacci-Daniel
Pharm/Tox	The proposed limits for the 3 ^{(b) (4)}  are considered qualified.*	04/15/2014	By Wendelyn Schmidt
Biopharm	Recommended for approval	7/15/2014	By Elsbeth Chikhale
Methods Validation	N/A, according to the current ONDQA IQP 5105		
Office of Drug Safety	No proprietary name was proposed. Labeling revisions were recommended.	07/03/2014	Aleksander P Winiarski
EA	Categorical exclusion (see this review)	07/07/2014	Jane Chang
Microbiology	Recommended for approval	7/11/2014	By Jessica Cole

* ^{(b) (4)}  are also known as ^{(b) (4)} , respectively. See page 63.

Executive Summary Section

Chemistry Review

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

While adequate CMC information was provided to ensure the identity and strength and quality of the drug product, this NDA has not provided sufficient information to assure the purity of the drug product. The extractable and leachable data with a medium representative of the formulation vehicle for the container closure system have not been provided.

The Office of Compliance has made an overall "Acceptable" recommendation for the facilities involved in this NDA. However, labeling issues are still pending. Therefore, from the ONDQA perspective, this NDA is not ready for approval per 21 CFR 314.125(b)(1),(6) in its present form until all issues are satisfactorily resolved.

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

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

(1) Drug Product

Linezolid Injection, 600 mg/300 mL, is a sterile aqueous solution for intravenous infusion. The drug product is comprised of a clear, colorless to slightly yellow solution with a pH range of 4.4 to 5.2. It is a (b) (4) sterilized product containing no antimicrobial preservatives. Linezolid Injection is presented in a (b) (4) mL VisIV flexible container with a 300 mL fill in a foil laminate overwrap. The flex bag will be closed with administration and additive port assemblies.

The manufacture of Linezolid Injection involves the following units of operation:

(b) (4)

Executive Summary Section

(b) (4)

No novel excipients are used. Inactive ingredients include: citric acid anhydrous USP 1.92 mg/mL, sodium chloride USP 9 mg/mL, and sodium hydroxide NF 0.76 mg/mL, and water for injection USP. Sodium hydroxide NF and/or hydrochloric acid NF are used to adjust the pH.

The proposed specification (see page 55) for Linezolid Injection is acceptable. The specification include clarity, volume, color (visual and instrumental), particulate matter, bacterial endotoxins, sterility, assay, pH, related substances, total sodium, osmolality, and identification (UV and HPLC). The analytical procedures and their method validations were reviewed and found to be adequate to support their intended purpose.

The manufacturing process that relates to product quality microbiology and the analytical procedures and acceptance criteria for sterility and endotoxins were reviewed by Product Quality Microbiology Reviewer, Dr. Jessica Cole, and found to be acceptable.

Per Biopharmaceutics Review dated 7/15/2014 by Dr. Elsbeth G Chikhale, the applicant's request for a biowaiver is granted.

The stability data support the proposed expiration dating period of 24 months when stored at 20° – 25°C (68° – 77°F), excursions permitted to 15° – 30°C (59° – 86°F).

The request for a categorical exclusion from the preparation of an environmental assessment (EA) under 21 CFR 25.31(a) is acceptable.

Quality risk assessment for Linezolid Injection is summarized in the following table.

Executive Summary Section

From Initial Quality Assessment ¹			Review Assessment		
Product Attribute/ CQA	Factors that can impact the CQA	Risk Ranking ²	Risk Mitigation Approach	Risk Evaluation	Lifecycle Considerations/ Comments ³
Sterility	Formulation Raw materials Container closure Process parameters Scale/Equipment/Site	H	Environmental monitoring including product bioburden (b) (4) as well as adequate safety margin for the proposed lower limit of (b) (4)	Acceptable	(b) (4) control and evaluation is critical for this (b) (4) sterilization process.
Endotoxin	See Sterility	M	Environmental monitoring and control of endotoxin for API, citric acid, sodium chloride, and water for injection.	Acceptable	
Particulate matter	See Sterility	M	Environmental monitoring and (b) (4)	Acceptable	
Related substances	See Sterility	L	The limits for specified impurities (b) (4) have been qualified. Establishment of an upper limit of (b) (4) minimizes formation of degradation products.	Acceptable	See page 66
Assay	See Sterility	L	Control of (b) (4) to facilitate dissolution of linezolid	Acceptable	
Appearance	See Sterility	L	-	Acceptable	
Leachable/ extractable	See Sterility	L	Acceptable leachable/extractable data for (b) (4). Lack of product specific extractable/leachable data for the container closure system.	Not acceptable	See page 36 for (b) (4).
Osmolality	Formulation Raw materials Process Parameters	L	-	Acceptable	
pH	See Osmolality	L	The product solution contains (b) (4) to maintain pH of the formulation.	Acceptable	
Deliverable volume	Container closure Process parameter Equipment	M	The acceptance criterion of deliverable volume, (b) (4) has been revised to (b) (4) mL.	Acceptable	

¹ See Attachment 1, page 101.

² Risk ranking applies to product attribute/CQA.

³ For example, post marketing commitment, knowledge management post approval, etc.

⁴ Information from Microbiology Review #1 was summarized by this reviewer.

⁵ The comment was provided by Microbiology Reviewer, Dr. Jessica Cole, through email. See Attachment 2.

Executive Summary Section

(2) Drug Substance

The drug substance is linezolid, which is manufactured by (b) (4). CMC information for linezolid is referenced to (b) (4) DMF (b) (4) and a letter of authorization has been provided. DMF (b) (4) has been reviewed by this reviewer and found to be adequate.

Linezolid exhibits multiple (b) (4). Linezolid (b) (4) is used for the manufacture of Linezolid Injection. The proposed linezolid specification (see page 16) includes testing for appearance, color, identification (IR and HPLC), (b) (4) loss on drying, heavy metals, residue on ignition, (b) (4), assay, related substances, residual solvents (GC), particle size distribution, and bacterial endotoxins. The analytical procedures and their validations were reviewed and found to be adequate to support their intended purpose. A retest date of (b) (4) months has been established by (b) (4).

B. Description of How the Drug Product Is Intended to Be Used

Infection*	Dosage and Route, and Frequency of Administration		Recommended Duration of Treatment (consecutive days)
	Pediatric Patients† (b) (4)	Adults and Adolescents (12 Years and Older)	
Nosocomial pneumonia Community-acquired pneumonia, including concurrent bacteremia Complicated skin and skin structure infections	10 mg/kg intravenous infusion every 8 hours	600 mg intravenous infusion every 12 hours	10 to 14
Vancomycin-resistant <i>Enterococcus faecium</i> infections, including concurrent bacteremia	10 mg/kg intravenous infusion every 8 hours	600 mg intravenous infusion every 12 hours	14 to 28

* Due to the designated pathogens [see *Indications and Usage (1)*]

† (b) (4)

Linezolid Injection should be administered by intravenous infusion over a period of 30 to 120 minutes. This intravenous container should not be used in series connections. Additives should not be introduced into this solution. If Linezolid Injection is to be given concomitantly with another drug, each drug should be given separately in accordance with the recommended dosage and route of administration for each product.

C. Basis for Not-Approval Recommendation

Executive Summary Section

- 21 CFR 314.125 (b)(1)
The submitted information does not assure the purity because of the following reason:
 - Extractable data from an aqueous solution of a pH similar (or a lower pH as the worst case scenario) to the drug product solution for the container closure system have not been provided.
- 21 CFR 314.125 (b)(6)
Labeling issues have not been resolved.

