CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208562Orig1s000

CHEMISTRY REVIEW(S)

Office of Pharmaceutical Quality (OPQ) Review

NDA 208562 Resubmission

OPQ Review # 3

Review Date: March 7, 2017
Submission: NDA 208562 Resubmission (Class 1); SDN#14
Submission date: January 9, 2017
OND Division: Division of Anti-Infective Products (DAIP)
Product Name: Voriconazole for Injection, 200 mg/vial
Applicant: Xellia Pharmaceuticals, ApS

Executive Summary:

NDA 208562 was originally submitted on July 24, 2015 and issued a Tentative Approval letter on May 24, 2016 due the pending patent issues. The original NDA was recommended for approval from the Product Quality perspective via the OPQ Review # 2 dated May 24, 2016, in Panorama. The current NDA resubmission (Class 1) contains only minor CMC and labeling updates; specifically, the drug product section includes updates to the excipient (hydroxypropylbetadex) and the container closure system (a vial and a stopper) specifications. In addition, a description of the manufacturing process was updated to include process validation recommendations resulting from the manufacture of three commercial scale batches. These updated sections were reviewed by Drs. Yushi Feng and Steve Rhieu, respectively, who found the proposed revisions acceptable (Attachments I and II, respectively). In addition, the status of the manufacturing facilities was assessed by Dr. Christina Capacci-Daniel who found them acceptable in support of this NDA (Attachment III). The overall recommendation of "Approve" was entered by the Office of Process and Facilities (OPF) into Panorama on March 6, 2017.

Recommendation:

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

Application Technical Lead (*on behalf of the OPQ team*):

Dorota M. Matecka -S

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Dorota Matecka, Ph.D.
Branch III; Division of New Drug Products I; OPQ

Attachments

Attachment I (Drug Product Review - **Dr. Yushi Feng**)

Attachment II (Process Review - **Dr. Steve Rhieu**)

Attachment III (Facilities Review - **Dr. Christina Capacci-Daniel**)

Attachment I

APPEARS THIS WAY ON ORIGINAL

Drug Product Review

NDA 208562 (Request for Final Approval Amendment)

OPQ Division of New Drug Products I

Branch III

Review date: 03/06/2017

Submission: NDA 208562 Resubmission Class 1, Supp. Document Number: 14, eCTD Sequence Number 0013

Submission date: 01/09/2017

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

Product Name: Voriconazole for Injection, 200 mg

Applicant: Xellia Pharmaceuticals, ApS

Background:

NDA 208562 was granted tentative approval on May 24, 2016. The sponsor submits this patent amendment requesting for final approval.

Recommendation:

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

Executive Summary

In addition to the information pertinent to patent issues, this amendment contains updates to the following CMC sections:

- Description of Manufacturing Process and Process Controls: refer to the Process review.
- Control of Excipients: the specification for Hydroxypropyl betadex, NF is updated to include a different way of expressing results (b) (4)
- Container/Closure System: the vial specification is revised to meet the requirements of current USP39 General Chapter <660> on the specific tests for Type I glass container; the standard test procedure for vials is revised accordingly; a new version of standard test procedure for stoppers is provided with updated test procedure on identification by IR.

The CMC changes are minor and have no impact from the product quality microbiology perspective – per email correspondence with the Quality Micro reviewer Dr. Lisa Shelton on 2/23/2017.

Facilities status update for NDA 208562 (resubmission 14): refer to the Facilities review.

This amendment also contains labeling updates reflect changes due to revision of the labeler to (b) (4)

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Derek Smith

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Christina Capacci-Daniel

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Date: 3/06/2017 09:55:39AM
GUID: 51dc71a50000c6c3f0b616578caafab6

Recommendation: Approval

NDA 208562
Review # 2*

Drug Name/Dosage Form	Voriconazole for Injection /Lyophilized Powder for Injection
Strength	200 mg
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Xellia Pharmaceuticals, ApS
US agent, if applicable	Mr. Edward Eichmann

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	07/24/2015	All
Amendment	12/16/2015	Micro, DP, Process
Amendment	03/04/2016	Micro
Amendment	05/19/2016	Labeling
Amendment	05/23/2016	Micro, Biopharmaceutics, Labeling

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Yushi Feng	ONPD/DNDP I/Branch III
Drug Product	Yushi Feng	ONPD/DNDP I/Branch III
Process	Steve Rhieu	OPF/DPA III/Branch VII
Microbiology	Lisa S.G. Shelton	OPF/DMA/Branch II
Facility	Christina Capacci-Daniel	OPF/DIA/Branch II
Biopharmaceutics	Gerlie Gieser	ONDP/DBP/Branch I
Regulatory Business Process Manager	Navi Bhandari	OPRO
Application Technical Lead	Dorota Matecka	ONPD/DNDP I/Branch III
Laboratory (OTR)	N/A	N/A
ORA Lead	N/A	N/A
Environmental Assessment (EA)	Yushi Feng	ONPD/DNDP I/Branch III

***NOTE:** This review includes labeling revisions and revisions to the Biopharmaceutics section as compared with Review # 1 (entered into Panorama on April 30, 2016). All other sections in the current review are the same as in the Review # 1. Therefore, the current document, Review # 2, should be considered the final Product Quality Review (OPQ Integrated Quality Assessment) for this NDA. For details refer to the Executive Summary below (Section II. Summary of Quality Assessments).*

Table of Contents

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		Active	01/08/2015	Adequate by Chem review No. 7 for an ANDA; LoA for Xellia is located in the DMF (b) (4)
	III			Active	04/24/2002	Adequate for NDA20280, lyophilized powder for subcutaneous injection. LoA for Xellia is located in the DMF (b) (4)
	III			Active	04/07/2015	Adequate by Chem review No. 1 for an NDA
	IV			Active	03/22/1999	Adequate for NDA20966, solution for IV injection, no deficiencies. LoA for Xellia is located in the DMF (b) (4) (b) (4)
	V			Adequate	03/25/15	Microbiology reviews No. 12, 12a1and 9 dated 10/15/14 and 03/25/15, by Y. Chabrier-Roselló, and 12/08/11 by Y. Smith, respectively (reviewed for ANDAs)

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21267	Listed Drug

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	Complete	Acceptable	09/02/2015 02/23/2016	Owen McMaster
CDRH	N/A			
Clinical	N/A			
Other				

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA, as amended, has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product, voriconazole for injection. Based on the overall stability information submitted in the NDA, the expiration dating of 24 months may be granted for the proposed drug product, Voriconazole for Injection, 200 mg, stored at 20°- 25°C (68° - 77°F) excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. The container and carton labels, and the package insert, as revised, have been found acceptable. 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 on January 19, 2016. Therefore, this NDA is recommended for approval from the Product Quality perspective.

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

II. Summary of Quality Assessments

The recommendation in the OPQ Review # 1 entered into Panorama on April 30, 2016 was "Approval pending labeling revisions". The current review (Review # 2) captures the labeling revisions recommended by the OPQ team in the proposed container and carton labels, and the package insert, which were accepted by the Applicant via NDA amendments dated May 19 and 23, 2016, respectively. In addition, the current review includes several revisions in the Biopharmaceutics Section. Specifically, a reference to [redacted] (b) (4) (to which the Applicant has no right of reference) has been removed. The recommendation regarding the biowaiver request has remained unchanged (i.e., the biowaiver request has been granted), now per 21 CFR 320.24(b)(5) (a revised CFR citation). All other sections in the current review are the same as in Review # 1.

Therefore, the current document, Review # 2, should be considered the final Product Quality Review (OPQ Integrated Quality Assessment) for this NDA.

Summary of Quality Assessments

The chemistry manufacturing and controls information for voriconazole drug substance has been provided via a reference to DMF Type II (b) (4) DMF (b) (4) has been found to be adequate via a chemistry review dated January 8th, 2015.

