

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206110Orig1s000**

**CHEMISTRY REVIEW(S)**

# OPQ, Division of New Drug Products I, Branch III

## CMC Review

### NDA 206110 (Class 1) Resubmission

**Review Date:** December 18, 2016

**Submission:** NDA 206110 Resubmission (Class 1); SDN #21

**Submission date:** October 31, 2016

**OND Division:** Division of Anti-Infective Products (DAIP)

**Product Name:** Caspofungin Acetate for Injection, 50 mg/vial and 70 mg/vial

**Applicant:** Fresenius Kabi USA, LLC

#### **Background:**

The original submission of NDA 206110 (dated December 27, 2013) was issued a Complete Response (CR) letter on October 21, 2014 due to several Product Quality deficiencies, which included issues related to the manufacturing facilities and a deficient DMF referenced for the caspofungin acetate drug substance (for details refer to the CMC Review dated October 24, 2014 in DARRTS). These deficiencies were adequately addressed via the first (Class 2) NDA resubmission dated May 27, 2015 (refer to the CMC Review dated November 16, 2015). However, the NDA was again issued a CR letter on November 20, 2015 due to the pending patent issues. The current (Class 1) NDA resubmission addressed only the patent issues and does not contain any CMC changes other than minor updates to the labeling and labels, following labeling revisions approved by the Agency for the listed drug, Cancidas®, via supplements NDA 21227/S-034 and S-035. *(Comment: The labeling review was conducted in the previous review cycle and several revisions recommended by the Agency were incorporated by the Applicant. It should be noted that, as stated in the CMC Review dated November 16, 2015, the established name of the proposed drug product, caspofungin acetate for injection, follows the established name of the listed drug, Cancidas®,*

(b) (4)

(b) (4)

In addition, the manufacturing facilities for the drug substance and the drug product have been found acceptable by the Office of Process and Facilities (OPF) in Panorama on November 18, 2016 (*Attachment below*).

#### **Recommendation:**

This NDA is recommended for approval from the Product Quality perspective.

**Attachment**

**(OPF Overall Manufacturing Inspection Recommendation from Panorama)**



Updated Inspection View for OPQ Layout Template

Task Number	Task Name	Comments	Assignments	Pln Comp	Act Comp	Task Status	Actions	Additional Information
<b>Parent: Manufacturing Facility Inspection (2)</b>								
7	Enter Application Specific Inspection Criteria	If you are finished with this task, change the Task Status to Complete.	Team: IM - Filing PM/Coordinator	11/29/16	11/18/16	Complete	Go to Form	
9	Overall Manufacturing Inspection Recommendation	No change in facilities or in facility statuses since last evaluation in ORIG-1-RESUB-15.	Christina Capacci-Daniel	12/29/16	11/18/16	Complete	Go to Form	Recommendation: Approve

**Signature block:**

**Dorota Matecka, Ph.D.**

\_\_\_\_\_  
**CMC Lead**

**December 19, 2016**

\_\_\_\_\_  
**Date**

**Balajee Shanmugam, Ph.D.**

\_\_\_\_\_  
**Acting Branch Chief**

**December 19, 2016**

\_\_\_\_\_  
**Date**



**Balajee  
Shanmugam**

Digitally signed by Balajee Shanmugam  
Date: 12/19/2016 11:11:08AM  
GUID: 50758d500003e1b1862e038ea11002c  
Comments: Thanks, Dorota.



**Dorota  
Matecka**

Digitally signed by Dorota Matecka  
Date: 12/19/2016 02:07:06PM  
GUID: 508173530000858082c689508374d0011

**OPQ, Division of New Drug Products I  
Branch III**

**CMC Review**

**NDA 206110 Resubmission**

**Review Date:** November 13, 2015

**Submission:** NDA 206110 Resubmission (Class 2); SDN #13

**Submission date:** May 27, 2015

**OND Division:** Division of Anti-Infective Products (DAIP)

**Product Name:** Caspofungin Acetate for Injection, 50 mg/vial and 70 mg/vial

**Applicant:** Fresenius Kabi USA, LLC

**Background:**

The CMC review of the original NDA submission dated October 21, 2014 recommended Complete Response (CR) due to several product quality deficiencies including the overall "Withhold" recommendation for manufacturing facilities from the Office of Compliance and a deficient DMF (b)(4) referenced in the NDA for the caspofungin drug substance. The CR letter for the original NDA 206110 submission issued on October 21, 2014 included mainly Product Quality deficiencies, which are reproduced below (in the Review Notes, for quick reference). The current CMC review covers the Applicant's responses to these deficiencies, which have been addressed in the NDA resubmission dated May 27, 2015.

**Recommendation:**

The product quality deficiencies listed in the CR letter of the original NDA have been addressed satisfactorily in the current NDA resubmission. DMF (b)(4) referenced for the caspofungin drug substance has been found adequate to support this NDA. The drug product manufacturing process issues have been addressed satisfactorily. Also, the drug product specification has been revised and is now found acceptable. The resubmission includes 24-month room temperature stability data for the three registration batches of the drug product (both strengths). The proposed expiration dating of 24 months and the room temperature storage conditions have been found acceptable for the proposed drug product. Several labeling revisions have been recommended for the package insert and the vial, and carton labels. In addition, all manufacturing facilities for the drug substance and the drug product have been found acceptable by the Office of Process and Facilities.

Therefore, this NDA is recommended for approval from the Product Quality perspective.

## Review Notes

This NDA resubmission includes a response to several deficiencies listed in the CR letter dated October 21, 2014. They included the following:

1. During a recent inspection of the Fresenius Kabi USA, LLC, Grand Island, NY, manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.
2. Your application referenced the Drug Master File (DMF) (b) (4). This DMF was found inadequate to support your submission and a deficiency letter was sent to the DMF holder on September 23, 2014. These deficiencies must be adequately addressed before this application can be approved. As part of your response to this letter, include the date the DMF holder amended their DMF to address the deficiencies.



5. Stability data provided shows that the stability profile of the drug product is strongly temperature dependent. Therefore, we recommend that the drug product be stored at refrigerated condition. Revise the storage conditions to recommend storing the drug product at 2° to 8°C (36° to 46°F). In addition, revise the acceptance criteria for the tests noted below:
  - a) Any other individual unspecified impurity: NMT (b) (4)%
  - b) Total impurities: NMT (b) (4)%
  - c) Assay: (b) (4)% - (b) (4)%
  - d) Water content: NMT (b) (4)%
6. Regarding the analytical procedures (10-08-03-6723 and 10-08-03-6712) and methods validation, provide the following:



7. Based on the pH results in the stability studies and the forced degradation results, revise the acceptance criteria for pH from (b) (4) to (b) (4) in the drug product specification.
8. Provide particulate matter testing results (USP <788>) for the infusion solutions of caspofungin acetate performed during the Large Volume Parenteral (LVP) Admixture Stability Study.

**CR Comment 1:**

*During a recent inspection of the Fresenius Kabi USA, LLC, Grand Island, NY, manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.*

*In response, the applicant stated that Fresenius Kabi USA, LLC overcame the compliance issues at the Grand Island, NY manufacturing facility in the most recent FDA inspection held on 20 - 24 October 2014 and, as a result, achieved the upgraded status to Voluntary Action Indicated (VAI).*

**Comment:**

*All facilities, including the drug product manufacturing facility, Fresenius Kabi USA, LLC, Grand Island, NY, were evaluated and found acceptable by the Office of Process and Facilities for this NDA. A copy the Overall Facilities Assessment issued by the Office of Process and Facilities has been attached as Attachment I, below.*

**CR Comment 2:**

*Your application referenced the Drug Master File (DMF) (b) (4). This DMF was found inadequate to support your submission and a deficiency letter was sent to the DMF holder on September 23, 2014. These deficiencies must be adequately addressed before this application can be approved. As part of your response to this letter, include the date the DMF holder amended their DMF to address the deficiencies.*

*In response, the applicant stated that the DMF holder amended their DMF on January 15, 2015 to address the deficiencies listed in the letter dated September 23, 2014.*

Comment:

*The responses to DMF deficiencies forwarded to the DMF holder on September 23, 2014, have been reviewed and found acceptable. Per CMC Review # 2 dated November 13, 2015 in DARRTS, this DMF is now considered adequate to support this NDA.*

**CR Comment 3:**



Comment:

*The response is acceptable.*

**CR Comment 4:**



Comment:

The response is acceptable.

