

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205645Orig1s000**

**CHEMISTRY REVIEW(S)**

**CMC Review**  
**NDA 205645 (Request for Final Approval Amendment)**

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

**Review date:** 11/08/2016

**Submission:** NDA 205645 Resubmission Class 2, Supp. Document Number: 19, eCTD Sequence Number 0017

**Submission date:** 06/01/2016

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

**Product Name:** Tigecycline for Injection, 50 mg/vial in 10 mL vial

**Applicant:** FRESENIUS KABI USA LLC

**Background:**

NDA 205645 was granted tentative approval on 25 Nov 2015. The sponsor submits this "Request for Final Approval Amendment" for full approval.

**Recommendation:**

This NDA is recommended for **Approval** from the Product Quality perspective.

**Executive Summary**

The following are included in this submission:

- The drug substance and drug product specifications have been updated to meet the USP monograph requirements that became effective on December 01, 2015.
- Updated analytical procedures for Assay and Organic Impurities for both drug substance and drug product, along with the respective validation/verification reports.
- The Certificate of Analysis for a recent batch (manufactured in Nov 2015)
- An updated package insert
- The vial label was rebranded and had the USP designation added. The tray label was rebranded and converted to a carton label with the USP designation added.

## Review Notes

### Drug Substance

#### Drug substance specifications

The drug substance specifications (Table 1) were updated in this amendment (SD-19) to meet the current USP monograph on Tigecycline.

The revisions include the following:

- HPLC identification and assay method.
- Assay is (b) (4) basis.
- Organic impurities method, specifications and limits.
- Removed (b) (4) since it is not used in the API manufacturing process.
- Yeast and Mold and Microbial count limits were tightened.
- Bacterial endotoxins limit.

Table 1. Drug substance specifications

Test	Acceptance Criteria	Test Method <sup>1</sup>
Appearance	Yellow to orange powder	Visual Examination
Identification		(b) (4)
B. HPLC Retention Time	<p>B. The chromatogram of the <i>Sample Preparation</i> exhibits a major peak for Tigecycline, the retention time of which corresponds to that exhibited in the chromatogram of the <i>Standard Preparation</i> at 248 nm wavelength and meets the criteria:</p> <p>(b) (4)</p> <p>Where:</p> <p><math>RT_U</math> is the retention time of the Tigecycline peak in the <i>Sample Preparation</i></p> <p><math>RT_S</math> is the retention time of the Tigecycline peak in the <i>Standard Preparation</i></p>	B. (b) (4)
		(b) (4)
Heavy Metals	NMT (b) (4) %	(b) (4)



**Drug Product**

Excipients of FK USA’s Tigecycline for Injection differ from those of the Listed Drug, Tygacil®. The following table presents the list of excipients or inactive ingredients contained in Fresenius Kabi USA, LLC’s (FK USA’s) Tigecycline for Injection, comparison to LD’s excipient, and their respective functions.

**Table 3.2.P.2 - 1 Excipient Comparison between Reference Listed Drug (Tygacil®) and FK USA Tigecycline for Injection**

Component	mg per vial		Functionality
	Tygacil®	FK USA Tigecycline for Injection	
Lactose Monohydrate	100	-	(b) (4)
Arginine	-	82.6	(b) (4)
Hydrochloric acid	As needed	As needed	pH adjuster
Sodium hydroxide	As needed	As needed	pH adjuster

Drug product specifications

The drug product specifications (Table 4) were updated in this amendment (SD-19) to meet the current USP monograph on Tigecycline for Injection.

The revisions include the following:

- The methods for identification, assay and impurities have been updated to be compliant to the USP monograph.
- The impurity specifications have been updated to be compliant to the USP monograph (new impurities added, acceptance criteria tightened to comply with USP monograph).

Table 4. Drug product specifications

Test	Acceptance Criteria	Test Method <sup>1</sup>
Description	Orange lyophilized cake in a (b) (4) glass vial	Visual Examination
Constituted Solution		
1. Completeness	1. The solid dissolves completely, leaving no visible residue as undissolved matter.	USP <1>
2. Clarity	2. The resultant solution is not significantly less clear than an equal volume of Water for Injection, USP (WFI) contained in a similar vessel and examined similarly.	10-08-05-6005
3. Particulate Matter	3. The resultant solution is essentially free from particles of foreign matter that can be observed on visual inspection.	Reconstitute with 5.3 mL of 0.9% Sodium Chloride Injection, USP
4. Visual Color	4. Yellow to orange	
Reconstitution Time	NMT (b) (4) minutes	10-08-05-6005  Reconstitute with 5.3 mL of 0.9% Sodium Chloride Injection, USP
pH	4.5 – 5.5	USP <791>  10-08-05-6001  Reconstitute with 5.3 mL of 0.9% Sodium Chloride Injection, USP
(b) (4)		
		Approximate sample size: 50 mg
Uniformity of Dosage Units	Meets Requirements	USP <905>  10-08-03-0001
Identification		
HPLC	<p>The Retention Time (RT) of the Tigecycline peak in the chromatogram of the <i>Finished Product Sample Preparation</i> corresponds to that of the <i>Tigecycline Reference Standard Preparation</i> at 248 nm and meets the following:</p> <p style="text-align: center;">(b) (4)</p> <p>Where,</p> <p>R<sub>s</sub>: RT Standard</p> <p>R<sub>u</sub>: RT Sample</p>	(b) (4)
UV	The extracted UV spectra collected on a photodiode array detector between 210 nm and 350 nm at the	10-08-03-6937

Test	Acceptance Criteria	Test Method <sup>1</sup>
	apex of the <i>Tigecycline</i> peak in the <i>Standard Preparation</i> and the <i>Finish Product Sample Preparation</i> exhibit maxima at the same wavelengths ( $\pm 2$ nm).	
Assay (% Label Claim)	(b) (4) %	(b) (4)
Impurities		
<i>Tigecycline open ring</i>	NMT (b) (4) %	(b) (4)
<i>Tigecycline 12-oxo-11-hydroxy</i>	NMT (b) (4) %	
<i>Tigecycline related compound B</i>	NMT (b) (4) %	
<i>Tigecycline epimer</i>	NMT (b) (4) %	
<i>Tigecycline quinone analog</i>	NMT (b) (4) %	
<i>Tigecycline tricyclic analog</i>	NMT (b) (4) %	
Any individual unspecified degradation product	NMT (b) (4) %	
Total Impurities	NMT (b) (4) %	
Container/Closure Integrity <sup>2</sup>	The differential pressure of all sample vials being tested for each lot must be below the two bracketing Self Tests	10-08-00-6031 10-08-00-6032
Particulate Matter	For the particles $\geq$ (b) (4) $\mu$ m, NMT (b) (4) per container For the particles $\geq$ (b) (4) $\mu$ m, NMT (b) (4) per container	USP <788> 10-08-03-6720 03-10-02-0002 Reconstitute with 5.3 mL of 0.9% Sodium Chloride Injection, USP
Sterility	Sterile	USP <71> 03-10-07-0001
Bacterial Endotoxins	NMT 1.75 EU/mg	USP <85> 03-10-08-0002 03-10-08-0005
(b) (4)		

<sup>1</sup> References 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.

<sup>2</sup> CCIT is not a release test. CCIT testing will be performed only on stability in lieu of sterility.

The analytical procedures for assay and organic impurities for the drug product were revised:

- Verification of the USP HPLC Method for Organic Impurities for Tigecycline, USP and Tigecycline for Injection, USP
- Verification of the USP HPLC Method for Assay for Tigecycline, USP and Tigecycline for Injection, USP Final Report

Refer to the drug substance section for details.

**Reviewer's assessment:**

Adequate

The revised drug product specifications comply with all required testing and acceptance criteria in the current USP monograph on Tigecycline for Injection.

**Labeling**

Package insert

Reference to USP added to the established name

The following IR was sent to the applicant on 10/18/2016:

We note that (b) (4) was not tested in the compatibility study submitted previously (supporting document number 13, eCTD Sequence Number 0011, submit date 05/29/2015). As a result, as presented in the package insert in the tentative approval letter dated 25 Nov 2015, (b) (4) was removed from the list of compatible drugs but note it has been included again in the recent resubmission. Since you have not demonstrated compatibility of the proposed drug product with (b) (4) remove (b) (4) from the list of compatible drugs.

Company Response (received as SD23, eCTD 0021, 10/25/2016) agreed with this assessment and has removed (b) (4) from the list of compatible drugs listed in the package insert.

**Reviewer's assessment: Acceptable**

Container closure labeling

Reference to USP added to the established name

Editorial changes

Balajee  
Shanmugam -S



Digitally signed by Balajee Shanmugam S  
DN: c=US, o=U S Government, ou=HHS  
ou=FDA, ou=People  
0.9.2342.192003001.1.1=1300217143  
cn=Balajee Shanmugam S  
Date: 2016.12.01 09:51:55 -05'00'

Signed for Dr. Yushi Feng



Balajee  
Shanmugam

Digitally signed by Balajee Shanmugam  
Date: 12/01/2016 09:55:18AM  
GUID: 50758d500003c1b1962e036ea11002c

## NDA 205645

Product Name: Tigecycline for Injection, 50 mg/vial in 10 mL vial

Product Quality Assessment (Addendum #1 to Review dated 11/08/2016)

From: Yushi Feng, Drug Product CMC Reviewer, Branch 3, ONDPI

Date: Nov-22-2016

Re: Facilities status for NDA 205645

-----  
This addendum is to document the facilities status for this NDA:

All facilities are acceptable for NDA 205645 (resubmission 19). An acceptable Overall Manufacturing Inspection Recommendation has been entered in Panorama on 9/21/2016:

NDA/BIA > NDA 205645

**NDA-205645-ORIG-1-RESUB-19** Request More Access | Project Actions

Project Owner

Status: **Current** Condition: **At Risk** Planned Completion: **Feb 16, 2017** Percent Complete: **7.7%**

Project Summary | Project Details | Application Life Cycle | Application History | **Inspection View** | Tasks | Submission Facility Status View

As of Nov 16, 2016 3:17 pm GMT

**Inspection View** Export Details Summary

Task Number	Task Name	Comments	Assignments	Pln Comp	Act Comp	Task Status	Actions	Additional Information
7	Application specific inspection criteria	If you are finished with the task, change the Task Status to Complete.	PI - filing PM/Coordinator	6/5/16		New	Go to Form	
9	Overall Manufacturing Inspection Recommendation	NDA 205645-ORIG-1-RESUB-13 was tentatively approved on 11/25/2015. Facilities were evaluated as part of that submission and OMR for approval was recommended.  NDA 205645-ORIG-1-RESUB-19 was submitted to request final approval. There have been no changes to the facilities (based upon review and comparison of submitted 356i form for 05/29/2015 and 09/16/2016) and there are no alerts. Manufacturing facilities include: (b) (4) and Presonus Kabi USA, LLC (FEI 3001833549). Testing facilities include: Presonus Kabi USA, LLC (FEI 3008604776), Presonus Kabi USA, LLC (FEI 1000115163), DUBS 284336252, 61 3045 North Comet Ave., Malvern Park, IL, (b) (4)	Frank Wackes	2/16/17	9/21/16	Complete	Go to Form	Recommendation: Approve

Showing all 2 tasks

OPQ's Review dated 11/08/2016 recommended Approval and this Addendum upholds the **Approval** recommendation from overall Product Quality perspective. Please refer to the previous review for all other details.