The proposed drug product is as a white to off-white cake or powder which contains 200 mg of voriconazole (USP grade) and 3200 mg HPβCD (NF grade). The proposed drug product contains the same active ingredient in the same amount as the listed drug VFEND®. However, the (b) (4) sulfobutylether β-cyclodextrin (SBEβCD) in VFEND® has been replaced with the same amount of (b) (4), hydroxypropyl β-cyclodextrin (HPβCD) in the currently proposed formulation. The Applicant requested a waiver of the bioequivalence (BE) requirement for their product, Voriconazole for Injection, 200 mg/vial. The information provided in the NDA, i.e., pH range of the currently proposed voriconazole drug product upon reconstitution, the osmolality/osmolarity of the infusion solution upon reconstitution and dilution, and the *in vitro* antifungal activity was found comparable to the listed drug, VFEND® and adequate to support the biowaiver request.

The proposed drug product specification includes relevant tests for the proposed dosage form (i.e., lyophilized powder for injection) such as: description, identification, water content, reconstitution characteristics (completeness of solution, clarity of solution, reconstituted volume, and color of solution), particulate matter, uniformity of dosage forms, assay, related substances, enantiomeric purity, assay of HPβCD, (b) (4) bacterial endotoxins, and sterility. In addition, the drug product meets the requirements of USP <1> (Injections). The proposed specification (tests, analytical procedures and acceptance criteria) as consulted with other review team members was found acceptable. The manufacturing process for the proposed drug product includes: (b) (4) Several information requests were sent to the Applicant in the course of the NDA review and additional information regarding the proposed sampling plan for the drug product commercial batches and in-process controls for (b) (4) was provided. The overall information on the manufacturing process provided in the original NDA submission and subsequent amendments was found acceptable. In addition, information provided for the proposed drug product from the product quality microbiology perspective (b) (4) was also found acceptable.

The proposed container closure system for the drug product is a glass vial with a rubber stopper, which was found acceptable based on the overall information provided (including compliance with the USP General Chapters 381> and <87>). Also, compatibility data of the proposed drug product with several drugs listed in the proposed package insert was found adequate. The long term and accelerated stability data provided in the NDA included data for three representative batches of the proposed drug product stored for 24 months at 25°C ± 2°C/60% RH ± 5% RH, for 12 months at 30°C ± 2°C/75% RH ± 5% RH, and for 6 months at 40°C ± 2°C/75% RH ± 5% RH (samples placed in inverted and upright orientations). Based on the overall stability information submitted in the NDA, the expiration dating of 24 months is granted for the proposed drug product, Voriconazole for Injection, 200 mg, stored at 20°- 25°C (68°-77°F) with excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

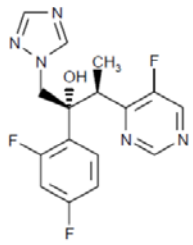
Several revisions were included in the package insert and the container labels, e.g., a change from the (b) (4) to the "single dose vial" statement in all parts of the product labeling and revisions to the proposed in the package insert storage time and conditions for the powder, and reconstituted and further diluted solutions of the proposed drug product.

All manufacturing and testing facilities for this NDA have been found acceptable by the Office of Process and Facilities (OPF) and an overall "Approve" recommendation was entered into Panorama on January 19, 2016.

A. Drug Substance [voriconazole] Quality Summary

Chemical Name: (2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl) butan-2-ol

Structure:



Voriconazole drug substance is a white or almost white powder, very slightly soluble in water, freely soluble in acetone and in methylene chloride. Voriconazole is a weak base,

with two pKa values reported as - 4.98 and 12.00; it is moderately lipophilic and classified as a low solubility, high permeability compound.

The chemistry manufacturing and controls information for voriconazole drug substance has been provided via a reference to DMF Type II (b) (4). DMF (b) (4) has been found to be adequate via a chemistry review dated January 8 , 2015. The retest period for voriconazole, USP, per drug substance manufacturer is (b) (4) if stored in (b) (4) However, the retest period established by the current drug product manufacturer (b) (4) for voriconazole drug substance is (b) (4).

B. Drug Product [voriconazole for injection] Quality Summary

1. *Strength*: Voriconazole for Injection, 200 mg

2. *Description/Commercial Image*: White to off white cake or powder supplied in a glass vial with a rubber stopper

3. *Summary of Product Design*: Lyophilized powder for injection

4. *List of Excipients*: Hydroxypropyl ß-cyclodextrin (HPβCD), Water for Injection (q.s.). (b) (4) (q.s.)

5. (b) (4)

6. *Container Closure*: 30 mL Clear glass vials (Type I) with (b) (4) rubber stoppers (b) (4) and aluminum seals with red plastic flip off button

7. *Expiration Date & Storage Conditions*: 24 months at 20°- 25°C (68° - 77°F) excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

8. *List of co-packaged components*: None

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	None
Non Proprietary Name of the Drug Product	Voriconazole for Injection

Non Proprietary Name of the Drug Substance	Voriconazole
Proposed Indication(s) including Intended Patient Population	From the proposed package insert: • Invasive aspergillosis • Candidemia (nonneutropenics) and disseminated candidiasis in skin, abdomen, kidney, bladder wall, and wounds • Serious infections caused by Scedosporium apiospermum and Fusarium species including Fusarium solani, in patients intolerant of, or refractory to, other therapy
Duration of Treatment	Varies, see the proposed package insert for details
Maximum Daily Dose	(b) (4) mg
Alternative Methods of Administration	None

D. Biopharmaceutics Considerations

1. BCS Designation: Not Applicable. The proposed drug product is a powder for reconstitution to an injectable solution.
   - Drug Substance: N/A
   - Drug Product: N/A

2. Biowaivers/Biostudies
   - Biowaiver Request: The Applicant's request to waive the required *in vivo* BE study between the proposed drug product and the Listed Drug VFEND is granted, per 21 CFR 320.24(b)(5).

E. Novel Approaches N/A

F. Any Special Product Quality Labeling Recommendations N/A

G. Life Cycle Knowledge Information (see Attachment A)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

Dorota M. Matecka -S

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Dorota Matecka, Ph.D., CMC Lead; Branch III; Division of New Drug Products I

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ASSESSMENT OF MICROBIOLOGY

2.3.P DRUG PRODUCT

34. Do the proposed manufacturing process and controls assure sterility/microbial limits of the final drug product?

Applicant's Response: Information is provided as presented below.

Product Quality Microbiology Assessment

Notes to reviewer:

- The pertinent CTD sections are included below. Except where noted otherwise, all references to Module, Section, and pdf documents in this microbiology assessment are from the 07/24/15 original NDA submission.
- See NDA 208562 Information Requests (IR) dated 10/26/15, 11/24/15, and 02/27/16 for microbiology deficiencies and 05/16/16 for labeling deficiencies conveyed to the applicant in support of this review.

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- **Drug product composition –** See the Assessment of Drug Product section of this review.

- **Description of container closure system –**

Component	Item Code #	Description	Manufacturer
Vial	PPVIA-025007	30 mL USP Type I clear glass vials with 20 mm neck size	(b) (4)
Stopper	PPSTO-015039	20 mm USP (b) (4) rubber stoppers	
Seal	PPSEA-011055	20 mm aluminum flip off seals with red color flip off button	

Acceptable

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- **Container-Closure and Package integrity -**
(3.2.P.2, pharmaceutical-development.pdf, pp. 242-251 of 257)

The container/closure system used for validation was the same as the drug product:

Component	Item Code #	Description	Manufacturer
Vial	PPVIA-025007	30 mL USP Type I clear glass (b) (4) vials with 20 mm neck size	(b) (4)
Stopper	PPSTO-015039	20 mm USP (b) (4) rubber stoppers	
Seal	PPSEA-011055	20 mm aluminum flip off seals with red color flip off button	

Study/Report # and date: Dye Immersion test for container closure integrity of Voriconazole for injection, 200 mg/vial, Report No. CCIR13010-01, 02/10/14

Test method: Dye ingress

Brief description: Vials of the subject drug product (20 total) were completely immersed in a vessel containing methylene blue dye solution at a concentration of 0.01%w/v. The vessel was placed in a vacuum chamber and vacuum of 360 mm of Hg applied and maintained for 30 minutes. Vacuum and pressure were slowly released and allowed to equilibrate to 1 atmosphere. The vials were removed from the dye solution and thoroughly rinsed with water and wiped with Isopropanol, and then each reconstituted with 19 mL purified water. All vials were examined visually and by UV-Visible spectrophotometer from 800 nm to 400 nm against drug solution from the negative control vials as blank. Intentionally breached positive controls (5 total), prepared by removing the flip-top and puncturing the closure with a sterile 26 gauge ½ inch needle, left in place, were subjected to the same conditions as the test containers. Spiked positive controls (5 total) were prepared by deliberate injection of the intrusion volume of 0.1% methylene blue corresponding to the previously determined limit of detection (LOD) (see below). Negative controls (5 total) were unspiked. Spiked positive controls and negative controls were not subjected to dye immersion or vacuum.