III. Administrative**A. Reviewer's Signature**

See appended electronic signature page

B. Endorsement Block

See appended electronic signature page

C. CC Block

Entered electronically in DARRTS

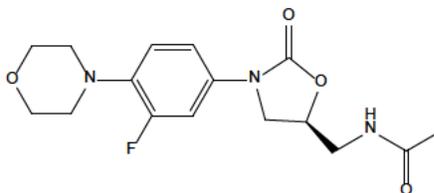
Chemistry Assessment Section

Chemistry Assessment**I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2:
Body of Data****S DRUG SUBSTANCE****S.1 General Information****S.1.1 Nomenclature**

INN: Linezolid
USAN: Linezolid
Chemical name: (*S*)-*N*-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide

Or

(b) (4)

S.1.2 Structure

CAS No [165800-03-3]

Molecular formula: C₁₆H₂₀FN₃O₄
Molecular weight: 337.35**S 1.3 General Properties**

General description: (b) (4) powder
Melting point: 178 - 182°C
pKa: 1.7
Chirality: one chiral center as *S*-isomer

(b) (4)

Solubility: Slightly soluble in methanol and soluble in chloroform
Hygroscopicity: Non-hygroscopic

¹ Reviewer's Comment:

(b) (4)

Chemistry Assessment Section

Partition Coefficient: 0.55
 Particle Size: $D(v, 0.5) \leq (b) (4) \mu\text{m}$
 $D(v, 0.9) \leq (b) (4) \mu\text{m}$
 $D(v, 0.99) \leq (b) (4) \mu\text{m}$

S.2 Manufacture

S.2.1 Manufacturers

Name and Address	Responsibility	Reference
(b) (4)	Drug Substance manufacture; release testing; stability testing	(b) (4)
(b) (4)	Particle Size Distribution Testing*	(b) (4)
Hospira, Inc. Highway 301 North Rocky Mount, NC 27801	Drug substance acceptance testing	FEI No: 1021343 DUNS No: 093132819

The responsibility was added in the 7/21/2014 amendment.

Reviewer's Assessment: Establishment evaluation was requested for each site listed above. The Office of Compliance has issued an "acceptable" recommendation for each site used in the manufacture and control of the drug substance (see page 103).

S.2.2 Description of Manufacturing Process and Process Controls

See DMF (b) (4)

S.2.3 Control of Materials

See DMF (b) (4)

S.2.4 Controls of Critical Steps and Intermediates

See DMF (b) (4)

S.2.5 Process Validation and/or Evaluation

See DMF (b) (4)

S.2.6 Manufacturing Process Development

See DMF (b) (4)

Chemistry Assessment Section

(b) (4)

A APPENDICES**A.1 Facilities and Equipment (biotech only)**

N/A

A.2 Adventitious Agents Safety Evaluation

N/A

A.3 Novel Excipients

N/A

R REGIONAL INFORMATION**R.1 Executed Batch Records**

Representative executed batch records were provided for the registration batches (Batch Numbers: 12-094-SB, 12-095-SB, and 12-096-SB).

R.2 Comparability Protocols

N/A

R.3 Methods Validation Package

See section I.P.5.2 on page 55 of this review for the analytical procedures. The analytical procedures and their validation were reviewed and found to be adequate. Methods validation packages will not be sent to FDA laboratories because the methods do not meet the “method validation request criteria” according to the current ONDQA IQP 5105 effective 3/31/2012.

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1**A. LABELING & PACKAGE INSERT**

Labeling information provided in the original submission is summarized below.

1. Physician’s Labeling Rule Prescription Drug Labeling**1) “Highlights” Section**

Chemistry Assessment Section

Linezolid Injection

Initial U.S. Approval: 2000

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

Injection: 600 mg (b) (4)

Reviewer's Assessment:

Item	Comments	Conclusions
Proprietary name and established name	Proprietary name is not required for NDA approval. Because there is no proprietary name, the established name should be presented in all capital letters.	Unsatisfactory
Dosage forms and strengths	(b) (4) the strength should be expressed as "600 mg in 300 mL" per USP <1>.	Unsatisfactory
Route of administration	"for intravenous use" was not provided.	Unsatisfactory

Conclusion: The "Highlights" section is unsatisfactory.

In July 2014, this reviewer provided the following edits for the labeling in the Division's bugs drive:

~~Linezolid Injection~~ **LINEZOLID INJECTION, for intravenous use**

Initial U.S. Approval: 2000

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

Injection: 600 mg (b) (4) **in 300 mL**

2) **"Full Prescribing Information" Section**

a. Section 2.3 Compatibilities

Compatible intravenous solutions include 0.9% Sodium Chloride Injection, USP, 5% Dextrose Injection, USP, and Lactated Ringer's Injection, USP.

Conclusion: This section is satisfactory. The data provided in Section P.2.6 support the labeling statement.

b. Section 3 Dosage Forms and Strengths

Linezolid Injection: (b) (4) single-use, ready-to-use flexible

Chemistry Assessment Section

plastic VisIV™ containers in a foil laminate overwrap. (b) (4)

Reviewer's Assessment:

Item	Comments	Conclusions
Dosage form and strength	The correct dosage form, i.e. injection, is provided. Per USP <1151>, solutions administered by injection are officially titled injections. This reviewer recommend revising expression of strength to "600 mg linezolid in 300 mL" per USP <1>.	Unsatisfactory
Others	The statement of (b) (4) should be deleted because (b) (4)	Unsatisfactory

Conclusion: This section is unsatisfactory.

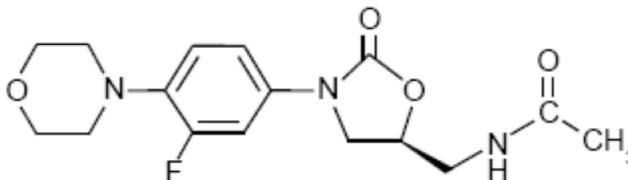
In July 2014, this reviewer provided the following edits for the labeling in the Division's bugs drive:

Linezolid Injection (b) (4) in 300 mL in a single-use, ready-to-use flexible plastic VisIV containers in a foil laminate overwrap. (b) (4)

c. Section 11 Description

Linezolid Injection, contains linezolid, which is a synthetic antibacterial agent of the oxazolidinone class. The chemical name for linezolid is (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl] methyl]-acetamide.

The empirical formula is C₁₆H₂₀FN₃O₄. Its molecular weight is 337.35, and its chemical structure is represented below:



Linezolid Injection is supplied as a ready-to-use sterile isotonic solution for intravenous infusion. Each (b) (4) contains (b) (4) mg of linezolid. Inactive ingredients (b) (4)

The sodium (Na) content is 3.98 mg/mL (52 mEq/300-mL container).

Reviewer's Assessment:

Chemistry Assessment Section

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name and established name*	Established name "Linezolid Injection" is provided. Proprietary name is not provided. Proprietary name is not a requirement for NDA approval.	Satisfactory
Dosage form and route of administration	The correct dosage form, injection, and route of administration, intravenous, are provided.	Satisfactory
Active moiety expression of strength	This reviewer recommend revising expression of strength to "600 mg of linezolid in 300 mL" per USP <1>.	Unsatisfactory
Inactive ingredient information (quantitative, if injectables per 21 CFR 201.100(b)(5)(iii))	(b) (4) inactive ingredients are: citric acid, sodium chloride, sodium hydroxide and hydrochloric acid (for pH adjustment), and water for injection. Furthermore, quantitative information for inactive ingredients (except that ingredients added to adjust the pH (b) (4) may be declared by name and a statement of their effect) must be provided per 21 CFR 201.100(b)(5)(iii).	Unsatisfactory
Statement of being sterile	The sterile statement is provided.	Satisfactory
Pharmacological/therapeutic class	The pharmacological class, oxazolidinone antibacterial, is provided.	Satisfactory
Chemical name, structural formula, molecular weight	Chemical name, molecular formula, structural formula and molecular weight are correctly described in this section.	Satisfactory
Other important chemical or physical properties (such as pKa or pH)	The sodium (Na ⁺) content is 3.98 mg/mL (52 mEq/300-mL container).	Satisfactory

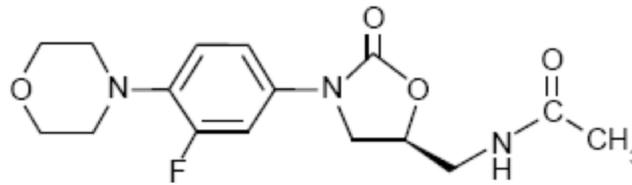
Conclusion: The "Description" section is unsatisfactory.

