CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212156Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 212156
Assessment # 2

Drug Product Name	Micafungin for injection
Dosage Form	Powder for injection
Strength	50 mg/vial and 100 mg/vial
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Par Sterile Products, LLC
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
eCTD 0014	April 6, 2020	Drug Product
eCDT 0016 (**NDA Resubmission**)	December 21, 2020	All
eCDT 0017	March 9, 2021	Drug Product
eCDT 0018	April 29, 2021	Drug Product
eCDT 0019	May 13, 2021	Drug Product
eCDT 0020	May 17, 2021	Drug Product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Katherine Windsor	Ali Al Hakim
Drug Product	Yang Nan	Thomas Oliver
Manufacturing	Ying Zhang	Frank Wackes
Labeling	N/A	N/A
Microbiology	Jason God	Julie Nemecek
Biopharmaceutics	N/A	N/A
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A
Regulatory Business Process Manager	Anh-Thy Ly	
Application Technical Lead	Dorota Matecka	

QUALITY ASSESSMENT DATA SHEET

IQA NDA Assessment Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Adequate	8/4/2020*	Review by Hongbiao Liao*
	III	*Refer to the OPQ Review # 1 dated April 10, 2020*				

**This is the only update to the table from OPQ Review # 1*

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
NDA	21506	Mycamine (micafungin for injection), 50 mg and 100 mg (*Listed Drug*)

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	Adequate	*Refer to the Drug Product and P/T reviews for details*		Dr. Kelly Brant
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			
Other	N/A			

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed drug product, micafungin for injection. All manufacturing and testing facilities are deemed acceptable and an overall "Approve" recommendation was entered into Panorama by the Office of Pharmaceutical Manufacturing Assessment (OPMA) on January 15, 2021. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ).

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Micafungin is a member of the echinocandin class of antifungal agents. This 505(b)(2) NDA provides for a new formulation of micafungin for injection, 50 mg/mL and 100 mg/mL, to be used for the treatment of the same indications as for the listed drug (LD), Mycamine® (micafungin for injection) from Astellas Pharma approved under NDA 21506. Micafungin for injection proposed by the current Applicant, Par Sterile Products, LLC, contains the same drug substance as Mycamine® (micafungin free base, as micafungin sodium) but a different excipient. Both drug products contain (b) (4) citric acid and sodium hydroxide, but the LD contains lactose, whereas Par Sterile Products, LLC's micafungin for injection formulation contains sucrose (b) (4).

The Par Sterile Products, LLC's drug product is a sterile, lyophilized powder for intravenous (IV) administration available in single-dose vials in two strengths: 50 mg and 100 mg. It is to be reconstituted by adding 5 mL of 0.9% sodium chloride injection, USP (b) (4) or 5% Dextrose injection, USP, and then further diluted with 0.9% Sodium Chloride Injection or 5% Dextrose injection for intravenous infusion.

Proposed Indication(s) including Intended Patient Population	Treatment of candidemia, acute disseminated candidaiasis, and candida peritonitis and abscesses in adult and pediatric patients, 4 months and older.
Duration of Treatment	Varies for different conditions (*refer to the Package Insert*)
Maximum Daily Dose	150 mg
Alternative Methods of Administration	None

B. Quality Assessment Overview

This NDA was originally submitted on November 19, 2018 and, following the initial review, it was refused to file (RTF) due to the lack of sufficient drug product stability data. The NDA, which was resubmitted after RTF on July 18, 2019, was issued a Complete Response (CR) letter on May 18, 2020 due to a number of deficiencies identified by the OPQ Review Team. These deficiencies included inadequate status of one of the manufacturing facilities, drug substance intermediate manufacturer, (b) (4) inadequate data from in-use stability studies and lack of proper justification for acceptance criteria proposed for several impurities, including any unspecified impurity. In addition, several other Product Quality comments, which were not considered approvability issues, were also included in the CR letter (refer to the OPQ Review # 1, dated April 10, 2020, and the NDA CR letter dated May 18, 2020, in DARRTS).

The current NDA resubmission provides information to address all of the above defficiencies and comments included in the CR letter; in addition, several minor updates from the product quality microbiology perspective have been also included. These issues are assessed in the current review, which also includes an assessment of the extractable/leachable report submitted in eCTD 0014, the amendment dated April 6, 2020 that was not reviewed in the previous review cycle.

Drug Substance: Adequate

The NDA was recommended for approval from the drug substance perspective in the previous review cycle. The CMC information for micafungin sodium drug substance is cross-referenced the to DMF (b) (4), which was recently assessed and found adequate for another application (refer to the DMF review dated August 4, 2020). There have been no amendments submitted to the DMF since the last review; the DMF remains adequate to support the current NDA.

With the NDA resubmission, the drug substance specification and associated analytical procedure descriptions have been updated to align with those included in the DMF for micafungin sodium. These updates have been found acceptable by the Drug Substance Reviewer (r*efer to the Drug Substance review, below)*.

