

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211158Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: *Approval*

NDA 211158

Review # 1

Drug Name/Dosage Form	Tigecycline for Injection*
Strength	50 mg/vial
Route of Administration	Intravenous infusion
Rx/OTC Dispensed	Rx
Applicant	Amneal Pharmaceuticals LLC
US agent, if applicable	N/A

**No proprietary name was proposed*

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	September 29, 2017	All
Amendment (eCTD 003)	December 14, 2017	Drug Product
Amendment (eCTD 008)	February 9, 2018	Biopharmaceutics
Amendment (eCTD 010)	March 16, 2018	Drug Product, Process
Amendment (eCTD 013)	April 12, 2018	Drug Product
Amendment (eCTD 014)	April 13, 2018	Drug Product
Amendment (eCTD 016)	April 20, 2018	Microbiology
Amendment (eCTD 017)	April 24, 2018	Drug Product
Amendment (eCTD 018)	April 25, 2018	Microbiology
Amendment (eCTD 019)	May 10, 2018	Drug Product, Process
Amendment (eCTD 018)	May 28, 2018	Drug Product

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Haripada Sarker	Charles Jewell
Drug Product	Erika Englund	Balajee Shanmugam
Process	Nancy Waites	Daniel Obrzut
Microbiology	Jonathan Burgos	Elizabeth Berr
Facilities	Ebber Dobbin	Ying Zhang
Biopharmaceutics	Om Anand	Elsbeth Chikhale
Environmental Assessment*	Erika Englund	Balajee Shanmugam
Regulatory Business Process Manager	Anh-Thy Ly	N/A
Application Technical Lead	Dorota Matecka	N/A

** Environmental Assessment is captured in the Drug Product Chapter*

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Review Completed	Comments
(b) (4)	Type II	(b) (4)	(b) (4)	Adequate	April 18, 2018	Review by Jizhou Wang
	Type III			Adequate	February 13, 2018	Review by Erika Englund
	Type III			N/A*		
	Type V			N/A*		

*Sufficient information for the container closure systems was submitted in the NDA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	128826	Presubmission

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	Complete	Acceptable (refer to DS and DP reviews)		
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The NDA, as amended, has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed drug product, tigecycline for injection. All information requests and review issues have been addressed and there are no pending approvability issues. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall “Approve” recommendation was entered into Panorama by the Office of Process and Facilities (OPF) on May 16, 2018. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ).

II. Summary of Quality Assessments

A. Product Overview

Tigecycline is a tetracycline class antibacterial indicated for the treatment of the bacterial infections (as listed in the table below), which are the same indications included in the labeling of the listed drug (LD), Tygacil® (tigecycline for injection), 50 mg/vial, approved in 2005 via NDA 21821.

The proposed drug product, tigecycline for injection, 50 mg, similarly to the LD, is a sterile lyophilized powder that needs to be reconstituted and further diluted for intravenous infusion. The proposed drug product differs from the LD in the excipients used in the formulation; specifically, it contains a different (b) (4) (i.e., arginine instead of lactose). In view of the similarities between the proposed drug product and the LD, a biowaiver for conducting in-vivo bioequivalence studies was requested by the Applicant. The Applicant is relying on previous findings of efficacy and safety for Tygacil® for approval of the proposed drug product.

Proposed Indication(s) including Intended Patient Population	Tigecycline is indicated in patients 18 years of age and older for the treatment of: <ul style="list-style-type: none"> • Complicated skin and skin structure infections • Complicated intra-abdominal infections • Community-acquired bacterial pneumonia
Duration of Treatment	The recommended dosage regimen for tigecycline for injection is an initial dose of 100 mg, followed by 50 mg every 12 hours. Intravenous infusions of tigecycline for injection should be administered over approximately 30 minutes to 60 minutes every 12 hours. Treatment up to 14 days for the above indications.
Maximum Daily Dose	150 mg (<i>see the package insert for details</i>)
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

The chemistry, manufacturing and controls (CMC) information for tigecycline drug substance in support of this NDA is provided via a reference to DMF (b) (4) (held by the manufacturer, (b) (4)). This DMF was found to be adequate via a review dated April 18, 2018 referenced for another application in CDER. Although most CMC information is provided by reference to the above DMF, general information on properties, a brief description of the manufacturing process and impurities (including elemental analysis), and a specification and batch analysis data were provided in the NDA. The retest period for the tigecycline drug substance established by the drug product manufacturer is (b) (4) months when stored (b) (4). The overall information provided in support of the tigecycline drug substance was found acceptable by the Drug Substance Reviewer.

Tigecycline for injection, 50 mg/vial, is a sterile, lyophilized orange (b) (4) cake or powder supplied in a 5 mL Type I glass vial with a (b) (4) rubber stopper and (b) (4) flip off seal. The excipients used in the proposed drug product formulation include L-arginine (b) (4) and sodium hydroxide and/or hydrochloric acid used as pH adjusting agents. To allow withdrawal of the labeled amount of tigecycline, a 6% overfill is used in the vial. The product is to be reconstituted and further diluted prior to the intravenous administration, and the Applicant provided adequate in-use stability data to support the use of the diluents listed in the proposed package insert (PI). Adequate data were also provided to support the co-administration of the proposed drug product with several drugs described in the PI.

The drug product specification includes tests for description, appearance of the reconstituted solution, identification, assay, related substances, water content, pH, reconstitution time, extractable volume, uniformity of dosage units, particulate matter, endotoxins and sterility. During the review cycle, the applicant agreed to revise the limit for the tigecycline (b) (4) from NMT (b) (4) % to NMT (b) (4) % to comply with the USP monograph for tigecycline for injection. In addition, at the FDA recommendation and based on the available batch data, the limit for (b) (4) was also tightened. The proposed specification (tests, acceptance criteria and analytical procedures), as revised, was found acceptable. The assessment of elemental impurities was submitted in the NDA and found acceptable. In addition, information submitted in the NDA for the container closure system, including the results of extractable/leachable studies, was also found adequate to demonstrate its safety and suitability for intended use. The drug product stability information submitted in the NDA includes acceptable 24-month long-term and 6-month accelerated stability data for three registration batches manufactured at the proposed commercial manufacturing site, which support the proposed in the NDA expiration dating of 24 month for a drug product to be stored at 25°C ± 2°C and 60% ± 5% RH. The overall information submitted in the NDA for the drug product was found acceptable by the Drug Product Reviewer.

The proposed manufacturing process consists of the following steps:

(b) (4)

(b) (4)

(b) (4). The overall information regarding the manufacturing process including (b) (4) (b) (4) controls provided in the initial NDA and subsequent amendments was found acceptable by the Process Reviewer.

The product quality microbiology review focused on the overall sterility assurance information submitted in the NDA for the proposed drug product that included issues such as container closure integrity, sterilization/depyrogenation of packaging components, (b) (4), proposed microbiological controls for the drug product, proposed hold times for the reconstituted and further diluted solutions in support of the proposed storage statements in the package insert, etc. During the NDA review, additional information was provided by the Applicant at the FDA request regarding the container closure integrity validation study, (b) (4) testing, proposed holding times (b) (4), validation of the sterilization/depyrogenation of packaging components, and media fill simulation. The overall product quality microbiology information provided in the NDA and subsequent amendments was found acceptable by the Microbiology Reviewer.