**CR Comment 5:**

(Please note that the discussion of the response to this comment contains information regarding the listed drug, Cancidas®, which is proprietary and should not be released to the applicant of the current NDA)

Stability data provided shows that the stability profile of the drug product is strongly temperature dependent. Therefore, we recommend that the drug product be stored at refrigerated condition. Revise the storage conditions to recommend storing the drug product at 2° to 8°C (36° to 46°F). In addition, revise the acceptance criteria for the tests noted below:

- a) Any other individual unspecified impurity: NMT (b) (4) %
- b) Total impurities: NMT (b) (4) %
- c) Assay: (b) (4) % - (b) (4) %
- d) Water content: NMT (b) (4) %

In response, the applicant proposed the following acceptance criteria for the above attributes:

- a) Any other individual unspecified impurity: NMT (b) (4) %

Comments:

This is in agreement with the acceptance criterion recommended by the Agency and, therefore, it is acceptable. As a result of tightening the limit for Any Other Individual Unspecified Impurity to NMT (b) (4) %, the applicant has identified two additional known impurities, (b) (4) (b) (4) which have been now incorporated into the drug product specification (with a limit of (b) (4) % for each). The applicant provided a toxicity evaluation indicating that (b) (4) do not pose any greater toxicity risk than the drug substance. In addition, the proposed limit of NMT (b) (4) % is less than the qualification threshold of NMT (b) (4) % for a drug product with a maximum daily dose of 70 mg. This issue was discussed in detail with the Pharm/Tox Reviewer for this NDA, Dr. Owen McMaster, who found the proposed limits acceptable.

- b) Total impurities: NMT (b) (4) %



Comments:

Based on the provided calculation and upon further discussions with the Pharm/Tox Reviewer for this NDA, Dr. Owen McMaster, the proposed new limit for Total Impurities on NMT (b) (4) % (as revised from the originally proposed NMT (b) (4) %) appears acceptable.

The room temperature stability data submitted in the current NDA resubmission for the three registration batches of the drug product (for the two proposed strengths, 50 mg/vial and 70 mg/vial) indicate that the average level of total impurities among these six batches was (b) (4) % at the 24-month time point with the highest result of (b) (4) % for the batch R342-042. The largest increase in total impurities over the proposed shelf life (24 months) was (b) (4) % (from the initial (b) (4) % to (b) (4) % at the 24-month time point) for the same batch.

Of note, the applicant provided also the results of the 24-month total impurities testing for two batches of the Cancidas® stored under the refrigerated conditions, (b) (4)

[Redacted]

c) Assay: (b) (4) % - (b) (4) %

To justify the proposed limit, the applicant stated that an overfill of 9.2 % for 50 mg code and 10.3 % for 70 mg code was added in Fresenius Kabi USA product, (b) (4)

[Redacted]

Comments:

The proposed assay acceptance criteria are based on the labeled claim taking into consideration the overfill used, and, therefore, may be considered acceptable. An overfill of 9.2 % for 50 mg code and 10.3 % for 70 mg code was added in Fresenius Kabi USA product, (b) (4)

[Redacted]

d) Water content: NMT (b) (4)%

The applicant stated that the drug product has been found to be stable through the 24 month expiration date at 25 °C ± 2 °C/60 % ± 5% RH, meeting all other specification limits, with the maximum water content of (b) (4)%

Comment:

*The new limit for the water content as proposed and justified in the resubmission appears to be acceptable.*

Overall comment regarding the response to CR Comment 5:

*The specification limits as proposed via the current NDA resubmission are acceptable. The proposed drug product specification is provided in Attachment II, below. It should be noted that Comment 5 included also a recommendation for storing the proposed drug product at the refrigeration. Based on the review of the stability data submitted in the resubmission (24-month results of room temperature stability for the three registration batches of the drug product of both strengths) and reanalysis of the stability data submitted in the original NDA, the proposed room temperature storage conditions appear acceptable for the following reasons:*

- 1) *Stability data provided in the resubmission cover the proposed expiration dating (24 months) and appear reasonable; e.g., no major increases in the individual degradation products was observed (as shown in the table provided in Attachment III, below);*
- 2) *The proposed limits for impurities appear to be adequately justified based on discussions with (and agreed by) the Pharm/Tox Reviewer, Dr. Owen McMaster; the proposed limits for new specified impurities*
- 3) *As described above, the limit for Total Impurities for the FK's product includes drug substance process impurities contrary to the listed drug specification; therefore, it is difficult to compare these two numbers;*

- 4) *In addition, as discussed with Dr. McMaster, the limit for total impurities in the FK's caspofungin acetate drug substance specification is much lower than that for the listed drug;*
- 5) *The range of the assay changes (from the initial value to the value at the 24-month time point) for the six registration batches was (b) (4) % - (b) (4) % with an average change of (b) (4) % and with the change of more than (b) (4) % in only one batch (i.e., a change of (b) (4) % from the initial assay value was detected for batch R342-041); it should be noted that the assay results varied somewhat among six stability batches and from one time point to the next one with no remarkable trend;*
- 6) *The formulation of the proposed drug product is quite different from that of Cancida®; therefore, the stability behavior expressed by these two drug products may be quite different.*

**CR Comment 6:**

*Regarding the analytical procedures (10-08-03-6723 and 10-08-03-6712) and methods validation provide the following:*



Comment:

*The response is acceptable.*

**CR Comment 7:**

*Based on the pH results in the stability studies and the forced degradation results, revise the acceptance criteria for pH from (b) (4) to (b) (4) in the drug product specification.*

*In response, the applicant revised the acceptance criterion for pH as recommended (refer to the specification table below; Attachment II).*

Comment:

*The response is acceptable.*

**CR Comment 8:**

*Provide particulate matter testing results (USP <788>) for the infusion solutions of caspofungin acetate performed during the Large Volume Parenteral (LVP) Admixture Stability Study.*

*In response*, the applicant provided a copy of the report PR-14-00807 entitled “Additional LVP Admixture Compatibility Study for Caspofungin Acetate for Injection”. This report includes a description of the study design, test samples preparation, test methods and results of the USP <788> testing for the proposed formulation of caspofungin acetate for injection. The test samples were prepared using the combination of agents recommended for reconstitution and further dilution listed in the proposed drug product package insert. All testing results met the USP <788> requirements for the LVP admixture compatibility after 24 hours storage at 25°C ± 2°C or 48 hours storage at 5°C ± 3°C thus supporting the instructions for the preparation and storage of the diluted solutions of the proposed drug product described in the package insert.

Comment:

*The response is acceptable.*

Labeling

A copy of the revised product vial labels are attached in Attachment IV of this review. The labeling recommendations from the CMC perspective included:

- 1) Change of the statement from (b) (4) to “Single Dose Vial” in all parts of labeling
- 2) The proposed room temperature storage conditions statement has been found acceptable: “Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]”.