In July 2014, this reviewer provided the following edits for the labeling in the Division's bugs drive:

Linezolid Injection₇ contains linezolid, which is a synthetic antibacterial agent of the oxazolidinone class. The chemical name for linezolid is (*S*)-*N*-[[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl] methyl]-acetamide.

The empirical formula is C₁₆H₂₀FN₃O₄. Its molecular weight is 337.35, and its chemical structure is represented below:

Chemistry Assessment Section



Linezolid Injection is supplied as a ready-to-use sterile isotonic solution for intravenous infusion. Each (b) (4) container contains (b) (4) 600 mg of linezolid in 300 mL of a clear, colorless to slightly yellow solution. Inactive ingredients include: (b) (4) citric acid anhydrous USP 1.92 mg/mL, sodium chloride USP 9 mg/mL, (b) (4) sodium hydroxide NF 0.76 mg/mL, and water for injection USP (b) (4) Sodium hydroxide NF and/or hydrochloric acid NF are used to adjust the pH. The sodium (Na⁺) content is 3.98 mg/mL (52 mEq/300-mL container).

d. *Section 16 How Supplied/Storage and Handling*

(b) (4)
Linezolid Injection is available in single-use, ready-to-use flexible plastic container (VisIV™ Container) in a foil laminate overwrap. (b) (4)
The container (b) (4) available in the following package size (b) (4)
(b) (4) NDC 0409-4883-01

(b) (4)
Store at 20 to 25°C (68 to 77°F) [see USP Controlled Room Temperature]. Protect from light. It is recommended that the containers be kept in the overwrap until ready to use. Protect containers from freezing.

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Strength of dosage form in metric system	This reviewer recommend revising expression of strength to "600 mg in 300 mL" per USP <1>.	Unsatisfactory
Units of dosage form	Available unit is correctly described as 300 mL.	Satisfactory
Identification of dosage forms, NDC number	The dosage form injection is correctly described. NDC Number is stated:	Satisfactory
Special handling (e.g., protect from light)	The statements that the containers be kept in the overwrap until ready to use and be protected from freezing are provided.	Satisfactory
Storage condition	Inclusion of permitted excursion temperature is recommended.	Unsatisfactory
Others	The statement of (b) (4) should be deleted.	Unsatisfactory

Conclusion: The "How Supplied/Storage and Handling" section is unsatisfactory.

Chemistry Assessment Section

In July 2014, this reviewer provided the following edits for the labeling in the Division's bugs drive:

(b) (4)

Linezolid Injection is available in a single-use, ready-to-use flexible plastic container (VisIV™ Container) in a foil laminate overwrap. (b) (4)

The container (b) (4) is available in the following package size (b) (4)
600 mg in 300 mL (b) (4) NDC 0409-4883-01

(b) (4)

Store at 20 to 25°C (68 to 77°F), **excursion permitted to 15 – 30°C (59-86°F)** [see USP Controlled Room Temperature]. Protect from light. It is recommended that the containers be kept in the overwrap until ready to use. Protect containers from freezing.

e. *Manufacturer's or Distributor's name*

Hospira, Inc., Lake Forest, IL 60045 USA

Reviewer's Assessment: *The information was provided at the end of labeling.*

Conclusion: ***Satisfactory***

2. Labels

1) *Immediate Container Label*

Chemistry Assessment Section

(b) (4)



Chemistry Assessment Section

Item	Comments	Conclusions
Proprietary name, established name	The applicant did not propose a proprietary name. (b) (4) The established name should be "Linezolid Injection".	Unsatisfactory
Route of administration	The route of administration, intravenous, is correctly described. However, it should be placed in a prominent place, i.e. under the strength.	Unsatisfactory
Strength	Strength (600 mg/300 mL) is correctly expressed. However, the statement "(2 mg/mL)" should be deleted.	Unsatisfactory
Net contents	The net content 300 mL is correctly described	Satisfactory
Lot number per 21 CFR 201.18	A space for this information is not indicated.	Unsatisfactory
Expiration date per 21 CFR 201.17	A space for this information is not indicated.	Unsatisfactory
"Rx only" statement	The statement is displayed.	Satisfactory
Storage	Storage condition should include permitted excursion temperature.	Unsatisfactory
Name of all inactive ingredients and quantitative ingredient information	Quantitative information for inactive ingredients, including citric acid anhydrous, sodium chloride, and sodium hydroxide, is provided. Quantitative information is not required for water as vehicle and for inactive ingredients used for pH adjustment.	Satisfactory
NDC number	NDC number is indicated.	Satisfactory
Bar Code	Barcode is indicated.	Satisfactory
Name of manufacturer/distributor	The name of manufacturer is correctly described.	Satisfactory
Others	(b) (4)	Unsatisfactory

Conclusion: The immediate container was unsatisfactory. See the comments on pages 92 and 94.

2) Overwrap

Front:

Chemistry Assessment Section

(b) (4)



Chemistry Assessment Section

Item	Comments	Conclusions
Proprietary name, established name	The applicant did not propose a proprietary name. (b) (4) The established name should be "Linezolid Injection".	Unsatisfactory
Strength	Strength, 600 mg/300 mL, is correctly expressed. However, the statement "(2mg/mL)" should be deleted.	Unsatisfactory
Net contents	The net content 300 mL is correctly described	Satisfactory
Lot number per 21 CFR 201.18	A space for this information is not indicated.	Unsatisfactory
Expiration date per 21 CFR 201.17	A space for this information is not indicated.	Unsatisfactory
Name of all inactive ingredients and quantitative ingredient information	Quantitative information for inactive ingredients, including citric acid anhydrous, sodium chloride, and sodium hydroxide, is provided. Quantitative information is not required for water as vehicle and for inactive ingredients used for pH adjustment.	Satisfactory
"Rx only" statement	The statement is displayed on the main panel.	Satisfactory
Storage Conditions	Inclusion of permitted excursion temperature is recommended.	Unsatisfactory
NDC number	NDC number is indicated.	Satisfactory
Bar Code	Bar code is indicated.	Satisfactory
Name of manufacturer/distributor	The name of manufacturer is correctly described.	Satisfactory
(b) (4)	The statement is present.	Satisfactory
Route of Administration	The route of administration, intravenous, is correctly described. However, it should be placed in a prominent place, i.e. under the strength.	Unsatisfactory
Others	(b) (4)	Unsatisfactory

Conclusion: The overwrap labeling was unsatisfactory.

The following comments were conveyed to the applicant on 5/27/2014.

Regarding the container label and overwrap labeling:

- Revise the established name to "Linezolid Injection". The established name should be displayed in the same line with the same font size. The statement (b) (4)
- Indicate the locations where lot number and expiration date will be placed.
- Include permitted excursion temperature "excursions permitted to 15-30°C (59-86°F).

In the 6/16/2014 amendment, revised container label and overwrap labeling, together with the following information, were provided.