The Biopharmaceutics review focused on the assessment of a waiver request for the conduct of bioavailability/bioequivalence studies. Based on supporting data submitted in the NDA, such as pH and osmolality comparisons, an in vitro protein binding study, and literature information, the differences in the inactive ingredients (arginine in the proposed drug product versus lactose in the LD) are not expected to affect the disposition kinetics of tigecycline in the proposed drug product when administered via the IV route, and the disposition kinetics of tigecycline should be similar after intravenous administration of these two products. The Biopharmaceutics Reviewer concluded that the data and information submitted in the Application demonstrate that the proposed drug product has been adequately bridged to the LD; therefore, per 21 CFR 320.24(b)(6), an in vivo pharmacokinetic study is not needed.

The Applicant has requested a categorical exclusion from the requirements of an environmental assessment (EA) preparation, which was found acceptable (as indicated in the Drug Product Chapter). Several labeling revisions have been recommended in the proposed package insert from the product quality perspective. The proposed package insert and container and carton labels are currently under review by the NDA review team.

The tigecycline drug substance is manufactured by (b) (4) (b) (4), and the drug product is manufactured at the Gland Pharma Limited facility, located in India. Following the review of the application and inspectional history of the facilities associated with the NDA, no significant outstanding facility risks that

would prevent approval of this NDA were identified by the Facilities Reviewer. Therefore, the overall recommendation of “Approve” was entered for this NDA into Panorama by OPF on May 16, 2018.

Based on the above assessments, this NDA is recommended for approval by the OPQ Review Team.

C. Special Product Quality Labeling Recommendations (*labeling review pending*)

D. Final Risk Assessment (*see Attachment I*)

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MICROBIOLOGY

Product Background:

NDA: 211158

**Drug Product Name/
Strength:** Tigecycline for Injection USP (50 mg/Vial)

**Route of
Administration:** Intravenous (IV)

Applicant Name: Amneal Pharmaceuticals LLC

Manufacturing Site: Gland Pharma Limited
Survey No. 143 - 148, 150 & 151,
Near Gandimaisamma Cross Roads,
D P Pally, Quthbullapur Mandal,
Ranga Reddy District, Dundigal (Post),
Hyderabad, Telangana - 500043, India (IND)

Method of Sterilization: (b) (4)

Review Recommendation: Adequate

Review Summary:

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
09/29/2017	10/02/2017	N/A	10/06/2017
04/20/2018			04/23/2018
04/25/2018			04/25/2018

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

Supporting/Related Documents:

- (b) (4) (04/05/2017): For the (b) (4) stopper (b) (4) (Review, Adequate).
- (b) (4).doc (08/06/2014): For (b) (4) validation studies (Adequate; overall review, Not Adequate).
- A207092MR01 (09/22/2017): For (b) (4) validation studies (Review, Adequate).
- 204289.doc (06/24/2013): For (b) (4) validation studies (Adequate; overall review, not adequate).
- 204289a1 (08/31/2015): For (b) (4) validation studies (Review, Adequate).

206398.doc (03/09/2016):

For (b) (4) validation studies (Review, Adequate).

(b) (4).doc (04/16/2016):

For pediatric dose calculations of maximum endotoxin levels due to drug product (Review, Adequate).

Remarks Section:

This ANDA was submitted in E-CTD format.

S Drug Substance

N/A, drug substance is nonsterile, (b) (4).

P.1 Description of the Composition of the Drug Product

(Information Located at: Sections 1.14.3, Final Labeling Text; 3.2.P.1, Description and Composition, Page 1/4; 3.2.P.7, Container Closure System, Pages 9-10/227)

The drug product, Tigecycline for Injection, is a sterile lyophilized powder supplied as a single dose 50mg/Vial configuration. The (b) (4) fill is contained in 5 mL vials. Exact formulation is described in the table below.

Ingredient	Quality Standard	Function	Quantity, mg/Vial
Tigecycline	USP	Active Ingredient	50
L-Arginine	IH	(b) (4)	50 (b) (4)
Hydrochloric acid	NF	pH adjustment	(b) (4)
Sodium Hydroxide	NF	pH Adjustment	(b) (4)

- Description of container closure system**

Configuration	Component	Description	Manufacturer
50 mg/Vial	Vial	5 mL (b) (4) Type I Glass (b) (4)	(b) (4)
	Stopper	Rubber (b) (4) (b) (4)	
	Flip-off-Seal	(b) (4) Flip Off Aluminum Seal (b) (4) (b) (4)	

Reviewer's Assessment: The information provided by the applicant was adequate.

Acceptable

P.2 Pharmaceutical Development

N/A

P.2.5 Microbiological Attributes

N/A

Container/Closure and Package Integrity

(Information Located at: Section 3.2.P.3.5, Process Validation, Page 395/404)

In the submission dated 10/02/2017, it was indicated the dye immersion test was performed by (b) (4) (b) (4) to assess the container/closure integrity of a total of 60 drug product samples (20 vials from each of the tested batches, ADT403, ADT404, ADT405) in November 2016. However, upon a request for additional information (see IRs-a-e below), a separate CCIT report, dated May 2015, was provided (Report Number: (CCIR15006-00)). In the report described below, a total of 20 test drug product vials and 5 positive control vials were immersed into a 0.1% methylene blue solution under a vacuum of 360 mm of Hg. Following a 30-minute immersion, the vials were removed, rinsed, and evaluated for dye ingress by UV-spectrophotometry. Negative control vials, which were not subjected to the dye immersion, were used as blanks during the spectrophotometry evaluations. An LOD of 0.013 Absorbance Units, equivalent to 0.25 μL of methylene dye solution, was implemented. The acceptance criterion employed was: Blue color is not evident in the vials. While dye ingress was not evident in the test vials, the positive control vials showed dye ingress.

The following deficiency was issued in the 06 April 2018 microbiology information request

The container-closure integrity (CCI) validation study provided in Section 3.2.P.2.4 is acknowledged. More information is needed for review. Please address the following:

a. Describe the method used to evaluate the presence or absence of dye ingress (e.g. spectrophotometry, visual inspection).

In the 20 April 2018 response, the sponsor indicated UV-visible spectrophotometry is used in the CCIT to detect the presence of dye ingress.

b. Describe the test that was performed to determine the limit of detection (LOD) for the CCI test method and provide the LOD. It is noted that the CCI method should be capable of detecting $\leq 5 \mu\text{L}$, although a detection capability of $< 1 \mu\text{L}$ is preferred.

In the 20 April 2018 response, the sponsor specified an LOD of 0.013 Absorbance Units (at 663 nm), which is equivalent to $< 0.25 \mu\text{L}$ of 0.1% methylene blue solution per 5 mL of product solution. A report (Report Number: CCIR15006-00) describing the LOD determination was provided.

c. If a visual detection method was used, provide information to demonstrate the reproducibility of the LOD. Examples of this information may include the results of blinded testing of a panel of visual examiners.

As indicated in the response to IR-a above, the immersed vials were not visually inspected. Therefore, additional visual detection of the challenged vials was not necessary.

d. Describe any positive or negative controls used.

In the 20 April 2018 response, the positive and negative controls were described in Report CCIR15006-00. While the 5 positive control vials were punctured with 26 gauge 0.5 inch needles and submerged into the dye solution vessel alongside the test vials, the 5 negative control vials were not exposed to the methylene blue solution.

e. Provide the actual test results, including the results of any positive or negative controls.