Yushi Feng, Ph.D.  
Drug Product CMC Reviewer



Balajee  
Shanmugam

Digitally signed by Balajee Shanmugam  
Date: 11/22/2016 02 01:16PM  
GUID: 50758d500003c1b1962e036ea11002c



Yushi  
Feng

Digitally signed by Yushi Feng  
Date: 11/22/2016 02 00:17PM  
GUID: 55916712002d8bbbf81fd3d0ab963187

**CMC Review  
NDA 205645 (Resubmission)**

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

**Review date:** 11/19/2015

**Submission:** NDA 205645 Resubmission Class 2, Supp. Document Number: 13, eCTD Sequence Number 0011

**Submission date:** 05/29/2015

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

**Product Name:** Tigecycline For Injection, 50 mg/vial

**Applicant:** FRESENIUS KABI USA LLC

**Background:**

The CMC review dated 29 May 2014 stated that "from the CMC perspective, this NDA is not recommended for approval until all pending issues are resolved." A Complete Response (CR) letter, which was issued on 30 May 2014 listed several product quality deficiencies including deficiencies related to the drug product manufacturing facility, Fresenius Kabi USA, LLC, Grand Island, NY. This review covers the responses to the CR product quality deficiencies provided by the Applicant in the NDA resubmission dated 29 May 2015.

**Recommendation:**

The responses to the Product Quality deficiencies provided by the Applicant in this resubmission have been found to be adequate. The (b) (4) impurity was not found to be mutagenic. The acceptable data were provided to demonstrate compatibility of the proposed drug product with several other drugs listed in the package insert except for haloperidol. In addition, data were not provided to support compatibility of the proposed drug product with (b) (4) therefore, these two drugs will not be included in the list of compatible drugs in Section 2.4 of the proposed package insert. Adequate extractable/leachable information was provided for the proposed drug product container closure, (b) (4) rubber stopper. Also, several labeling revisions have been made in 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.

## Executive Summary

- Facilities inspection – Resolved
  - All facilities are acceptable for NDA 205645 (resubmission), with an acceptable Overall Manufacturing Inspection Recommendation in Panorama, per Christina Capacci-Daniel of OPF.
- (b) (4) impurity mutagenicity – Resolved
  - Pharm/Tox reviewer reviewed the applicant's response in the resubmission. (b) (4) has not been found mutagenic. For details, refer to the Pharm/Tox review dated 16 Nov 2015 in DARRTS.
- Compatibility study – Resolved
  - In addition to removing (b) (4) from the list of compatible drugs in Section 2.4 of the proposed package insert, (b) (4).
  - (b) (4) should be deleted from the list of compatible drugs in Section 2.4 of the proposed package insert until test results are submitted to confirm its compatibility.
- Extractable & leachable studies – Resolved
  - The metal extractable study assessment on Permitted Daily Exposures for Elemental Impurities followed a previous version of the ICH Q3D guideline (Step 2), not the current version Step 4. The Pharm/Tox reviewer has been consulted on this issue and concluded that since this application was submitted in May 2015, while ICH Q3D Step 4 was finalized in September 2015, the PDE values listed are in compliance. For details, refer to the Pharm/Tox review dated 16 Nov 2015.
  - The extractable compounds study Report I&D15-CLR-A-002 is adequate.
  - The leachable study (REPORT# I&D15-CLR-A-001) observed one volatile peak, (b) (4) above the reporting threshold. The Applicant claimed that since it was not detected in the extractable study it is not likely to originate as a leachable from the container closure system. The Pharm/Tox reviewer concurred that the applicant's conclusion is acceptable.
  - The method qualification spike/recovery study (Report I&D15-CLR-A-010) is adequate.
- Labeling – Resolved
  - All deficiencies/recommendations cited in the CR letter have been addressed and/or adopted.
  - Recommended revisions to the CMC sections of the proposed package insert and the rationales are documented here.

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

5. Labeling

**From the CR letter dated 30 May 2014:**

*We reserve comment on the proposed package insert labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.*

*Please submit draft carton and container labeling revised as follows.*

**A. Vial Labels**

- 1. The Principal Display Panel (PDP) contains the I.V. abbreviation, which is listed on Institute for Safe Medication Practices' (ISMP) list of error-prone abbreviations. Replace the I.V. abbreviation with the word "Intravenous" for clarity.*
- 2. For consistency with the insert labeling, revise the statement [REDACTED] (b) (4) to "Single Dose Vial" and relocate it to appear directly under the "For Intravenous Infusion Only" statement for increased prominence.*
- 3. To improve prominence of important use information, relocate the statement "Discard Unused Portion" from the side panel to under the "Single Dose Vial" statement.*
- 4. The Statement "Not Made with Natural Rubber Latex" should be removed from the side panel.*
- 5. To improve readability, revise the letter case of the established name "TIGECYCLINE FOR INJECTION" from all capitals to title case to read "Tigecycline for Injection."*

**B. Carton Labeling**

- 1. See A2, A3 and A5 above*
- 2. To improve readability revise the letter case of the statement [REDACTED] (b) (4) [REDACTED] (b) (4) from all capitals to title case to read: [REDACTED] (b) (4)*
- 3. Currently, the Usual Dosage statement, [REDACTED] (b) (4) [REDACTED] provides one of the recommended dosage regimens. To help ensure correct dosing revise the Usual Dosage statement to read "Dosage and Administration: See package insert".*

*Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.*

*To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations that support any proposed changes.*

**Review of the current resubmission:**

A. Vial Label

All deficiencies/recommendations cited in the Complete Response letter on 30 May 2014 have been addressed/adopted in the proposed label:

1. Replace the I.V. abbreviation with the word "Intravenous" for clarity.
2. Revise the statement (b) (4) to "Single Dose Vial" and relocate it to appear directly under the "For Intravenous Infusion Only".
3. Relocate the statement "Discard Unused Portion" from the side panel to under the "Single Dose Vial" statement.
4. The Statement "Not Made with Natural Rubber Latex" should be removed from the side panel.
5. Revise the letter case of the established name "TIGECYCLINE FOR INJECTION" from all capitals to title case to read "Tigecycline for Injection".

In addition, responses to the following comments are also adopted into the label.

**Comments from the CMC review dated 25 Apr 2014:**

Please add the following information to the immediate container label:

- a. Storage conditions
- b. A statement of being sterile

Per the draft guidance *Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex*: The preferred statements on claims regarding Natural Rubber Latex in product container are: "Not made with natural rubber latex" or "The <vial stopper> is not made with natural rubber latex". Therefore, inclusion of the texts "not made with natural rubber latex" in the container label is acceptable.

B. Carton Label

All deficiencies/recommendations cited in the CR letter on 30 May 2014 have been addressed/adopted in the proposed label:

1. See A2, A3 and A5 below
  2. Revise the statement (b) (4) to "Single Dose Vial" and relocate it to appear directly under the "For Intravenous Infusion Only".
  3. Relocate the statement "Discard Unused Portion" from the side panel to under the "Single Dose Vial" statement.
  5. Revise the letter case of the established name "TIGECYCLINE FOR INJECTION" from all capitals to title case to read "Tigecycline for Injection".
2. Changed (b) (4) to: (b) (4)
3. Changed the Usual Dosage statement: (b) (4) to "Dosage and Administration: See package insert".

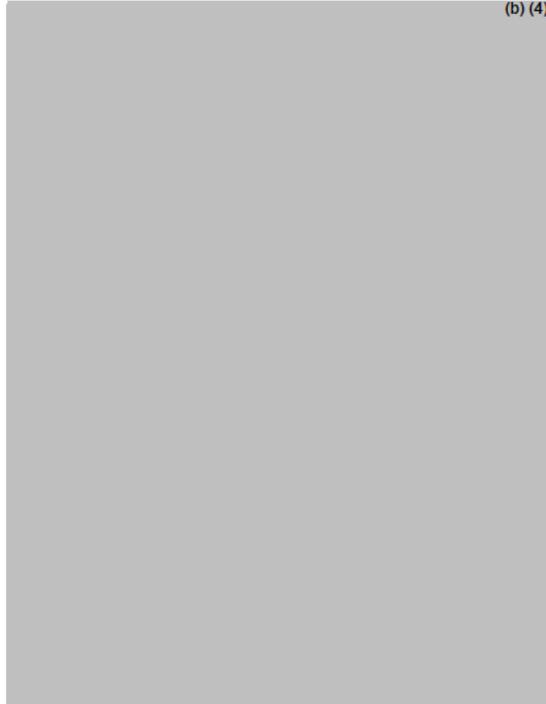
NDA 205645

Some minor formatting changes are also proposed as highlighted in the following comparison figure:

**NDA 205645** **Response to Complete**  
**Tigecycline for Injection** **Response Letter dated 5-30-14**

**Product Code 961110**

**Current Tray Label**



- Revised text per Complete Response Letter dated 5-30-14.
- Revised container closure statement

**Reviewer's Evaluation:**

Acceptable.