Comments:

*The above recommendations have been included in the labeling of the proposed drug product. It should be noted that the established name of the proposed drug product caspofungin acetate for injection follows the established name of the listed drug (Cancidas®).*

(b) (4)  
(b) (4)

**Attachment I**

**(OPF Overall Manufacturing Inspection Recommendation from Panorama)**

**Facility Status View for NDA 206110**

Displays information for the facilities that are associated to NDA 206110. It also shows the Overall Manufacturing  
Time out: 11/12/2015 9:47:24 PM

**Overall Manufacturing Inspection Recommendations for NDA 206110**

Project Name	Sponsor Name	Overall Manufacturing Inspection Recommendation	Overall Manufacturing Inspection Task Status	Overall Manufacturing Inspection Recommendation Task Completion Date
NDA 206110-Orig 1- Re-submission/Class 2(15)	FREDENIUS KABI USA LLC	Approve	Complete	8/10/2015
NDA 206110-Orig 1-New/NDA 1	FREDENIUS KABI USA LLC	Pending	New	

Attachment II (Drug Product Specification)

**Table 3.2.P.5.1- 1 Regulatory Specification for Caspofungin Acetate for Injection, 50 mg/vial and 70 mg/vial**

Test	Acceptance Criteria	Test Method <sup>1</sup>
Description	White to off-white lyophilized cake or powder in a (b) (4) glass vial	Visual Inspection 10-08-05-6005
Reconstitution Time	NMT (b) (4)	10-08-05-6005
Constituted Solution		
1. Completeness	1. The solid dissolves completely, leaving no visible residue or undissolved matter.	1. USP <1>
2. Clarity	2. The resultant solution is not significantly less clear than an equal volume of diluent contained in a similar vessel and examined similarly.	2. USP <1>
3. Particulate Matter	3. The resultant solution is essentially free from particles of foreign matter that can be observed on visual inspection.	3. USP <1>
4. Visual Color	(b) (4)	4. 10-08-05-6005
pH	(b) (4)	USP <791>
Water Content	NMT (b) (4)	USP <921>, Method 1c
Uniformity of Dosage Units	Meets requirements of USP <905>	USP <905>
Instrumental Color	(b) (4)	99-08-00-6016 OR 03-08-07-0057

**Table 3.2.P.5.1- 1 Regulatory Specification for Caspofungin Acetate for Injection, 50 mg/vial and 70 mg/vial (Cont.)**

Test	Acceptance Criteria	Test Method <sup>1</sup>
Identification	(b) (4)	10-08-03-6723
1. HPLC	(b) (4)	
2. (b) (4)	(b) (4)	
	(b) (4)	10-08-03-6725
Assay (% Label Claim): 50 mg/vial (code 356110); 70 mg/vial (code 358110)	(b) (4) <sub>o</sub> to (b) (4) <sub>o</sub>	10-08-03-6723
Impurities (%):		
(b) (4)	1. NMT (b) (4) %	1. 10-08-03-6712
	2. NMT %	2. 10-08-03-6712
	3. NMT %	3. 10-08-03-6712
	4. NMT %	4. 10-08-03-6712
	5. NMT %	5. 10-08-03-6712
6. Total Impurities	6. NMT %	6. 10-08-03-6712 10-08-03-6723
Container Closure Integrity	(b) (4)	10-08-00-6031 10-08-00-6032
	(b) (4)	
Particulate Matter in Injection:	1. For particles: (b) (4) m. NMT (b) (4) per container 2. For particles: (b) (4) m. NMT (b) (4) per container	USP 788
Sterility	Sterile	USP 71
Bacterial Endotoxins	NMT (b) (4) EU/mg	USP 85
Other Requirements	Meets the requirements under Injection USP 1	USP 1
		(b) (4)

<sup>1</sup> Reference: to compendia signify current compendia. If a compendial monograph or test changes, Fresenius Kabi USA, LLC (FK USA) will implement the changes and report them via annual report.

3 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

Signature block:

Dorota Matecka, Ph.D.

11/16/15

CMC Lead

Date

Dorota M.  
Matecka -S

Digitally signed by Dorota M. Matecka, DN: cn=Dorota M. Matecka, o=FDA, ou=FDA, email=Dorota.Matecka@FDA.gov, c=US, email=Dorota.Matecka@FDA.gov, cn=Dorota M. Matecka, o=FDA, ou=FDA, email=Dorota.Matecka@FDA.gov, c=US

Balajee Shanmugam, Ph.D.

11/16/15

Acting Branch Chief

Date

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# **NDA 206110**

**Caspofungin Acetate for Injection  
50 mg/vial and 70 mg/vial**

**Fresenius Kabi USA, LLC**

**Lin Qi**

**Review Chemist**

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

**For the Division of Anti-Infective Products**

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**CMC Review Data Sheet**

# CMC Review Data Sheet

1. NDA 206110
2. REVIEW #: 1-Addendum #1
3. REVIEW DATE: Oct 21, 2014
4. REVIEWER: Lin Qi
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

**6. SUBMISSION(S) BEING REVIEWED:**

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original NDA Submission	12/27/2013
Amendment	1/31/2014
Amendment	2/19/2014
Amendment	3/4/2014
Amendment	4/1/2014
Amendment	6/24/2014
Amendment	9/2/2014
Amendment	9/12/2014

**7. NAME & ADDRESS OF APPLICANT:**

Name: Fresenius Kabi USA, LLC  
Address: Three Corporate Drive  
Lake Zurich, IL 60047  
Representative: Jenna Holm  
Telephone: 847-550-2300

**8. DRUG PRODUCT NAME/CODE/TYPE:**

- a) Proprietary Name: N/A
- b) Non-Proprietary Name: Caspofungin Acetate for Injection
- c) Code Name/# (ONDQA only):
- d) Chem. Type/Submission Priority (ONDQA only):

## CMC Review Data Sheet

- Chem. Type: Type 5
- Submission Priority: Standard

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

10. PHARMACOL. CATEGORY: Anti-fungal

11. DOSAGE FORM: Sterile Lyophilized Powder for Injection

12. STRENGTH/POTENCY: 50 mg/vial and 70 mg/vial

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED:  Rx  OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

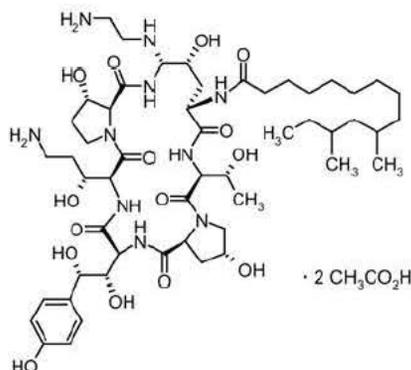
SPOTS product – Form Completed

Not a SPOTS product

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

**Chemical name:** 1-[(4*R*,5*S*)-5-[(2-aminoethyl)amino]-*N*2-(10,12-dimethyl-1-oxotetradecyl)-4-hydroxy-*L*-ornithine]-5-[(3*R*)-3-hydroxy-*L*-ornithine] pneumocandin B0 diacetate (salt)

**Structural formula:**



**Molecular formula:**  $C_{52}H_{88}N_{10}O_{15} \cdot 2 C_2H_4O_2$

**Molecular weight:** 1213.42 g/mol (as diacetate salt); 1093.31 g/mol as free base

**CMC Review Data Sheet**

**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Inadequate	9/19/14	
	III			4			
	III			4			
	III			4			

<sup>1</sup> 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")

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

**B. Other Documents:**

**18. STATUS:**

**ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		
Pharm/Tox			Owen McMaster
Biopharm	Acceptable	9/17/2014	Houda Mahayni
LNC	N/A		
Methods Validation	Inadequate	10/21/2014	Lin Qi
DMEPA*	See consult review	9/11/2014	Christine Corser
EA	Categorical exclusion	9/19/2014	Lin Qi
Microbiology	Acceptable	8/8/2014	Bryan Riley

\*DMEPA: Division of Medication Error Prevention and Analysis



# The CMC Review for NDA 206110

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The overall recommendation from the Office of Compliance is "Withhold". There are outstanding CMC issues regarding the manufacturing process and the product control. The labeling issues are pending the team review. Therefore, the recommendation for this application is "Complete Response".