In the 20 April 2018 response, the sponsor provided results for the positive and negative control vials in Report CCIR15006-00. Positive controls showed blue coloration greater than the spiked sample vials. The negative control vials were not spectrophotometrically analyzed. They were instead used as blanks when test and positive control vials were evaluated by UV-Visible spectrophotometry.

Reviewer's Assessment: The information provided by the applicant was adequate.

Acceptable

Antimicrobial Effectiveness Testing

Not applicable since the drug product is provided as a single dose vial and does not contain preservatives.

Reviewer's Assessment: The information provided by the applicant was adequate.

Acceptable

P.3 Manufacture

P.3.1 Manufacturers

Gland Pharma Limited
Survey No. 143 - 148, 150 & 151,
Near Gandimaisamma Cross Roads,
D P Pally, Quthubullapur Mandal,
Ranga Reddy District, Dundigal (Post),
Hyderabad, Telangana - 500043, India (IND)

(b) (4)

Reviewer's Assessment: The information provided by the applicant was adequate.

Acceptable

P. 3.3 Description of the Manufacturing Process and Process Controls

(b) (4)



QUALITY ASSESSMENT



Reviewer's Assessment: The information provided by the applicant was adequate.

Acceptable

Overall Manufacturing Operation

(b) (4)

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Reviewer's Assessment: The information provided by the applicant was adequate.

Acceptable

P.5 Control of Drug Product

N/A

P. 5.1 Specification

(Information Located at: Section 3.2.P.5.1, Specifications, Pages 4/8 and 7/8)

The product release specification includes the following microbiological tests:

Test	Test Method	Acceptance Criteria	Batch Numbers	Exhibit Batch Results
Bacterial Endotoxins	USP<85>	≤ (b) (4) EU/mg*	ADT403 ADT404 ADT405	All Exhibit Batches Meet Acceptance Criteria**. Please See Section P.8.3
Sterility	USP<71>	Sterile		

*, The endotoxin specification was changed (b) (4) on 05/26/2017 (Section 3.2.P.5.1, Page 7/8). A justification was not provided.

** ,All tested batches met both the previous and current endotoxin acceptance criterion.

Reviewer's Assessment: The information provided by the applicant was adequate.

Acceptable

P.5.2 Analytical Procedures

N/A

P.5.3 Validation of Analytical Procedures

N/A

Endotoxins

(Information Located at: Section 3.2.P.5.3, Validation of Analytical Procedures [Endotoxin Test Method Validation], Pages 1-67/67)

<USP 85> BET gel clot method was used to evaluate one drug product vial from each of the exhibit batches (ADT403, ADT404, and ADT405) in March 2015 (Report Number: VBER15011-00). Each vial was reconstituted with 2 mL of LAL reagent water (50 mg/2 mL = 25 mg/mL). The applicant indicated the lysate sensitivity of the LAL reagent was 0.03 EU/mL and the proposed endotoxin specification of the 25 mg/mL drug product was NMT (b) (4) EU/mg (at the time of testing). Based on the previous endotoxin specification, both the reviewer and the applicant calculated an MVD of (b) (4). Using the revised endotoxin specification of (b) (4) EU/mg, the reviewer calculated an MVD of (b) (4). Identical results were observed in the analyses of the three exhibit batches: Clotting was observed at 2λ and λ but not at $\lambda/4$ or at $\lambda/2$. These results indicate that the exhibit batch is free from interfering/enhancing factors under the tested conditions. The tests described above were conducted at an effective dilution of (b) (4). Although data to support the new endotoxin specification of NMT (b) (4) EU/mg was not provided, it was indicated the same procedure described above, including the effective dilution of (b) (4) will be employed during routine drug product testing. The (b) (4) dilution is within the new MVD of (b) (4).

Note to Reviewer: Release testing will be performed on a pooled sample comprised of units (b) (4) (b) (4) (i.e. 3 units). For stability testing, analysis will be performed on one vial representing the entire batch. It is unclear whether sample pooling occurred during the test for interfering factors. Pooling 3 samples results in a (b) (4) dilution of endotoxins should only 1 sample exceed the endotoxins limit. Diluting the pooled sample (b) (4) results in a dilution of (b) (4) which is within the MVD of (b) (4). The MVD for each of the unpooled vials is (b) (4) (b) (4) pooled vials). The dilution for each vial is (b) (4) which is within the MVD of (b) (4) for each vial.

Adult Dose:

Taking into account the current endotoxin specification, the maximum adult dose is 100 mg administered intravenously over 30 to 60 minutes.

(b) (4)

Pediatric Dose (Although the drug product is not recommended for pediatric patients, the following doses are suggested if no alternative antibacterial drugs are available):

(A) For patients 8-11, 1.2 mg/Kg every 12 hours

(b) (4)

(B) For patients 12-17, 50 mg every 12 hours.

(b) (4)

The maximum potential endotoxin exposure due to the drug product is less than the USP <85> recommended maximum level of NMT 5 EU/Kg/Hour for adult and pediatric patients.

Note to Reviewer: Similar pediatric calculations were performed in (b) (4).doc, dated 16 April 2016. It is also noted that to exceed the USP limit, patients 12-17 would have to weigh less than 17.5 kg (b) (4) (b) (4). The CDC published growth chart for US children indicates that 12 year-old girls and boys in the 50 percentile weigh about 40 kg. See <https://www.cdc.gov/growthcharts/data/set1clinical/cj411021.pdf> and <https://www.cdc.gov/growthcharts/data/set1clinical/cj411022.pdf>

Reviewer's Assessment: The information provided by the applicant was adequate.

Acceptable

Sterility

(Information Located at: Section 3.2.P.5.3, Validation of Analytical Procedures [Sterility Test Method Suitability], Pages 1-69/69)

(b) (4)

Exhibit batches ADT403, ADT404, and ADT405 met the release specification of sterile (Section 3.2.P.5.4).

Reviewer’s Assessment: The information provided by the applicant was adequate.

Acceptable

P.7 Container Closure

Summary table of the container closure system proposed

See P.1.

P.8 Stability

N/A

P. 8.1 Stability Summary and Conclusion

(Information Located at: Section 3.2.P.8.1, Stability Summary and Conclusion, Pages 1-10/10; Section 3.2.P.8.3, Stability Data, Pages 11-25/167)

Proposed Expiry: 24 Months. The expiry date is based on data obtained from Long Term Storage (25±2°C/60±5% RH) and Accelerated Storage (40±2°C/75±5% RH) condition studies. Sterility (per USP <71>) and endotoxin (per USP<85>) analyses were conducted on exhibit batches at 0, 12, and 24 months (long term storage conditions) as well as at 0 and 6 months (accelerated storage conditions). While the sterility specification was the same as the proposed release specification, the endotoxins specification changed from NMT (b) (4) EU/mg on 05/26/2017 (Section 3.2.P.5.1, Page 7/8) to NMT (b) (4) EU/mg, after the 12-month evaluation.

Reviewer’s Assessment: The information provided by the applicant was adequate.