Chemistry Assessment Section

- The established name has been revised to “Linezolid Injection” (b) (4)

- Hospira prints the product expiration date and lot number on the primary container and the foil overwrap during batch manufacture. The location for the information on lot number and expiration date is indicated with a red box.
- The statement “excursions permitted to 15 to 30°C (59 to 86°F)” has been added.

Revised container label:**Revised overwrap labeling:**(b) (4)


Chemistry Assessment Section

The issue regarding the location for the route of administration has also been identified by DMEPA reviewer, Aleksander P Winiarski, dated 03-Jul-2014.

The container label and the overwrap labeling contain (b) (4) (b) (4)

Furthermore, the pH range should be changed from (b) (4) to "4.4 – 5.2" (see page 55).

The following comments were conveyed to the applicant on 7/18/2014:

1. *Regarding the container label and overwrap labeling:*
 - a) *Place the route of administration "for intravenous infusion" under the strength to ensure appropriate prominence.*
 - b) *Express the strength only by 600 mg/300 mL. Delete "(2 mg/mL)".*
 - c) (b) (4)
 - d) *Change pH range from (b) (4) to "4.4 – 5.2".*
2. (b) (4)

In the 8/7/2014 amendment, the applicant provided updated container label and carton labeling, which have incorporated all of the above recommendations except for Item 1b). The strength "(2 mg/mL)" is expressed using a smaller font size.

The response is acceptable. Inclusion of "(2 mg/mL)" at a smaller font size (less prominent) is acceptable per USP <1>. The strength per mL is used for calculation of the dose for pediatric patients based on body weight.

Chemistry Assessment Section

(b) (4)

3. Product Data Elements in Structured Product Labeling

Chemistry Assessment Section

Item		Information Provided in NDA		
Trade name	None			
Established name	Linezolid Injection			
Product Code	NDC:0409-4883			
Route of Administration	INTRAVENOUS			
DEA Schedule	None			
Active Ingredient/Active Moiety	Ingredient Name	Basis of Strength	Strength	
	LINEZOLID (LINEZOLID)	LINEZOLID	2 mg in 1 mL	
Inactive Ingredients	Ingredient Name	Strength		
	SODIUM HYDROXIDE			
	ANHYDROUS CITRIC ACID			
	SODIUM CHLORIDE			
	WATER			
	HYDROCHLORIC ACID			
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0409-4883-01	10 in 1 CASE		
1		1 in 1 POUCH		
1		300 mL in 1 BAG		
Marketing Information				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	
NDA	NDA206473			

Labeler - Hospira, Inc. (141588017)		
Establishment		
Name	ID/FEI	Business Operations
	(b) (4)	api manufacture(0409-4883)
Hospira, Inc.	093132819	analysis(0409-4883), manufacture(0409-4883)
Hospira, Inc.	827731089	analysis(0409-4883)
	(b) (4)	analysis(0409-4883)
		analysis(0409-4883)

Reviewer's Assessment: The labeling information in drug listing data elements is unsatisfactory. Quantitative information for excipients should be provided. The following comment was conveyed to the applicant on 5/27/2014:

Provide the strength of inactive ingredients, including anhydrous citric acid, sodium chloride, and sodium hydroxide in Product Data Elements in Structured Product Labeling.

In the 6/16/2014 amendment, the Product Data Elements in Structured Product Labeling has been revised to include strength of inactive ingredients, including anhydrous citric

Chemistry Assessment Section

acid (1.92 mg in 1 mL), sodium chloride (9 mg in 1 mL), and sodium hydroxide (0.76 mg in 1 mL). *The response is acceptable.*

B. ENVIRONMENTAL ASSESSMENT OR CLAIM OF CATEGORICAL EXCLUSION

A categorical exclusion from the preparation of an environmental assessment (EA) was requested under 21 CFR 25.31. The basis of this exclusion is the fact that Linezolid Injection will not be indicated for administration at a higher dose level, nor for a longer duration, or for different indications than those that are in effect.

Reviewer's Assessment: The (b) (4) for Linezolid Injection (in 0.9% sodium chloride) is (b) (4) to Zyvox (linezolid) injection with the same dosage and route of administration. Hospira's formulation does not contain dextrose, but contains higher amount of sodium. It is expected that action on the NDA will not increase the use of the active moiety. Thus, the claim of categorical exclusion is acceptable per 21 CFR 25.31 (a).

III. List Of Deficiencies**A. Regarding CMC**

1. Extractable data from an aqueous solution of a pH similar (or a lower pH as the worst case scenario) to the drug product solution for the container closure system have not been provided.

B. Regarding Labeling

1. All labeling should be revised as is recommended in the bugs drive of the Division of Anti-Infective Products.

Except for the highlighted item in **bold** type, which is captured above, all other deficiencies have been addressed adequately.

The following information was requested from the applicant in the 3/27/2014 FDA information request letter. The applicant has responded adequately in the 4/18/2014 amendment for all items except for Items 4, 5, 7, and 15a). The response for Item 4 was provided in the 6/16/2014 amendment.

1. Provide the analytical procedure for instrumental color testing for the drug substance. Provide information on the standards as to whether they are (b) (4). If they are (b) (4), please provide the (b) (4).
2. Regarding linezolid drug substance specification, tighten the acceptance criterion for each unspecified impurity to NMT (b) (4)%, which corresponds to (b) (4) mg per day, per ICH Q3A.
3. Regarding the drug substance container closure system, clarify whether the (b) (4). The information appears to be inconsistent with the description in DMF (u) (4).

Chemistry Assessment Section

4. Provide linezolid (b) (4) solubility data in the formulation vehicle, i.e. (b) (4). The solubility of the (b) (4) should be characterized because your formulation uses (b) (4).
5. Provide data on extractables/leachables for (b) (4) as well as (b) (4) that are in direct contact with the product. The data should be obtained using Linezolid Injection or the vehicle solution.
6. To support the proposed hold time of (b) (4) hours for the bulk solution, provide data to demonstrate its quality is not adversely affected. In the absence of such data, limit the hold time to (b) (4) hours, which was used for the registration stability batches.
7. Your proposed acceptance criterion of (b) (4) mL to (b) (4) mL (target (b) (4) mL), which corresponds to (b) (4)% to (b) (4)% of the label claim, for fill volume is not acceptable. Please tighten the acceptance criterion to comply with the USP <1151> recommendation of 2% excess for injectable drug products of 50.0 mL or more.
8. Regarding the non-compendial analytical procedures for testing of the drug product:
 - a) Provide the analytical procedures and the respective method validation data for total sodium.
 - b) Provide the analytical procedures for color by instrumental, identification by UV, and identification by HPLC.
 - c) Clarify the analytical procedure for osmolality. The following analytical procedures are listed: "in house" in Section 3.2.P.5.1; "USP <785>, C-1191" in Sections 3.2.P.8.1 and 3.2.P.8.2. If non-compendial analytical procedure is used, please provide the procedure.
9. Please clarify the amount of (b) (4) impurity for the three registration batches of the drug product. The amount reported in the certificate of analysis for each registration batch is (b) (4). However, the amount reported in the summary table (Table 2 of Section 3.2.P.5.4) is (b) (4)%.
10. Please provide a summary in Section 3.2.P.5.5 for the analytical techniques used in structural characterization of potential impurities, including Impurities (b) (4).
11. Address the following items regarding the drug product specification:
 - a) Provide specific acceptance criterion for identification by HPLC and by UV. The proposed acceptance criterion of "Meets test requirements" is not acceptable because the test requirements are not provided.
 - b) Revise the acceptance criterion for fill volume from "NLT labeled volume" to "(b) (4) mL - (b) (4) mL".
 - c) Revise the acceptance criteria for particulate matter from "NMT (b) (4)" to "NMT (b) (4) per mL" for particles $\geq 10 \mu\text{m}$ and from "NMT (b) (4)" to "NMT (b) (4) per mL" for particles $\geq 25 \mu\text{m}$.
 - d) Delete testing for (b) (4). The specification should reflect actual testing performed for release and stability study.
 - e) Revise the acceptance criterion for pH for release and stability from "(b) (4)" to "4.4 to 5.2". Please note that your proposed release acceptance criterion in Section 2.3 (b) (4) is inconsistent with that in Section 3.2.P.5.1 (4.3 – 5.3).
 - f) Tighten the acceptance criterion for total impurities from (b) (4)% to (b) (4)%.
 - g) Tighten the acceptance criterion for color APHA from NMT (b) (4) to NMT (b) (4). This limit is supported by the regression analysis of the long-term stability data of the registration batches.