C. Package Insert

Following are the recommended revisions to the CMC sections of the proposed package insert and the rationales:

**2.5 Drug Compatibilities**

Compatible intravenous solutions include 0.9% Sodium Chloride Injection, USP, 5% Dextrose Injection, USP, and Lactated Ringer's Injection, USP. When administered through a Y-site, tigecycline for injection is compatible with the following drugs or diluents when used with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP: amikacin, dobutamine, dopamine HCl, gentamicin, Lactated Ringer's, lidocaine HCl, metoclopramide, morphine, norepinephrine, (b) (4), potassium chloride, propofol, ranitidine HCl, theophylline, and tobramycin.

(b) (4) *should be deleted from the compatible drugs list.*

**Rationale:** Due to its unavailability, this drug was not tested in the compatibility study the applicant submitted in the resubmission.

The same compatibility study found that haloperidol is not compatible with this drug product. (b) (4)

**2.6 Drug Incompatibilities**

The following drugs should not be administered simultaneously through the same Y-site as tigecycline for injection: amphotericin B, amphotericin B lipid complex, diazepam, esomeprazole, haloperidol, and omeprazole.

*Haloperidol should be added into the incompatible drugs list.*

**Rationale:** The compatibility study submitted in the resubmission found that haloperidol is not compatible with this drug product.

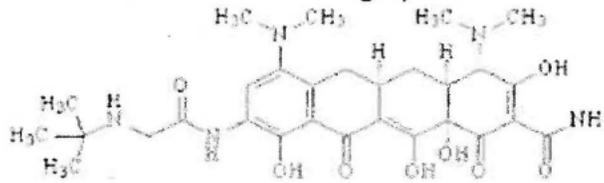
**11 DESCRIPTION**

Tigecycline for Injection is a (b) (4), tetracycline class antibacterial for intravenous infusion. The chemical name of tigecycline is (4S,4aS,5aR,12aS)-9-[2-(tert-butylamino)acetamido]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide.

(b) (4) *to be changed to tetracycline class antibacterial.*

**Rationale:** To maintain consistent with the established pharmacologic class in the Highlights section.

The following represents the chemical structure of tigecycline:



$C_{29}H_{39}N_5O_8$  M.W. 585.65

Figure 1. Chemical structure of tigecycline

Tigecycline for injection is an orange lyophilized powder or cake. Each tigecycline single-dose 10 mL vial contains 50 mg tigecycline and 82.6 mg of arginine as lyophilized powder for reconstitution for intravenous infusion and 82.6 mg of arginine. The pH is adjusted with hydrochloric acid, and if necessary sodium hydroxide. The product does not contain preservatives.

*Revision for better specificity and clarity.*

**Rationale:** During the manufacturing process, [REDACTED] (b) (4)

If the sentence [REDACTED] (b) (4)

[REDACTED] were to move to before [REDACTED] (b) (4)

[REDACTED] The words "reconstitution for intravenous infusion" removes this potential confusion.

Signature block

Yushi Feng

CMC Reviewer

Yushi  
Feng -S

Digitally signed by Yushi Feng -S  
DN: c=US, o=U.S. Government,  
ou=HHS, ou=FDA, ou=People,  
cn=Yushi Feng -S,  
0.9.2342.19200300.100.1.1=20017  
26281  
Date: 2015.11.19 17:22:39 -05'00'

11/19/2015

Date

Dorota Matecka

CMC Lead

11/19/2015

Date

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: 2015.11.19 17:26:16 -05'00'

MEMORANDUM



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

**DATE:** October 15, 2015  
**TO:** File – NDA 205645  
**FROM:** Vinayak B. Pawar, Ph.D., Senior Microbiology Reviewer, CDER/OPQ/DMA  
**THROUGH:** John W, Metcalfe, Ph.D., Senior Microbiology Reviewer, CDER/OPQ/DMA  
**SUBJECT:** Amended NDA 205645, May 29, 2015 received in response to CR issued on May 30, 2014.  
**Product:** Tigecycline for Injection, 50 mg/vial.  
**Sponsor:** Fresenius Kabi

---

**Reviewer's Conclusion:** NDA 205645 is recommended for approval from microbiology product quality standpoint.

**Review Summary:** Reference is made to the New Drug Application (NDA) dated July 31, 2013, received August 1, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Tigecycline for Injection, 50 mg/vial. It was determined at the completion of review of this application could not be approved due to Product Quality & Labeling issues and a CR was issued on May 30, 2014.

The outstanding issues to be addressed were listed in the CR and consisted of deficiencies resulting from field inspection of the Fresenius Kabi USA facility; lack of evaluation of mutagenic potential of (b) (4) impurity, statement of compatibility to other drugs, extractables and leachables from the rubber stopper and labeling issues unrelated to microbiology product quality.

The amended "Quality Information Amendment" was reviewed for updated microbiology product quality information and it is determined that the sterilization process validation information has not been updated since the original submission. Therefore, the application remains approved from microbiology product quality standpoint based on the information provided in the original submission.

**END**

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

/s/  
-----

VINAYAK B PAWAR  
10/16/2015

JOHN W METCALFE  
10/16/2015  
I concur.

# **NDA 205-645**

**Tigecycline for Injection, 50 mg**

**Fresenius Kabi USA, LLC**

**Maotang Zhou, Ph.D.**

**Review Chemist**

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

**CMC REVIEW OF NDA 205-645  
For the Division of Anti-Infective Products (DAIP)**

# Table of Contents

<b>Table of Contents .....</b>	<b>2</b>
<b>CMC Review Data Sheet .....</b>	<b>3</b>
<b>The Executive Summary .....</b>	<b>7</b>
I. Recommendations .....	7
A. Recommendation and Conclusion on Approvability .....	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable .....	7
II. Summary of CMC Assessments .....	7
A. Description of the Drug Product and Drug Substance .....	7
B. Description of How the Drug Product is Intended to be Used .....	9
C. Basis for Approvability or Not-Approval Recommendation .....	9
III. Administrative .....	10
<b>CMC Assessment.....</b>	<b>11</b>
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data .....	11
A.1 Facilities and Equipment (biotech only) .....	12
A.2 Adventitious Agents Safety Evaluation .....	12
A.3 Novel Excipients .....	12
R. REGIONAL INFORMATION .....	12
R1 Executed Batch Records .....	12
R2 Comparability Protocols .....	12
R3 Methods Validation Package .....	12
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 .....	12
A. Labeling & Package Insert .....	12
B. Environmental Assessment Or Claim Of Categorical Exclusion .....	12
C. Establishment Evaluation Report .....	13

CMC Review Data Sheet

# CMC Review Data Sheet

1. NDA 205-645
2. REVIEW #: 1, Addendum #1
3. REVIEW DATE: 29-May-2014
4. REVIEWER: Maotang Zhou, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original IND	N/A
Original IND	N/A
End-of-phase-2 meeting (No CMC issues discussed)	N/A
Pre-NDA meeting	N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date	Stamp Date
Original NDA Submission	0000	7/31/2013	8/1/2013
Resubmission/After Refusal to File			
Quality Amendment (Response to Agency Questions)	0001	8/16/2013	8/20/2013
Labeling/Package Insert Draft	0002	11/8/2013	11/8/2013
Quality Amendment (Response to Agency Questions)	0005	1/16/2014	1/16/2014
Quality Amendment (Response to Information Request)	0006	2/27/2014	2/27/2014
Quality Amendment (Response to Information Request)	0007	4/4/2014	4/4/2014
Quality Amendment (Response to Information Request)	0008	4/4/2014	4/4/2014
Quality Amendment (Response to Information Request)	0009	4/17/2014	4/17/2014
Quality Amendment (Response to Information Request)			

## CMC Review Data Sheet

## 7. NAME &amp; ADDRESS OF APPLICANT:

Name: Fresenius Kabi USA, LLC  
Address: Three Corporate Drive  
Lake Zurich, IL 60047  
Representative: Anne Huffman, Sr. Director of QA/QC  
Telephone: 716-773-3715

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

- a) Proprietary Name: Tygacil®
- b) Non-Proprietary Name: Tigecycline
- c) Code Name/# (ONDQA only): D-18506
- d) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: 5
  - Submission Priority: Standard

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

## 10. PHARMACOL. CATEGORY:

11. DOSAGE FORM: Powder for Injection

12. STRENGTH/POTENCY: 50 mg

13. ROUTE OF ADMINISTRATION: Intravenous infusion

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

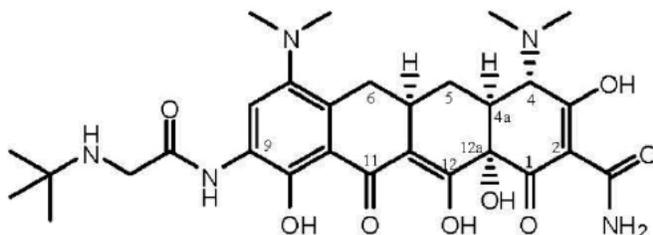
SPOTS product – Form Completed

Not a SPOTS product

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

CMC Review Data Sheet

Tigecycline: (4S, 4aS, 5aR, 12aS)-9-[2-(tert-butylamino)acetamido]-4,7-bis(dimethylamino)-1,4,4a,5,5a, 6,11,12a -octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide



C<sub>29</sub>H<sub>39</sub>N<sub>5</sub>O<sub>8</sub>  
MW = 585.65

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)	Tigecycline	1	2	M Zhou	
	III	(b) (4)	(b) (4)	4			
	III	(b) (4)	(b) (4)	4			
	III	(b) (4)	(b) (4)	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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	N/A	N/A
NDA	N/A	N/A

## CMC Review Data Sheet

## 18. STATUS:

## ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Withhold	5/28/2014	S Hertz
Pharm/Tox	Approval	9/26/2013	W Schmidt
Biopharm	Approval	3/12/2014	E Chikhale
LNC	N/A		
Methods Validation	Not required		
DMEPA*	Review in DARRTS	3/20/2014	A Winiarski
EA	Categorical exclusion (see review)	4/22/2014	M Zhou
Microbiology	Approval	1/27/2014	V Pawar

\*DMEPA: Division of Medication Error Prevention and Analysis

## Executive Summary Section

# The CMC Review for NDA 205-645

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This NDA has not provided sufficient information to assure identity, strength, purity, and quality of the drug product. The Office of Compliance has made an overall “Withhold” site recommendation for this NDA. Therefore, from the CMC perspective, this NDA is not recommended for approval until all pending issues are resolved.