Acceptable

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

(Information Located at: Section 3.2.P.8.2, Post-Approval Stability Protocol, Pages 1-12/12; Section 3.2.P.8.3, Stability Data, Pages 11-25/167)

Strength	Test	Test Method	Acceptance Criteria
50 mg/Vial	Bacterial Endotoxins	USP<85>	≤ (b) (4) EU/mg
	Sterility	USP<71>	Sterile

The testing schedule in the post-approval protocol is as follows:

Stability storage conditions: Long Term Storage Conditions (25±2°C/60±5% RH, Inverted Position)

Test	Time (Months)							
	0	3	6	9	12	15	18	24
Bacterial Endotoxins	X*	-**	-	-	X	-	-	X
Sterility	X	-	-	-	X	-	-	X

*, X = Test will be performed
 **, - = Test will not be performed

Stability Commitment - The applicant commits to placing the first three commercial drug product batches in the long-term stability program, with a minimum of 1 lot per year thereafter, if produced. Vials will be stored in an inverted orientation. Moreover, the applicant commits to withdrawing any production lots from the market if any of the approved drug product specifications are not met.

Reviewer’s Assessment: The information provided by the applicant was adequate.

Acceptable

P.8.3 Stability Data

(Information Located at: Section 3.2.P.8.3, Stability Data, Pages 11-25/167)

Strength	Batch Number	Stability Conditions and Orientation	Sterility USP<71>	Endotoxin* USP<85>
50 mg/Vial	ADT403 (Inverted)	25±2°C/60±5% RH	Sterile at 0, 12 and 24 Months	<2.5 EU/mg at 0 Months; <0.8 EU/mg at 12 Months; <0.31 EU/mg at 24 Months
		30±2°C/65±5% RH		
		40±2°C/75±5% RH	Sterile at 0 and 6 Months	<2.5 EU/mg at 0 Months; <0.8 EU/mg at 6 Months
	ADT404 (Inverted)	25±2°C/60±5% RH	Sterile at 0, 12 and 24 Months	<2.5 EU/mg at 0 Months; <0.8 EU/mg at 12 Months; <0.31 EU/mg at 24 Months
		30±2°C/65±5% RH		
		40±2°C/75±5% RH	Sterile at 0 and 6 Months	<2.5 EU/mg at 0 Months; <0.8 EU/mg at 6 Months
	ADT405 (Inverted)	25±2°C/60±5% RH	Sterile at 0, 12 and 24 Months	<2.5 EU/mg at 0 Months; <0.8 EU/mg at 12 Months; <0.31 EU/mg at 24 Months
		30±2°C/65±5% RH		
		40±2°C/75±5% RH	Sterile at 0 and 6 Months	<2.5 EU/mg at 0 Months; <0.8 EU/mg at 6 Months

*, The endotoxin specification was changed from NMT (b) (4) EU/mg on 05/26/2017 (Section 3.2.P.5.1, Page 7/8) to NMT (b) (4) EU/mg, after the 12-month evaluation.

Reviewer’s Assessment: The information provided by the applicant was adequate.

Acceptable

A Appendices

N/A

A.2 Adventitious Agents Safety Evaluation

N/A

A.2.1 Materials of Biological Origin

N/A

A.2.2 Testing at Appropriate Stages of Production

N/A

A.2.3. Viral Testing of Unprocessed Bulk

N/A

A. 2.4 Viral Clearance Studies

N/A

R Regional Information

Executed Batch Records

Executed lot #(s): Executed batch record summaries were available for batches ADT403, ADT404, and ADT405. The batches were aseptically sterilized according to the proposed parameters.

Reviewer's Assessment: The information provided by the applicant was adequate.

Acceptable

Comparability Protocols

N/A

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Package Insert

(Information Located at: Sections 1.14.3, Final Labeling Text; Section 3.2.P.8.3, Stability Data, Pages 29-38/167)

(b) (4)

In-Use Post Reconstitution Studies (Report: S16/336-GC, June 2016): Drug product vials from exhibit batches ADT403 and ADT404 were reconstituted with 5.3 mL of either 0.9% NaCl, 5% Dextrose, or Ringer’s lactate (10 mg/mL final concentration). The individual suspensions were then inoculated with NMT ^{(b) (4)} CFU of *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Escherichia coli*, *Candida albicans*, or *Aspergillus brasiliensis* and incubated at 20-25°C for 6 hours (see table below). Microbial viability was assessed at 0 and 6 hours by filtering 1 mL of suspension through a 0.45 µm membrane, which was rinsed 3X with NaCl-peptone solution and subsequently placed on either Soybean Casein Digest Agar (SCDA) (bacterial suspensions) or Sabouraud Dextrose Agar (SDA) (fungi suspensions) plates. The SCDA and SDA plates were incubated at 30-35°C for NLT 3 days and 20-25°C for NLT 5 days, respectively. A viability study was also performed with the proposed dilutions. After resuspending and inoculating the drug product vials with the aforementioned diluents and microorganisms, 5 mL of the suspension was diluted into 100 mL of the identical diluent (0.5 mg/mL final concentration). Vials were stored at 20-25°C for up to 48 hours or at 2-8°C for up to 72 hours (see table below). Positive and negative controls were included in the studies. The acceptance criteria were: (1) The negative control should not yield microbial growth while (2) the positive control should not show less than ^{(b) (4)} % of the original inoculum. (3) The CFU count between sampling points should not be higher than ^{(b) (4)} Log.

In-Use Reconstitution Study: Reconstitution Analysis.

Initial Reconstitution Analysis (1 Vial + 5.3 mL Diluent)	Storage Condition	Time point Sample *
0.9% NaCl (5.3 ml)	20-25°C	0 and 6 Hours
5% Dextrose (5.3 ml)		
Ringer’s Lactate (5.3 mL)		

*, Samples were plated onto Soybean Casein Digest Agar (SCDA) (bacterial suspensions) or Sabouraud Dextrose Agar (SDA) (fungi suspensions) plates, which were incubated at 30-35°C for NLT 3 days and 20-25°C for NLT 5 days, respectively.

In-Use Reconstitution Study: Dilution Analysis.

Dilution Study (5 mL from Original 5.3 mL Reconstitution into 100 mL of Diluent)	Storage Condition	Time point Sample *
0.9% NaCl (5.3 ml)	20-25°C	0, 6, 12, 24, and 48 Hours
	2-8°C	0, 24, 48, 72 Hours
5% Dextrose (5.3 ml)	20-25°C	0, 6, 12, 24, and 48 Hours
	2-8°C	0, 24, 48, 72 Hours
Ringer's Lactate (5.3 mL)	20-25°C	0, 6, 12, 24, and 48 Hours

*, Samples were plated onto Soybean Casein Digest Agar (SCDA) (bacterial suspensions) or Sabouraud Dextrose Agar (SDA) (fungi suspensions) plates, which were incubated at 30-35°C for NLT 3 days and 20-25°C for NLT 5 days, respectively.

In-Use Reconstitution Study: Reconstitution Analysis Results (Batch ADT 403)*

Strain	0 Hours		6 Hours	
	CFU/Plate	Log	CFU/Plate	Log
<i>P. aeruginosa</i>	(b) (4)			
<i>E. coli</i>				
<i>S. aureus</i>				
<i>C. albicans</i>				
<i>A. brasiliensis</i>				

*, Diluent: NaCl; Storage Conditions: 25°C.

In-Use Reconstitution Study: Dilution Analysis Results (Batch ADT 403)*

Strain	0 Hours		24 Hours		48 Hours		72 Hours	
	CFU/Plate	Log	CFU/Plate	Log	CFU/Plate	Log	CFU/Plate	Log
<i>P. aeruginosa</i>	(b) (4)							
<i>E. coli</i>								
<i>S. aureus</i>								
<i>C. albicans</i>								
<i>A. brasiliensis</i>								

*, Diluent: NaCl; Storage Conditions: 5°C.