Chemistry Assessment Section

3. **Your response on the extractable/leachable study for the container closure system for the drug product (Item 15a of the 3/27/2014 FDA Letter) in the April 18, 2014 amendment is not acceptable because** (b) (4). **The extractable data from an aqueous solution of a pH similar (or a lower pH as the worst case scenario) to the drug product solution should be provided since different pH solutions may result in different extractable profiles.**

If the data have been submitted, please provide the exact location (e.g. date of submission, Section, DMF, etc.) where the information is presented.

4. Regarding the container label and overwrap labeling:
- Revise the established name to “Linezolid Injection”. The established name should be displayed in the same line with the same font size. (b) (4)
 - Indicate the locations where lot number and expiration date will be placed.
 - Include permitted excursion temperature “excursions permitted to 15-30°C (59-86°F).
5. Provide the strength of inactive ingredients, including anhydrous citric acid, sodium chloride, and sodium hydroxide in Product Data Elements in Structured Product Labeling.

The following information was requested from the applicant in the 7/11/2014 FDA information request letter. The applicant has responded adequately in the 7/21/2014 and 8/4/2014 amendments.

Revise the drug substance specification to include testing for (b) (4). Your solubility data as provided in the 6/16/2014 amendment show that both quality attributes affect the dissolution rate of linezolid in the formulation vehicle.

The following information was requested from the applicant in the 7/18/2014 FDA information request letter. The applicant has responded adequately in the 8/7/2014 amendment.

- Regarding the container label and overwrap labeling:
 - Place the route of administration “for intravenous infusion” under the strength to ensure appropriate prominence.
 - Express the strength only by 600 mg/300 mL. Delete “(2 mg/mL)”.
 - (b) (4)
 - Change pH range from (b) (4) to “4.4 – 5.2”
- (b) (4)

Refer to pertinent sections of this review for the evaluation of the applicant’s response.

Chemistry Assessment Section

IV. Attachments

1. Initial Quality Risk Assessment

The following is initial quality risk assessment for Linezolid Injection 600 mg/300 mL, jointly conducted by CMC Lead Dr. Dorota Matecka and this reviewer.

Product attribute/CQA	Factors that can impact the CQA	Probability of Occurrence (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number*	Comment, if any
Sterility	Formulation Raw materials Container closure Process parameters Scale/Equipment/Site	4	5	5	100	(b) (4) sterilization: (b) (4)
Endotoxin	See Sterility	2	4	4	32	
Particulate matter	See Sterility	3	5	3	45	
Related substances	See Sterility	3	2	1	6	(b) (4) sterilization (b) (4)
Assay	See Sterility	2	3	1	6	Assign independent RPN numbers for assay and related substances.
Appearance	See Sterility	3	3	1	9	
Leachable/extractable	See Sterility	2	4	3	24	
Osmolality	Formulation Raw materials Process Parameters	2	5	2	20	
pH	See Osmolality	2	2	1	4	Target pH 4.8. Use (O)(S)(D) values of low pH.
Deliverable volume	Container closure Process parameter Equipment	5	2	5	50	Target fill volume (b) (4) mL. Only the lower limit was proposed per USP <1>.

*Risk Ranking:

Low (L): 25 ≤ RPN

Medium (M): 26 ≤ RPN ≤ 60

High (H): RPN > 60

Chemistry Assessment Section

2. Email Communication with Microbiology Reviewer

Chang, Jane

From: Cole, Jessica
Sent: Wednesday, July 16, 2014 8:48 AM
To: Chang, Jane
Subject: RE: Micro Risk Assessment for NDA 206473

One comment below regarding the life cycle management.

Jessica Cole, PhD
 301-796-5148

From: Chang, Jane
Sent: Tuesday, July 15, 2014 11:41 AM
To: Cole, Jessica
Subject: Micro Risk Assessment for NDA 206473

Hi Jessica,

As you may be aware that ONDOA reviewers are required to include a risk assessment for NDAs with GRMP dates after August 1, 2014. Because your review does not include a formal risk assessment template (see below), I would like to seek your input on this subject for microbiological quality attributes for NDA 206473. Below is a template that ONDOA use. Please let me know if you have any comments on Risk Mitigation Approach and Lifecycle Considerations/Comments.

From Initial Quality Assessment			Review Assessment		
Product attribute/CQA	Factors that can impact the CQA	Risk Ranking*	Risk Mitigation approach	Risk Evaluation	Lifecycle Considerations/Comments**
Sterility	Formulation Raw materials Container closure Process parameters Scale/Equipment/Site	H	Environmental monitoring including product bioburden (b) (4) as well as adequate safety margin for the proposed lower limit of (b) (4)	Acceptable	(b) (4) control and evaluation is critical for this (b) (4) sterilization process.
Endotoxin	See Sterility	M	Environmental monitoring and control of endotoxin for API, citric acid, sodium chloride, and water for injection.	Acceptable	

*Risk ranking applies to product attribute/CQA

**For example, post marketing commitment, knowledge management post approval, etc.

***Information from Microbiology Review #1 was summarized by this reviewer.

Please Note that The Initial Quality Assessment Section has yet to be generated by Dorota and filed in DARRTS.
 Thanks.

Jane

CMC REVIEW NDA 206473

Chemistry Assessment Section

3. EES Report

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: NDA 206473/000 Sponsor: HOSPIRA INC
Org. Code: 520 275 NORTH FIELD DR DEPT 0389 BLDG H2 2
Priority: LAKE FOREST, IL 60045
Stamp Date: 26-NOV-2013 Brand Name: LINEZOLID IN 0.9% SODIUM CHLORIDE
PDUFA Date: 26-SEP-2014 Estab. Name:
Action Goal: Generic Name: LINEZOLID IN 0.9% SODIUM CHLORIDE
District Goal: 27-MAR-2014 Product Number; Dosage Form; Ingredient; Strengths
001: INJECTABLE; LINEZOLID; 2MG

FDA Contacts: J. CHANG Prod Qual Reviewer 3017961973
N. BHANDARI Product Quality PM 2404023815
S. SAMANTA Regulatory Project Mgr (HFD-520) 3017960803

Overall Recommendation: ACCEPTABLE on 30-JAN-2014 by C. CAPACCI-DANIEL () 3017963532

Establishment: CFN: (b) (4) FEI: (b) (4)
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE OTHER TESTER
FINISHED DOSAGE RELEASE TESTER
Profile: CONTROL TESTING LABORATORY OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 23-DEC-2013
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: CFN: FEI: (b) (4)
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER
Profile: NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 23-DEC-2013
Decision: ACCEPTABLE
Reason: BASED ON PROFILE



Chemistry Assessment Section

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: CFN: 1021343 FEI: 1021343
HOSPIRA WORLDWIDE, INC

DMF No: ROCKY MOUNT, , UNITED STATES 27804 **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER
FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE OTHER TESTER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STERILITY TESTER