Drug Product: Adequate

Several deficiencies and comments were identified for the drug product in the previous review cycle. These issues have been adequately addressed in the current resubmission, specifically:

- The root cause of lower assay values observed in the compatibility studies was identified; the repeated study shows the assay values in the diluted micafungin solutions have been found acceptable.
- The Applicant developed new assay and related substance analytical procedures; both methods were validated. The new assay method can identify a new impurity at (b) (4) which is controlled at NMT (b) (4)%.
- The impurity acceptance criteria in the drug product specification have been revised as follows: from (b) (4)% to NMT (b) (4)% for the Impurity (b) (4), and from NMT (b) (4)% to NMT (b) (4)% for the impurity at (b) (4), and any unspecified impurity.
- The results of the extractable/leachable study report have been found acceptable.

The overall information submitted in the NDA resubmission and additional amendments has been found adequate. Based on the overall information and updated stability data submitted in the NDA resubmission, the proposed shelf-life 24 months can be granted for the drug product when stored at room temperature, 20°C to 25°C (*refer to the Drug Product Review, below*).

Labeling: Adequate

N/A (*refer to the OPQ Review # 1 dated April 10, 2020, in DARRTS*)

Manufacturing: Adequate

The drug product manufacturing process was found adequate in the previous OPMA assessment of this NDA. However, one of the manufacturing facilities (the drug substance intermediate manufacturer, (b) (4) was found inadequate and this facility was not considered ready for commercial manufacturing. Following the 704(a)(4) review, this facility has been now found acceptable and all associated facilities are now considered adequate to support this NDA with an overall "Approve" recommendation for this NDA entered into Panorama by OPMA on January 15, 2021 (*refer to the Manufacturing Review, below*).

Biopharmaceutics: Adequate

N/A (*refer to the OPQ Review # 1 dated April 10, 2020, in DARRTS*)

Microbiology (if applicable): Adequate No deficiencies from the Product Quality Microbiology perspective were identified in the first review cycle and the overall microbiology information submitted in the original NDA was found acceptable (refer to the OPQ Review # 1 dated April 10, 2020, in DARRTS). However, in the current resubmission, the Applicant

has proposed revisions to the container closure system integrity test method; in addition, the endotoxin release acceptance criterion was revised from NMT (b) (4) EU/mg to NMT (b) (4) EU/mg (b) (4) (b) (4) (b) (4) These changes have been found acceptable (*refer to the Microbiology Review, below*).

C. Risk Assessment*

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**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	Low	*Adequate stability data including assay results in the in-use stability studies were provided* *Acceptance criteria for impurities revised*	Acceptable	
Particulate Matter	Formulation Raw materials Process parameters Scale/equipment Site	Medium	Adequate procedure and data provided; test included in drug product specification (OPQ Review # 1)	Acceptable	
Bacterial endotoxins	Formulation Raw materials Process parameters Scale/equipment Site	High	*Adequate controls established for the intended patient population*	Acceptable	
Sterility	Formulation Raw materials Process parameters Scale/equipment	High	Adequate microbiological controls (OPQ Review # 1)	Acceptable	

	Site				
Extractable /leachable	Formulation Raw materials	Medium	*The leachable assessment was found adequate by DP and P/T review teams*	Acceptable	
Facilities	Site	High	*All facilities, including the DS Intermediate site are now adequate*	Acceptable	

** The risk table included in the OPQ Review # 1 has been updated and modified based on the information submitted in the NDA resubmission*

D. List of Deficiencies for Complete Response

N/A

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

MICROBIOLOGY

Product Information	Lyophilized powder for injection
NDA Number	212156
Assessment Cycle Number	2
Drug Product Name/ Strength	Micafungin for Injection / 50 mg/vial, 100 mg/vial
Route of Administration	IV
Applicant Name	Par Sterile Products, LLC
Therapeutic Classification/ OND Division	OND/OAP/DAIP
Manufacturing Site	Par Sterile Products, LLC 870 Parkdale Road Rochester, MI 48307
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

List Submissions being assessed (table):

Document(s) Assessed	Date Received
eCTD 0016	12/21/2020

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: The subject submission is a complete response to a Complete Response (CR) Letter issued by the Agency, dated 18 May 2020. The first cycle Microbiology review was adequate, so there are no deficiencies to address from the Agency's CR Letter. However, in addition to responding to deficiencies issued by other review disciplines, the applicant has proposed revisions to the container-closure integrity test method for stability studies and the endotoxin release specification. These changes are addressed in this review.

Concise Description of Outstanding Issues: None

Supporting Documents: N212156MR01.docx, dated 6 March 2019 (adequate).

Container-Closure Integrity Testing (CCIT)

In the original re-submission (eCTD 0003, 7/18/2019) the applicant proposed to perform CCIT (b) (4)

The information provided demonstrates the suitability of the proposed CCIT method to confirm container integrity during stability studies.

Endotoxin Specification

The applicant has revised the endotoxin specification from NMT (b) (4) EU/mg to NMT (b) (4) EU/mg. The cause for the change is (b) (4)

(b) (4)

Although the original endotoxin specification was NMT (b) (4) EU/mg, testing was performed such that the routine release would be (b) (4) EU/mg (see the discussion in N212156MR01.docx, 6 March 2019). Thus, additional method suitability testing is not necessary. (b) (4)

(b) (4)

Primary Microbiology Reviewer Name and Date: Jason M. God, Ph.D, 1/19/2021

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Julie Nemecek, Ph.D., SPQA, 1/19/2021

Jason God

Digitally signed by Jason God
Date: 5/24/2021 10:31:35AM
GUID: 56e1bae0001680fc58a5ce226a4481ab