In-Use Reconstitution Study: Dilution Analysis Results (Batch ADT 403)*

Strain	0 Hours		12 Hours		24 Hours		48 Hours	
	CFU/Plate	Log	CFU/Plate	Log	CFU/Plate	Log	CFU/Plate	Log
<i>P. aeruginosa</i>	(b) (4)							
<i>E. coli</i>								
<i>S. aureus</i>								
<i>C. albicans</i>								
<i>A. brasiliensis</i>								

*, Diluent: NaCl; Storage Conditions: 25°C.

Conclusion: None of the microorganisms resulted in growth higher than (b) (4) Log under the tested conditions. The criteria were met under the evaluated incubation conditions.

Note to Reviewer: Similar results were seen for drug product batches ADT 403 and ADT 404 when they were evaluated in the different diluents and incubation conditions. Data from batch ADT 403, analyzed in NaCl at 5°C or 25°C, serve as representative data samples.

Although results from the negative and positive controls were not provided, the applicant indicated all of the criteria were met. Regarding the 20-25°C hold studies, it is likely the initial reconstitution study was performed independently from the dilution study. This is based on the very low CFU counts seen after 6 hour incubation and the high CFU counts seen at the start of the dilution experiment. Clarification will not be requested from the sponsor since it is clear the diluents do not promote microbial growth under the proposed temperature conditions and times.

Reviewer's Assessment: The information provided by the applicant was adequate.

Acceptable

Post-Approval Commitments:

N/A

Lifecycle Management Considerations

N/A

List of Deficiencies: N/A

Primary Microbiology Reviewer Name and Date: Jonathan Burgos, Ph.D.
17 May 2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
Elizabeth Berr, Ph.D.
17 May 2018



Jonathan
Burgos

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Elizabeth
Barr

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QUALITY A QUALITY ASSESSMENT Chapter VII-Biopharmaceutics



NDA: 211158-ORIG-1

Drug Product Name/Strength: Tigecycline for Injection [50 mg/vial]

Route of Administration: Injectable /Intravenous (IV) infusion

Applicant Name: Amneal Pharmaceuticals.

Submission Date: 10/02/2017 (Original Submission);

02/09/2018 (Response to Information Request (IR))

04/10/2018 (Response to IR)

EXECUTIVE SUMMARY:

Amneal Pharmaceuticals is seeking approval for Tigecycline for Injection [50 mg/vial] indicated for the treatment of complicated skin and skin structure infections, complicated intra-abdominal infections, community-acquired bacterial pneumonia.

This 505 (b)(2) Application relies, for its approval, on FDA's previous findings of safety and effectiveness for the listed drug (LD), Tygacil (tigecycline) for injection, 50 mg/vial (NDA 021821). In addition, the NDA includes a waiver request for the conduct of bioavailability/bioequivalence study(ies).

The proposed product is a lyophilized powder for solution, for intravenous (IV) administration after reconstitution and dilution. The proposed drug product has the same active moiety (tigecycline), and is the same dosage form, for the same route of administration [IV use] and indication as the listed drug (LD), Tygacil (tigecycline) for injection, 50 mg/vial (NDA 021821).

The proposed product and the reference product are different with regards to the excipients (lactose and arginine). Based on supporting data from pH and osmolality comparisons, an in vitro protein binding study, and literature information, differences in the inactive ingredients are not expected to affect the disposition kinetics of tigecycline in the proposed drug product when administered via the IV route. The disposition kinetics of tigecycline should be similar after administration of these two products.

The data and information submitted in the Application demonstrate that the proposed drug product has been adequately bridged to the listed drug; therefore, per 21 CFR 320.24(b)(6), an in vivo pharmacokinetic study is not needed.

From the Biopharmaceutics perspective, NDA-211158-ORIG-1 for Tigecycline for Injection [50 mg/vial], is recommended for APPROVAL

SUBMISSION:

Anneal submitted the current NDA for Tigecycline for Injection [50 mg/vial] under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. This 505 (b)(2) Application relies for approval, on FDA's previous findings of safety and effectiveness for the listed drug (LD), Tygacil[®] (tigecycline) for Injection, which is the subject of approved NDA 021821.

BIOPHARMACEUTICS REVIEW:

The LD, Tygacil[®] is an orange lyophilized powder or cake. Each Tygacil[®] single-dose 5 mL or 10 mL vial contains 50 mg tigecycline and 100 mg of lactose monohydrate lyophilized powder for reconstitution for intravenous infusion. The pH is adjusted with hydrochloric acid, and if necessary sodium hydroxide. The product does not contain preservatives¹.

Anneal's proposed product Tigecycline for injection, 50 mg/vial, is also a lyophilized orange (b) (4) cake or powder, and contains the same active ingredient, is the same dosage form for the same route of administration as the LD. However, the formulation of Anneal's proposed drug product is qualitatively different from Tygacil (Tigecycline) for Injection, 50 mg/vial, as described below. The comparison of qualitative and quantitative composition of the proposed drug product and the listed drug [LD] is provided below in Table 1.

There are two principle components of the proposed intravenous formulation for tigecycline; the active ingredient, tigecycline (50 mg/vial), and the excipient, L-arginine (50 mg/vial). This differs from the LD., which is composed of Tigecycline (50 mg/vial) and lactose (100 mg/vial). Similar to the LD, the proposed product is a lyophilized dosage form for injection, which upon reconstitution is further diluted for infusion. The instructions for dosage and administration will be the same as that of Tygacil.

The comparative osmolality and pH of the exhibit batches vs. Tygacil[®] are summarized below in Tables 2-3:

¹ Tygacil label: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021821s0431b1.pdf

Table 1. Formulation comparison between the proposed and the listed product

Name of the Ingredient	Pharmaceutical function	RLD Formulation	Proposed Formulation
		Quantity (mg/Vial) #	Quantity (mg/Vial)
Tigecycline	Active ingredient	50.0 mg	50.0 mg*
L-Arginine	(b) (4)	-	50.0 mg
Lactose Monohydrate		100.0 mg	(b) (4)
Hydrochloric acid		pH adjustment	
Sodium Hydroxide	pH adjustment	q. s.	(b) (4)

* The actual quantity of Tigecycline is calculated by considering the assay on as is basis.

Vials will be overfilled 6% to allow the withdrawable volume.

(b) (4)

q. s. Quantity sufficient

\$ complies with EP, JP, USP and FCC monographs current edition

Table 2: Comparison of pH and osmolality between Amneal’s proposed product and the LD, Tygacil® for Injection: reconstituted product (10 mg/mL of Tigecycline)

	LD: TYGACIL		Proposed Drug Product: Tigecycline for Injection-		
	AK8M12	AKDR12	ADT403	ADT404	ADT405
	Upon reconstitution with 0.9% sodium chloride				
Osmolality	(b) (4)				
pH	(b) (4)				
	Upon reconstitution with 5% Dextrose				
Osmolality	(b) (4)				
pH	(b) (4)				
	Upon reconstitution with Ringer Lactate				
Osmolality	(b) (4)				
pH	(b) (4)				

Table 3: Comparison of pH and osmolality between Amneal’s proposed product and the LD, Tygacil® for Injection: reconstituted and diluted product (0.5 mg/mL of Tigecycline)

	LD: TYGACIL		Proposed Drug Product: Tigecycline for Injection-		
	AK8M12	AKDR12	ADT403	ADT404	ADT405
Upon reconstitution and dilution with 0.9% sodium chloride					
Osmolality	(b) (4)				
pH	(b) (4)				
Upon reconstitution and dilution with 5% Dextrose					
Osmolality	(b) (4)				
pH	(b) (4)				
Upon reconstitution and dilution with Ringer Lactate					
Osmolality	(b) (4)				
pH	(b) (4)				

Effect of arginine in the proposed product: L-Arginine, an essential amino acid included in parenteral formulations (b) (4). The Applicant described it (b) (4). Arginine has a low urinary excretion (5% of administered dose). Most of arginine in the glomerular filtrate is effectively reabsorbed.