Profile: LARGE VOLUME PARENTERALS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 30-JAN-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: FEI: 3004591926
HOSPIRA WORLDWIDE, INC

DMF No: LAKE FOREST, , UNITED STATES 60045 **AADA:**

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 23-DEC-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 23-DEC-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Chemistry Assessment Section

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER
FINISHED DOSAGE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 23-DEC-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JANE L CHANG
08/20/2014

DOROTA M MATECKA
08/21/2014

ONDQA Initial Quality Assessment (IQA) and Filing Review
CMC and Biopharmaceutics

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: **206473**

2. DATES AND GOALS:

Letter Date: November 25, 2013	Submission Received Date: November 26, 2013
PDUFA Goal Date: September 26, 2014	

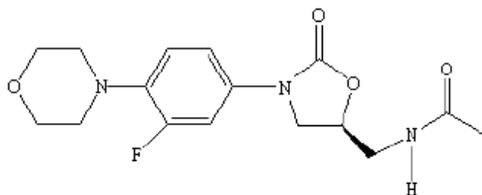
3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	<i>None currently proposed</i>
Established or Non-Proprietary Name (USAN):	Linezolid Injection
Dosage Form:	Injection (intravenous solution)
Route of Administration	Intravenous
Strength/Potency	2 mg/mL (600 mg/300 mL)
Rx/OTC Dispensed:	Rx

4. INDICATION:

Linezolid Injection is indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms: Vancomycin-Resistant *Enterococcus faecium* infections; Nosocomial pneumonia; Complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis; (b) (4)
Community acquired pneumonia.

5. DRUG SUBSTANCE STRUCTURAL FORMULA:



Molecular Formula: $C_{16}H_{20}FN_3O_4$

Molecular Weight: 337.35

6. NAME OF APPLICANT (as indicated on Form 356h):

Hospira, Inc.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
CMC and Biopharmaceutics**

7. SUBMISSION PROPERTIES:

Review Priority:	Standard
Submission Classification (Chemical Classification Code):	Type 5 (new formulation)
Application Type:	505(b)(2)
Breakthrough Therapy	No
Responsible Organization (Clinical Division):	DAIP

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		X	
Clinical Pharmacology			<i>TBD</i>
Establishment Evaluation Request (EER)	X		<i>Submitted on December 20, 2013</i>
Pharmacology/Toxicology	X		<i>TBD</i>
Methods Validation		X	
Environmental Assessment		X	<i>Categorical exclusion</i>
CDRH			N/A
Other			N/A

ONDQA Initial Quality Assessment (IQA) and Filing Review
CMC and Biopharmaceutics

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective?	
Yes	No
CMC Filing Issues:	
1. None	

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter?	
Yes	No
CMC Comments for 74-Day Letter (<i>draft comments – to be finalized in the 74-Day Letter</i>):	
1. <i>The draft labeling (Section 2.3 Compatibilities) includes a list of intravenous solutions compatible with the proposed linezolid formulation. Please provide compatibility data for your proposed drug product to support this statement or indicate where this data can be located in the NDA.</i>	
2. <i>Please revise Section 11 of the labeling (Description) to reflect the composition of your proposed linezolid drug product.</i>	
3. <i>The container closure system for the proposed linezolid drug product is described as (b)(4) mL VisIV flexible container whereas the fill volume of the proposed drug product (2 mg/mL strength, 600 mg dose) is 300 mL. Please explain and provide a sample of the proposed drug product in the proposed container closure system.</i>	

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective?	
Yes	No
Biopharmaceutics Filing Issues:	
1. None	

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter?	
Yes	No
Biopharmaceutics Comments for 74-Day Letter:	
1. None	

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective?	
Yes	No
Microbiology Filing Issues:	
See Microbiology Filing Review for details and for any potential Microbiology review issues.	

**ONDQA Initial Quality Assessment (IQA) and Filing Review
CMC and Biopharmaceutics**

Summary of Initial Quality Assessment

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain
	X		

Is a team review recommended?	Yes	No
Suggested expertise for team:		
CMC Reviewer: Jane Chang, Ph.D.		
Quality Microbiology Reviewer: Jessica Cole, Ph.D.		
Biopharmaceutics Reviewer: Elsbeth Chikhale, Ph.D.		

Summary of Critical Issues and Complexities
<i>Refer to IQA (below)</i>

**ONDQA Initial Quality Assessment (IQA) and Filing Review
CMC and Biopharmaceutics**

Initial Quality Assessment

Linezolid drug substance has been previously approved as injection (IV solution), tablets and oral solution. The current 505(b)(2) NDA provides for a new IV formulation of linezolid (linezolid in 0.9 % sodium chloride solution) to be used for the treatment of (b) (4) infections as the listed drug, Zyvox IV, which was approved via NDA 21131 on April 8, 2000.

The applicant states that the vehicle of the proposed drug product via the current NDA was modified from 5% dextrose to 0.9% sodium chloride (b) (4). In addition, (b) (4) in the proposed linezolid formulation (by removing sodium citrate and adjusting the contents of citric acid (b) (4)). The current NDA contains mainly CMC data. In addition, a biowaver request has been submitted in the current application. The comparison of the proposed drug product and the Zyvox IV formulations has been attached below (Appendix 1). The quantitative composition of the proposed formulation is provided in Attachment 2 (below).

Comment: It should be noted that there are several unexpired patents listed in the Orange Book for Zyvox®. The applicant of the current NDA (Hospira, Inc.) submitted the appropriate Paragraph III and Paragraph IV Certifications.

It should be noted that Hospira has also submitted an application to the Office of Generic Drugs for another (b) (4) Zyvox IV) formulation of linezolid (600 mg/300 mL) via ANDA 205442 (submitted on February 28, 2013 and currently pending).

Drug Substance

For the majority of the CMC information for linezolid drug substance, the reference is made to DMF Type II (b) (4) held by (b) (4). *Comment: DAARTS indicates there the DMF was reviewed for completeness by the Office of Generic Drugs and found complete on October 24, 2013. However, a technical review of this DMF has not been conducted as of the date of this IQA and it will need to be performed for the purpose of the current NDA.*

In addition, some general information (Section 3.2.S.1), a specification, information on impurities including residual solvents, batch analysis for the linezolid drug substance have been also included in the NDA. The proposed drug substance specification is attached below (Appendix 3).

Drug Product

Linezolid Injection is available as a sterile aqueous solution, which is intended for intravenous administration. The drug product is described as a clear, colorless to slightly yellow solution, free from visible particulate, presented in a VisIV flexible container in a foil laminate overwrap. The flexible container is (b) (4) mL flex bags with a 300 mL fill and will be closed with administration and additive port assemblies. The pH range is (b) (4). This is a (b) (4)

ONDQA Initial Quality Assessment (IQA) and Filing Review CMC and Biopharmaceutics

sterilized product containing no antimicrobial preservatives. *Comment: The container closure system for the proposed linezolid drug product is described as (b) (4) mL VisIV flexible container whereas the fill volume of the proposed product strength (2 mg/mL) is 300 mL. The applicant will be asked to explain that and provide a sample of the proposed drug product in the proposed container closure system.*

Pharmaceutical Development section describes the product and process development using a Quality by Design (QbD) elements. The quality target product profile (QTPP) and critical quality attributes (CQAs) have been identified and discussed. In addition, a risk assessment approach used throughout the product development to identify potentially high risk formulation and process variables and to develop a control strategy has also been described.