Julie Nemecek

Digitally signed by Julie Nemecek
Date: 5/24/2021 10:36:49AM
GUID: 5277e82100088e39e79f3393e72134cf

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DOROTA M MATECKA
06/03/2021 01:34:29 PM

QUALITY ASSESSMENT

Recommendation: COMPLETE RESPONSE

NDA #212156

Review #1

Drug Name/Dosage Form	Micafungin for injection
Strength	50 mg and 100 mg
Route of Administration	Intravenous Infusion
Rx/OTC Dispensed	Rx
Applicant	Par Pharmaceuticals
US agent, if applicable	Not Applicable

SUBMISSION(S) REVIEWED		DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Resubmission	SD #0003	*18-Jul-2019*	All
Quality Response to IR	SD #0004	*28-Aug-2019*	Drug Product
Quality Response to IR	SD #0006	*18-Oct-2019*	Biopharmaceutics
Quality Response to IR	SD #0007	*22-Nov-2019*	Drug Product
Quality Response to IR	SD #0008	*13-Dec-2019*	Multiple
Quality Response to IR	SD #0009	*3-Feb-2020*	Drug Product
Labeling	SD #0010	*10-Feb-2020*	Drug Product
Quality Response to IR	SD #0011	*12-Feb-2020*	Drug Substance
Quality Response to IR	SD #0012	*9-Mar-2020*	Multiple
Quality Response to IR	SD #0013	*25-Mar-2020*	Drug Product

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Katherine Windsor	Suong Tran
Drug Product	Yang Nan	Thomas Oliver
Process and Facilities	Ying Zhang	Frank Wackes
Microbiology	Jason God	Denise Miller
Biopharmaceutics	Akm Khairuzzaman	Elsbeth Chikhale
Environmental Assessment	Yang Nan	Thomas Oliver
Laboratory (OTR)	-	-
ORA Lead	Caryn McNab	-
Regulatory Business Process Manager	Anh-Thy Ly	-
Application Technical Lead	Andrei Ponta	-

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Active	See DS review	-
	Type III			Adequate	See DP review	-

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
#0001	NDA #21506	Mycamine
This product was not developed under an IND, and no IND was referenced.		

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA	-	-	-
Pharm/Tox	Pending	Pending	-	-
CDRH	NA	-	-	-
Clinical	NA	-	-	-
Other	NA	-	-	-

Executive Summary

I. Recommendations and Conclusion on Approvability

This NDA is recommended for a **Complete Response** from a chemistry, manufacturing, and controls (CMC) perspective. The overall manufacturing inspection recommendation for this NDA was **Withhold**, as entered into Panorama by the Office of Pharmaceutical Manufacturing Assessment on 3-Apr-2020. Additionally, the drug product review team determined the submission was **Inadequate** from a product quality perspective.

II. Summary of Quality Assessments

A. Product Overview

The proposed product, micafungin for injection, is indicated for the treatment of Candidemia, acute disseminated Candidiasis, Candida peritonitis and abscesses in adult and pediatric patients 4 months of age and older; treatment of Candidemia, acute disseminated Candidiasis, Candida peritonitis and abscesses without meningoencephalitis and/or ocular dissemination in pediatric patients younger than 4 months of age; treatment of esophageal Candidiasis in adult and pediatric patients 4 months of age and older; and prophylaxis of Candida infections in adult and pediatric patients 4 months of age and older undergoing hematopoietic stem cell transplantation (b) (4) The drug product is a sterile, lyophilized product for intravenous (IV) infusion available in single-dose vials in two strengths: 50 mg and 100 mg. It is to be reconstituted by adding 5 mL of: 0.9% sodium chloride injection, USP (without a bacteriostatic agent) or 5% Dextrose injection, USP. It is then further diluted with 0.9% sodium chloride injection or 5% Dextrose injection.

This 505(b)(2) NDA lists the listed drug (LD) as NDA#21506: Mycamine (micafungin for injection, for intravenous use). There is no USP monograph for micafungin. The Applicant described that the only difference is the inactive ingredient (sucrose in the proposed drug product instead of lactose in the LD). There are no novel excipients in this product.

Proposed Indication(s) including Intended Patient Population	Micafungin for injection is indicated for: • Treatment of Candidemia, Acute Disseminated Candidiasis, Candida Peritonitis and Abscesses in adult and pediatric patients 4 months of age and older • Treatment of Candidemia, Acute Disseminated Candidiasis, Candida Peritonitis and Abscesses without meningoencephalitis and/or ocular

	dissemination in pediatric patients younger than 4 months of age • Treatment of Esophageal Candidiasis in adult and pediatric patients 4 months of age and older • Prophylaxis of Candida Infections in adult and pediatric patients 4 months of age and older undergoing hematopoietic stem cell transplantation
Duration of Treatment	Mean duration of treatment is 15-19 days (range 10 to 47 days)
Maximum Daily Dose	150 mg
Alternative Methods of Administration	Not Applicable

B. Quality Assessment Overview

The original NDA was submitted 19-Nov-2018 and after a preliminary review, the Agency determined that the NDA was not sufficiently complete to permit a substantive review due to lack of drug product stability data. Therefore, the Application was refused to file. The Applicant resubmitted the application 18-Jul-2019 with the appropriate amount of stability data.