Determination of Limit of Detection (LOD): 10 µL, 20 µL, 40 µL, 80 µL, and 120 µL of 0.01 %w/v solution of methylene blue solution were diluted to 20 mL with the subject drug product in individual volumetric flasks to provide standard series of methylene blue at effective concentrations of 0.05 µg/mL, 0.1 µg/mL, 0.2 µg/mL, 0.4 µg/mL, and 0.6 µg/mL, respectively. The absorbance of each solution was read on a UV-Visible spectrophotometer using unspiked drug solution as a blank. The test identified the LOD as 0.05 µg/mL, showing absorbance of 0.011 AU at 668 nm (data provided). The

LOD concentration of 0.05 µg/mL was correlated with an intrusion volume of <1.0 µL per 20 mL product solution (explanation provided).

Results:
- The LOD concentration was identified as 0.05 µg/mL (absorbance 0.011AU).
- None of the 20 test vials subjected to the dye immersion test showed absorbance greater than the lowest absorbance shown by any spiked sample vials. Results were reported as "none detected at 668 nm."
- Spiked sample vials showed the absorbance in the same order as the LOD concentration (0.010-0.011 at 668 nm).
- Breached positive control vials showed blue coloration greater than the spiked sample vials when visually compared.

Acceptable

- **Antimicrobial Effectiveness Testing** - N/A. The subject drug product is a single dose; antimicrobial effectiveness testing is not required.

Acceptable

- **Reconstitution, Dilution and Storage (package insert and product labeling)** (1.14.1.3, draft-package-insert.pdf, 3.2.P.2, pharmaceutical-development.pdf, pp. 252-257 of 257, 03/04/16 Amendment, draft-package-insert-0005.pdf, 05/23/16 Amendment, 1.14.1.3, draft-package-insert-clean-0011.pdf)

  Module 1: Package Insert
  Storage temperature: 15-30°C
  Route of administration: IV infusion
  Container: Single dose

  Reconstituted/Further Diluted Drug Product
  Pre-use storage: As stated above
  Reconstitution and further dilution: The subject drug product requires reconstitution to 10 mg/mL and subsequent dilution to a final concentration of not less than 0.5 mg/mL and not greater than 5 mg/mL prior to administration as an infusion, at a maximum rate of 3 mg/kg per hour over 1-2 hours. The reconstituted solution can be diluted with:
  - 9 mg/mL (0.9%) Sodium Chloride USP
  - 5% Dextrose and Lactated Ringers USP
  - 5% Dextrose USP
  - 0.45% Sodium Chloride USP
  - Lactated Ringers USP
  - 5% Dextrose and 0.45% Sodium Chloride USP
  - 5% Dextrose and 20 mEq Potassium Chloride USP
  - 5% Dextrose and 0.9% Sodium Chloride USP

Compatibility with other diluents is unknown.

The package insert in the original NDA submission states:

- (b) (4) (b) (4) If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2° to 8°C (36° to 46°F). (b) (4)
- "Voriconazole for injection must be infused over 1-2 hours, at a concentration of 5 mg/mL or less. Therefore, the required volume of the 10 mg/mL Voriconazole for injection concentrate should be further diluted as follows (appropriate diluents listed below):" The dilution scheme, where the final concentration is stated to be "not less than 0.5 mg/mL nor greater than 5 mg/mL" is provided, and the target doses for various patient body weights are presented (not shown here), followed by this statement: "The final Voriconazole for injection solution must be infused over 1-2 hours at a maximum rate of 3 mg/kg per hour." No storage condition for the further diluted product in the infusion fluids is stated.

Note to reviewer: A reconstitution microbial challenge study to support the storage time stated in the package insert for the reconstituted product (final concentration 10 mg/mL) has been performed (reviewed below). The storage conditions, if any, for the further diluted product in the second container (final concentration 0.5 mg/mL to 5 mg/mL using various infusion fluids) were not addressed in the package insert in the original NDA submission and were not simulated in this study; clarification was requested. In the 12/16/15 Amendment, response to Questions #3a and 3b (see IR dated 11/24/15), the applicant clarifies the following:

- Storage is recommended in the labeling only for the reconstituted product (final concentration 10 mg/mL) and not for the further diluted product (final concentration 0.5 mg/mL and 5 mg/mL). The further diluted product is expected to be used immediately without any storage and infused over 1-2 hours.
- A compatibility study is provided in the original NDA submission (3.2.P.2.6, p. 83 of 261) where testing was performed using diluents considered to be worst-case and under conditions considered to be worst case (i.e., 30°C during 3 hours to cover the 1-2 hour infusion). Results were within specified limits.
- The applicant interprets the package insert for the RLD and the subject drug product to say that the further diluted product (0.5 mg/mL and 5 mg/ml) should be used immediately after second step dilution. Therefore, they contend that the package insert need not be revised to specify permitted storage conditions.

Since the package insert in the original NDA submission did not state clearly that the further diluted product is to be administered immediately after dilution, the applicant was requested to add a statement to the package insert that the infusion should commence immediately after dilution. In the 03/04/16 Amendment, the applicant provided a revised package insert in the response to Question #1 (see IR dated 12/27/16). Thereafter, additional revisions to the labeling were discussed by the review team and in a collaborative effort a revised package insert including Agency-recommended revisions was prepared and sent to the applicant for their consideration; this included Agency-recommended revisions that better clarified which storage instructions were applicable for the reconstituted drug concentrate and which were applicable for the further diluted drug solution for infusion (see IR dated 05/16/16). The applicant agreed to accept all the Agency-recommended revisions and provided a revised package insert in the 05/23/16 Amendment. The revisions in Sections 2.5 Preparation and Intravenous Administration and 16.2 Storage and Handling were deemed acceptable to this reviewer.

Reconstitution/dilution hold study (a.k.a. Microbial challenge test)

Study/Report # and date: Evaluation of microbial growth inhibition in Voriconazole vial, 200 mg per vial, reconstituted for use, Document No. CK-V-3314R, 03/19/14

A study was performed to demonstrate if adventitious contamination occurring at reconstitution would result in growth during storage, before use. The study included reconstitution of each container with 19 mL WFI, inoculation with one of 5 test strains as per USP <51>, storage at 2-8°C for 48 hours, and then enumeration by membrane filtration method. Membranes were plated on TSA and incubated at 30-35°C for 3-5 days. Each test condition was performed in triplicate using 1 product lot for the first replicate and the a second product lot for replicates 2 and 3. The size of each inoculum was verified by the average of triplicate plates. Positive controls (growth promotion) were performed by inoculating a closed media filled vial containing 19 mL TSB. Positive controls performed in parallel using diluent and including no drug product were not performed.

Test conditions

Final concentration after reconstitution as per package insert	Diluent	Storage condition	Testing intervals*
10 mg/mL	WFI	2-8°C	0-1, 12, 24, 48 hrs

* Study design included storage for an additional 24 hours beyond what is stated in the package insert.

Acceptance criteria:

- All controls show good visible growth after 1-2 days incubation. Samples are identified as identical to the added test strain.
- Inoculum size is verified as NMT (b) (4) CFU per 100-200 µL.

- No growth is observed in test vials, where growth is defined as a (b) (4) log increase in average cell count (CFU/vial) at each testing time point with reference to the count at 0-1 hours.