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

None

### II. Summary of CMC Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### (1) Drug Substance

Caspofungin Acetate is a white to off-white powder that is freely soluble in water and methanol, and is slightly soluble in ethanol. The proposed storage condition is

(b) (4)

The manufacturing facilities include

(b) (4)

(b) (4)

(b) (4) The complete drug substance information regarding is provided in DMF (b) (4), which is held by (b) (4)

A letter of authorization dated 6/18/2013 was provided to reference for this NDA. DMF (b) (4) was found inadequate to support the current NDA in review #1 dated September 19, 2014.

##### (2) Drug Product

The drug product, Caspofungin Acetate for Injection, is a white to off-white cake or powder for intravenous infusion available in 50 mg/vial or 70 mg/vial. The 50 mg vial also contains 100 mg of L-arginine, hydrochloric acid and sodium hydroxide. The 70 mg vial also contains 140 mg of L-arginine, hydrochloric acid and sodium hydroxide. All excipients are of the compendial grades, USP/NF. Although the formulation is different (the listed drug contains sucrose and mannitol as (b) (4), and glacial acetic



acid (b) (4), the current drug product is designed to be the same as the listed drug, Cancidas<sup>®</sup> in the quality target product profile, such as dosage form, route of administration, dosage strength, reconstitution solutions, and container/closure system. The proposed overage for the current product (b) (4) (9.2% for 50 mg and 10.3% for 70 mg), resulting the reconstituted solutions of 5 mg/mL and 7 mg/mL, respectively. The infusion solution is prepared by adding appropriate volume of reconstituted solution into the infusion bags to achieve the target concentration of NMT 0.5 mg/mL.

The drug product is manufactured by Fresenius Kabi USA, LLC at Grand Island, NY.

(b) (4)  
 (b) (4) The proposed commercial batch size is (b) (4) L. The process temperatures and hold times are considered as critical process parameters for this product, (b) (4)

(b) (4) The drug product release tests include Description, Reconstitution Time, Constituted Solution USP tests, Visual Color, pH, Water Content, Uniformity of Dosage Units, Instrumental Color, Identification by HPLC and (b) (4), Assay, Impurities, Particulate Matter in Injection (USP), Container Closure Integrity, Sterility, and Bacterial Endotoxins.

The drug product will be filled into (b) (4) Type I USP glass vials (10 mL, 20 mm), with (b) (4) rubber, (b) (4) stoppers (20 mm) and aluminum crimped flip cap seals. An expiration dating period of (b) (4) months at (b) (4) is requested for this drug product. However, the FDA recommended storage condition is refrigerated condition, 2° to 8°C (36° to 46°F), based on the available product information.

#### **B. Description of How the Drug Product is Intended to be Used**

Caspofungin acetate for injection is an echinocandin antifungal drug for the treatment of Candidemia and Candida infections, as well as Aspergillosis and Aspergillus infections in patients 3 months of age and older. The proposed product is intended to be administered intravenously over a period of 60 minutes.

Caspofungin acetate for injection is reconstituted by adding 10.8 mL of 0.9% Sodium Chloride Injection, Sterile Water for Injection, Bacteriostatic Water for Injection with methylparaben and propylparaben, or Bacteriostatic Water for Injection with 0.9% benzyl alcohol to the vial. The reconstituted solution (5 mg/ml or 7 mg/ml) may be stored for up to one hour at ≤ 25°C (≤ 77°F). Aseptically transfer the appropriate volume (mL) of reconstituted caspofungin acetate for injection to an IV bag (or bottle) containing 250 mL of 0.9%, 0.45%, or 0.225% Sodium Chloride Injection or Lactated Ringers Injection. Alternatively, the volume (mL) of reconstituted caspofungin acetate for injection can be added to a reduced volume of 0.9%, 0.45%, or 0.225% Sodium Chloride Injection or Lactated Ringers Injection, not to exceed a final concentration of



0.5 mg/mL. This infusion solution must be used within 24 hours if stored at ≤25°C (≤77°F) or within 48 hours if stored refrigerated at 2° to 8°C (36° to 46°F).

**C. Basis for Approvability or Not-Approval Recommendation**

Basis for Approval:

- Dr. Bryan Riley recommended “Approval” in the most recent microbiology review dated 8/8/2014.
- Dr. Houda Mahayni recommended “Approval” in the biopharmaceutics review dated 9/17/2014.

Basis for Not-Approval:

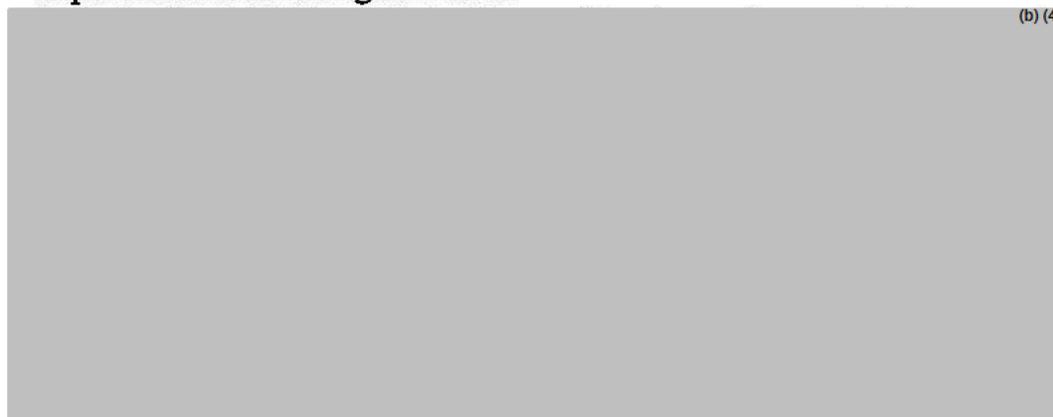
- Risk Assessment:

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**
Formulation Design	Use Arginine as (b) (4)		Pharm/Tox and Biopharm consult	Acceptable See P.2	None
Manufacturing and Facility	Commercial Process capability, Process controls		Satisfactory Responses to IR needed	Not acceptable See P.2.3 and P.3	None
Product Control	Assay, pH, Water content, Impurities, method validation		Satisfactory Responses to IR needed	Not acceptable See P.5.6	None

\*Risk ranking applies to product attribute/CQA

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

- An acceptable recommendation on this application depends on satisfactory responses to the following comments:



(b) (4)



(b) (4)

3. Stability data provided shows that the stability profile of the drug product is strongly temperature dependent. Therefore, we recommend that the drug product be stored at refrigerated condition. In addition, we recommended that the acceptance criteria for the following tests be revised as follows:
- Any other individual unspecified impurity: NMT (b) (4)%
  - Total impurities: NMT (b) (4)%
  - Assay: (b) (4)% - (b) (4)%
  - Water content: NMT (b) (4)%
- Update the NDA with the revised specifications and labeling.