Drug Substance: Adequate

Micafungin, an antifungal agent, is a semi-synthetic echinocandin derivative. The drug substance is isolated as the sodium salt, which is soluble in water.

The Applicant cross-references the CMC information for micafungin sodium drug substance to DMF (b) (4) DMF (b) (4) is adequate to support NDA 212156, as noted in a product quality memo (Katherine Windsor, Ph.D., final signature 18-Mar-2020). Specified and unspecified impurity controls are sufficient. Stability data in the referenced DMF support the Applicant's proposed retest period of (b) (4) months for micafungin sodium drug substance stored (b) (4) (b) (4)

This NDA is recommended for approval from a drug substance perspective.

For additional details, refer to the Drug Substance Review by Katherine Windsor, Ph.D.

Drug Product: Inadequate

Micafungin for injection is a sterile, lyophilized product for intravenous (IV) infusion. The drug product is a white cake or powder supplied in a 10 mL clear vial available in

two strengths (50 mg/vial and 100 mg/vial). The strength is expressed in terms of the free acid. The drug product contains micafungin sodium and the following USP/NF excipients: sucrose, citric acid, sodium hydroxide, (b) (4) The excipient levels are within the IIG limits. There are no novel excipients in this product. All excipients are the same as RLD with the exception of sucrose.

The drug product contains (b) (4)% overfill (b) (4) however, the Applicant has not provided adequate justification for the overfill.

The drug product is to be reconstituted and subsequently further diluted in 0.9% sodium chloride or 5% dextrose prior to administration. Results from the study reconstituted and further diluted with 0.9% sodium chloride are acceptable. Results demonstrated that there is an (b) (4)% drop in assay when the drug product is further diluted with 5% dextrose solution. The Applicant has not addressed this drop in assay in this review cycle. Other drug product attributes remained within specifications over the 24 hours in-use stability study regardless of dilution solution.

The Applicant has performed extractable/leachable studies that appear to be in line with the FDA guidance (refer to FDA Comment #2 listed in Refuse to File (RTF) letter dated 18-Jan-2019). However, the final determination of the adequacy of extractable/leachable studies cannot be made in this review cycle due to the lack of justification for the of (b) (4) mcg/mL analytical evaluation threshold (AET). The Applicant has provided additional information regarding the proposed AET on 6-Apr-2020; however, this information was provided too late in the review cycle and was not reviewed.

Drug product specifications include controls of critical quality attributes for lyophilized powder for injection such as: description, identification, completeness and clarity of solution, container content for injection, pH, reconstitution time, water content, uniformity of dosage units by weight, assay, related substances, particulate matter, sterility, bacteria endotoxins, and container closure integrity. The proposed limits are acceptable with the exception of impurities, as the acceptance criteria for several impurities are above ICH qualification thresholds. The Applicant has yet to submit adequate justification for the proposed limits.

There are outstanding concerns with the related substance and assay methods. The related substance method does not have adequate (b) (4) for many impurities. The assay method does not include resolution in (b) (4) The Applicant has not addressed either concern.

Twelve-month long term and six-month accelerated stability data have been provided. No out of specification results have been observed. The proposed shelf-life of 24 months is acceptable if the Application is approved.

In a response to an information request, the Applicant indicated that a response to all of the outstanding drug product issues would be 31-Jul-2020. The PDUFA date for this

Application is 18-May-2020. The timeline proposed by the Applicant is not acceptable. This NDA is not recommended for approval from a drug product perspective.

For additional details, refer to the Drug Product Review by Yang Nan, Ph.D.

Environmental Assessment: Adequate

Pursuant to 21 CFR Sections 25.15(d) and 25.31(a), Par Sterile Products, LLC claims a categorical exclusion from the requirement to prepare an Environmental Assessment Statement. The Applicant confirms that its proposed drug product is to be administered at the same dosage level, for the same duration and for the same indications as the reference listed drug, Mycamine®. Pursuant to 21 CFR 25.15(d), Par Sterile Products, LLC describes that no extraordinary circumstances exist. The categorical exclusion is granted.

For additional details, refer to the Drug Product Review by Yang Nan, Ph.D.

Biopharmaceutics: Adequate

Due to differences in formulation composition between the proposed and listed drug product (sucrose is used in proposed product instead of lactose), a biowaiver based on 21 CFR 320.22(b)(1) is not appropriate. However, a bridge based on 21 CFR 320.24(b)(6), between the proposed product and the listed drug product has been established.

This NDA is recommended for approval from a Biopharmaceutics perspective.

For additional details, refer to the Biopharmaceutics Review by Akm Khairuzzaman, Ph.D.

Process and Facilities: Inadequate

The drug product is manufactured via (b) (4) (b) (4) (b) (4) Adequate process development data has been provided to justify the process. Sufficient controls are also proposed.

The drug product facility has an acceptable history of lyophilization product manufacture, (b) (4) (b) (4) The proposed drug substance intermediate manufacturer, (b) (4) (b) (4) was found unacceptable following a recent 704(a)(4) documentation review in lieu of the pre-approval inspection. The other sites are acceptable based on the previous inspection history.

The overall manufacturing process assessment for this NDA is adequate; however, the facility assessment for this NDA is **inadequate**. This NDA is not recommended for approval from an OPMA perspective.

For additional details, refer to the Process and Facilities Reviews by Ying Zhang, Ph.D.