Similarly to the innovator's product, the proposed by Hospira Linezolid Injection, 2 mg/mL, will be packaged in the flexible bags and is intended to be labeled for storage at 25°C (77°F); excursions permitted to 15-30°C (59-86°C) [USP Controlled Room Temperature]. Table 1 in Section 3.2.P.2.4 (reproduced below) provides a comparison between the Hospira and RLD container closure systems:

Table 1. Container - Closure System Comparison, Hospira vs. RLD

Components	Reference Listed Drug	Hospira
Container	FreeFlex® IV bag; PVC- and latex-free	VisIV™ flexible container; PVC-, DEHP- and latex-free
Ports	Dual ports; blue and white	Dual ports; blue and white
Overwrap	Foil laminated overwrap	Foil laminated overwrap

The applicant states that all packaging components have been qualified for use based on the results of USP/Ph.Eur. biological, physicochemical, and other characterization tests, including extractables and leachables. *Comment: Supportive qualification data for the proposed container closure system have been submitted in both Pharmaceutical Development and Stability sections. These data will need to be reviewed in detail and discussed with the pharm/tox reviewer.*

The specification proposed for the drug product in the current NDA has been reproduced in Attachment 4 (below). The drug product stability section includes data for three representative batches of Linezolid Injection, 2 mg/mL manufactured at the Rocky Mount, NC, facility of Hospira and placed on long term (25°C/40% RH, 30°C/35% RH, 30°C/75% RH) and accelerated (40°C/<25% RH and 40°C/75% RH) conditions. This includes 12-month and 6-month of data under long-term and accelerated stability conditions, respectively. Hospira proposes 24-month expiration dating for their linezolid drug product, stored at controlled room temperature (20 - 25°C; 68 – 77°F).

A request for inspection for all manufacturing facilities listed in the application for the drug substance and the drug product has been submitted to the EES. *Comment: It should be noted that the proposed drug product manufacturing facility (Hospira, Rocky Mount, NC) is under OAI alert as of the date of this IQA.*

**ONDQA Initial Quality Assessment (IQA) and Filing Review
CMC and Biopharmaceutics**

Biopharmaceutics Assessment

Biopharmaceutics Critical Issues or Complexities

The Applicant is seeking approval of a New Drug Application (NDA) for Linezolid Injection under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act and is referencing Zyvox Solution approved under NDA 21131 on 04/18/2000 (marketed by Pharmacia and Upjohn) as the listed drug.

The proposed product is a 600 mg linezolid in 300 mL 0.9% sodium chloride sterile solution for administration by IV infusion over a period of 30 to 120 minutes. This solution formulation has the same active ingredient (linezolid), concentration (2 mg/mL) and routes of administration (IV infusion) as the listed drug, Zyvox Solution; however, the inactive ingredients are different. The comparison of the proposed formulation and the Zyvox formulation is shown in the table below.

Component	Hospira Quantity per Milliliter (mL)	Innovator Quantity per Milliliter (mL)	Function	Reference to Standards
Linezolid ¹	2 mg	2 mg	Active Ingredient	Hospira In-house Standard
Sodium Citrate, Dihydrate	N/A	1.64 mg	(b) (4)	N/A
Citric Acid, Anhydrous ²	1.92 mg	0.85 mg		USP, Ph.Eur, BP
Dextrose, Monohydrate	N/A	50.24 mg		USP, Ph.Eur, BP
Sodium Chloride	9 mg	N/A		USP, Ph.Eur, BP
Sodium Hydroxide ²	0.76 mg	A.R.		NF, Ph.Eur, BP
Hydrochloric Acid	q.s. to pH (b) (4)	A.R.		pH adjustment
Sodium Hydroxide	q.s. to pH	A.R.	pH adjustment	NF, Ph.Eur, BP
Water for Injection	q.s. to 1.00 mL	A.R.	Vehicle	USP, Ph.Eur, BP
Total Volume	1.00 mL	1.00 mL		

q.s. = Quantity sufficient; A.R. = As required.

¹ This is a non-compendial item and tested according to specifications provided in [Section 3.2.S.4.1 Specifications](#). Factored to 100% basis. Refer to [Section 3.2.P.2 Pharmaceutical Development](#) for the formulation development.

(b) (4)

The Applicant is requesting a waiver for *in-vivo* bioavailability/bioequivalence requirements for the proposed drug product based on 21 CFR § 320.22.

The Biopharmaceutics review of this NDA will be focused on the evaluation of the information supporting the approvability of the biowaiver request for the proposed Linezolid Injection, 2 mg/mL product. There is sufficient Biopharmaceutics information/data to permit a substantive review and from the Biopharmaceutics perspective this NDA is fileable.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
CMC and Biopharmaceutics**

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?			<i>Not applicable</i>

B. FACILITIES*				
* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a potential filing issue or a potential review issue.				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	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? This question is not applicable for synthesized API.	X		

**ONDQA Initial Quality Assessment (IQA) and Filing Review
CMC and Biopharmaceutics**

	Parameter	Yes	No	Comment
7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • 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) 	X		
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • 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) 	X		

**ONDQA Initial Quality Assessment (IQA) and Filing Review
CMC and Biopharmaceutics**

	Parameter	Yes	No	Comment
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • 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) 	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

C. ENVIRONMENTAL ASSESMENT

	Parameter	Yes	No	Comment
11.	Has an environmental assessment or claim of categorical exclusion been provided?	X		

**ONDQA Initial Quality Assessment (IQA) and Filing Review
CMC and Biopharmaceutics**

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		Reference to DMF Type II (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Reference to DMF Type II (b) (4)
14.	Does the section contain information regarding the characterization of the DS?	X		Reference to DMF Type II (b) (4)
15.	Does the section contain controls for the DS?	X		Reference to DMF Type II (b) (4)
16.	Has stability data and analysis been provided for the drug substance?	X		Reference to DMF Type II (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?			<i>Not immediately obvious (but not required either)</i>
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?			<i>Not immediately obvious (but not required either)</i>

**ONDQA Initial Quality Assessment (IQA) and Filing Review
CMC and Biopharmaceutics**

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?			<i>Not applicable</i>
23.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		
24.	Does the section contain controls of the final drug product?	X		
25.	Has stability data and analysis been provided to support the requested expiration date?	X		
26.	Does the application contain Quality by Design (QbD) information regarding the DP?	X		<i>QbD elements: CQAs, risk assessment, control strategy</i>
27.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?			<i>Not immediately obvious (but not required either</i>

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
28.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment

**ONDQA Initial Quality Assessment (IQA) and Filing Review
CMC and Biopharmaceutics**

29.	If appropriate, is a separate microbiological section included assuring sterility of the drug product	X		
-----	---	---	--	--

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
30.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF # (b) (4)	TYPE	HOLDER	ITEM REFERENCED (b) (4)	LOA DATE	COMMENTS
	II			November 7, 2012	<i>Not previously reviewed</i>
	III			February 28, 2013	<i>Last review dated September 3, 2013</i>
	III			February 28, 2013	<i>Last review dated September 3, 2013</i>

I. LABELING				
	Parameter	Yes	No	Comment
31.	Has the draft package insert been provided?	X		
32.	Have the immediate container and carton labels been provided?	X		

J. BIOPHARMACEUTICS				
	Parameter	Yes	No	Comment
33.	Does the application contain dissolution data?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
34.	Is the dissolution test part of the DP specifications?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
35.	Does the application contain the dissolution method development report?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
36.	Is there a validation package for the analytical method and dissolution methodology?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A

**ONDQA Initial Quality Assessment (IQA) and Filing Review
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37.	Does the application include a biowaiver request?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	A BA/BE waiver request is included in section 1.12.15 of the submission.
38.	Does the application include data supporting the biowaiver?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Comparative formulation information and other supportive information and references are provided.
39.	Does the application include an IVIVC model?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
40.	Is information such as BCS classification mentioned, and supportive data provided?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
41.	Is information on mixing the product with foods or liquids included?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
42.	Is there any <i>in vivo</i> BA or BE information in the submission?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	A BA/BE waiver request is included in the submission
FILING CONCLUSION				
	Parameter	Yes	No	Comment
43.	ARE THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
44.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	<input type="checkbox"/>	<input type="checkbox"/>	N/A (fileable)
45.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.	<input type="checkbox"/>	<input type="checkbox"/>	N/A (fileable)
46.	Are there any potential review issues identified?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<i>See draft CMC comments for 74-Day letter (page 3 of this review)</i>