The Applicant stated that there is no direct evidence in the literature of the effect of arginine of the disposition of Tigecycline. Indirect evidence can be inferred from the analysis of the disposition processes of both substances. Arginine and Tigecycline are not substrates of the same transporters. Arginine and Tigecycline do not share any disposition mechanism, thus the probability of any interaction at this level is very low. The Applicant also performed simulation of the plasma levels of a 30-minute infusion of a dose of 50 mg of L Arginine and demonstrated that, taking into account that the average baseline L-arginine levels in healthy volunteers are 15.1+-2.6 µg/mL, the administration of a dose of 50 mg arginine would not produce any significant change in the normal baseline levels². The Applicant concluded that interaction at the disposition level between Tigecycline and Arginine is not expected.

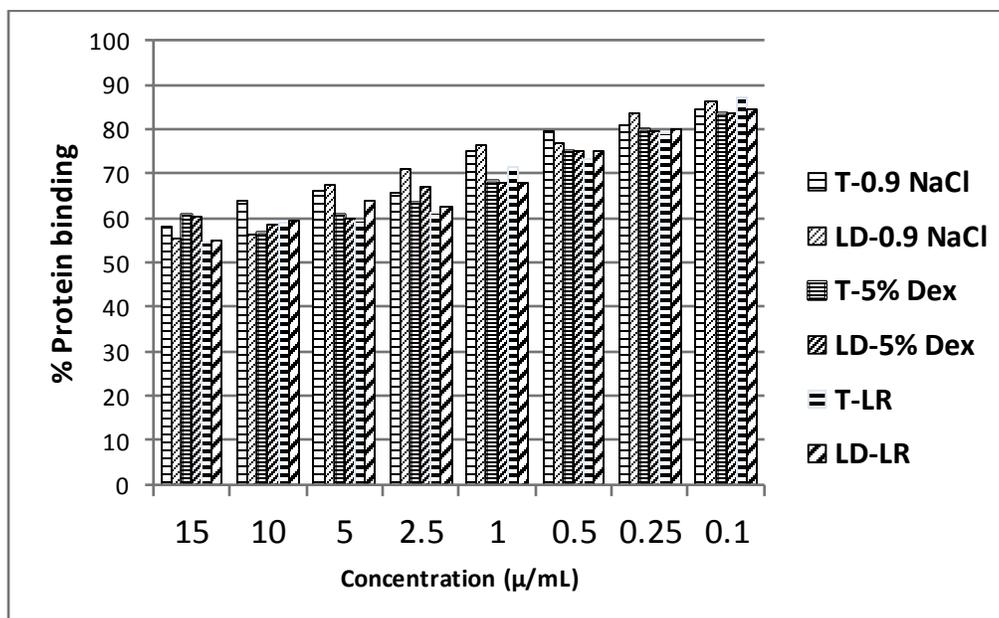
² Details in section 5.3.5.4: <\\cdsesub1\evsprod\nda211158\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\antibacterial\5354-other-stud-rep\disposition-kinetics\5-3-5-4-study-report-disposition.pdf>

Effect of lack of lactose in the proposed product: The Applicant stated that removal of lactose monohydrate in the proposed drug product (compared to the listed drug) should have no significant effect on the disposition kinetics of Tigecycline in human subjects. In support, the Applicant cited NDA 205645 Clinical Review³ which concluded that the substitution (arginine instead of Lactose) is not expected to affect the excretion, metabolism, and/or distribution and therefore will not affect the systemic exposure (both maximum plasma concentration [C_{max}] and area under the plasma concentration-time curve [AUC]) to tigecycline or the pharmacologic activity of tigecycline.

Protein binding study⁴: To assess the impact of differences in excipients, the Applicant conducted an in-vitro protein binding study in human plasma and determined the concentrations of total and free tigecycline using the proposed drug product and the listed drug product. The in vitro protein binding study is briefly summarized in Appendix 1 of this Review.

In this study, Tigecycline for Injection (Test) and Tygacil (LD) reconstituted in different solvents showed similar protein binding. Therefore, the Applicant concluded that the excipient change in the formulation of the test product has no impact on the protein binding capacity of tigecycline. Table 4 below, provides a comparison of in vitro protein binding between reconstituted and diluted Amneal's proposed product (T) and LD Tygacil® (LD) for Injection.

Table 4: Comparison of in vitro protein binding between Amneal's proposed product (T) and LD Tygacil® (LD) for Injection: reconstituted and diluted product



³ https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/205645Orig1s000PharmR.pdf

⁴ Submitted in response (dated: 02/09/2018) to IR (dated: 11/30/2017):

<https://cdsesub1\evsprod\nda211158\0008\ml\us\1-2-cover-letter-esigned-seq-0008-20180209.pdf>

Waiver Request:

In this NDA submission, the Applicant is requesting that the FDA waives the CFR requirement to provide in vivo bioavailability/bioequivalence (BA/BE) data for their product under 21 CFR § 320.24(b)(6) i.e. an alternative approach for measuring bioavailability or establishing bioequivalence. The Applicant stated that the proposed drug product contains the same concentration, is for the same route of administration and is intended for the same indications as the listed drug, Lilly's Tygacil®, NDA 021821.

Amneal's proposed product contains the same active and inactive ingredients in the same concentration as the LD, except that L-arginine has been added to Amneal's formulation (b) (4), and the RLD's (b) (4) lactose monohydrate has been removed from Amneal's formulation (Table 1).

In Summary, to support the waiver request for the proposed Amneal' Tigecycline for Injection, the Applicant submitted the following data and information:

- Qualitative and quantitative composition (Table 1)
- Comparative physicochemical data between the proposed drug product and the LD product (Tables 2-3)
- Effect of the difference in the excipients on the disposition kinetics of tigecycline
- In vitro protein binding study demonstrating the effect of the difference in the excipients on in vitro protein binding (Table 4 and Appendix 1)

Reviewer's Final Assessment: Adequate

The data from pH and osmolality comparisons, in vitro protein binding study and literature information, shows that the differences in the inactive ingredients are not expected to affect the disposition kinetics of tigecycline in the proposed drug product when administered via the IV route.

Per 21 CFR 320.24(b)(6), FDA can rely on any other approach deemed adequate to establish the bridge (bioavailability/bioequivalence) between the listed and proposed drug products. Therefore, based on the totality of the information provided, the Applicant has established an appropriate bridge between the proposed drug product and the LD.

RECOMMENDATION:

Based on the data submitted, the proposed drug product, Tigecycline for Injection [50 mg/vial], has been demonstrated to be adequately bridged to the listed drug, Tygacil. The Division of Biopharmaceutics therefore recommends **APPROVAL** for NDA 211158.