Microbiology: Adequate

The drug product is formulated, sterile (b) (4) and lyophilized. The manufacturing, sterilization processes, and process controls are adequate.

The drug product specification (sterility and bacterial endotoxins testing) and validations comply with USP <1> Injections, <71> Sterility Test, and <85> Bacterial Endotoxins Test.

Results provided demonstrate the ability of the proposed container-closure system to effectively maintain a sterile barrier at release and the ability of the proposed container-closure system to effectively exclude microbial contamination through proposed expiry date. The in-use stability study results support the proposed storage time of NMT 12 hours at room temperature for both the reconstituted drug product and the diluted drug product.

This NDA is recommended for approval from a microbiology perspective.

For additional details, refer to the Microbiology Review by Jason God, Ph.D.

C. Special Product Quality Labeling Recommendations

The recommendations in Yang Nan's labeling review were conveyed to the OND PM for consideration as the labeling is finalized.

D. Final Risk Assessment

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Eval.**	**Lifecycle Considerations/ Comments**
Assay, Stability		**L**	Drug product met specifications	**Unac**	There are outstanding issues with the assay method
In-use stability		**M**		**Unac.**	Reconstitution with dextrose leads to low assay ((b) (4) %)
Extractable/Leachables		**M**		**Unac.**	The AET is not adequately justified
Microbial limits		**M**	Microbiology and OPMA reviews found testing and controls acceptable	Acc	

Sterility	Manufacture, formulation	**H**	Microbiology and OPMA reviews found testing and controls acceptable	Acc	
Drug Product Impurity Control		**L**		**Unac.**	The Applicant has not justified impurity limits. There are outstanding issues with methods.

E. Deficiencies

1. ***An inspection of the (b) (4) facility is required before the application can be approved as the FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with CGMP. Due to U.S. Government and/or Agency-wide restrictions on travel, we were unable to conduct an inspection during the current review cycle for your application. We will schedule and perform an inspection of this facility as soon as we can. We must perform a complete evaluation of the information associated with the inspection before determining that the site is satisfactory, and this application may be approved.***
2. ***We note that (b) (4) for drug substance in drug product composition. Provide additional justification (b) (4) We recommend that you provide experimental data (b) (4) (b) (4) (b) (4) Provide the experimental results (b) (4) and corresponding assays in tabular format.***
3. ***Regarding the compatibility studies in your Pharmaceutical Development Report, we have the following comments and recommendations:***
    a. ***We note the assay values are (b) (4) mg/mL at time (b) (4) and (b) (4) mg/mL at (b) (4) hours for the 5% dextrose diluted admixture of 100 mg drug product as shown in Table 7-4 on page 126 of 134. The assay value of (b) (4) mg/mL is more than (b) (4) % off from the target 0.5 mg/mL concentration, and this could affect the efficacy of the drug product. Conduct a root cause analysis to determine the reason for the low assay value. After determining the cause and correcting, reconduct the assay test of the in-use-stability study to support your labeling.***
    b. ***It appears that Table 7-3 and Table 7-4 are the same. Comment on why the extra table is listed.***
4. ***Regarding the drug product specification, we have the following comments and recommendations:***
    a. ***The proposed acceptance criterion for Impurity (b) (4) is NMT (b) (4) %. Tighten the limit to NMT 0.2% per ICH Q3B or provide toxicology data to justify the limit.***
    b. ***The proposed acceptance criterion for specified impurity at (b) (4) is NMT (b) (4) %. The limit is above the qualification threshold; therefore,***

justify the limit with toxicology data. Alternatively, tighten the limit to NMT 0.2% per ICH Q3B.

c. *The limit NMT (b) (4) % for any unspecified impurity is above the qualification threshold. Tighten the limit per ICH Q3B.*

5. *With respect to your response to Deficiency #2 and the related substance method (MET-00698) dated 22-Nov-2019, we have the following comments and recommendations:*

(b) (4)

6. *Regarding the assay method for Micafungin Sodium in Drug Product, we have the following recommendations:*

(b) (4)

7. *We note that in your amendment dated 12-Feb-2020, the structure for Micafungin Impurity (b) (4) has been corrected in Section 3.2.S.3.2, but not in Section 3.2.P.5.5. Update Section 3.2.P.5.5 accordingly for Micafungin Impurity (b) (4)*

83 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

CHAPTER VI: BIOPHARMACEUTICS

Product Information	
NDA Number	212156-ORIG-1-RESUB-3
Assessment Cycle Number	SDN 003 (Resubmission)
Drug Product Name/ Strength	Micafungin for Injection, 50 mg/vial and 100 mg/vial
Route of Administration	Intravenous
Applicant Name	Par Sterile Products, LLC
Therapeutic Classification/ OND Division	Anti-Infective Products/Office of Antimicrobial Products
LD Number	Mycamine [NDA-021506]
Proposed Indication	Treatment of patients with candidemia, acute disseminated candidiasis, candida peritonitis and abscesses

Assessment Recommendation: **Adequate**

Assessment Summary: The Applicant is seeking approval for Micafungin Sodium for Injection, 50 mg/vial, 100 mg/vial under the 505(b)(2) path, relying upon FDA's previous findings of safety and efficacy for the approved MYCAMINE® injection (NDA 021506) as the listed drug. The drug product is to be administered by intravenous administration after reconstitution either with 5 ml of 0.9% NaCl or 5 ml of 5% dextrose for the treatment of symptoms of Esophageal Candidiasis. The proposed drug product is a sterile lyophilized powder which forms a solution after reconstitution. The Biopharmaceutics review was focused on the evaluation of the adequacy of the overall information/data supporting; 1) biowaiver request and 2) bridging of formulations. Based on the review of the provided information/data, Biopharmaceutics has the following comments:

1. BIOWAIVER REQUEST:

Due to differences in formulation composition between the proposed and listed drug product (sucrose is used in proposed product instead of lactose), a biowaiver request is not appropriate. However, a bridge based on 21 CFR 320.24(b)(6), between the proposed product and the listed drug product has been established. ***Acceptable***.