4. Regarding the analytical procedures (10-08-03-6723 and 10-08-03-6712) and methods validation, please provide the following:

(b) (4)

5. Based on the pH results in the stability studies and the forced degradation results, it is recommended that the acceptance criteria for pH be revised from (b) (4) to (b) (4) in the drug product specification.
6. The particulate matter (USP<788>) test results were not found in the "Large Volume Parenteral (LVP) Admixture Stability Study Report". Please provide particulate matter testing results (USP <788>) performed during the Large Volume Parenteral (LVP) Admixture Stability Study.
- DMF (b) (4) is inadequate to support the current NDA.
  - The storage condition is to be finalized pending the satisfactory responses to the information requests listed above. The outstanding labeling issues are pending the team review in the next review cycle.
  - The overall recommendation from the Office of Compliance is "Withhold" dated 10/21/14.

Therefore, the recommendation for this application is "Complete Response".



**III. Administrative**

**A. Reviewer's Signature:**

*(See appended electronic signature page)*

Lin Qi Ph.D., CMC Reviewer, ONDQA

**B. Endorsement Block:**

*(See appended electronic signature page)*

Mark Seggel, Ph.D., Acting for Dorota Matecka, Ph. D., CMC Lead, ONDQA

Stephen Miller, Ph.D. Acting for Rapti Madurawe, Ph.D., Branch Chief, ONDQA

**C. CC Block: Entered electronically in DFS**

## CMC Assessment Section

**CMC Assessment**

This is an addendum to the CMC review#1 dated 9/19/2014 to include the overall recommendation (WH) from OC.

**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****R1 Executed Batch Records**

Reviewed in the manufacturing section of CMC review #1 dated 9/19/2014.

**R2 Comparability Protocols**

N/A

**R3 Methods Validation Package**

Inadequate. A comment regarding the method validation was sent in an information request letter dated 8/22/2014. The partial responses submitted in 10/2/2014 are to be evaluated in the next review cycle when complete responses are provided by the applicant.

**II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1****A. Labeling & Package Insert**

The storage condition (Amendment dated 10/10/2014) is to be finalized pending the satisfactory responses to the information requests listed in section II.C of the Executive Summary. The outstanding labeling issues are pending the team review in the next review cycle.

**B. Environmental Assessment Or Claim Of Categorical Exclusion**

A categorical exclusion is requested by the applicant pursuant to 21 CFR § 25.31(a) as the applicant states that the action of this application does not increase the use of the active moiety, Caspofungin Acetate. The applicant also certifies that its Grand Island, New York, USA manufacturing facility is in compliance with all federal, state, and local environmental protection requirements and that it has a certified waste disposal program as committed in their EPA COMPLIANCE STATEMENT.

**C. Establishment Evaluation Report**

See the GMP Establishment Review dated 10/21/2014 in DARRTS.

## CMC Assessment Section

**III. List Of Deficiencies Communicated and Resolved**

Comments Sent on August 22, 2014.

(b) (4)



3. Stability data provided shows that the stability profile of the drug product is strongly temperature dependent. Therefore, we recommend that the drug product be stored at refrigerated condition. In addition, we recommended that the acceptance criteria for the following tests be revised as follows:

- Any other individual unspecified impurity: NMT (b) (4)%
- Total impurities: NMT (b) (4)%
- Assay: (b) (4)% - (b) (4)%
- Water content: NMT (b) (4)%

Update the NDA with the revised specifications and labeling.

4. Regarding the analytical procedures (10-08-03-6723 and 10-08-03-6712) and methods validation, please provide the following:

(b) (4)



**CMC Assessment Section****Comments Sent on Sept 22, 2014:**

5. Based on the pH results in the stability studies and the forced degradation results, it is recommended that the acceptance criteria for pH be revised from (b) (4) to (b) (4) (b) (4) in the drug product specification.
  
6. The particulate matter (USP<788>) test results were not found in the "Large Volume Parenteral (LVP) Admixture Stability Study Report". Please provide particulate matter testing results (USP <788>) performed during the Large Volume Parenteral (LVP) Admixture Stability Study.

**CMC Assessment Section**

APPEARS THIS WAY ON ORIGINAL

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

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/s/

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LIN QI  
10/21/2014

MARK R SEGCEL  
10/21/2014  
for Dorota Matecka

STEPHEN MILLER  
10/21/2014

I concur for R.Madurawe - at this time this NDA is recommended for a CR action from the CMC perspective

# **NDA 206110**

**Caspofungin Acetate for Injection  
50 mg/vial and 70 mg/vial**

**Fresenius Kabi USA, LLC**

**Lin Qi**

**Review Chemist**

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

**For the Division of Anti-Infective Products**

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## CMC Review Data Sheet

# CMC Review Data Sheet

1. NDA 206110
2. REVIEW #: 1
3. REVIEW DATE: Sept 19, 2014
4. REVIEWER: Lin Qi
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original NDA Submission

12/27/2013

Amendment

1/31/2014

Amendment

2/19/2014

Amendment

3/4/2014

Amendment

4/1/2014

Amendment

6/24/2014

Amendment

9/2/2014

Amendment

9/12/2014

7. NAME & ADDRESS OF APPLICANT:

Name: Fresenius Kabi USA, LLC

Address: Three Corporate Drive

Lake Zurich, IL 60047

Representative: Jenna Holm

Telephone: 847-550-2300

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A

b) Non-Proprietary Name: Caspofungin Acetate for Injection

c) Code Name/# (ONDQA only):

d) Chem. Type/Submission Priority (ONDQA only):

## CMC Review Data Sheet

- Chem. Type: Type 5
- Submission Priority: Standard

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

10. PHARMACOL. CATEGORY: Anti-fungal

11. DOSAGE FORM: Sterile Lyophilized Powder for Injection

12. STRENGTH/POTENCY: 50 mg/vial and 70 mg/vial

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED:  Rx  OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

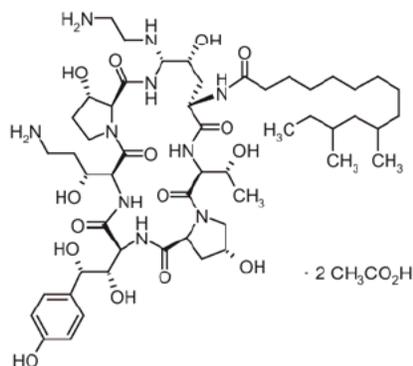
SPOTS product – Form Completed

Not a SPOTS product

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

**Chemical name:** 1-[(4*R*,5*S*)-5-[(2-aminoethyl)amino]-*N*2-(10,12-dimethyl-1-oxotetradecyl)-4-hydroxy-*L*-ornithine]-5-[(3*R*)-3-hydroxy-*L*-ornithine] pneumocandin B0 diacetate (salt)

**Structural formula:**



**Molecular formula:** C<sub>52</sub>H<sub>88</sub>N<sub>10</sub>O<sub>15</sub> · 2 C<sub>2</sub>H<sub>4</sub>O<sub>2</sub>

**Molecular weight:** 1213.42 g/mol (as diacetate salt); 1093.31 g/mol as free base

CMC Review Data Sheet

**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Inadequate	9/19/14	
	III			4			
	III			4			
	III			4			

<sup>1</sup> 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")

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

**B. Other Documents:**

**18. STATUS:**

**ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		
Pharm/Tox			Owen McMaster
Biopharm	Acceptable	9/17/2014	Houda Mahayni
LNC	N/A		
Methods Validation	N/A		
DMEPA*	See consult review	9/11/2014	Christine Corser
EA	Categorical exclusion	9/19/2014	Lin Qi
Microbiology	Acceptable	8/8/2014	Bryan Riley

\*DMEPA: Division of Medication Error Prevention and Analysis



# The CMC Review for NDA 206110

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The overall recommendation from the Office of Compliance is pending. There are outstanding CMC issues regarding the manufacturing process and the product control. Therefore, this NDA is not recommended for approval.