SIGNATURE BLOCK:

Om Anand, Ph.D. [Date: 05/14/2018]

Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Products/OPQ

Elsbeth Chikhale, Ph.D. [Date: 05/17/2018]

Acting Biopharmaceutics Lead
Division of Biopharmaceutics
Office of New Drug Products/OPQ

Appendix 1

In vitro protein binding study⁵: Determination of plasma protein binding of tigecycline using rapid equilibrium dialysis method in human plasma (test and reference formulations).

Objective: To evaluate and compare the impact of the excipient change in the formulation of the test and the reference product, by conducting an in vitro protein binding study in human plasma and determining the concentration of total and free tigecycline using the test and reference products.

Method: This study was performed to evaluate the plasma protein binding of Tigecycline for Injection USP, 50 mg/vial (Test Product), and Tygacil® (tigecycline) for injection (Reference Product) in three different reconstitution solvents (0.9% Sodium Chloride Injection, 5% Dextrose injection and Lactated Ringer's solution) each at eight different concentrations (0.1 µg/mL, 0.25 µg/mL, 0.5 µg/mL, 1 µg/mL, 2.5 µg/mL, 5 µg/mL, 10 µg/mL and 15 µg/mL along with the reference compounds Atenolol and Propranolol representing positive and negative controls using a rapid equilibrium dialysis method in human plasma

Treatment:

- Test formulation: Tigecycline for injection 50mg/vial manufactured by: Gland Pharma Limited. B.No. ACT701.
- Reference product: Tigecycline for injection 50mg/via Tigecycline for injection 50mg/vial Manufactured By: (b) (4). B.No. AKFD12.

Summary of Bioanalytical Method:

The plasma concentrations of Tigecycline in the test and reference formulation samples were determined by a LC-MS/MS method using Tigecycline-d9 as the internal standard and an eight-point calibration curve.

Concentration of the Test item free fraction and percent parent bound was calculated using the following equation:

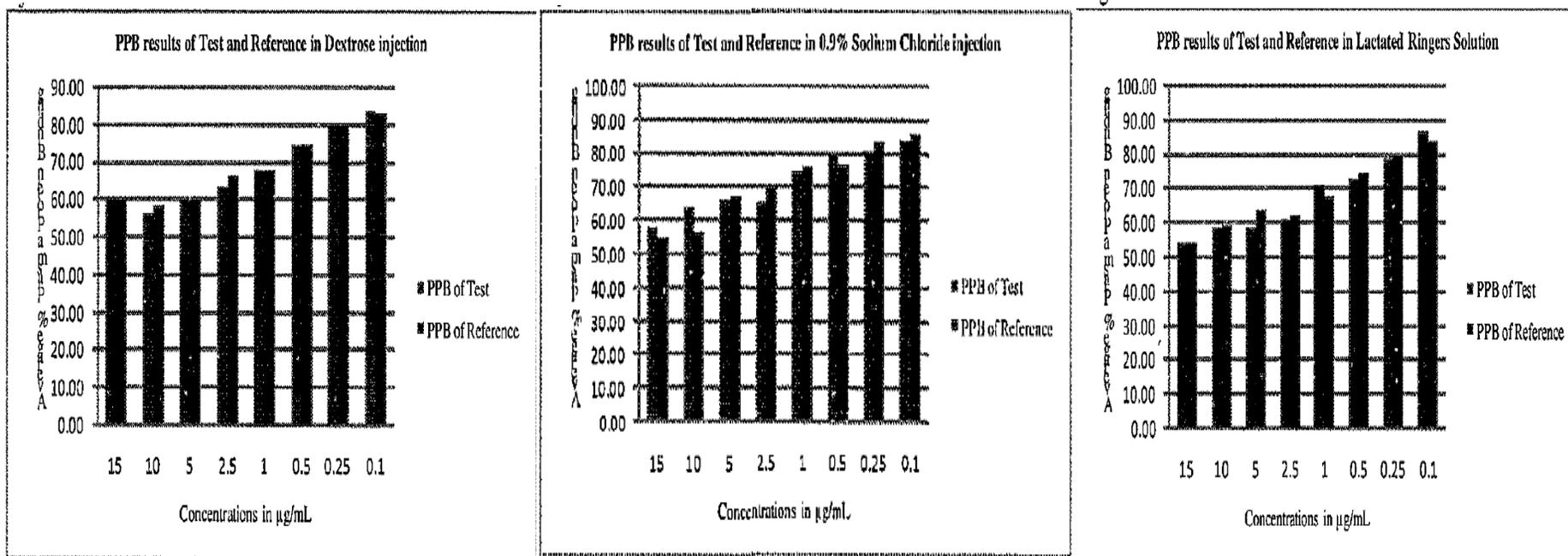
$$\begin{aligned}\text{Free fraction (Fu)} &= [\text{free}] / \{[\text{free}]+[\text{bound}]\} \\ &= [\text{Peak area of receiver}] / [\text{peak area of donor}/0.1]\end{aligned}$$

$$\text{Percent Protein Binding} = 100 * (1-\text{Fu}).$$

⁵ Details of this study are located at the following link: <\\cdsesub1\evsprod\nda211158\0008\m5\53-clin-stud-rep\531-rep-biopharm-stud\5313-in-vitro-in-vivo-corr-stud-rep\vll-0118-ng-d002\vll-0118-ng-d002.pdf>

Summary of Results:

Table 7: Comparison of plasma protein binding (PPB) of tigecycline from the reference and the test product, diluted in various diluents (NaCl, Dextrose and Lactated Ringer Solution)



Conclusion: The Applicant concluded that based on the results of this study, Tigecycline for Injection USP, 50 mg/vial (Test Product-VPCD/TC/18/8) reconstituted in different solvents showed a moderate binding to human plasma. Similar results were recorded Tygacil (tigecycline) for injection (Reference Product- VPCD/RC/18/5). Therefore, it is concluded that the excipient change in the formulation of the test product has no impact in its protein binding capacity.



Om
Anand

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Elsbeth
Chikhale

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LABELING

I. Package Insert

1. Highlights of Prescribing Information

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	TIGECYCLINE for injection
Dosage form, route of administration	for intravenous use
Controlled drug substance symbol (if applicable)	N/A
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	<p>The Highlights section currently states: “For Injection: 50 mg, lyophilized powder for reconstitution in a single-dose (b) (4) vial.”</p> <p>The following proposed edit will be sent to OND: “50 mg of tigecycline as a lyophilized powder in a single-dose vial for reconstitution”</p>

2. Section 2 Dosage and Administration

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	The description of the reconstitution procedure is provided in this section along with stability data for the reconstituted solutions. The drug compatibility with co-administered drugs information is consistent with the supporting data in the NDA.

3. Section 3 Dosage Forms and Strengths

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	<p>“For Injection: Each single-dose (b) (4) glass vial contains 50 mg of tigecycline, USP as an orange lyophilized powder for reconstitution.”</p> <p>Our proposed edit is to remove (b) (4).</p>
Strengths: in metric system	50 mg
Active moiety expression of strength with equivalence statement (if applicable)	N/A. Tigecycline is not a salt
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Each single-dose (b) (4) glass vial contains 50 mg of tigecycline, USP as an orange lyophilized powder for reconstitution.