Results: The data sheet for the study performed is provided that includes growth promotion controls (growth/no growth) and triplicate counts and average count for each test condition (p. 257 of 257). The results are summarized as follows:

Test strain	Control	Average cell counts					Increase
		Inoculum size	0 days	12 hours	24 hours	48 hours	
Candida albicans	Growth	20	22	21	19	12	No
Aspergilius brasiliensis	Growth	24	1	1	2	0	No
Escherichia coli	Growth	44	54	40	47	31	No
Pseudomonas aeruginosa	Growth	37	42	6	3	0	No
Staphylococcus aureus	Growth	18	20	14	11	13	No

(Table excerpted from 3.2.P.2, pharmaceutical-development.pdf, p. 255 of 257. Based on the study description, "0 days" actually means "0-1 hours.")

All acceptance criteria were met.

Note to reviewer: For the reported study, it is noted that growth promotion positive controls to show viability in a media filled vials were performed and acceptable, but no positive controls were performed in parallel, simulating the test conditions in the diluent (WFI) without drug product, to demonstrate viability over the duration of the test. Based on the reported results, it is presumed that sustained growth would have been observed for *C. albicans*, *E. coli*, and *S. aureus* over the duration of the test, but one cannot assume this for *A. brasiliensis* and *P. aeruginosa*. Since the proposed storage condition for the reconstituted product in the original container is refrigerated for NMT 24 hours, and the Agency does not require a reconstitution microbial challenge study under these conditions, this reviewer sees no need to point this out to the applicant.

Acceptable

Reviewer's Assessment: Information provided in Section P.2 and in the labeling are acceptable as far as sterility assurance is concerned.

P.3.3 Description of the Manufacturing Process and Process Controls

(b) (4)

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(b) (4)

Acceptable

Reviewer's Assessment: Information provided in Section R is acceptable as far as sterility assurance is concerned.

R.2 Comparability Protocol – The applicant is not submitting any comparability protocols at this time.

Reviewer's Assessment: N/A

40. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response: See Section P.5 of the Product Quality Microbiology Assessment above.

Reviewer's Assessment: Adequate

2.3.P.7 Container/Closure System

41. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant's Response: See Section P.2.5 of the Product Quality Microbiology Assessment above.

Reviewer's Assessment: Adequate

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

42. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response: See Section A.2 of the Product Quality Microbiology Assessment above.

Reviewer's Assessment: Adequate

43. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response: See Section A.2 of the Product Quality Microbiology Assessment above.

Reviewer's Assessment: Adequate

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: Recommended/Adequate
Lisa S.G. Shelton 05/23/16

Secondary Review Comments and Concurrence: I concur with the primary microbiology reviewer's assessment.
Bryan S. Riley, Ph.D. 05/24/2016

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

1. Is the applicant's claim for categorical exclusion acceptable?

2. Is the applicant's Environmental Assessment adequate for approval of the application?

The applicant claims categorical exclusion under 21 CFR 25.31 (a) from filing Environmental Impact Assessment Statement with respect to this application.
Under 21 CFR 25.31(a), a categorical exclusion exists for:
"Action on an NDA, abbreviated application, application for marketing approval of a biologic product, or a supplement to such applications, or action on an OTC monograph, if the action does not increase the use of the active moiety".

The applicant certifies that no extraordinary circumstances exist, and the firm is in compliance with all applicable Federal, State and Local environmental laws and regulations.

Reviewer's Assessment: ADEQUATE

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature: ADEQUATE
The claim is reasonable and is acceptable.
Yushi Feng, Ph.D.; Staff Fellow; Branch 3; Division of New Drug Product I.
Mar 23, 2016.

Secondary Review Comments and Concurrence: I concur.
Balajee Shanmugam, Ph.D. Division of New Drug Product 1.
April 29, 2016

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

VORICONAZOLE for injection, for intravenous use

_____DOSAGE FORMS AND STRENGTHS_____

For Injection: lyophilized white to off white cake or powder containing 200 mg voriconazole and 3200 mg of hydroxypropyl ß-cyclodextrin (HPβCD); after reconstitution 10 mg/mL of voriconazole and 160 mg/mL of HPβCD

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name		ADEQUATE
Dosage form, route of administration		ADEQUATE
Controlled drug substance symbol (if applicable)		N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths		ADEQUATE

Conclusion: ADEQUATE

(b) "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

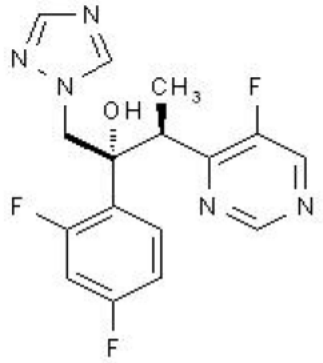
Powder for Solution for Injection
Voriconazole for injection is supplied in a single dose vial as a sterile lyophilized white to off white cake or powder equivalent to 200 mg voriconazole and 3200 mg hydroxypropyl ß-cyclodextrin (HPβCD).

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms		ADEQUATE
Strengths: in metric system		ADEQUATE
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.		ADEQUATE

Conclusion: ADEQUATE

#11: Description (21CFR 201.57(c)(12))

Voriconazole for injection, an azole antifungal is available as a sterile lyophilized cake or powder for solution for intravenous infusion. The structural formula is:



Voriconazole is designated chemically as (2R,3S)-2-(2, 4-difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol with an empirical formula of $C_{16}H_{14}F_3N_5O$ and a molecular weight of 349.3.

Voriconazole drug substance is a white or almost white powder.

Voriconazole for injection, is a white to off white lyophilized cake or powder containing nominally 200 mg voriconazole and 3200 mg hydroxypropyl ß-cyclodextrin (HPβCD) in a 30 mL Type I clear glass vial.

Voriconazole for injection is intended for administration by intravenous infusion. It is an unpreserved product in a single dose vial. Vials containing 200 mg lyophilized voriconazole are intended for reconstitution with Water for Injection to produce a solution containing 10 mg/mL Voriconazole for injection and 160 mg/mL of hydroxypropyl ß-cyclodextrin (HPβCD). The resultant solution is further diluted prior to administration as an intravenous infusion [*see Dosage and Administration (2)*].

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name		ADEQUATE
Dosage form and route of administration		ADEQUATE
Active moiety expression of strength with equivalence statement for salt (if applicable)		ADEQUATE
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.		ADEQUATE
Statement of being sterile (if applicable)		ADEQUATE
Pharmacological/ therapeutic class		ADEQUATE
Chemical name, structural formula, molecular weight		ADEQUATE
If radioactive, statement of important nuclear characteristics.		N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)		N/A

Conclusion: ADEQUATE

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

16.1 How Supplied

Voriconazole for Injection is supplied in a single dose vial as an unpreserved, sterile white to off white lyophilized cake or powder equivalent to 200 mg voriconazole and 3200 mg hydroxypropyl ß-cyclodextrin (HPβCD).

Individually packaged vials of Voriconazole for Injection, 200 mg, NDC (b) (4)

16.2 Storage and Handling

Storage

Powder for Injection: Voriconazole for Injection unreconstituted vials should be stored at 20° – 25°C (68° – 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

Reconstituted Drug Solution: From a microbiological point of view, following reconstitution of the lyophile with Water for Injection, the reconstituted solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2° to 8°C (36° to 46°F). Chemical and physical in-use stability has been

demonstrated for 24 hours at 2° to 8°C (36° to 46°F). Discard Unused Portion. [*see Dosage and Administration (2.5)*].

Further Diluted Drug Solution for Infusion: Once the reconstituted product is further diluted for infusion, it should be used immediately. Discard Unused Portion. [*see Dosage and Administration (2.5)*].

This medicinal product is for single use only and any unused solution should be discarded. Only clear solutions without particles should be used [*see Dosage and Administration (2.5)*].