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

None

### II. Summary of CMC Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### (1) Drug Substance

Caspofungin Acetate is a white to off-white powder that is freely soluble in water and methanol, and is slightly soluble in ethanol. The proposed storage condition is

(b) (4)

The manufacturing facilities include (b) (4)

The complete drug substance information regarding is provided in DMF (b) (4) which is held by (b) (4)

A letter of authorization dated 6/18/2013 was provided to reference for this NDA. DMF (b) (4) was found inadequate to support the current NDA in review #1 dated September 19, 2014.

##### (2) Drug Product

The drug product, Caspofungin Acetate for Injection, is a white to off-white cake or powder for intravenous infusion available in 50 mg/vial or 70 mg/vial. The 50 mg vial also contains 100 mg of L-arginine, hydrochloric acid and sodium hydroxide. The 70 mg vial also contains 140 mg of L-arginine, hydrochloric acid and sodium hydroxide. All excipients are of the compendial grades, USP/NF. Although the formulation is different (the listed drug contains sucrose and mannitol as (b) (4), and glacial acetic acid (b) (4)), the current drug product is designed to be the same as the listed



(b) (4) Cancidas® in the quality target product profile, such as dosage form, route of administration, dosage strength, reconstitution solutions, and container/closure system. The proposed overage for the current product (b) (4) (9.2% for 50 mg and 10.3% for 70 mg), resulting the reconstituted solutions of 5 mg/mL and 7 mg/mL, respectively. The infusion solution is prepared by adding appropriate volume of reconstituted solution into the infusion bags to achieve the target concentration of NMT 0.5 mg/mL.

The drug product is manufactured by Fresenius Kabi USA, LLC at Grand Island, NY. The manufacturing process consists of the following process operation units: (1)

(b) (4)

(b) (4) The proposed commercial batch size is (b) (4) L. The process temperatures and hold times are considered as critical process parameters for this product, (b) (4). The drug product release tests include Description, Reconstitution Time, Constituted Solution USP tests, Visual Color, pH, Water Content, Uniformity of Dosage Units, Instrumental Color, Identification by HPLC and (b) (4), Assay, Impurities, Particulate Matter in Injection (USP), Container Closure Integrity, Sterility, and Bacterial Endotoxins.

The drug product will be filled into (b) (4) Type I USP glass vials (10 mL, 20 mm), with (b) (4) rubber, (b) (4) stoppers (20 mm) and aluminium crimped flip cap seals. An expiration dating period of (b) (4) months at (b) (4) is requested for this drug product. However, the FDA recommended storage condition is refrigerated condition, 2° to 8°C (36° to 46°F), based on the available product information.

## B. Description of How the Drug Product is Intended to be Used

Caspofungin acetate for injection is an echinocandin antifungal drug for the treatment of Candidemia and Candida infections, as well as Aspergillosis and Aspergillus infections in patients 3 months of age and older. The proposed product is intended to be administered intravenously over a period of 60 minutes.

Caspofungin acetate for injection is reconstituted by adding 10.8 mL of 0.9% Sodium Chloride Injection, Sterile Water for Injection, Bacteriostatic Water for Injection with methylparaben and propylparaben, or Bacteriostatic Water for Injection with 0.9% benzyl alcohol to the vial. The reconstituted solution (5 mg/ml or 7 mg/ml) may be stored for up to one hour at  $\leq 25^{\circ}\text{C}$  ( $\leq 77^{\circ}\text{F}$ ). Aseptically transfer the appropriate volume (mL) of reconstituted caspofungin acetate for injection to an IV bag (or bottle) containing 250 mL of 0.9%, 0.45%, or 0.225% Sodium Chloride Injection or Lactated Ringers Injection. Alternatively, the volume (mL) of reconstituted caspofungin acetate for injection can be added to a reduced volume of 0.9%, 0.45%, or 0.225% Sodium Chloride Injection or Lactated Ringers Injection, not to exceed a final concentration of



0.5 mg/mL. This infusion solution must be used within 24 hours if stored at ≤25°C (≤77°F) or within 48 hours if stored refrigerated at 2° to 8°C (36° to 46°F).

**C. Basis for Approvability or Not-Approval Recommendation**

Basis for Approval:

- Dr. Bryan Riley recommended “Approval” in the most recent microbiology review dated 8/8/2014.
- Dr. Houda Mahayni recommended “Approval” in the biopharmaceutics review dated 9/17/2014.

Basis for Not-Approval:

- Risk Assessment:

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**
Formulation Design	Use Arginine as (b) (4)		Pharm/Tox and Biopharm consult	Acceptable See P.2	None
Manufacturing and Facility	Commercial Process capability, Process controls		Satisfactory Responses to IR needed	Not acceptable See P.2.3 and P.3	None
Product Control	Assay, pH, Water content, Impurities, method validation		Satisfactory Responses to IR needed	Not acceptable See P.5.6	None

- \*Risk ranking applies to product attribute/CQA
- \*\*For example, post marketing commitment, knowledge management post approval, etc.

- An acceptable recommendation on this application depends on satisfactory responses to the following comments:



(b) (4)



(b) (4)

3. Stability data provided shows that the stability profile of the drug product is strongly temperature dependent. Therefore, we recommend that the drug product be stored at refrigerated condition. In addition, we recommended that the acceptance criteria for the following tests be revised as follows:
- Any other individual unspecified impurity: NMT (b) (4)%
  - Total impurities: NMT (b) (4)%
  - Assay: (b) (4)% - (b) (4)%
  - Water content: NMT (b) (4)%

Update the NDA with the revised specifications and labeling.

4. Regarding the analytical procedures (10-08-03-6723 and 10-08-03-6712) and methods validation, please provide the following:

(b) (4)

5. Based on the pH results in the stability studies and the forced degradation results, it is recommended that the acceptance criteria for pH be revised from (b) (4) to (b) (4) in the drug product specification.
6. The particulate matter (USP<788>) test results were not found in the “Large Volume Parenteral (LVP) Admixture Stability Study Report”. Please provide particulate matter testing results (USP <788>) performed during the Large Volume Parenteral (LVP) Admixture Stability Study.
- The status of the drug product manufacturer has been “OAI” since the application was submitted. Concerns regarding the drug product manufacturing process were conveyed to the Office of Compliance for consideration. The



overall recommendation from the Office of Compliance is still pending at the date of this review.

Therefore, the recommendation for this application is “Complete Response”.

### III. Administrative

#### A. Reviewer's Signature:

*(See appended electronic signature page)*

Lin Qi Ph.D., CMC Reviewer, ONDQA

#### B. Endorsement Block:

*(See appended electronic signature page)*

Dorota Matecka, Ph. D., CMC Lead, ONDQA

Rapti Madurawe, Ph.D., Branch Chief, Branch V, ONDQA

#### C. CC Block: entered electronically in DFS

36 Page(s) have been Withheld in Full as b4 (CCI/TS)  
immediately following this page

CMC Assessment Section

- N/A
- A.3 Novel Excipients  
N/A

R. REGIONAL INFORMATION

- R1 Executed Batch Records
- R2 Comparability Protocols
- R3 Methods Validation Package

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

A. Labeling & Package Insert

The following is a summary of the labeling review.

1. Package Insert

(a) “Highlights” Section

Item	Information Provided in NDA
<b>Drug name (201.57(a)(2))</b>	
Proprietary name and established name	Caspofungin Acetate for Injection
Dosage form, route of administration	Intravenous
Controlled drug substance symbol (if applicable)	--
<b>Dosage Forms and Strengths (201.57(a)(8))</b>	
Whether the drug product is scored	

(b) “Full Prescribing Information” Section

#2.6 Preparation (b) (4) for Administration

Do not mix or co-infuse caspofungin acetate for injection with other medications, as there are no data available on the compatibility of caspofungin acetate for injection with other intravenous substances, additives, or medications. DO NOT USE DILUENTS CONTAINING DEXTROSE (α-D-GLUCOSE), as caspofungin acetate for injection is not stable in diluents containing dextrose.