**ONDQA Initial Quality Assessment (IQA) and Filing Review
CMC and Biopharmaceutics**

Attachment 1

Table 1. Comparison Between Generic Drug and Reference Listed Drug

	Reference Listed Drug	Generic Equivalent
	Pharmacia and Upjohn Zyvox	Hospira, Inc. Linezolid in 0.9% Sodium Chloride Injection
Conditions of Use	ZYVOX formulations are indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms: Vancomycin-Resistant <i>Enterococcus faecium</i> infections; Nosocomial pneumonia; Complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis; Uncomplicated skin and skin structure infections; Community-acquired pneumonia.	Linezolid Injection is indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms: Vancomycin-Resistant <i>Enterococcus faecium</i> infections; Nosocomial pneumonia; Complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis; (b) (4) (b) (4) Community-acquired pneumonia.
Active Ingredient(s)	Linezolid	Linezolid
Inactive Ingredient(s)	Dextrose Citric acid ¹ Sodium citrate ¹ Sodium hydroxide Hydrochloric acid Water for Injection	Citric acid ¹ Sodium Chloride Sodium hydroxide ¹ Hydrochloric acid Water for Injection
Route of Administration	Injection (Intravenous)	Injection (Intravenous)
Dosage Form	Injectable	Injectable
Strength	200 mg/100 mL 400 mg/200 mL 600 mg/300 mL	600mg/300 mL ²

(b) (4)

² Hospira is choosing to develop only the 600 mg/300 mL (2 mg/ml) product presentation.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
CMC and Biopharmaceutics**

Attachment 2

Table 1. Qualitative Composition

Component	Hospira Code Number	Quality Standard	Function
Linezolid	HS116	In-house	Active Ingredient
Citric Acid, Anhydrous	HS144	USP, Ph.Eur, BP	(b) (4)
Sodium Chloride	64847	USP, Ph.Eur, BP	
Sodium Hydroxide	34654	NF, Ph.Eur, BP	
Hydrochloric Acid	33420	NF, Ph.Eur, BP	pH adjustment
Water for Injection	87222	USP, Ph.Eur, BP	Vehicle

Table 2. Quantitative Composition

Component	Quantity per Milliliter (mL)	Strength: 2 mg/mL
		600 mg/300 mL
		Quantity per unit
Linezolid ¹	2 mg	600 mg
Citric Acid, Anhydrous ²	1.92 mg	576 mg
Sodium Chloride	9 mg	2700 mg
Sodium Hydroxide	0.76 mg	228 mg
Hydrochloric Acid	q.s. to pH (b) (4)	A.R.
Sodium Hydroxide	q.s. to pH (b) (4)	A.R.
Water for Injection	q.s. to 1.00 mL	q.s. to 300 mL
Total Volume	1.00 mL	300 mL

q.s. = Quantity sufficient; A.R. = As required

¹ Factored to 100% basis. Refer to Section 3.2.P.2 for the formulation development.

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Attachment 3

DS Specification:

Table 1. Specifications

Standard Claimed		Professed	
Specification Reference Number		HS116	
Test	Acceptance Criteria	Regulatory Analytical Procedure	Alternative Analytical Procedure
Physical Examination: Appearance	(b)(4) powder	In-House: Visual ^a	N/A
Assay (HPLC)	NLT (b)(4)% and NMT (b)(4)% calculated on dried basis	In-House: HPLC ^a	N/A
Identification by IR	Conform to Reference Spectrum	USP <197K>	N/A
Identification by HPLC	Conform to Standard	In-House: HPLC ^a	N/A
Residue on Ignition	NMT (b)(4)% w/w	USP <281>	N/A
Loss on drying	NMT (b)(4)% w/w	USP <731>	N/A
Heavy Metals	NMT (b)(4)ppm	USP <231> Method II	N/A
Related Substances: 1. (b)(4) 2. Individual Unspecified Impurity 3. Total Impurities	1. NMT (b)(4)% 2. NMT (b)(4)% 3. NMT (b)(4)%	In-House: HPLC ^a	N/A
(b)(4)	NMT (b)(4)%	In-House: HPLC	N/A
Residual Solvents 1. (b)(4) 2. (b)(4) 3. (b)(4) 4. (b)(4) 5. (b)(4)	1. NMT (b)(4) ppm 2. NMT (b)(4) ppm 3. NMT (b)(4) ppm 4. NMT (b)(4) ppm 5. NMT (b)(4) ppm	In-House: GC ^a	N/A
Color, Instrumental	NMT (b)(4)APHA	In-House ^a	N/A
Bacterial Endotoxins	NMT (b)(4)EU/mg	USP <85> ^a	N/A

IR = Infrared; NMT = Not more than; HPLC = High pressure chromatography; NLT = Not less than

^a In-house (non-USP) analytical procedures are provided in *Section 3.2.S.4.2 Analytical Procedures*.

^b The validation data for the analytical procedures are provided in *Section 3.2.S.4.3 Validation of Analytical Procedures*.

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Attachment 4

DP Specification:

Table 1. Release Specification

Standard Claimed		Professed	
Specification Reference Number		04883	
Test	Acceptance Criteria	Regulatory Analytical Procedure	Alternate Analytical Procedure
Clarity	Solution must be clear. Solution must be free of visible particles.	Visual	N/A
Volume	NLT labeled volume	USP<1>	N/A
Color, Visual	Colorless to slightly yellow	Visual	N/A
Color, Instrumental	NMT (b) (4) APHA	In-house	N/A
Particulate Matter	NMT (b) (4) μ m NMT (b) (4) μ m	USP <788>	N/A
Bacterial Endotoxin	NMT (b) (4) EU/mL (NMT (b) (4) EU/mg)	USP <85> Gel Clot	In-house ^{a,b}
Sterility	Meets Test Requirements	USP<71>	N/A
Linezolid	(b) (4) %	In-house ^{a,b}	N/A
pH	(b) (4)	USP <791>	N/A
Related Substances: A. (b) (4) B. (b) (4) C. (b) (4) D. (b) (4) E. Individual Unspecified Degradation Product F. Total	A. NMT (b) (4) % B. NMT (b) (4) % C. NMT (b) (4) % D. NMT (b) (4) % E. NMT (b) (4) % F. NMT (b) (4) %	In-house ^{a,b,c}	N/A
(b) (4)			
Total Sodium	(b) (4) %	In-house ^{a,b}	N/A
Osmolality	(b) (4) mOsmol/kg	In-house ^{a,b}	N/A
Identification (HPLC)	Meets test requirements	In-house ^{a,b}	N/A
Identification (UV)	Meets test requirements	In-house ^{a,b}	N/A

HPLC = High pressure liquid chromatography; UV = Ultraviolet Visible Spectromphotometer; NLT = Not less than; NMT = Not more than

- ^a Non-USP – analytical and microbiological procedures are provided in *Section 3.2.P.5.2 – Analytical Procedures*.
- ^b The validation data for the analytical and microbiological procedures are provided in *Section 3.2.P.5.3 - Validation of Analytical Procedures*
- ^c All future batches will be tested with the procedure described in *Section 3.2.P.5.2 – Analytical Procedures Related Substances Current*.
- ^d Refer to *Section 3.2.P.5.6 Justification of Specifications*.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
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