Handling

Not made with natural rubber latex.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form		ADEQUATE
Available units (e.g., bottles of 100 tablets)		ADEQUATE
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number		ADEQUATE
Special handling (e.g., protect from light, do not freeze)		ADEQUATE
Storage conditions		ADEQUATE

Manufacturer/distributor name listed at the end of PI, following Section #17

(b) (4)

Made in India

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)		ADEQUATE

Conclusion: ADEQUATE

2. Container and Carton Labeling

1) Immediate Container Label

Zoom Size 200%

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))		ADEQUATE
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))		ADEQUATE
Route of administration 21.CFR 201.100(b)(3))		ADEQUATE
Net contents* (21 CFR 201.51(a))		ADEQUATE
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**		ADEQUATE
Lot number per 21 CFR 201.18		ADEQUATE
Expiration date per 21 CFR 201.17		ADEQUATE
"Rx only" statement per 21 CFR 201.100(b)(1)		ADEQUATE
Storage (not required)		ADEQUATE
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		ADEQUATE
Bar Code per 21 CFR 201.25(c)(2)***		ADEQUATE
Name of manufacturer/distributor (21 CFR 201.1)		ADEQUATE
Others		

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.

**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label

**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: ADEQUATE

2) Carton Labeling

(b) (4)

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))		ADEQUATE
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))		ADEQUATE
Net contents (21 CFR 201.51(a))		ADEQUATE
Lot number per 21 CFR 201.18		ADEQUATE
Expiration date per 21 CFR 201.17		ADEQUATE
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]		ADEQUATE
Sterility Information (if applicable)		ADEQUATE
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)		ADEQUATE
Storage Conditions		ADEQUATE
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		ADEQUATE
Bar Code per 21 CFR 201.25(c)(2)**		ADEQUATE
Name of manufacturer/distributor		ADEQUATE
"See package insert for dosage information" (21 CFR 201.55)		ADEQUATE
"Keep out of reach of children" (optional for Rx, required for OTC)		ADEQUATE
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))		ADEQUATE

Conclusion: ADEQUATE

OVERALL ASSESSMENT AND SIGNATURES: CONTAINER AND CARTON LABELING

Reviewer's Assessment and Signature: ADEQUATE
Review is based on the package insert information submitted in Supporting Document Number: 12, eCTD Sequence Number 0011, Submit Date: 5/23/2016; and the container closure labeling information submitted in Supporting Document Number: 10, eCTD Sequence Number 0009, Submit Date: 5/19/2016.
Yushi Feng, Ph.D.; Staff Fellow; Branch 3; Division of New Drug Product I.
May 23, 2016.

Secondary Review Comments and Concurrence: I concur.
Balajee Shanmugam, Ph.D., ONDP I; May 23, 2016

II. List of Deficiencies To Be Communicated

N/A

III. Attachments

A. Lifecycle Knowledge Management

a) Drug Product

From Initial Risk Identification			Review 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 of Voriconazole	Quality of the incoming API; analytical method	L	The DMF was found adequate.	Acceptable	
Impurities/ Degradation Products	Quality of the API, and excipient	L	The DMF of DS and excipient were both adequate.	Acceptable	
Particulate matter (reconstituted solution)	Quality of the API, excipient, and container closure	M	The DMF of DS and excipient were both adequate.	Acceptable	

Leachables/ extractables	Quality of the API, excipient, and container closure	L	The DMF of DS, excipient and container closure were adequate.	Acceptable	
Sterility	Starting materials, manufacturing process, and container/ closure integrity.	H	Evaluate (b) (4) and validation data.	Acceptable	
Endotoxins	Starting materials and processing of container closure components	M	Evaluate depyrogenation of container closure components and final product specification.	Acceptable	

Recommendation: ***Approval pending labeling revisions***

NDA 208562
Review # 1

Drug Name/Dosage Form	Voriconazole for Injection /Lyophilized Powder for Injection
Strength	200 mg
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Xellia Pharmaceuticals, ApS
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	07/24/2015	All
Amendment	12/16/2015	Micro, DP, Process
Amendment	03/04/2016	Micro

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Yushi Feng	ONPD/DNDP I/Branch III
Drug Product	Yushi Feng	ONPD/DNDP I/Branch III
Process	Steve Rhieu	OPF/DPA III/Branch VII
Microbiology	Lisa S.G. Shelton	OPF/DMA/Branch II
Facility	Christina Capacci-Daniel	OPF/DIA/Branch II
Biopharmaceutics	Gerlie Gieser	ONDP/DBP/Branch I
Regulatory Business Process Manager	Navi Bhandari	OPRO
Application Technical Lead	Dorota Matecka	ONPD/DNDP I/Branch III
Laboratory (OTR)	N/A	N/A
ORA Lead	N/A	N/A
Environmental Assessment (EA)	N/A	N/A

Table of Contents

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		Active	01/08/2015	Adequate by Chem review No. 7 for an ANDA; LoA for Xellia is located in the DMF (b) (4)
	III			Active	04/24/2002	Adequate for NDA20280, lyophilized powder for subcutaneous injection. LoA for Xellia is located in the DMF (b) (4)
	III			Active	04/07/2015	Adequate by Chem review No. 1 for an NDA
	IV			Active	03/22/1999	Adequate for NDA20966, solution for IV injection, no deficiencies. LoA for Xellia is located in the DMF (b) (4)
	V			Adequate	03/25/15	Microbiology reviews No. 12, 12a1and 9 dated 10/15/14 and 03/25/15, by Y. Chabrier-Roselló, and 12/08/11 by Y. Smith, respectively (reviewed for ANDAs)

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21267	Listed Drug

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	Complete	Acceptable	09/02/2015 02/23/2016	Owen McMaster
CDRH	N/A			
Clinical	N/A			
Other				

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA, as amended, has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product, voriconazole for injection. Based on the overall stability information submitted in the NDA, the expiration dating of 24 months may be granted for the proposed drug product, Voriconazole for Injection, 200 mg, stored at 20°- 25°C (68° - 77°F) excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. 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 on January 19, 2016. However, the labeling review is currently pending. Therefore, this NDA is recommended for approval pending satisfactory resolution of the labeling issues and recommendations (to be addressed in Review # 2).

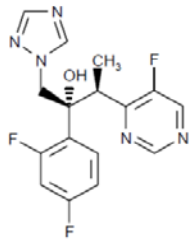
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable N/A

II. Summary of Quality Assessments

A. Drug Substance [voriconazole] Quality Summary

Chemical Name: (2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1H-1,2,4-triazol-1-yl) butan-2-ol

Structure:



Voriconazole drug substance is a white or almost white powder, very slightly soluble in water, freely soluble in acetone and in methylene chloride. Voriconazole is a weak base,

with two pKa values reported as - 4.98 and 12.00; it is moderately lipophilic and classified as a low solubility, high permeability compound.

The chemistry manufacturing and controls information for voriconazole drug substance has been provided via a reference to DMF Type II (b) (4). DMF (b) (4) has been found to be adequate via a chemistry review dated January 8 , 2015. The retest period for voriconazole, USP, per drug substance manufacturer is (b) (4) if stored in (b) (4) . However, the retest period established by the current drug product manufacturer (b) (4) for voriconazole drug substance is (b) (4)

B. Drug Product [voriconazole for injection] Quality Summary

1. *Strength*: Voriconazole for Injection, 200 mg

2. *Description/Commercial Image*: White to off white cake or powder supplied in a glass vial with a rubber stopper

3. *Summary of Product Design*: Lyophilized powder for injection

4. *List of Excipients*: Hydroxypropyl ß-cyclodextrin (HPβCD), Water for Injection (q.s.), (b) (4) (q.s.)