(b) (4)

## CMC Assessment Section

- A. Aseptically add 10.8 mL of 0.9% Sodium Chloride Injection, Sterile Water for Injection, Bacteriostatic Water for Injection with methylparaben and propylparaben, or Bacteriostatic Water for Injection with 0.9% benzyl alcohol to the vial.

Each vial of caspofungin acetate for injection contains an intentional overfill of caspofungin acetate for injection. Thus, the drug concentration of the resulting solution is listed in Table 1 below.

**Table 1: Information for Preparation of Caspofungin Acetate for Injection**

<b>Caspofungin Acetate for Injection vial</b>	<b>Total Drug Content (including overfill)</b>	<b>Reconstitution Volume to be added</b>	<b>Resulting Concentration following Reconstitution</b>
50 mg	54.6 mg	10.8 mL	5 mg/mL
70 mg	77.2 mg	10.8 mL	7 mg/mL

The white to off-white cake will dissolve completely. Mix gently until a clear solution is obtained. Visually inspect the reconstituted solution for particulate matter or discoloration during reconstitution and prior to infusion. Do not use if the solution is cloudy or has precipitated.

The reconstituted solution may be stored for up to one hour at  $\leq 25^{\circ}\text{C}$  ( $\leq 77^{\circ}\text{F}$ ).

Caspofungin acetate for injection vials are for single use only; the remaining solution should be discarded.

- B. Aseptically transfer the appropriate volume (mL) of reconstituted caspofungin acetate for injection to an IV bag (or bottle) containing 250 mL of 0.9%, 0.45%, or 0.225% Sodium Chloride Injection or Lactated Ringers Injection. Alternatively, the volume (mL) of reconstituted caspofungin acetate for injection can be added to a reduced volume of 0.9%, 0.45%, or 0.225% Sodium Chloride Injection or Lactated Ringers Injection, not to exceed a final concentration of 0.5 mg/mL.

CMC Assessment Section

This infusion solution must be used within 24 hours if stored at  $\leq 25^{\circ}\text{C}$  ( $\leq 77^{\circ}\text{F}$ ) or within 48 hours if stored refrigerated at  $2^{\circ}$  to  $8^{\circ}\text{C}$  ( $36^{\circ}$  to  $46^{\circ}\text{F}$ ). (b) (4)

[Redacted]

# 3: Dosage Forms and Strengths

(b) (4) 50 mg is a white to off-white cake or powder for (b) (4) contains 54.6 mg of caspofungin.

(b) (4) 70 mg is a white to off-white cake or powder for (b) (4) contains 77.2 mg of caspofungin.

Item	Information Provided in NDA
Available dosage forms	Included
Strengths: in metric system	Included
Active moiety expression of strength with equivalence statement (if applicable)	Included
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Included

**Comments:** The drug name should be “caspofungin acetate for injection”, not

(b) (4)

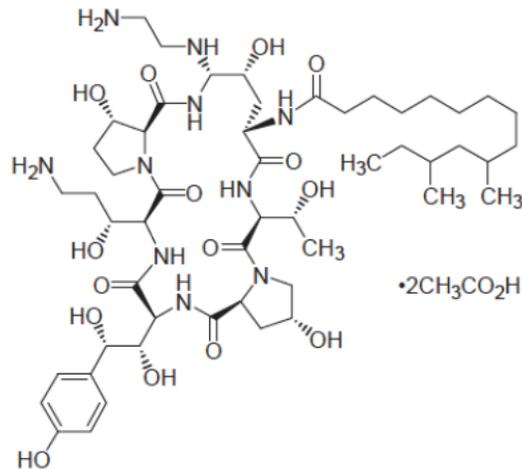
#11: Description

Caspofungin acetate for injection is a sterile, lyophilized product for intravenous (IV) infusion that contains a semisynthetic lipopeptide (echinocandin) compound synthesized from a fermentation product of *Glarea lozoyensis*. Caspofungin acetate is an echinocandin that inhibits the synthesis of  $\beta$  (1,3)-D-glucan, an integral component of the fungal cell wall.

Caspofungin acetate is 1-[(4R,5S)-5-[(2-aminoethyl)amino]-N<sup>2</sup>-(10,12-dimethyl-1-oxotetradecyl)-4-hydroxy-L-ornithine]-5-[(3R)-3-hydroxy-L-ornithine] pneumocandin B<sub>0</sub> diacetate (salt). Caspofungin acetate for injection 50 mg (b) (4) contains 100 mg arginine and hydrochloric acid/sodium hydroxide required for pH adjustment. Caspofungin acetate for injection 70 mg (b) (4) contains 140 mg arginine and hydrochloric acid/sodium hydroxide required for pH adjustment. Caspofungin

## CMC Assessment Section

acetate is a hygroscopic, white to off-white powder. It is freely soluble in water and methanol, and slightly soluble in ethanol. The pH of a saturated aqueous solution of caspofungin acetate is approximately 6.6. The structural formula is:



M.W. 1213.42

Item	Information Provided in NDA
Proprietary name and established name	Included
Dosage form and route of administration	Included
Active moiety expression of strength with equivalence statement (if applicable)	Included
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Included
Statement of being sterile (if applicable)	Included
Pharmacological/ therapeutic class	Included
Chemical name, structural formula, molecular weight	Included
If radioactive, statement of important nuclear characteristics.	--
Other important chemical or physical properties (such as pKa or pH)	Included

**Comments:** *The content of this section is similar to that for the listed drug. Acceptable.*

#### #16: How Supplied/Storage and Handling

Caspofungin acetate for injection is a white to off-white cake or powder for infusion, supplied in single-use vials as follows:

CMC Assessment Section

Product No.	NDC No.	Strength	
356110	63323-356-10	50 mg per vial	Packaged in trays of 10.
358110	63323-358-10	70 mg per vial	Packaged in trays of 10.

**Storage and Handling**

(b) (4)

The lyophilized vials should be stored at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

**Reconstituted Concentrate**

Reconstituted caspofungin acetate for injection in the vial may be stored at ≤ 25°C (≤ 77°F) for one hour prior to the preparation of the patient infusion solution.

**Diluted Product**

The final patient infusion solution in the IV bag or bottle can be stored at ≤ 25°C (≤ 77°F) for 24 hours or at 2° to 8°C (36° to 46°F) for 48 hours.

This container closure is not made with natural rubber latex.

(b) (4)

Item	Information Provided in NDA
Strength of dosage form	Included
Available units (e.g., bottles of 100 tablets)	Included
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Included
Special handling (e.g., protect from light)	N/A
Storage conditions	To be revised
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Included

**Comments:**

- The material and color of the cap/seal should be included.
- The storage condition should be changed to “The lyophilized vials should be stored refrigerated at 2° to 8°C (36° to 46°F)”.

CMC Assessment Section

- What does (b) (4) represent and why is it included in the manufacturer name?