2. BRIDGING:

Adequate bridging data and information was provided in the application. Therefore, the bridge between the proposed and Listed Drug (LD) products has been established based on 21 CFR §320.24(b)(6). ***Acceptable***.

3. ***RISK ASSESSMENT:*** The table below shows the initial and final review assessment from a Biopharmaceutics perspective.

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
Physicochemical attributes of the formulation	Low	Dissolution is irrelevant, but bridging between the proposed drug product and the LD is required as per 505(b)(2) regulation	Low	The proposed drug product, upon reconstitution, forms an injectable solution. Bridging between the proposed drug product and the LD has been established based on the submitted information.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
SDN-001	**11/19/2018 (RTF)**
SDN-003	**07/18/2019**
SDN-006	**10/18/2019**

Highlight Key Issues from Last Cycle and Their Resolution: None

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): Original submission was "Refuse to File" (RTF).

B.1 BCS DESIGNATION

Solubility data:

Micafungin sodium API is soluble in water as supported by the provided data below.

Table 1. pH Solubility Data for Micafungin Sodium, Study NBD107-15

Target pH	pH of the dispersion	Solubility of Micafungin (mg/mL)
pH 4.0	4.00	≥ 39.765*
pH 5.0	4.89	≥ 44.878*
pH 5.5	5.41	≥ 44.590*
pH 7.0	6.91	≥ 42.882*

Assessment: N/A
BCS designation is not applicable for this dosage form.

B.2 BRIDGING OF FORMULATIONS

The comparative formulation composition of the proposed 505(b)(2) drug product vs the listed drug product, MYCAMINE® injection is provided in Table 2 below. Both products are "lyophilized dry powder for solution for infusion".

Table 2. Comparison of the proposed product composition to the LD

Ingredient	Grade	Function	Par Composition (mg/vial)		RLD Mycamine® Composition (mg/vial)	
Micafungin Sodium	N/A	Active Pharmaceutical Ingredient	50 mg	100 mg	50 mg	100 mg
Sucrose	NF	(b) (4)	200 mg (4% w/v)[b]	400 mg (8% w/v)[b]	N/A	N/A
Lactose	NF		N/A	N/A	200 mg	200 mg
Citric Acid	USP	pH Adjustment	QS	QS	QS	QS
Sodium Hydroxide	NF/EP	pH Adjustment	QS	QS	QS	QS
(b) (4)						

[b] Amount after reconstitution with 5 mL of diluent.

As shown in the above table, the proposed drug product contains sucrose instead of lactose in the LD. However, both formulations form a concentrated solution upon reconstitution. After dilution (in 100 mL solution for administration

via IV infusion), both products contain the same amount of micafungin at the same concentration, as described below.

The proposed drug product is reconstituted with 5 mL of 0.9% NaCl or 5% dextrose. A study was conducted to evaluate the pH, assay, impurity, completeness and clarity of the reconstituted product (submitted under the pharmaceutical development). The study was conducted to evaluate the stability of the reconstituted product at room temperature for 24 hours. All results were acceptable after 24 hours for chemical attributes (refer to Table 7-1 and 7-2 for results in Pharmaceutical Development report FRD-18-001)

After reconstitution, the reconstituted drug product can also be further diluted with 0.9% NaCl or 5% dextrose in an IV bag and the final concentration of the drug could be 0.5 mg/ml. The Applicant has also conducted an admixture study for 30 hours to evaluate the pH, assay, impurity, and clarity of this diluted product and compared with that of the listed drug product (after similar dilution). The reconstituted drug product was injected into a commercially prepared IV bag and the resulting concentration was 0.5 mg/ml. The admixture solution was then evaluated for stability. A separate study for risk assessment of microbial contamination of diluted solutions was also conducted for up to 48 hours). Results indicate (table 3 below) that there was a (b) (4) (b) (4) The assay value was low (below (b) (4) % of label claim) for the dextrose admixture as highlighted in red in table 3 below. This has been communicated to the drug product CMC reviewer. The acceptability of these admixture stability data will be determined by the drug product reviewer.