#### 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 and Drug Substance

Tigecycline is approved for the treatment of complicated skin and skin structure infections, complicated intra-abdominal infections, and community-acquired bacterial pneumonia by intravenous administration and is marketed in the US as Tygacil® (approved in 2005 via NDA 21821 for Wyeth Pharmaceuticals, Inc.). There are currently no alternative tigecycline formulations approved for use in humans in the US. Tygacil® is an orange lyophilized powder or cake. Each Tygacil® vial contains 50 mg tigecycline lyophilized powder for reconstitution for intravenous infusion and 100 mg of lactose monohydrate. The pH is adjusted with hydrochloric acid, and if necessary sodium hydroxide. The product does not contain preservatives.

The current 505(b)(2) NDA provides for a new IV formulation of tigecycline that is intended to be therapeutically equivalent to and to be used for the treatment of the same infections as listed in the labeling of the reference listed drug (LISTED DRUG), Tygacil®. The proposed drug product contains 50 mg tigecycline lyophilized cake for reconstitution for intravenous infusion and 82.6 mg of arginine. The pH is adjusted with hydrochloric acid, and if necessary, with sodium hydroxide.

#### (1) Drug Substance

For the majority of the CMC information for tigecycline drug substance, the reference is made to DMF Type II (b)(4) held by (b)(4). Some general information (Section 3.2.S.1), a specification, information on impurities including residual solvents, batch analysis for the tigecycline drug substance have been also included in the NDA.

## Executive Summary Section

**(2) Drug Product**

The proposed drug product is a new formulation of tigecycline IV solution which contains 50 mg tigecycline lyophilized cake for reconstitution for intravenous infusion and 82.6 mg of arginine. Therefore, the proposed drug product differs from the LISTED DRUG in the inactive ingredients, i.e., it contains a different (b) (4). The applicant stated that the proposed formulation of Tigecycline for Injection was developed to have the same drug content with an overage of 6% as stated in the LISTED DRUG labeling.

Pharmaceutical Development section (3.2.P.2) describes the drug product formulation and process development issues. The Quality Target Product Profile (QTPP) and Critical Quality Attributes (CQAs) are discussed in this section. In addition, a risk assessment has been conducted on the CQAs of the drug product (DP) to form a basis for product development studies in order to mitigate the risk through design and control of formulation as well as process.

A description of the manufacturing process that includes (b) (4) has been provided in section 3.2.P.3.3. The batch analysis data have been provided for three exhibit batches of the drug product (Product Code 961110) manufactured at the proposed commercial manufacturing facility in FK USA Grand Island, NY. These batches (R341-041, R342-025, and R342-026) are (b) (4) L size each, whereas the proposed commercial batch size is (b) (4) L (the proposed drug product has strength of 50 mg/vial and is filled in a 10 mL vial). The master batch record (product code 961110) has been included in section P.3.3. The exhibit and proposed commercial batches process comparison has also been provided. The proposed sterilization process, including validation and other microbiological quality aspects of the proposed drug substance and drug product, has been evaluated and found adequate by Dr. Vinayak Pawar who is the product quality microbiology reviewer of this NDA.

Drug product specification includes description, reconstitution time, pH, (b) (4), uniformity of dosage units, identification, assay, impurities, container closure integrity, particulate matter, sterility, bacterial endotoxins, and statement of compliance (b) (4). In addition, several attributes are included for the reconstituted solution (completeness, clarity, visual color, and particle matter). The justification of specification including statistical evaluation of results observed on stability are provided in the NDA to justify the proposed acceptance criteria including limits for impurities. As revised, the acceptance criteria are found adequate except for one specified impurity (b) (4). The structure of (b) (4) constitutes a structural alert for potential mutagenicity. In response to a deficiency letter issued by the FDA on 3/21/2014, the applicant is conducting an Ames test on this particular impurity. Therefore, the adequacy of the overall control strategy for (b) (4) will be dependent on the pending Ames test results.

Information on the proposed commercial container closure system has been provided in Section 3.2.P.7. This includes a description of the proposed container closure, results of container/closure system testing (USP <660>, <381>, etc.), specifications and test results of the individual components, and information of the component suppliers. The container closure integrity issues are discussed in section 3.2.P.2 (Pharmaceutical Development section).

## Executive Summary Section

Stability information submitted in section 3.2.P.8.3 include six-month accelerated ( $40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \pm 5\% \text{RH}$ ) twelve-month long term room temperature ( $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \pm 5\% \text{RH}$ ) data for three exhibit batches (R341-041, R342-025, and R342-026) of the drug product manufactured at the proposed manufacturing facility. Based on these data, an expiration dating period of 24 months has been requested for the commercial drug product when stored at controlled room temperature ( $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \pm 5\% \text{RH}$ ) in the proposed commercial container closure system.

In addition, the results of compatibility studies of the proposed drug product with the proposed reconstitution agents: 0.9% Sodium Chloride Injection, USP, 5% Dextrose Injection, USP, and Lactated Ringer's Injection, USP have also been provided in the Pharmaceutical Development section. That includes stability data for these solutions stored over a period of 24 hours at  $25^{\circ}\text{C}$ . Since the reconstituted drug product solution will be in contact with the container/closure system including the rubber stopper for up to 6 hours, the applicant is recommended to conduct a one-time extractable/leachable studies to demonstrate the compatibility of the proposed stopper with the proposed drug product. An information request was forwarded to the applicant; however, this information has not been yet submitted.

Prior to administration, Tigecycline for Injection should be reconstituted and diluted with 0.9% Sodium Chloride Injection, USP, 5% Dextrose Injection, USP, or Lactated Ringer's Injection, USP. The detailed preparation instructions of the reconstituted solution are provided in the package insert. The package insert also allows for co-administration (via a Y-site) of tigecycline with a number of other drugs. However, no compatibility data were submitted in the NDA to support this statement. An information request was forwarded to the applicant; however, this information has not been yet submitted.

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

Tigecycline for injection is a tetracycline-class antibacterial drug indicated in patients 18 years of age and older for complicated skin and skin structure infections, complicated intra-abdominal infections, and community-acquired bacterial pneumonia. The tigecycline concentration, route of administration, dose, and dosing regimen for the proposed drug product are identical to those of the listed drug, Tygacil<sup>®</sup> (NDA 021821). The proposed drug product is intended to be administered intravenously over a period of 30 to 60 minutes as an initial loading dose of 100 mg followed by 50 mg every 12 hours.

Prior to administration, Tigecycline for injection should be reconstituted and diluted with 0.9% Sodium Chloride Injection, USP, 5% Dextrose Injection, USP, or Lactated Ringer's Injection, USP. The maximum concentration of the reconstituted solution in the intravenous bag should be 1 mg/mL. The detailed preparation instruction of the reconstituted solution is provided in the package insert.

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

This NDA has not provided sufficient information on raw material controls, manufacturing processes and process controls, adequate specifications, and stability data for assuring consistent product quality of the drug substance and drug product. This NDA is not recommended for approval from a CMC perspective due to the following unresolved issues.

## Executive Summary Section

- The CGMP status of the drug product manufacturing facilities is not acceptable.
- The mutagenicity potential of (b) (4) impurity needs to be addressed.
- Compatibility with several drugs to be co-administered with tigecycline was not demonstrated.
- Extractable/leachable profile was not established for the rubber stopper.

**The following deficiencies should be included in the Complete Response Letter:**

1. *The facility used for the manufacture of the drug product is inadequate.*
2. *The (b) (4) impurity contains a structural alert for mutagenicity. Evaluate the mutagenic potential of (b) (4). If (b) (4) is confirmed to be mutagenic, provide an appropriate control strategy for (b) (4).*
3. *In Section 2.4 of the proposed package insert, the drug product is stated to be compatible with several other drugs. To support this statement, for each drug listed, provide physical and chemical compatibility data with your drug product. This should include tests for appearance, description (color, visible particulates, turbidity), sub-visible particulates (i.e., USP <788> compliance), and assay, at a minimum data.*

*In addition, the following outstanding issue should also be addressed in the NDA resubmission:*

1. *Provide results of the extractable and leachable studies for the proposed (b) (4) rubber stopper using suitable solvents and the reconstituted solutions of the proposed drug product, tigecycline for injection, with the proposed reconstitution diluents.*

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

*(See appended electronic signature page)*

Maotang Zhou, Ph.D., Reviewer, ONDQA

**B. Endorsement Block:**

*(See appended electronic signature page)*

Dorota Matecka, Ph.D., CMC Lead, Branch V, Division of New Drug Quality Assessment II, ONDQA

Rapti Madurawe, Ph.D., Branch Chief, Branch V, Division of New Drug Quality Assessment II, ONDQA

**C. CC Block:** entered electronically in DARRTS

## CMC Assessment Section

**CMC Assessment****I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2:  
Body Of Data**

See CMC Review #1.

## CMC Assessment Section

**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**

Executed batch records for three exhibit lots (#R342-025, #R341-041, and R342-026) are provided.

**R2 Comparability Protocols**

N/A

**R3 Methods Validation Package**

Provided references to various sections of the NDA.

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

See CMC Review #1.

**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(b). The basis of this exclusion is the fact that the estimated concentration of the active ingredient at the point of entry into the aquatic environment will be less than 1 ppb from all products using this material as the active ingredient.