3. Immediate container labels

A copy of the container label is provided below:



Item	Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Caspofungin Acetate for Injection
Dosage strength	50 mg & 70 mg
Net contents (See USP <1> for presentation of strength and content for injections.)	Included
“Rx only” displayed prominently on the main panel	Included
NDC number (21 CFR 207.35(b)(3)(i)) (Appear prominently in the top third of the principal display panel or it may appear as part of and contiguous to any bar-code symbol)	Included
Lot number and expiration date (21 CFR 201.17)	Included
Storage conditions	To be revised
Bar code (21CFR 201.25)	Included
Name of manufacturer/distributor	Included
Instruction for Medication Guide, if any (21CFR 208.24(d)) appears prominently	Included
And others, if space is available	--

***Comments:*** The storage condition on the proposed container label needs to be revised as in the PI.

## CMC Assessment Section

4. Proposed Tray Label

***Comments:** The storage condition on the proposed tray label needs to be revised as in the PI. In addition, the following are missing from the proposed tray label:*

- Statement of being sterile*
- See package insert for dosage and reconstitution information*

**B. Environmental Assessment Or Claim Of Categorical Exclusion****C. Establishment Evaluation Report****III. List Of Deficiencies Communicated and Resolved**

Comments Sent on August 22, 2014.



## CMC Assessment Section

3. Stability data provided shows that the stability profile of the drug product is strongly temperature dependent. Therefore, we recommend that the drug product be stored at refrigerated condition. In addition, we recommended that the acceptance criteria for the following tests be revised as follows:

- Any other individual unspecified impurity: NMT (b) (4) %
- Total impurities: NMT (b) (4) %
- Assay: (b) (4) % - (b) (4) 0%
- Water content: NMT (b) (4) %

Update the NDA with the revised specifications and labeling.

4. Regarding the analytical procedures (10-08-03-6723 and 10-08-03-6712) and methods validation, please provide the following:



Comments to be Sent:

5. Based on the pH results in the stability studies and the forced degradation results, it is recommended that the acceptance criteria for pH be revised from (b) (4) to (b) (4) (b) (4) in the drug product specification.
6. The particulate matter (USP<788>) test results were not found in the “Large Volume Parenteral (LVP) Admixture Stability Study Report”. Please provide particulate matter testing results (USP <788>) performed during the Large Volume Parenteral (LVP) Admixture Stability Study.



CMC Assessment Section

Attachment:

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT

<b>Application:</b>	NDA 206110/000	<b>Action Goal:</b>	
<b>Stamp Date:</b>	27-DEC-2013	<b>District Goal:</b>	28-AUG-2014
<b>Regulatory:</b>	27-OCT-2014		
<b>Applicant:</b>	FRESENIUS KABI USA 3 CORPORATE DR LAKE ZURICH, IL 60047	<b>Brand Name:</b>	CASPOFUNGIN ACETATE FOR INJECTION
<b>Priority:</b>	5	<b>Estab. Name:</b>	
<b>Org. Code:</b>	520	<b>Generic Name:</b>	
<b>Application Comment:</b>		<b>Product Number; Dosage Form; Ingredient; Strengths</b>	001; POWDER, FOR INJECTION SOLUTION, LYOPHILIZED; CASPOFUNGIN ACETATE; 50MG 002; POWDER, FOR INJECTION SOLUTION, LYOPHILIZED; CASPOFUNGIN ACETATE; 70MG
<b>FDA Contacts:</b>	L. QI	Prod Qual Reviewer	3017961438
	S. DONALD	Micro Reviewer	(HFD-805) 4107795444
	N. BHANDARI	Product Quality PM	2404023815
	A. RODGERS	Regulatory Project Mgr	(HFD-520) 3017960797
<b>Overall Recommendation:</b>			



CMC Assessment Section

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT

Establishment: CFN: 1321116 FEI: 3001833549  
FRESENIUS KABI USA, LLC  
3150 STALEY RD  
GRAND ISLAND, NY 140722028

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER  
FINISHED DOSAGE MANUFACTURER  
FINISHED DOSAGE PACKAGER  
FINISHED DOSAGE RELEASE TESTER  
FINISHED DOSAGE STABILITY TESTER

Establishment Comment: DRUG SUBSTANCE RELEASE TESTING,  
DRUG PRODUCT MANUFACTURING, RELEASE/STABILITY TESTING, AND PACKAGING (b) (4)

Profile: SMALL VOLUME PARENTERAL, LYOPHILIZED OAI Status: OAI ALERT

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
REQUEST CANCELLED	03-FEB-2014				BHANDARIN
SUBMITTED TO OC	03-FEB-2014				BHANDARIN
SUBMITTED TO DO OAI	04-FEB-2014	10-Day Letter			CAPACCIDANIC
DO RECOMMENDATION	06-FEB-2014			WITHHOLD	MSPATARO
W/L ISSUED 2/22/12; RE-INSPECTION COMPLETED 1/11/13, CLASSIFIED AS OAI; SEVERAL PRELIMINARY ASSESSMENT CALLS FOR INJECTION HAVE BEEN HELD. FK GMP STATUS IS BEING HANDLED USING CDER'S DRUG SHORTAGE PROTOCOL.					



CMC Assessment Section

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT

Establishment: CFN: 1421790 FEI: 1000115163  
 FRESENIUS KABI USA, LLC  
 2045 CORNELL AVE  
 MELROSE PARK, IL 601601002

DMF No: AADA:  
 Responsibilities: FINISHED DOSAGE STABILITY TESTER

Establishment Comment: DRUG PRODUCT STABILITY TESTING, ALTERNATE CONTAINER CLOSURE INTEGRITY TESTING (on 31-JAN-2014 by N. BHANDARI (J 2404023815))

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
<b>Comment</b>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<b>Reason</b>					
SUBMITTED TO OC	31-JAN-2014				BHANDARIN
OC RECOMMENDATION	31-JAN-2014			ACCEPTABLE	CAPACCIDANIC



CMC Assessment Section

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT

Establishment: CFN: FEI: 3008604776  
 FRESENIUS KABI USA, LLC  
 8045 LAMON AVE STE 300  
 SKOKIE, IL 600775318

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER  
 FINISHED DOSAGE RELEASE TESTER  
 FINISHED DOSAGE STABILITY TESTER

Establishment Comment: CONTAINER CLOSURE INTEGRITY TESTING  
 ALTERNATE DRUG SUBSTANCE RELEASE TESTING  
 ALTERNATE DRUG PRODUCT RELEASE/STABILITY TESTING (on 06-JAN-2014 by N. BHANDARI () 2404023815)

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	31-JAN-2014				BHANDARIN
OC RECOMMENDATION	31-JAN-2014			ACCEPTABLE	CAPACCIDANIC

**CMC Assessment Section****FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

Establishment: [REDACTED] (b) (4)

DMF No: [REDACTED]

Responsibilities: [REDACTED] (b) (4)  
 DRUG SUBSTANCE PACKAGER  
 DRUG SUBSTANCE RELEASE TESTER  
 DRUG SUBSTANCE STABILITY TESTER

Establishment Comment: [REDACTED] (b) (4) RELEASE/STABILITY TESTING, AND PACKAGING. (on [REDACTED] (b) (4) by N. BHANDARI (I) 2404023815)

Profile: [REDACTED] (b) (4) OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					
SUBMITTED TO OC	31-JAN-2014				BHANDARIN
OC RECOMMENDATION	23-MAY-2014			ACCEPTABLE	WILLIAMSJU

CMC Assessment Section

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT

Establishment: (b) (4)

DMF No: (b) (4)

Responsibilities: (b) (4)

Establishment Comment: (b) (4)

Profile: (b) (4) OAI Status: NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	21-FEB-2014				BHANDARIN

(b) (4)

(b) (4)

(b) (4)

INSPECTION SCHEDULED	(b) (4)	(b) (4)	(b) (4)		
DO RECOMMENDATION	29-AUG-2014			ACCEPTABLE	MROSE
OC RECOMMENDATION	29-AUG-2014			ACCEPTABLE	RHX

CMC Assessment Section

APPEARS THIS WAY ON ORIGINAL

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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LIN QI  
09/19/2014

DOROTA M MATECKA  
09/19/2014

RAPTI D MADURawe  
09/19/2014