Table 3. Micafungin for Injection 0.5 mg/mL Admixture Study

Diluent	Admixture Study	Batch #	Diluent	Time (Hours)	Desc.	pH	Assay (mg/mL)	% IMP	% IMP (b) (4)	% Imp. (b) (4)	% Unk. Imp. (b) (4)	% Total Impurities
Saline	50	308975	Saline	0	(b) (4)	5.2						(b) (4)
				24		5.3						
				30		5.3						
	100	308975		0		5.3						
				24		5.4						
				30		5.4						
Dextrose	50	308975	Dextrose	0		4.2						
				24		4.2						
				30		4.3						
	100	308975		0		4.3						
				24		4.3						
				30		4.4						

The Applicant has provided the following comparative physicochemical characteristics of the two products (proposed and LD product) as follows:

Table 4. Comparison between the proposed drug product and LD product:

Micafungin Analysis		Test#	50-mg Vial				100-mg Vial				Release Specification
			Mycamine Lot A000001655	Par Lot 308974	Par Lot 308973	Par Lot 308972	Mycamine Lot A000002491	Par Lot 308968	Par Lot 308967	Par Lot 308966	
Description		MET-00003	Satisfactory	Satisfactory	Satisfactory	Satisfactory	Satisfactory	Satisfactory	Satisfactory	Satisfactory	White Cake or Powder
Completeness and Clarity of Solution	0.9% Saline	MET-00705	Passes	Passes	Passes	Passes	Passes	Passes	Passes	Passes	Meets USP requirements for constitutes solutions under Injection <1>
	5% Dextrose		Passes	Passes	Passes	Passes	Passes	Passes	Passes	Passes	
pH		MET-00706	5.2	5.1	5.2	5.9	5.3	5.0	5.5	5.5	4.5-7.0
Reconstitution Time (Seconds)	0.9% Saline	MET-00707	23	18	45	18	24	22	26	19	NMT (b) (4)
	5% Dextrose		25	20	50	16	29	29	33	23	
											(b) (4)
Assay (micafungin)		MET-00689									(b) (4)
Related Substances (%)	Impurity (b) (4)	MET-00698									(b) (4)
	Impurity										
	Impurity										
	Impurity (b) (4)										
	Any Unspecified Impurities										
	Total										

The Applicant completed a search of the available published literature; and compared the levels of sucrose in their proposed formulation of Micafungin for Injection with the levels of sucrose used in other approved products administered by the i.v. route. The following list of literature was submitted in the application:

(i) Norman M. Keith & Marschelle H. Power, The Urinary Excretion of Sucrose and its Distribution in the Blood After Intravenous Injection into Normal Men., Division of Medicine, The Mayo Clinic and Division of Biochemistry, The Mayo Foundation, Rochester, Minnesota.1937

(ii) Jules H. Masserman, Effect of the Intravenous Administration of Hypertonic Solution of Sucrose., Johns Hopkins University, Baltimore, 1935.

(iii) Elliot Wester and Marvin H. Sleisenger, Metabolism of Circulating Disaccharides in Man and the Rat., Journal of Clinical Investigation, Vol., 46., NO. 4, 1967.

(iv) Listed Drug Product's Package Insert

No published literature was identified that indicates that i.v. sucrose could alter the distribution and elimination of micafungin. The above literature indicates that lactose and sucrose are disaccharides that, when administered intravenously, are not metabolized; both are excreted unchanged in urine. In contrast, micafungin is metabolized to a modest degree by arylsulfatase and subsequently catechol-O-methyltransferase or by cytochrome P450 hydroxylation, with fecal excretion being the major route of elimination (total radioactivity recovered in feces at 28 days following a single i.v. dose of ^{14}C-micafungin was 71% of the administered dose).

Initial Assessment: *Inadequate*
The study for physicochemical property of the reconstituted solution does not include some important physicochemical attributes of the reconstituted product such as osmolality and tonicity. The Applicant has claimed that *"Osmolality of the final dosing solutions is not expected to differ, as both products are diluted in isotonic intravenous solution (0.9% sodium chloride or 5% dextrose) prior to administration."* However, based on previous experience, sucrose could increase the osmolality of the solution.

With respect to the Applicant's provided literature citations, this reviewer agrees that that the elimination pathway for micafungin is separate from that of lactose and sucrose and therefore substituting the lactose with sucrose is unlikely to influence the elimination of the proposed product.

The following IR was sent out on October 4th, 2019:
IR Request:

1. *Provide (in module 1.12.15) comparative physicochemical data (osmolality and tonicity) for at least 3 lots of the listed drug product and 3 lots of the proposed drug product after reconstitution and dilution. The measurements should be done in triplicate for each lot tested*

Applicant's response[1] dated 10/18/2019: The Applicant has provided (see table 1 through 13 under module 1.12.15) comparative physicochemical data (osmolality and tonicity) for the listed drug (5 lots of LD) and the proposed drug product (6 lots of Par's product). The 6th lot of the LD was unavailable). The measurements were done in triplicate for each lot tested.

Reviewer's Final Assessment*:* Data of the reconstituted solution shows no significant difference in pH and osmolality between the LD and proposed drug product and therefore the data support the bridging. Considering the overall information submitted in the NDA (some dosage form, drug concentration, route of administration, pH, and osmolality, and no expected difference in PK) the bridge between the proposed drug product and the LD has been established. ***Acceptable***.

[1] \\cdsesub1\evsprod\NDA212156\0006\m1\us

B. 3 BIOWAIVER REQUEST

The Applicant requests a waiver of in vivo bioequivalence studies under 21 CFR §320.21(a)(2).