**Evaluation:** *Acceptable.*



CMC Assessment Section

C. Establishment Evaluation Report

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: NDA 205645/000 Sponsor: FRESENIUS KABI USA
Org. Code: 520 3 CORPORATE DR
Priority: 5N LAKE ZURICH, IL 60047
Stamp Date: 01-AUG-2013 Brand Name: TIGECYCLINE FOR INJECTION, 50 MG/VIAL
PDUFA Date: 01-JUN-2014 Estab. Name:
Action Goal: Generic Name: TIGECYCLINE FOR INJECTION, 50 MG/VIAL
District Goal: 02-APR-2014 Product Number; Dosage Form; Ingredient; Strengths
001; POWDER, FOR INJECTION SOLUTION, LYOPHILIZED; TIGECYCLINE; 50MG

FDA Contacts: M. ZHOU Prod Qual Reviewer 3017962163
V. PAWAR Micro Reviewer (HFD-305) 3017961587
N. BHANDARI Product Quality PM 2404023815
C. DEBELLAS Regulatory Project Mgr (HFD-520) 3017961203
R. MADURAWA Team Leader 3017961408

Overall Recommendation: WITHHOLD on 28-MAY-2014 by S. HERTZ (HFD-320) 3017963203
PENDING on 22-APR-2014 by EES\_PROD
PENDING on 18-APR-2014 by EES\_PROD

Establishment: (b) (4)
DMF No:
AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER
Profile: NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 19-AUG-2013
Decision: ACCEPTABLE
Reason: BASED ON PROFILE



CMC Assessment Section

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

**Establishment:** CFN: 1321116 FEI: 3001833549  
FRESENIUS KABI USA, LLC

**DMF No:** GRAND ISLAND, , UNITED STATES 140722028 **ADA:**

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

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

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 28-MAY-2014

**Decision:** WITHHOLD

**Reason:** DISTRICT RECOMMENDATION

---

**Establishment:** CFN: 1421790 FEI: 1000115163  
FRESENIUS KABI USA, LLC

**DMF No:** MELROSE PARK, , UNITED STATES 601601002 **ADA:**

**Responsibilities:** FINISHED DOSAGE RELEASE TESTER  
FINISHED DOSAGE STABILITY TESTER

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

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 08-OCT-2013

**Decision:** ACCEPTABLE

**Reason:** BASED ON PROFILE

---



CMC Assessment Section

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

Establishment: CFN: FEI: 3008604776  
FRESENIUS KABI USA, LLC

DMF No: SKOKIE, , UNITED STATES 600775318 AADA:

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

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 20-AUG-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

---

Establishment: (b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 24-APR-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

---

Establishment: (b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Profile: CONTROL TESTING LABORATORIES "ALSO"  
(DRUGS) OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 22-APR-2014

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

---

CMC Assessment Section

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

Establishment: [REDACTED] (b) (4)

DMF No: [REDACTED] AADA:

Responsibilities: [REDACTED] (b) (4)

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 22-APR-2014

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

---

Establishment: [REDACTED] (b) (4)

DMF No: [REDACTED] AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Profile: CONTROL TESTING LABORATORIES "ALSO" (DRUGS) OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 22-APR-2014

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

---

## CMC Assessment Section

## III. List Of Deficiencies communicated and to be resolved

**Deficiencies to be resolved (from the IR letters dated 4/22/2014 and 5/1/2014.)**

- Please refer to Section P.5.3 of this review. The API supplier is currently performing an Ames test on a drug product impurity, (b) (4), whose structure contains a (b) (4) which makes it a structural alert for potential mutagenicity. Once results are collected and evaluated, appropriate action will be taken to ensure a new limit for the impurity is imposed if necessary and that the method for quantitating the (b) (4) impurity can quantitate the (b) (4) peak at a possible lower level. The CMC reviewer agrees with the applicant's approach. If the results from the Ames test are positive, then both the analytical procedure and the overall control strategy for this particular impurity should be reevaluated.
- In Section 2.4 of the proposed package insert, the drug product is stated to be compatible with several other drugs. To support this statement, for each drug listed, provide physical and chemical compatibility data with your drug product. This should include tests for appearance, description (color, visible particulates, turbidity), sub-visible particulates (i.e., USP <788> compliance), and assay, at a minimum.
- Please provide results of the extractable and leachable studies for the proposed (b) (4) rubber stopper using suitable solvents and the reconstituted solutions of the proposed drug product, tigecycline for injection, with the proposed reconstitution diluents.

**Information requests communicated to the applicant:** the applicant has adequately responded all the IR (DR) questions listed here except for the one listed above concerning the (b) (4) impurity.

**IR Letter Dated 12/3/2013**

1. In reference to Section 3.2.P.4.1 of the NDA submission concerning the drug substance specification:
  - a) Please add a test with appropriate acceptance criteria (b) (4);
  - b) Please add a test with appropriate acceptance criteria for pH;
  - c) In addition to the heavy metal test by USP <231>, add a test with appropriate acceptance criteria for (b) (4) content. Please refer to USP <232>, USP <233>, and ICH Q3D for further guidance.
2. In reference to Section 3.2.P.3.3 of the NDA submission concerning the manufacturing process description:



## CMC Assessment Section

3. The information provided in Section 3.2.P.3.4 of the NDA is not adequate. Please refer to ICH M4Q(R1) and submit the necessary information accordingly. In this section, all critical process controls and their associated numeric ranges, limits, or acceptance criteria should be identified and justified and a brief description of the test provided. Any experimental data to support the justification should be included in this section as well. Critical process control values from relevant batches should be provided only as part of the justification.
4. In reference Section 3.2.P.5.1 of the NDA submission concerning the drug product specification:
- Update the acceptance criteria for Particular Matter test (b) (4)
  - Given that the API is (b) (4) we recommend a test with an appropriate acceptance criterion (b) (4) be included in the drug product specification. The acceptance criteria should be adequately justified by experimental data;
  - The drug product specification in Table 2.3.P-15 lists (b) (4) as one of the identity tests. This is not consistent with the information provided in other section of the NDA submission. Please reconcile.
  - Please tighten the (b) (4) limit from NMT (b) (4) % to NMT (b) (4) % based on available batch analysis data and stability data.
5. Your interpretation of the ICH Q6A, (b) (4) value in your equation should be the estimated “maximum increase in the degradation product at shelf life”, not the projected value as you stated. As such, some of the proposed acceptance criteria are not fully justified. Based on the available batch data and stability data, we recommend that acceptance criteria be tightened for the following attributes:
- (b) (4)
6. In reference to Section 3.2.P.5.3 concerning the method validation (PR-10-00185):
- Your acceptance criteria of %RSD (b) (4) % for precision (b) (4) are considered high. We recommend that these acceptance criteria be tightened to NMT (b) (4) % for (b) (4) precision for impurity tests.
  - In the validation report (PR-10-00185), you state that the impurity (b) (4) degraded from (b) (4) % in the test solution. Please discuss the suitability of the analytical method for this particular impurity.
  - It appears that only precision test has been revalidated after the HPLC method revision. We recommend that (b) (4) precision tests be repeated after the revision of the HPLC method.

## CMC Assessment Section

**DR Letter dated 3/21/2014**

Reference is made to your communication dated February 27, 2014 containing a response to FDA's CMC Information Request letter dated December 3, 2013. We have reviewed your response to Question 6(b) concerning the suitability of the analytical method for the (b) (4) impurity and find your response inadequate. (b) (4), it appears unlikely you are able to quantify this particular impurity accurately with the current HPLC method. Although you stated that (b) (4) is a process impurity as well as a degradation product, this impurity was not included in Table 3.2.P.5.5-1. In order to continue evaluation of the (b) (4) impurity, we request a written response to the following deficiencies on or before April 4, 2014.

1. The (b) (4) impurity contains a structural alert for mutagenicity. Evaluate the mutagenic potential of (b) (4).
2. How did you determine that (b) (4) is a degradation product? Provide supporting data.
3. Propose a possible mechanism for the formation of (b) (4) as a degradation product.
4. Develop an appropriate analytical procedure that is capable of accurately quantitating (b) (4) levels and provide representative batch analysis data for the (b) (4) impurity using this method. Note that the appropriate limit of detection and limit of quantitation for the (b) (4) analytical method would be based on the outcome of item #1 above. If (b) (4) is confirmed to be mutagenic, provide an appropriate control strategy for (b) (4).

**IR Letter dated 4/14/2014**

1. The drug substance establishments provided to-date in your NDA 205645 are inconsistent with those provided in DMF (b) (4). Amend the drug substance establishment information in the NDA with a complete and accurate list of ALL facilities involved in the manufacture and testing of the drug substance. Include all necessary information for each establishment such as contact name(s), address, phone number, fax number, and email addresses.

**IR Letter dated 5/1/2014**

1. In Section 2.4 of the proposed package insert, the drug product is stated to be compatible with several other drugs. To support this statement, for each drug listed, provide physical and chemical compatibility data with your drug product. This should include tests for appearance, description (color, visible particulates, turbidity), sub-visible particulates (i.e., USP <788> compliance), and assay, at a minimum.
2. Please provide results of the extractable and leachable studies for the proposed (b) (4) rubber stopper using suitable solvents and the reconstituted solutions of the proposed drug product, tigecycline for injection, with the proposed reconstitution diluents.

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

/s/  
-----

MAOTANG ZHOU  
05/30/2014

DOROTA M MATECKA  
05/30/2014

RAPTI D MADURawe  
05/30/2014

# **NDA 205-645**

**Tigecycline for Injection, 50 mg**

**Fresenius Kabi USA, LLC**

**Maotang Zhou, Ph.D.**

**Review Chemist**

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

**CMC REVIEW OF NDA 205-645  
For the Division of Anti-Infective Products (DAIP)**

# Table of Contents

<b>Table of Contents .....</b>	<b>2</b>
<b>CMC Review Data Sheet .....</b>	<b>4</b>
<b>The Executive Summary .....</b>	<b>8</b>
I. Recommendations .....	8
A. Recommendation and Conclusion on Approvability .....	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable .....	8
II. Summary of CMC Assessments .....	8
A. Description of the Drug Product and Drug Substance .....	8
B. Description of How the Drug Product is Intended to be Used .....	10
C. Basis for Approvability or Not-Approval Recommendation .....	10
III. Administrative .....	11
<b>CMC Assessment.....</b>	<b>12</b>
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data .....	12
S. DRUG SUBSTANCE .....	12
S.1 General Information .....	12
S.1.1 Nomenclature & Structure .....	12
S.1.2 General Properties .....	13
S.2 Manufacture .....	13
S.2.1 Manufacturers .....	13
S.2.2 Description of Manufacturing Process and Process Controls .....	15
S.2.3 Control of Materials .....	15
S.2.4 Controls of Critical Steps and Intermediates .....	15
S.2.5 Process Validation and/or Evaluation .....	15
S.2.6 Manufacturing Process Development .....	15
S.3 Characterization .....	15
S.3.1 Elucidation of Structure and other Characteristics .....	15
S.3.2 Impurities .....	16
S.4 Control of Drug Substance .....	17
S.4.1 Specification .....	17
S.4.2 Analytical Procedures .....	19
S.4.3 Validation of Analytical Procedures .....	22
S.4.4 Batch Analyses .....	23
S.4.5 Justification of Specification .....	24
S.5 Reference Standards or Materials .....	24
S.6 Container Closure System .....	25
S.7 Stability .....	25
P. DRUG PRODUCT .....	26
P.1 Description and Composition of the Drug Product .....	26