4. Section 11 Description

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	tigecycline for injection, USP
Dosage form and route of administration	lyophilized powder for reconstitution for intravenous infusion
Active moiety expression of strength with equivalence statement (if applicable)	N/A. Tigecycline is not a salt
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	50 mg arginine. HCl and NaOH are added if necessary to adjust the pH.
Statement of being sterile (if applicable)	Refer to discussion below.
Pharmacological/ therapeutic class	antibacterial
Chemical name, structural formula, molecular weight	(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 ₂₉ H ₃₉ N ₅ O ₈ ; MW = 585.65
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	The product is an orange lyophilized powder or cake and does not contain preservatives.

5. Section 16 How Supplied/Storage and Handling

Item	Information Provided in NDA
(Refer to Labeling Review Tool and	21 CFR 201.57(c)(17))
Strength of dosage form	50 mg
Available units (e.g., bottles of 100 tablets)	50 mg/vial. Available in 10 vials/box
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	5 mL glass vial containing 50 mg tigecycline, USP - 10 vials/box. NDC 70121-1647-7
Special handling (e.g., protect from light)	Stability of reconstituted solution is provided in this section. A comment will be sent to OND that the stability of the reconstituted solutions should be referenced to Section 2.4.
Storage conditions	USP Controlled room temperature
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Amneal Biosciences LLC

Reviewer’s Assessment of Package Insert: {Adequate}

The highlights section for dosage forms and strengths currently states:

“For Injection: 50 mg, lyophilized powder for reconstitution in a single-dose (b) (4) vial.”

This is in a similar format to the labeling for Tygacil, which currently states:

“For Injection: 50 mg, lyophilized powder for reconstitution in a single-dose 5 mL vial or 10 mL vial.”

However, currently the preferred format for the description of the dosage form would be in the following format:

For injection: 50 mg of tigecycline as a lyophilized powder in a single-dose vial for reconstitution

The proposed edit above will be sent to OND for the labeling team discussion.

The dosage forms and strengths section currently states:

(b) (4)

Our proposed edit is to remove (b) (4). See comments for the NDA labeling review discussion below.

The labeling describes the in-use stability data of the reconstituted product, and also the list of acceptable co-administered drugs. Adequate supporting data was submitted for the in-use stability data. Refer to the drug product review. The PI was updated on 04/04/2018 to list the following drugs that the product is compatible with. Adequate supporting data was submitted to the NDA to support these drug compatibilities.

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, haloperidol, Lactated Ringer's, lidocaine HCl, metoclopramide, morphine, norepinephrine, piperacillin/tazobactam (EDTA formulation), potassium chloride, propofol, ranitidine HCl, theophylline, and tobramycin.

There is not currently a statement that the product is sterile in section 11. A comment was included in the PI that section 11 should be updated to state that the product is sterile.

Section 16 currently describes the stability of the reconstituted solution. The labeling for Tygacil also currently describes the stability of the reconstituted solution. However, currently the preference is to reference the stability information of the reconstituted solutions in section 2.4. Section 16 should replace the stability of the reconstituted solution with the following reference to section 2.4 in the PI:

“For storage conditions of reconstituted and further diluted solutions refer to Section 2.4”

(b) (4)

➤ *Any deficiencies should be listed at the end in the “List of Deficiencies”*

Refer to “Comments for NDA Labeling Team Discussion” below.

II. Labels:

1. Container and Carton Labels

(b) (4)



Container Label (above). Submitted 04/17/2018

(b) (4)



Carton Label (above). Submitted 04/17/2018.

Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Tigecycline for Injection, USP	Tigecycline for Injection, USP
Dosage strength	50 mg per vial	50 mg per vial
Net contents	Single-dose vial	10 single dose vials
“Rx only” displayed prominently on the main panel	Yes	Yes
NDC number (21 CFR 207.35(b)(3)(i))	70121-1647-1	70121-1647-7
Lot number and expiration date (21 CFR 201.17)	Space provided	Space provided
Storage conditions	Storage conditions on carton, not container. Adequate per 21 CFR 201.10(i)	Prior to Reconstitution: Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
Bar code (21CFR 201.25)	Yes	Yes
Name of manufacturer/distributor	Amneal Biosciences, Bridge Water NJ There is also a line “made in India”. Drug Product is manufactured in India	Amneal Biosciences, Bridge Water NJ There is also a line “made in India”. Drug Product is manufactured in India
And others, if space is available	Inactive ingredients, including quantity of arginine, listed. Package Insert referenced for dosage information	Inactive ingredients, including quantity of arginine, listed. A brief description of the dosing information is also provided.

Reviewer’s Assessment of Labels: {Adequate}

IRs were sent on 03/02/2018 for updates to the labeling. The IRs included a request for addition of product lot and space for the expiration date. In addition, the carton originally only described reconstitution with NaCl and dextrose, not Lactated Ringer’s Injection. The IR requested that Lactated Ringer’s injection be included in the list of

diluents to be consistent with the PI. The labeling was updated on 04/17/2018 to include the requested edits. This is adequate.

➤ *Any deficiencies should be listed at the end in the “List of Deficiencies”*

None

List of Deficiencies:

Comments for NDA Labeling Team Discussion:

The Highlights section of the PI currently has: “For Injection: 50 mg, lyophilized powder for reconstitution in a single-dose (b) (4) vial.” The following proposed change will be sent: “50 mg of tigecycline as a lyophilized powder in a single-dose vial for reconstitution”

The description (b) (4) should be removed from Section 3, Dosage Forms and Strengths.

A statement should be included in section 11 that the product is sterile.

Section 16 should replace the storage conditions with the following reference to section 2.4 in the PI: “For storage conditions of reconstituted and further diluted solutions refer to Section 2.4”

Overall Assessment and Recommendation:

The product labeling is adequate from a CMC perspective, but refer to the proposed edits above.

Primary Labeling Reviewer Name and Date:

Erika E. Englund, Ph.D.

CMC Reviewer

05/31/2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed):



Erika
Englund

Digitally signed by Erika Englund
Date: 6/01/2018 07:07:55AM
GUID: 51389ea30003450414230afb8c3e8114



Dorota
Matecka

Digitally signed by Dorota Matecka
Date: 6/01/2018 06:36:34PM
GUID: 508173530000859092c69506374d0011

ATTACHMENT I: Final Risk Assessments

From Initial Risk Identification			Review Assessment		
From Initial Risk Identification	Review Assessment	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
		H, M, or L		Acceptable or Not Acceptable	
Assay /Stability	Formulation Raw materials Process parameters Scale/equipment Site	L	Sufficient evaluation of impurities/degradation products provided in the NDA Adequate acceptance criteria proposed	Acceptable	The (b) (4) is near the USP limit at the end of the 24 month shelf life. During the lifecycle of this product, post-approval changes should consider the impact on the (b) (4) levels.
Uniformity of Dose	Formulation Process parameters Scale/equipment Site	L	Adequate (b) (4) controls implemented in the manufacturing process	Acceptable	
Reconstitution time	Formulation Raw materials Process parameters Scale/equipment Site	L	Data provided demonstrate adequate range	Acceptable	
Extractables and leachables	Formulation Container closure	L		Acceptable	E/L studies should be performed with stopper change
Endotoxins	Formulation Raw materials Process parameters Scale/equipment Site	M		Acceptable	
Sterility	Formulation Raw materials Process parameters Scale/equipment Site	H		Acceptable	

Particulate matter	Formulation Raw materials Process parameters Scale/equipment Site	M	Consistent data provided to demonstrate that the drug product meets <788>	Acceptable	
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OVERALL RECOMMENDATION:

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

On behalf of OPQ Review Team

Dorota Matecka, ATL for NDA 211158