5. (b) (4)

6. *Container Closure*: 30 mL Clear glass vials (Type I) with (b) (4) rubber stoppers (b) (4) and aluminum seals with red plastic flip off button

7. *Expiration Date & Storage Conditions*: 24 months at 20°- 25°C (68° - 77°F) excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

8. *List of co-packaged components*: None

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	None
Non Proprietary Name of the Drug Product	Voriconazole for Injection
Non Proprietary Name of the Drug	Voriconazole

Substance	
Proposed Indication(s) including Intended Patient Population	From the proposed package insert: • Invasive aspergillosis • Candidemia (nonneutropenics) and disseminated candidiasis in skin, abdomen, kidney, bladder wall, and wounds • Serious infections caused by Scedosporium apiospermum and Fusarium species including Fusarium solani, in patients intolerant of, or refractory to, other therapy
Duration of Treatment	Varies, see the proposed package insert for details
Maximum Daily Dose	(b) (4) mg
Alternative Methods of Administration	None

D. Biopharmaceutics Considerations

1. BCS Designation: Not Applicable. The proposed drug product is a powder for reconstitution to an injectable solution.
   - Drug Substance: N/A
   - Drug Product: N/A

2. Biowaivers/Biostudies
   - Biowaiver Request: Per 21 CFR 320.22(b), the *in vivo* bioequivalence of the proposed drug product to the Listed Drug (LD) is self-evident as it meets the following criteria: (1) a parenteral solution intended solely for administration by injection, (2) contains the same active ingredient in the same quantity as the LD, and (b) (4) in the form of a substituted β-cyclodextrin (HPβCD for the Applicant's product and SBEβCD for the LD).
   - PK studies – refer to Clinical Pharmacology review

E. Novel Approaches N/A

F. Any Special Product Quality Labeling Recommendations N/A

G. Life Cycle Knowledge Information (see Attachment A)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

Dorota M. Matecka -S

Digitally signed by Dorota M. Matecka -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300123291, cn=Dorota M. Matecka -S
Date: 2016.04.30 23:48:56 -04'00'

Dorota Matecka, Ph.D., CMC Lead; Branch III; Division of New Drug Products I

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ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION

This Biopharmaceutics review focuses on the Applicant's biowaiver request.

38. Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?

Not Applicable. The proposed drug product is a powder or cake for reconstitution as an injectable solution.

a. Is the Applicant's biowaiver request acceptable?

Yes.

The Applicant requested a waiver of the requirement to conduct a bioequivalence study between the proposed Voriconazole Injection and the approved VFEND® solution for injection. The Applicant considers the *in vivo* bioequivalence of their product as self-evident as it meets the following criteria: The drug product (1) is a parenteral solution intended solely for administration by injection, and (2) contains the same active drug substance in the same quantity (200 mg/vial) as the Listed Drug (LD), and (b) (4) both drug products contain a substituted ß-cyclodextrin.

Table 38.1-1 shows that the Applicant's product is formulated so that the SBEβCD of VFEND® is replaced [1:1 w/w] with HPβCD (b) (4).

Table 38.1-1
Comparison of the compositions of the Applicant's proposed voriconazole injection and the Listed Drug (VFEND®) before and after reconstitution

Ingredient		Function	Quantity	
Xellia's Product	VFEND (NDA 021267)		mg/vial	mg/mL*
Voriconazole	Voriconazole	Active Ingredient	200	10
Hydroxypropyl ß-cyclodextrin (HPβCD)	Sulfobutylether ß-cyclodextrin (SBECD)	(b) (4)	3,200	160

* Following reconstitution with 19 mL of water for injection.

Source: summary-biopharm.pdf

The *in vitro* comparability experiments conducted by the Applicant showed that: 1) when HPβCD or SBEβCD are added at 3200 mg/vial [equivalent to (b) (4) M SBEβCD and (b) (4) M HPβCD upon reconstitution with 19 mL Water for Injection (WFI)], the voriconazole solubilizing capability of HPβCD is similar to SBEβCD, i.e., at least 10 mg/mL or 200 mg/20 mL voriconazole will dissolve, 2) using samples prepared from VFEND® and the Applicant's drug product, the kinetics of release of voriconazole from βCD complexation in both aqueous and lipophilic environments did not appear to be influenced by the type of βCD (b) (4) used.

Additionally, when comparing the proposed drug product with the LD, the osmolality values of the infusion solutions prepared with the same diluents appear to be similar. For example, when diluted with 0.9% NaCl solution to yield the 0.5 mg/mL voriconazole infusion solution, the measured osmolalities were 0.283 and 0.292 osmol/kg for the proposed product and the LD, respectively. Likewise, the pH range of three exhibit or registration stability batches of the proposed drug product ((b) (4) upon reconstitution with 19 mL WFI, up to 18 months of long-term storage at inverted and upright positions) overlaps with the pH range of VFEND® injection reported in the literature (5.7 to 7.3 upon reconstitution). Moreover, the *in vitro* antifungal activity in terms of minimum inhibitory concentration (MIC) against *Candida* species was comparable between the proposed drug product and the LD.

Based on the Applicant's review of publicly available voriconazole PK data from the VFEND® development program, the pharmacokinetic parameters of voriconazole appear to be comparable between formulations containing HPβCD and SBEβCD (b) (4). The Applicant considers the amount of HPβCD in the proposed drug product to be safe because higher daily doses of HPβCD are received by patients using Sporanox® (itraconazole) injection [still marketed in Europe] than by patients who would be receiving the proposed Voriconazole Injection (approximately (b) (4) grams versus (b) (4) grams) at the recommended dosage. Additionally, the Applicant believes that the precautions for patients with renal impairment (attributable to the renal elimination of SBEβCD) in the VFEND® labeling could be applied to the proposed drug product. Based on literature information, HPβCD (like SBEβCD) is mainly eliminated unchanged via glomerular filtration and the PK characteristics (i.e., volume of distribution, renal clearance and elimination half-life) of the two βCDs following intravenous administration are similar.

Reviewer's Assessment:

Overall, the information provided in the NDA suggest that the formulation (i.e., (b) (4)) difference between the Applicant's proposed drug product and the Listed Drug (VFEND® Injection) is not anticipated to result in significant differences in the efficacy and safety of voriconazole. The pH range of the Applicant's Voriconazole Injection upon product reconstitution, the measured osmolality/osmolarity of the infusion solution upon reconstitution and dilution, and the *in vitro* antifungal activity are comparable to those of the Listed Drug. Per the proposed labeling of the Applicant's Voriconazole Injection, (b) (4) the labeling instructions for reconstitution and further dilution are the same as that in the approved VFEND® labeling.

Per the Clinical Pharmacology reviewer (Dr. Grace Yan), the replacement of HPβCD with the same concentration of SPEβCD (b) (4) in VFEND® (voriconazole) injection during its early development did not appear to significantly alter the pharmacokinetics of voriconazole. This FDA finding supports the Applicant's conclusion that the use of HPβCD as (b) (4) in the proposed drug product does not impact the bioavailability of voriconazole administered by injection.
Per previous FDA recommendation, the Drug Product specifications include Assay of

HPβCD. This reviewer defers to the Drug Product (DP) reviewer regarding the acceptability of the sponsor's proposed specification for HPβCD assay, i.e., not less than 90% and not more than 110% of the labeled amount (b) (4) mg/mL). Likewise, this reviewer defers to the DP reviewer regarding the acceptability of the proposed DP specification for pH range ((b) (4) upon reconstitution).

39. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

Not Applicable. No *in vivo* animal or clinical study was conducted to support this 505(b)(2) NDA. The exhibit batches and the post-approval commercial batches of the proposed drug product have the same composition and manufacturing process (unit operations, equipment design and operating principles). Therefore, no *in vitro* or *in vivo* studies were conducted nor required to bridge formulation and/or manufacturing process changes.

Per the Applicant, the optimal characteristics (i.e., molar substitution, pH) of the HPβCD used in the formulation were determined prior to conducting all laboratory and production scale studies. In addition, the process parameters were optimized on the scale-up batch manufactured in the production facility using the equipment intended for production of the exhibit or primary registration batches and the post-approval commercial batches.

Reviewer's Assessment:

The proposed commercial formulation of the Applicant's drug product was evaluated in the *in vitro* studies that compared its physicochemical properties (i.e., pH, osmolality), release kinetics, and antifungal activities to those of the Listed Drug (VFEND®). The overall provided information supports the biowaiver request. Therefore, the biowaiver request is granted.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Recommendation and Signature:

From a Biopharmaceutics perspective, NDA 208562 for Voriconazole Injection (200 mg) is recommended for **APPROVAL**.

12/3/2015

Gerlie Gieser, Ph.D.
Biopharmaceutics Reviewer,
Division of Biopharmaceutics/ONDP
Office of Pharmaceutical Quality

Secondary Concurrence and Signature:
I concur with Dr. Gieser's assessment and recommendation.