Assessment:
A biowaiver under 21 CFR §320.21(a)(2) is not feasible due to differences in formulation composition between the proposed and listed drug product. However, based on 21 CFR 320.24(b)(6), a "bridge" between the proposed product and the listed drug product can be established. Therefore, the following IR was sent out on October 4th, 2019:

> 2. *A biowaiver based on 21 CFR §320.21(a)(2) is not feasible due to differences in formulation composition between the proposed and listed drug product. However, based on 21 CFR 320.24(b)(6), a "bridge" between the proposed product and the listed drug product can been established. Therefore; please update the module 1.12.15 and include appropriate regulatory citation for bridging.*

Applicant's response[2] dated 10/18/2019: The Applicant acknowledged the Agency's request to updated module 1.12.15 to include the appropriate regulatory citation for bridging *21 CFR 320.24(b)(6)*.

Reviewer's Final evaluation: Acceptable

R. REGIONAL INFORMATION

Comparability Protocols

Assessment: *None*

Post-Approval Commitments

Assessment: *None*

Lifecycle Management Considerations

None.

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None.

[2] \\cdsesub1\evsprod\NDA212156\0006\m1\us

Primary Biopharmaceutics Assessor's Name and Date: Akm Khairuzzaman, Ph.D., 12/18/2019

Secondary Assessor Name and Date (and Secondary Summary, as needed): Elsbeth Chikhale, Ph.D., 01/02/2020

Akm Khairuzzaman

Digitally signed by Akm Khairuzzaman
Date: 4/10/2020 01:30:47PM
GUID: 502d1ab500002aef5afaa6f74ddf7e69

Elsbeth Chikhale

Digitally signed by Elsbeth Chikhale
Date: 4/10/2020 01:30:32PM
GUID: 50743ccc000031928b54eba1769a5df9

MICROBIOLOGY

Product Information	Lyophilized powder for injection
NDA Number	212156
Assessment Cycle Number	1
Drug Product Name/ Strength	Micafungin for Injection / 50 mg/vial, 100 mg/vial
Route of Administration	IV
Applicant Name	Par Sterile Products, LLC
Therapeutic Classification/ OND Division	OND/OAP/DAIP
Manufacturing Site	Par Sterile Products, LLC 870 Parkdale Road Rochester, MI 48307
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

List Submissions being assessed (table):

Document(s) Assessed	Date Received
eCTD 0001 (Original)	11/19/2018
eCTD 0003 (Resubmission)	07/18/2019
eCTD 0008 (Response to IR, addition of CP)	12/13/2019

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: Initial marketing of a sterile drug product. Proposed manufacturing facility currently manufactures other FDA-approved products. The original submission, received 11/19/2018, was refuse to file. The 07/18/2019 submission is the resubmission after refusal to file.

An IR was issued by the Agency, dated 15 November 2019. The applicant's responses, received 13 December 2019, are addressed in the appropriate sections of this review.

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed):
(None)

Supporting Documents:
DMF (b) (4)
Letter of Authorization dated 05/07/2018 for the Bacterial Endotoxin Reduction studies

on the (b) (4) Gray (b) (4) stoppers. This data was reviewed in (b) (4).doc, dated 02/03/2017 (Adequate)

(b) (4)

S Drug Substance

N/A. Drug substance is supplied non-sterile.

P.1 Description of the Composition of the Drug Product

- **Description of drug product –** Sterile, white powder/cake, 50 mg/vial and 100 mg/vial, single-dose

- **Drug product composition –** Drug product composition is shown in Table 1, below. The original submission described a (b) (4) L batch size for the 50 mg/vial drug product

presentation and a (b) (4) L batch size for the 100 mg/vial presentation. The 7/18/2019 resubmission adds a (b) (4) L scale-up batch size for the 50 mg/vial presentation.

Table 1: Composition of Micafungin for Injection

Ingredient	Grade	Function	Composition (mg/vial)		Unit Dose[4] (mg/mL)	
			50 mg	100 mg	50 mg	100 mg
Micafungin Sodium	N/A	Active Pharmaceutical Ingredient	(b) (4)		10 mg	20 mg
Sucrose	NF	(b) (4)	200 mg	400 mg	40 mg	80 mg
Citric Acid[1]	USP	pH Adjustment	QS	QS	QS	QS
Sodium Hydroxide[1]	NF/EP	pH Adjustment	QS	QS	QS	QS
(b) (4)						

Table 1 was reproduced from Table 2 in "Description and Composition" in Module 3.2.P.1

- **Description of container closure system –**
  - Vial: 10 mL, 20 mm, (b) (4) glass vial
  - Stopper: 20 mm (b) (4) rubber stopper (b) (4)
  - Cap: 20 mm flip-off cap.

P.2 Pharmaceutical Development

(b) (4)

17 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

Reviewer's Assessment: ***Adequate.***
The applicant has met regulatory expectations with regard to the information related to issues of product quality microbiology that is provided in the product labeling. Post-dilution/constitution hold times have been adequately validated.

List of Deficiencies: NA

Primary Microbiology Reviewer Name and Date: Jason M. God, Ph.D., 6 March 2019

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Denise A. Miller, Senior Microbiologist, 6 March 2019

Jason God

Digitally signed by Jason God
Date: 3/06/2020 12:37:27PM
GUID: 56e1bae0001680fc58a5ce226a4481ab

Denise Miller

Digitally signed by Denise Miller
Date: 3/06/2020 01:24:21PM
GUID: 508da7280002a5d546459b998253d1aa

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ANDREI PONTA
04/10/2020 04:40:40 PM