P.2	Pharmaceutical Development.....	27
P.2.1	Components of the Drug Product.....	27
P.2.1.1	Drug Substance.....	27
P.2.1.2	Excipients.....	27
P.2.2	Drug Product.....	27
P.2.2.1	Formulation Development.....	32
P.2.2.2	Overages.....	34
P.2.2.3	Physicochemical and Biological Properties.....	35
P.2.3	Manufacturing Process Development.....	35
P.2.4	Container Closure System.....	38
P.2.5	Microbiological Attributes.....	39
P.2.6	Compatibility.....	39
P.3	Manufacture.....	40
P.3.1	Manufacturers.....	40
P.3.2	Batch Formula.....	41
P.3.3	Description of Manufacturing Process and Process Controls.....	41
P.3.4	Controls of Critical Steps and Intermediates.....	45
P.3.5	Process Validation and/or Evaluation.....	46
P.4	Control of Excipients.....	46
P.5	Control of Drug Product.....	46
P.5.1	Specification.....	47
P.5.2	Analytical Procedures.....	49
P.5.3	Validation of Analytical Procedures.....	51
P.5.4	Batch Analyses.....	57
P.5.5	Characterization of Impurities.....	58
P.5.6	Justification of Specification.....	59
P.6	Reference Standards or Materials.....	63
P.7	Container Closure System.....	63
P.8	Stability.....	65
P.8.1	Stability Summary and Conclusion.....	65
P.8.2	Postapproval Stability Protocol and Stability Commitment.....	67
P.8.3	Stability Data.....	67
A.1	Facilities and Equipment (biotech only).....	73
A.2	Adventitious Agents Safety Evaluation.....	73
A.3	Novel Excipients.....	73
R.	REGIONAL INFORMATION.....	73
R1	Executed Batch Records.....	73
R2	Comparability Protocols.....	73
R3	Methods Validation Package.....	73
II.	Review Of Common Technical Document-Quality (Ctd-Q) Module 1.....	73
A.	Labeling & Package Insert.....	73
B.	Environmental Assessment Or Claim Of Categorical Exclusion.....	80
C.	Establishment Evaluation Report.....	81

CMC Review Data Sheet

# CMC Review Data Sheet

1. NDA 205-645
2. REVIEW #: 1
3. REVIEW DATE: 25-April-2014
4. REVIEWER: Maotang Zhou, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original IND	N/A
Original IND	N/A
End-of-phase-2 meeting (No CMC issues discussed)	N/A
Pre-NDA meeting	N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date	Stamp Date
Original NDA Submission	0000	7/31/2013	8/1/2013
Resubmission/After Refusal to File			
Quality Amendment (Response to Agency Questions)	0001	8/16/2013	8/20/2013
Labeling/Package Insert Draft	0002	11/8/2013	11/8/2013
Quality Amendment (Response to Agency Questions)	0005	1/16/2014	1/16/2014
Quality Amendment (Response to Information Request)	0006	2/27/2014	2/27/2014
Quality Amendment (Response to Information Request)	0007	4/4/2014	4/4/2014
Quality Amendment (Response to Information Request)	0008	4/4/2014	4/4/2014
Quality Amendment (Response to Information Request)	0009	4/17/2014	4/17/2014
Quality Amendment (Response to Information Request)			

## CMC Review Data Sheet

## 7. NAME &amp; ADDRESS OF APPLICANT:

Name: Fresenius Kabi USA, LLC  
Address: Three Corporate Drive  
Lake Zurich, IL 60047  
Representative: Anne Huffman, Sr. Director of QA/QC  
Telephone: 716-773-3715

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

- a) Proprietary Name: Tygacil®
- b) Non-Proprietary Name: Tigecycline
- c) Code Name/# (ONDQA only): D-18506
- d) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: 5
  - Submission Priority: Standard

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

## 10. PHARMACOL. CATEGORY:

11. DOSAGE FORM: Powder for Injection

12. STRENGTH/POTENCY: 50 mg

13. ROUTE OF ADMINISTRATION: Intravenous infusion

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

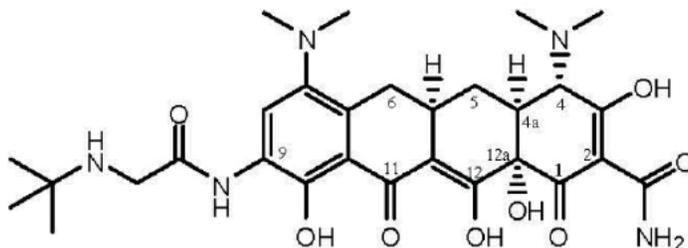
SPOTS product – Form Completed

Not a SPOTS product

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

CMC Review Data Sheet

Tigecycline: (4S, 4aS, 5aR, 12aS)-9-[2-(tert-butylamino)acetamido]-4,7-bis(dimethylamino)-1,4,4a,5,5a, 6,11,12a -octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide



C<sub>29</sub>H<sub>39</sub>N<sub>5</sub>O<sub>8</sub>  
MW = 585.65

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)	Tigecycline	1	2	M Zhou	
	III	(b) (4)	(b) (4)	4			
	III	(b) (4)	(b) (4)	4			
	III	(b) (4)	(b) (4)	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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	N/A	N/A

## CMC Review Data Sheet

NDA	N/A	N/A
-----	-----	-----

## 18. STATUS:

**ONDQA:**

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Biometrics	N/A		
EES	Pending		
Pharm/Tox	Approval	9/26/2013	W Schmidt
Biopharm	Approval	3/12/2014	E Chikhale
LNC	N/A		
Methods Validation	Not required		
DMEPA*	Review in DARRTS	3/20/2014	A Winiarski
EA	Categorical exclusion (see review)	4/22/2014	M Zhou
Microbiology	Approval	1/27/2014	V Pawar

\*DMEPA: Division of Medication Error Prevention and Analysis

## Executive Summary Section

# The CMC Review for NDA 205-645

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This NDA has not provided sufficient information to assure identity, strength, purity, and quality of the drug product. A site recommendation from the Office of Compliance has not been made as of the date of this review. Therefore, from the CMC perspective, this NDA is not recommended for approval until all pending issues are resolved (Refer to Section II.C).

#### 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 and Drug Substance

Tigecycline is approved for the treatment of complicated skin and skin structure infections, complicated intra-abdominal infections, and community-acquired bacterial pneumonia by intravenous administration and is marketed in the US as Tygacil® (approved in 2005 via NDA 21821 for Wyeth Pharmaceuticals, Inc.). There are currently no alternative tigecycline formulations approved for use in humans in the US. Tygacil® is an orange lyophilized powder or cake. Each Tygacil® vial contains 50 mg tigecycline lyophilized powder for reconstitution for intravenous infusion and 100 mg of lactose monohydrate. The pH is adjusted with hydrochloric acid, and if necessary sodium hydroxide. The product does not contain preservatives.

The current 505(b)(2) NDA provides for a new IV formulation of tigecycline that is intended to be therapeutically equivalent to and to be used for the treatment of the same infections as listed in the labeling of the reference listed drug (LISTED DRUG), Tygacil®. The proposed drug product is supplied as a lyophilized cake for reconstitution for intravenous infusion and contains 50 mg tigecycline and 82.6 mg of arginine. The pH is adjusted with hydrochloric acid, and if necessary, with sodium hydroxide.

#### (1) Drug Substance

For the majority of the CMC information for tigecycline drug substance, the reference is made to DMF Type II (b)(4) held by (b)(4). Some general information (Section 3.2.S.1), a specification, information on impurities including residual solvents, batch analysis for the tigecycline drug substance have been also included in the NDA.

## Executive Summary Section

**(2) Drug Product**

The proposed drug product is a new IV formulation of tigecycline, a lyophilized cake for reconstitution for intravenous infusion which contains 50 mg tigecycline and 82.6 mg of arginine. Therefore, the proposed drug product differs from the listed drug in the inactive ingredients, i.e., it contains a different (b) (4). The applicant stated that the proposed formulation of Tigecycline for Injection was developed to have the same drug content with an overage of 6% as stated in the listed drug labeling.

Pharmaceutical Development section (3.2.P.2) describes the drug product formulation and process development issues. The Quality Target Product Profile (QTPP) and Critical Quality Attributes (CQAs) are discussed in this section. In addition, a risk assessment has been conducted on the CQAs of the drug product (DP) to form a basis for product development studies in order to mitigate the risk through design and control of formulation as well as process.

A description of the manufacturing process that includes (b) (4) has been provided in section 3.2.P.3.3. The batch analysis data have been provided for three exhibit batches of the drug product (Product Code 961110) manufactured at the proposed commercial manufacturing facility in FK USA Grand Island, NY. These batches (R341-041, R342-025, and R342-026) are (b) (4) L size each, whereas the proposed commercial batch size is (b) (4) L (the proposed drug product has strength of 50 mg/vial and is filled in a 10 mL vial). The master batch record (product code 961110) has been included in section P.3.3. The exhibit and proposed commercial batches process comparison has also been provided. The proposed sterilization process, including validation and other microbiological quality aspects of the proposed drug substance and drug product, has been evaluated and found adequate by Dr. Vinayak Pawar who is the product quality microbiology reviewer of this NDA.

Drug product specification includes description, reconstitution time, pH, (b) (4), uniformity of dosage units, identification, assay, impurities, container closure integrity, particulate matter, sterility, bacterial endotoxins, and statement of compliance (b) (4). In addition, several attributes are included for the reconstituted solution (completeness, clarity, visual color, and particle matter). The justification of specification including statistical evaluation of results observed on stability are provided in the NDA to justify the proposed acceptance criteria including limits for impurities. As revised, the acceptance criteria are found adequate except for one specified impurity (b) (4). The structure of (b) (4) constitutes a structural alert for potential mutagenicity. In response to a deficiency letter issued by the FDA on 3/21/2014, the applicant is conducting an Ames test on this particular impurity. Therefore, the adequacy of the overall control strategy for (b) (4) will be dependent on the pending Ames test results.

Information on the proposed commercial container closure system has been provided in Section 3.2.P.7. This includes a description of the proposed container closure, results of container/closure system testing (USP <660>, <381>, etc.), specifications and test results of the individual components, and information of the component suppliers. The container closure integrity issues are discussed in section 3.2.P.2 (Pharmaceutical Development section).