12/4/15

Elsbeth Chikhale, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics/ONDP
Office of Pharmaceutical Quality

ASSESSMENT OF MICROBIOLOGY

2.3.P DRUG PRODUCT

34. Do the proposed manufacturing process and controls assure sterility/microbial limits of the final drug product?

Applicant's Response: Information is provided as presented below.

Product Quality Microbiology Assessment

Notes to reviewer:

- The pertinent CTD sections are included below. Except where noted otherwise, all references to Module, Section, and pdf documents in this microbiology assessment are from the 07/24/15 original NDA submission.
- See NDA 208562 Information Requests (IR) dated 10/26/15, 11/24/15 and 02/27/16 for microbiology deficiencies conveyed to the applicant in support of this review.

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- **Drug product composition –** See the Assessment of Drug Product section of this review.

- **Description of container closure system –**

Component	Item Code #	Description	Manufacturer
Vial	PPVIA-025007	30 mL USP Type I clear glass vials with 20 mm neck size	(b) (4)
Stopper	PPSTO-015039	20 mm USP (b) (4) rubber stoppers	
Seal	PPSEA-011055	20 mm aluminum flip off seals with red color flip off button	

Acceptable

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- **Container-Closure and Package integrity -**
(3.2.P.2, pharmaceutical-development.pdf, pp. 242-251 of 257)

The container/closure system used for validation was the same as the drug product:

Component	Item Code #	Description	Manufacturer
Vial	PPVIA-025007	30 mL USP Type I clear glass (b) (4) vials with 20 mm neck size	(b) (4)
Stopper	PPSTO-015039	20 mm USP (b) (4) rubber stoppers	
Seal	PPSEA-011055	20 mm aluminum flip off seals with red color flip off button	

Study/Report # and date: Dye Immersion test for container closure integrity of Voriconazole for injection, 200 mg/vial, Report No. CCIR13010-01, 02/10/14

Test method: Dye ingress

Brief description: Vials of the subject drug product (20 total) were completely immersed in a vessel containing methylene blue dye solution at a concentration of 0.01%w/v. The vessel was placed in a vacuum chamber and vacuum of 360 mm of Hg applied and maintained for 30 minutes. Vacuum and pressure were slowly released and allowed to equilibrate to 1 atmosphere. The vials were removed from the dye solution and thoroughly rinsed with water and wiped with Isopropanol, and then each reconstituted with 19 mL purified water. All vials were examined visually and by UV-Visible spectrophotometer from 800 nm to 400 nm against drug solution from the negative control vials as blank. Intentionally breached positive controls (5 total), prepared by removing the flip-top and puncturing the closure with a sterile 26 gauge ½ inch needle, left in place, were subjected to the same conditions as the test containers. Spiked positive controls (5 total) were prepared by deliberate injection of the intrusion volume of 0.1% methylene blue corresponding to the previously determined limit of detection (LOD) (see

below). Negative controls (5 total) were unspiked. Spiked positive controls and negative controls were not subjected to dye immersion or vacuum.

Determination of Limit of Detection (LOD): 10 µL, 20 µL, 40 µL, 80 µL, and 120 µL of 0.01 %w/v solution of methylene blue solution were diluted to 20 mL with the subject drug product in individual volumetric flasks to provide standard series of methylene blue at effective concentrations of 0.05 µg/mL, 0.1 µg/mL, 0.2 µg/mL, 0.4 µg/mL, and 0.6 µg/mL, respectively. The absorbance of each solution was read on a UV-Visible spectrophotometer using unspiked drug solution as a blank. The test identified the LOD as 0.05 µg/mL, showing absorbance of 0.011 AU at 668 nm (data provided). The LOD concentration of 0.05 µg/mL was correlated with an intrusion volume of <1.0 µL per 20 mL product solution (explanation provided).

Results:
- The LOD concentration was identified as 0.05 µg/mL (absorbance 0.011AU).
- None of the 20 test vials subjected to the dye immersion test showed absorbance greater than the lowest absorbance shown by any spiked sample vials. Results were reported as "none detected at 668 nm."
- Spiked sample vials showed the absorbance in the same order as the LOD concentration (0.010-0.011 at 668 nm).
- Breached positive control vials showed blue coloration greater than the spiked sample vials when visually compared.

Acceptable

- **Antimicrobial Effectiveness Testing** - N/A. The subject drug product is a single dose; antimicrobial effectiveness testing is not required.

Acceptable

- **Reconstitution, Dilution and Storage (package insert and product labeling)** (1.14.1.3, draft-package-insert.pdf, 3.2.P.2, pharmaceutical-development.pdf, pp. 252-257 of 257, 03/04/16 Amendment, draft-package-insert-0005.pdf)

  Module 1: Package Insert
  Storage temperature: 15-30°C
  Route of administration: IV infusion
  Container: Single dose

  Reconstituted/Further Diluted Drug Product
  Pre-use storage: As stated above
  Reconstitution and further dilution: The subject drug product requires reconstitution to 10 mg/mL and subsequent dilution to a final concentration of not less than 0.5 mg/mL and not greater than 5 mg/mL

prior to administration as an infusion, at a maximum rate of 3 mg/kg per hour over 1-2 hours. The reconstituted solution can be diluted with:

- 9 mg/mL (0.9%) Sodium Chloride USP
- 5% Dextrose and Lactated Ringers USP
- 5% Dextrose USP
- 0.45% Sodium Chloride USP
- Lactated Ringers USP
- 5% Dextrose and 0.45% Sodium Chloride USP
- 5% Dextrose and 20 mEq Potassium Chloride USP
- 5% Dextrose and 0.9% Sodium Chloride USP

Compatibility with other diluents is unknown.

The package insert states:

- (b) (4) (b) (4). If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2° to 8°C (36° to 46°F). (b) (4)
- "Voriconazole for injection must be infused over 1-2 hours, at a concentration of 5 mg/mL or less. Therefore, the required volume of the 10 mg/mL Voriconazole for injection concentrate should be further diluted as follows (appropriate diluents listed below):" The dilution scheme, where the final concentration is stated to be "not less than 0.5 mg/mL nor greater than 5 mg/mL" is provided, and the target doses for various patient body weights are presented (not shown here), followed by this statement: "The final Voriconazole for injection solution must be infused over 1-2 hours at a maximum rate of 3 mg/kg per hour." No storage condition for the further diluted product in the infusion fluids is stated.

Note to reviewer: A reconstitution microbial challenge study to support the storage time stated in the package insert for the reconstituted product (final concentration 10 mg/mL) has been performed (reviewed below). The storage conditions, if any, for the further diluted product in the second container (final concentration 0.5 mg/mL to 5 mg/mL using various infusion fluids) were not addressed in the package insert and were not simulated in this study; clarification was requested. In the 12/16/15 Amendment, response to Questions #3a and 3b (see IR dated 11/24/15), the applicant clarifies the following:

- Storage is recommended in the labeling only for the reconstituted product (final concentration 10 mg/mL) and not for the further diluted product (final concentration 0.5 mg/mL and 5 mg/mL). The further diluted product is expected to be used immediately without any storage and infused over 1-2 hours.

- A compatibility study is provided in the original NDA submission (3.2.P.2.6, p. 83 of 261) where testing was performed using diluents considered to be worst-case and under conditions considered to be worst case (i.e., 30°C during 3 hours to cover the 1-2 hour infusion). Results were within specified limits.
- The applicant interprets the package insert for the RLD and the subject drug product to say that the further diluted product (0.5 mg/mL and 5 mg/ml) should be used immediately after second step dilution. Therefore, they contend that the package insert need not be revised to specify permitted storage conditions.

Since the package insert did not state clearly that the further diluted product is to be administered immediately after dilution, the applicant was requested to add a statement to the package insert that the infusion should commence immediately after dilution. In the 03/04/16 Amendment, response to Question #1 (see IR dated 12/27/16), the applicant provides a revised package insert in which they have added the statement "Further diluted product (0.5 mg/mL and 5 mg/mL) should be used immediately after second step dilution." (Sections 2.5 and 16.2, pp. 7 and 40 of 41). However, this reviewer does not consider that the wording and placement of this statement in the context of Sections 2.5 and 16.2 provides sufficient clarity (see note to reviewer).