## Executive Summary Section

Stability information submitted in section 3.2.P.8.3 include six-month accelerated ( $40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \pm 5\% \text{RH}$ ) twelve-month long term room temperature ( $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \pm 5\% \text{RH}$ ) data for three exhibit batches (R341-041, R342-025, and R342-026) of the drug product manufactured at the proposed manufacturing facility. Based on these data, an expiration dating period of 24 months has been requested for the commercial drug product when stored at controlled room temperature ( $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \pm 5\% \text{RH}$ ) in the proposed commercial container closure system.

In addition, the results of compatibility studies of the proposed drug product with the proposed reconstitution agents: 0.9% Sodium Chloride Injection, USP, 5% Dextrose Injection, USP, and Lactated Ringer's Injection, USP have also been provided in the Pharmaceutical Development section. That includes stability data for these solutions stored over a period of 24 hours at  $25^{\circ}\text{C}$ .

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

Tigecycline for injection is a tetracycline-class antibacterial drug indicated in patients 18 years of age and older for complicated skin and skin structure infections, complicated intra-abdominal infections, and community-acquired bacterial pneumonia. The tigecycline concentration, route of administration, dose, and dosing regimen for the proposed drug product are identical to those of the listed drug, Tygacil<sup>®</sup> (NDA 021821). The proposed drug product is intended to be administered intravenously over a period of 30 to 60 minutes as an initial loading dose of 100 mg followed by 50 mg every 12 hours.

Prior to administration, Tigecycline for injection should be reconstituted and diluted with 0.9% Sodium Chloride Injection, USP, 5% Dextrose Injection, USP, or Lactated Ringer's Injection, USP. The maximum concentration of the reconstituted solution in the intravenous bag should be 1 mg/mL. The detailed preparation instruction of the reconstituted solution is provided in the package insert.

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

This NDA has not provided sufficient information on raw material controls, manufacturing processes and process controls, adequate specifications, and stability data for assuring consistent product quality of the drug substance and drug product. Prior to approval, the following pending issues must be satisfactorily resolved.

- Overall site recommendation: Office of Compliance has not yet issued an overall acceptable site recommendation in EES;
- The applicant has not responded to all CMC information requests. Specifically, the applicant is currently conducting an Ames test on the (b)(4) impurity for mutagenicity. The adequacy of the overall control strategy will be reevaluated based on the pending the testing results.
- Compatibility data for the proposed tigecycline drug product with several drugs to be administered through a Y-site (as proposed in section 2.4 of the package insert) has not been provided. In addition, several other minor revisions to the labeling and labels will need to be incorporated.

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

## Executive Summary Section

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

*(See appended electronic signature page)*

Maotang Zhou, Ph.D., Reviewer, ONDQA

**B. Endorsement Block:**

*(See appended electronic signature page)*

Dorota Matecka, Ph.D., CMC Lead, Branch V, Division of New Drug Quality  
Assessment II, ONDQA

**C. CC Block:** entered electronically in DARRTS

CMC Assessment Section

**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**  
Executed batch records for three exhibit lots (#R342-025, #R341-041, and R342-026) are provided.
- R2 Comparability Protocols**  
N/A
- R3 Methods Validation Package**  
Provided references to various sections of the NDA.

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

**A. Labeling & Package Insert**

1. Package Insert

(a) “Highlights” Section

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

**Evaluation:** Adequate.

## CMC Assessment Section

## (b) "Full Prescribing Information" Section

# 3: Dosage Forms and Strengths

Each single-dose 10 mL glass vial contains 50 mg of tigecycline as an orange lyophilized powder for reconstitution.

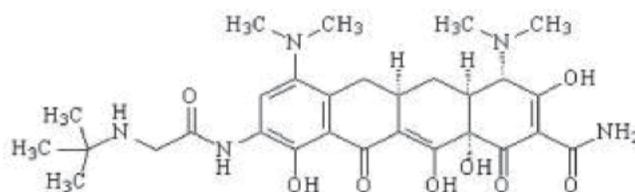
Item	Information Provided in NDA
Available dosage forms	Lyophilized powder for reconstitution
Strengths: in metric system	50 mg
Active moiety expression of strength with equivalence statement (if applicable)	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Orange lyophilized powder for reconstitution

**Evaluation:** adequate.

#11: Description

Tigecycline is a (b) (4) for intravenous infusion. The chemical name of tigecycline is (4*S*,4*aS*,5*aR*,12*aS*)-9-[2-(*tert*-butylamino)acetamido]-4,7-bis(dimethylamino)-1,4,4*a*,5,5*a*,6,11,12*a*-octahydro-3,10,12,12*a*-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamide. The empirical formula is  $C_{29}H_{39}N_5O_8$  and the molecular weight is 585.65.

The following represents the chemical structure of tigecycline:



$C_{29}H_{39}N_5O_8$

**M.W. 585.65**

Tigecycline for injection is ~~an~~ a sterile orange lyophilized powder or cake. Each tigecycline vial contains 50 mg tigecycline lyophilized powder for reconstitution for intravenous infusion and 82.6 mg of arginine. The pH is adjusted with hydrochloric acid, and if necessary sodium hydroxide. The product does not contain preservatives.

CMC Assessment Section

Item	Information Provided in NDA
Proprietary name and established name	Tigecycline
Dosage form and route of administration	Tigecycline for injection
Active moiety expression of strength with equivalence statement (if applicable)	N/A
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)	50 mg tigecycline lyophilized powder for reconstitution for intravenous infusion and 82.6 mg of arginine
Statement of being sterile (if applicable)	Not Included
Pharmacological/ therapeutic class	Not included
Chemical name, structural formula, molecular weight	Included
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	N/A

**Evaluation:**

*Not all the required CMC information was included in the originally submitted package insert. Minor comments were discussed during the internal labeling meeting on 4/21/2014.*

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

Tigecycline for injection is supplied in a single-dose 10 mL glass vial, containing 50 mg tigecycline lyophilized powder for reconstitution.

(b) (4)	<b>NDC</b>		
	<b>No.</b>	<b>Strength</b>	
	63323-960-10	50 mg per vial	10 mL vial in packages of ten.

Prior to reconstitution, tigecycline for injection should be stored at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Once reconstituted, tigecycline for injection may be stored at room temperature (not to exceed 25°C/77°F) for up to 24 hours (up to 6 hours in the vial and the remaining time in the intravenous bag). (b) (4)

[Redacted text block]

CMC Assessment Section

(b) (4)

(b) (4) ~~container closure is not made with natural rubber latex.~~

Item	Information Provided in NDA
Strength of dosage form	50 mg
Available units (e.g., bottles of 100 tablets)	10-mL vials in packages of ten
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	Included
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Not included. But this information is provided in Section 17

**Reviewer Notes:** prior to administration, tigecycline for injection should be reconstituted and diluted with 0.9% Sodium Chloride Injection, USP, 5% Dextrose Injection, USP, or Lactated Ringer’s Injection, USP. The maximum concentration of the reconstituted solution in the intravenous bag should be 1 mg/mL. The detailed preparation instruction of the reconstituted solution is provided in Section 2.4 of the package insert. The paragraph entitled “Compatibilities” in this section lists a number of drugs compatible with the proposed tigecycline injection when administered through a Y-site. However, it appears that the compatibility data has only been provided for the three diluents specified above (0.9% Sodium Chloride Injection, USP, 5% Dextrose Injection, USP, and Lactated Ringer’s Injection, USP). A request to provide the compatibility data for all the drugs listed in this paragraph (or indicate where this data can be located in the NDA) should be forwarded to the applicant.

**Evaluation:** The required CMC information is included. It is usual to include the statement: “(b) (4) container closure is not made with natural rubber latex.” This statement is therefore being crossed out.

CMC Assessment Section

2. 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))	Tigecycline For Injection
Dosage strength	50 mg per vial
Net contents (See USP <1> for presentation of strength and content for injections.)	<b>Not included</b>
“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	<b>Not included</b>
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	N/A

***Evaluation:*** It is noted that the proposed immediate container label does not contain some other information such as the storage conditions. This is acceptable as per 21 CFR 201.10(i) which states that a drug packaged in a container too small or otherwise unable to accommodate a label with sufficient space to bear the information required for compliance with section 502(e)(1)(A)(ii) and (B) of the act shall be exempt from compliance with those clauses: Provided (1) the label contains the four items listed in the table, i.e., the proprietary name, the established name, lot or control number, and the manufacturer name; (2) all the required information appears on the carton or other outer container or wrapper. In the current NDA, both conditions have been satisfied.

The following comments were forwarded to the applicant.

## CMC Assessment Section

*Please add the following information to the immediate container label:*

- a. Storage conditions*
- b. A statement of being sterile*

CMC Assessment Section

3. Carton labeling

A copy of the carton labels is provided below:



Item	Information Provided in NDA
Proprietary name, established name (font size, prominence)	Tigecycline For Injection
Dosage strength	50 mg per vial
Net quantity of dosage form	10 single use vials
“Rx only” displayed prominently on the main panel	Included
Lot number and expiration date	Not Included
Storage conditions	Included
Bar code (21CFR 201.25)	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
Manufacturer/distributor's name	Included
Quantitative ingredient information (injectables)	Yes
Statement of being sterile (if applicable)	Not included
“See package insert for dosage information”	Yes
Special instructions (“Keep out of reach of children” is required for OTC in CFR. Optional for Rx drugs)	Yes.

CMC Assessment Section

***Evaluation:*** *The proposed carton label does contain all required information. The followings comments are forwarded to the applicant. In addition, the statement “(b) (4) container closure is not made with natural rubber latex” should also be removed from the carton label.*

*Please add the following information to the carton label:*

- c. Lot number and expiration date*
- d. A statement of being sterile*

5. Unit-dose labeling (21 CFR 201.10(i)): N/A.

Item	Information Provided in NDA
Proprietary name, established name (font size and prominence)	
Dosage strength	
Net content (for injection only. See USP <1> for presentation of strength and content for injections.)	
“Rx only”	
Lot number and expiration date (21 CFR 201.17 & 201.18) (For single-dose containers, the expiration date may properly appear on the individual carton instead of the immediate product container.)	
Bar code (Not required for physician samples)	
NDC number	
Name of manufacturer/distributor	

***Evaluation:*** *This section is not applicable for this particular product as per FDA’s Compliance Policy Guide (CPG) Sec 430.100 (updated 01/20/2010). 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(b). The basis of this exclusion is the fact that the estimated concentration of the active ingredient at the point of entry into the aquatic environment will be less than 1 ppb from all products using this material as the active ingredient.

***Evaluation:*** *Acceptable.*



CMC Assessment Section

C. Establishment Evaluation Report

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 205645/000 Sponsor: FRESENIUS KABI USA
Org. Code: 520 3 CORPORATE DR
Priority: 5N LAKE ZURICH, IL 60047
Stamp Date: 01-AUG-2013 Brand Name: TIGECYCLINE FOR INJECTION, 50 MG/VIAL
PDUFA Date: 01-JUN-2014 Estab. Name:
Action Goal: Generic Name: TIGECYCLINE FOR INJECTION, 50 MG/VIAL
District Goal: 02-APR-2014 Product Number; Dosage Form; Ingredient; Strengths
001: POWDER, FOR INJECTION SOLUTION, LYOPHILIZED;
TIGECYCLINE; 50MG

Table with 4 columns: Name, Title, ID, and Contact Info. Rows include M. ZHOU (Prod Qual Reviewer), V. PAWAR (Micro Reviewer), N. BHANDARI (Product Quality PM), C. DEBELLAS (Regulatory Project Mgr), and R. MADURAWA (Team Leader).

Overall Recommendation: PENDING on 22-APR-2014 by EES\_PROD
PENDING on 18-APR-2014 by EES\_PROD

Establishment: (b) (4)

DMF No: AADA:

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

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 19-AUG-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE



CMC Assessment Section

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

<b>Establishment:</b>	<b>CFN:</b> 1321116	<b>FEI:</b> 3001833549	
	FRESENIUS KABI USA, LLC		
<b>DMF No:</b>	GRAND ISLAND, , UNITED STATES	140722028	<b>AADA:</b>
<b>Responsibilities:</b>	DRUG SUBSTANCE OTHER TESTER FINISHED DOSAGE MANUFACTURER FINISHED DOSAGE PACKAGER FINISHED DOSAGE RELEASE TESTER FINISHED DOSAGE STABILITY TESTER		
<b>Profile:</b>	SMALL VOLUME PARENTERAL, LYOPHILIZED	<b>OAI Status:</b>	OAI ALERT
<b>Last Milestone:</b>	DO RECOMMENDATION		
<b>Milestone Date:</b>	06-DEC-2013		
<b>Decision:</b>	WITHHOLD		
<b>Reason:</b>	PENDING REGULATORY ACTION WITHOUT PRODUCT SPECIFIC ISSUES AND/OR PREVIOUS DEVIATIONS PERSIST		
<b>Establishment:</b>	<b>CFN:</b> 1421790	<b>FEI:</b> 1000115163	
	FRESENIUS KABI USA, LLC		
<b>DMF No:</b>	MELROSE PARK, , UNITED STATES	601601002	<b>AADA:</b>
<b>Responsibilities:</b>	FINISHED DOSAGE RELEASE TESTER FINISHED DOSAGE STABILITY TESTER		
<b>Profile:</b>	CONTROL TESTING LABORATORY	<b>OAI Status:</b>	NONE
<b>Last Milestone:</b>	OC RECOMMENDATION		
<b>Milestone Date:</b>	08-OCT-2013		
<b>Decision:</b>	ACCEPTABLE		
<b>Reason:</b>	BASED ON PROFILE		



CMC Assessment Section

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

**Establishment:** CFN: FRESENIUS KABI USA, LLC FEI: 3008604776

**DMF No:** SKOKIE, , UNITED STATES 600775318 **AADA:**

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

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

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 20-AUG-2013

**Decision:** ACCEPTABLE

**Reason:** BASED ON PROFILE

**Establishment:** (b) (4)

**DMF No:** **AADA:**

**Responsibilities:** DRUG SUBSTANCE OTHER TESTER

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

**Last Milestone:** SUBMITTED TO DO

**Milestone Date:** 22-APR-2014

PDUFA GOAL DATE

**Establishment:** (b) (4)

**DMF No:** **AADA:**

**Responsibilities:** DRUG SUBSTANCE OTHER TESTER

**Profile:** CONTROL TESTING LABORATORIES "ALSO" (DRUGS) **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 22-APR-2014

**Decision:** ACCEPTABLE

**Reason:** BASED ON PROFILE

CMC Assessment Section

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

**Establishment:** [REDACTED] (b) (4)

**DMF No:** [REDACTED] **AADA:**

**Responsibilities:** [REDACTED] (b) (4)

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

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 22-APR-2014

**Decision:** ACCEPTABLE

**Reason:** BASED ON PROFILE

---

**Establishment:** [REDACTED] (b) (4)

**DMF No:** [REDACTED] **AADA:**

**Responsibilities:** DRUG SUBSTANCE OTHER TESTER

**Profile:** CONTROL TESTING LABORATORIES "ALSO" (DRUGS) **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 22-APR-2014

**Decision:** ACCEPTABLE

**Reason:** BASED ON PROFILE

---

## CMC Assessment Section

## III. List Of Deficiencies communicated and to be resolved

**Deficiency to be resolved (from the IR letter dated 4/22/2014.)**

- Please refer to Section P.5.3 of this review. The API supplier is currently performing an Ames test on a drug product impurity, (b) (4), whose structure contains a (b) (4) (b) (4) which makes it a structural alert for potential mutagenicity. Once results are collected and evaluated, appropriate action will be taken to ensure a new limit for the impurity is imposed if necessary and that the method for quantitating the (b) (4) impurity can quantitate the (b) (4) peak at a possible lower level. The CMC reviewer agrees with the applicant's approach. If the results from the Ames test are positive, then both the analytical procedure and the overall control strategy for this particular impurity should be reevaluated.

**Information requests communicated to the applicant:** the applicant has adequately responded all the IR (DR) questions listed here except for the one listed above concerning the (b) (4) impurity.

**IR Letter Dated 12/3/2013**

1. In reference to Section 3.2.P.4.1 of the NDA submission concerning the drug substance specification:
  - a) Please add a test with appropriate acceptance criteria (b) (4);
  - b) Please add a test with appropriate acceptance criteria for pH;
  - c) In addition to the heavy metal test by USP <231>, add a test with appropriate acceptance criteria for (b) (4) content. Please refer to USP <232>, USP <233>, and ICH Q3D for further guidance.
2. In reference to Section 3.2.P.3.3 of the NDA submission concerning the manufacturing process description:  
 (b) (4)
3. The information provided in Section 3.2.P.3.4 of the NDA is not adequate. Please refer to ICH M4Q(R1) and submit the necessary information accordingly. In this section, all critical process controls and their associated numeric ranges, limits, or acceptance criteria should be identified and justified and a brief description of the test provided. Any experimental data to support the justification should be included in this section as well. Critical process control values from relevant batches should be provided only as part of the justification.

## CMC Assessment Section

4. In reference Section 3.2.P.5.1 of the NDA submission concerning the drug product specification:
- Update the acceptance criteria for Particular Matter test (b) (4)
  - Given that the API is (b) (4), we recommend a test with an appropriate acceptance criterion (b) (4) be included in the drug product specification. The acceptance criteria should be adequately justified by experimental data;
  - The drug product specification in Table 2.3.P-15 lists (b) (4) as one of the identity tests. This is not consistent with the information provided in other section of the NDA submission. Please reconcile.
  - Please tighten the (b) (4) limit from NMT (b) (4)% to NMT (b) (4)% based on available batch analysis data and stability data.
5. Your interpretation of the ICH Q6A, (b) (4) value in your equation should be the estimated “maximum increase in the degradation product at shelf life”, not the projected value as you stated. As such, some of the proposed acceptance criteria are not fully justified. Based on the available batch data and stability data, we recommend that acceptance criteria be tightened for the following attributes:
- (b) (4)
6. In reference to Section 3.2.P.5.3 concerning the method validation (PR-10-00185):
- Your acceptance criteria of %RSD (b) (4)% for precision (b) (4) are considered high. We recommend that these acceptance criteria be tightened to NMT (b) (4)% for (b) (4) precision for impurity tests.
  - In the validation report (PR-10-00185), you state that the impurity (b) (4) degraded from (b) (4)% in the test solution. Please discuss the suitability of the analytical method for this particular impurity.
  - It appears that only precision test has been revalidated after the HPLC method revision. We recommend that (b) (4) precision tests be repeated after the revision of the HPLC method.

**DR Letter dated 3/21/2014**

Reference is made to your communication dated February 27, 2014 containing a response to FDA’s CMC Information Request letter dated December 3, 2013. We have reviewed your response to Question 6(b) concerning the suitability of the analytical method for the (b) (4) impurity and find your response inadequate. (b) (4), it appears unlikely you are able to quantify this particular impurity accurately with the current HPLC method. Although you stated that (b) (4) is a process impurity as well as a degradation

## CMC Assessment Section

product, this impurity was not included in Table 3.2.P.5.5-1. In order to continue evaluation of the (b) (4) impurity, we request a written response to the following deficiencies on or before April 4, 2014.

1. The (b) (4) impurity contains a structural alert for mutagenicity. Evaluate the mutagenic potential of (b) (4).
2. How did you determine that (b) (4) is a degradation product? Provide supporting data.
3. Propose a possible mechanism for the formation of (b) (4) as a degradation product.
4. Develop an appropriate analytical procedure that is capable of accurately quantitating (b) (4) levels and provide representative batch analysis data for the (b) (4) impurity using this method. Note that the appropriate limit of detection and limit of quantitation for the (b) (4) analytical method would be based on the outcome of item #1 above. If (b) (4) is confirmed to be mutagenic, provide an appropriate control strategy for (b) (4).

**IR Letter dated 4/14/2014**

1. The drug substance establishments provided to-date in your NDA 205645 are inconsistent with those provided in DMF (b) (4). Amend the drug substance establishment information in the NDA with a complete and accurate list of ALL facilities involved in the manufacture and testing of the drug substance. Include all necessary information for each establishment such as contact name(s), address, phone number, fax number, and email addresses.

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

/s/  
-----

MAOTANG ZHOU  
04/25/2014

DOROTA M MATECKA  
04/25/2014

RAPTI D MADURawe  
04/25/2014