Note to reviewer: Additional revisions to the labeling are being discussed by the review team (pending at the time of this review). The applicant's aforementioned revision to the package insert will be discussed by the review team and evaluated for its clarity within the context of the package insert in its entirety. Depending on the outcome of the discussion, further revision may be requested (see comment below).

Reconstitution/dilution hold study (a.k.a. Microbial challenge test)

Study/Report # and date: Evaluation of microbial growth inhibition in Voriconazole vial, 200 mg per vial, reconstituted for use, Document No. CK-V-3314R, 03/19/14

A study was performed to demonstrate if adventitious contamination occurring at reconstitution would result in growth during storage, before use. The study included reconstitution of each container with 19 mL WFI, inoculation with one of 5 test strains as per USP <51>, storage at 2-8°C for 48 hours, and then enumeration by membrane filtration method. Membranes were plated on TSA and incubated at 30-35°C for 3-5 days. Each test condition was performed in triplicate using 1 product lot for the first replicate and the a second product lot for replicates 2 and 3. The size of each inoculum was verified by the average of triplicate plates. Positive controls (growth promotion) were performed by inoculating a closed media filled vial containing 19 mL TSB. Positive controls performed in parallel using diluent and including no drug product were not performed.

Test conditions

Final concentration after reconstitution as per package insert	Diluent	Storage condition	Testing intervals*
10 mg/mL	WFI	2-8°C	0-1, 12, 24, 48 hrs

* Study design included storage for an additional 24 hours beyond what is stated in the package insert.

Acceptance criteria:

- All controls show good visible growth after 1-2 days incubation. Samples are identified as identical to the added test strain.
- Inoculum size is verified as NMT (b) (4) CFU per 100-200 µL.
- No growth is observed in test vials, where growth is defined as a (b) (4) log increase in average cell count (CFU/vial) at each testing time point with reference to the count at 0-1 hours.

Results: The data sheet for the study performed is provided that includes growth promotion controls (growth/no growth) and triplicate counts and average count for each test condition (p. 257 of 257). The results are summarized as follows:

Test strain	Control	Average cell counts					Increase
		Inoculum size	0 days	12 hours	24 hours	48 hours	
Candida albicans	Growth	20	22	21	19	12	No
Aspergilius brasiliensis	Growth	24	1	1	2	0	No
Escherichia coli	Growth	44	54	40	47	31	No
Pseudomonas aeruginosa	Growth	37	42	6	3	0	No
Staphylococcus aureus	Growth	18	20	14	11	13	No

(Table excerpted from 3.2.P.2, pharmaceutical-development.pdf, p. 255 of 257. Based on the study description, "0 days" actually means "0-1 hours.")

All acceptance criteria were met.

Note to reviewer: For the reported study, it is noted that growth promotion positive controls to show viability in a media filled vials were performed and acceptable, but no positive controls were performed in parallel, simulating the test conditions in the diluent (WFI) without drug product, to demonstrate viability over the duration of the test. Based on the reported results, it is presumed that sustained growth would have been observed for *C. albicans*, *E. coli*, and *S. aureus* over the duration of the test, but one cannot assume this for *A. brasiliensis* and *P. aeruginosa*. Since the proposed storage condition for the reconstituted product in the original container is refrigerated for NMT 24 hours, and the Agency does not require a reconstitution microbial challenge study under these conditions, this reviewer sees no need to point this out to the applicant.

Not Acceptable

Reviewer's Assessment: Information provided in Section P.2 is not acceptable as far as sterility assurance is concerned. Revisions to the product labeling (i.e., package insert) related to reconstitution, dilution, and storage are being discussed with the clinical review team. These include addition of the following statements:

- "Infusion should commence immediately after dilution of the concentrate." (in Section 2.5 Preparation and Intravenous Administration)
- "Once the reconstituted product is further diluted for infusion, it should be used immediately." (in Sections 2.5 Preparation and Intravenous Administration and 16.2 Storage and Handling)

Comments: Further revisions to the product labeling (i.e., package insert), regarding storage of the further diluted drug solution for infusion, are currently under discussion with the clinical review team and will be requested in the context of a labeling IR (yet to be sent to the Applicant). Any further revisions to the labeling submitted in the IR response will be reviewed in an Addendum to this review.

P.3.3 Description of the Manufacturing Process and Process Controls

(b) (4)

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

(b) (4)

Acceptable

Reviewer's Assessment: Information provided in Section R is acceptable as far as sterility assurance is concerned.

R.2 Comparability Protocol – The applicant is not submitting any comparability protocols at this time.

Reviewer's Assessment: N/A

40. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response: See Section P.5 of the Product Quality Microbiology Assessment above.

Reviewer's Assessment: Adequate

2.3.P.7 Container/Closure System

41. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant's Response: See Section P.2.5 of the Product Quality Microbiology Assessment above.

Reviewer's Assessment: Adequate

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

42. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response: See Section A.2 of the Product Quality Microbiology Assessment above.

Reviewer's Assessment: Adequate

43. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response: See Section A.2 of the Product Quality Microbiology Assessment above.

Reviewer's Assessment: Adequate

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: Not Recommended/Not Adequate
Lisa S.G. Shelton 04/29/16

Secondary Review Comments and Concurrence: I concur with the primary microbiology reviewer's assessment.
Bryan S. Riley, Ph.D. 04/29/2016

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

1. Is the applicant's claim for categorical exclusion acceptable?

2. Is the applicant's Environmental Assessment adequate for approval of the application?

The applicant claims categorical exclusion under 21 CFR 25.31 (a) from filing Environmental Impact Assessment Statement with respect to this application.
Under 21 CFR 25.31(a), a categorical exclusion exists for:
"Action on an NDA, abbreviated application, application for marketing approval of a biologic product, or a supplement to such applications, or action on an OTC monograph, if the action does not increase the use of the active moiety".

The applicant certifies that no extraordinary circumstances exist, and the firm is in compliance with all applicable Federal, State and Local environmental laws and regulations.

Reviewer's Assessment: ADEQUATE

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature: ADEQUATE
The claim is reasonable and is acceptable.
Yushi Feng, Ph.D.; Staff Fellow; Branch 3; Division of New Drug Product I.
Mar 23, 2016.

Secondary Review Comments and Concurrence: I concur.
Balajee Shanmugam, Ph.D. Division of New Drug Product 1.
April 29, 2016

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

Voriconazole for injection for intravenous use

_____DOSAGE FORMS AND STRENGTHS_____

For Injection: lyophilized white to off white cake or powder containing 200 mg voriconazole and 3200 mg of hydroxypropyl ß-cyclodextrin (HPβCD); after reconstitution 10 mg/mL of voriconazole and 160 mg/mL of HPβCD

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name		ADEQUATE
Dosage form, route of administration		ADEQUATE
Controlled drug substance symbol (if applicable)		N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths		ADEQUATE

Conclusion: ADEQUATE

(b) "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

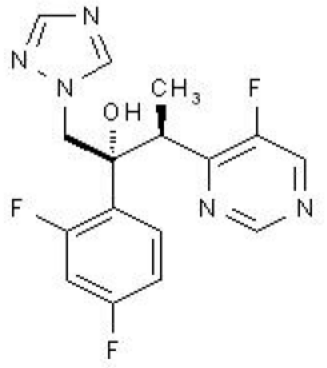
Powder for Solution for Injection
Voriconazole for injection is supplied in a single (b) (4) dose vial as a sterile lyophilized white to off white cake or powder equivalent to 200 mg voriconazole and 3200 mg hydroxypropyl ß-cyclodextrin (HPβCD).

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms		ADEQUATE
Strengths: in metric system		ADEQUATE
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.		ADEQUATE

Conclusion: ADEQUATE
Change from "single use" to "single dose"

#11: Description (21CFR 201.57(c)(12))

Voriconazole for injection, an azole antifungal agent is available as a sterile lyophilized cake or powder for solution for intravenous infusion. The structural formula is:



Voriconazole is designated chemically as (2R,3S)-2-(2, 4-difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)-1-(1H-1,2,4-triazol-1-yl)-2-butanol with an empirical formula of C16H14F3N5O and a molecular weight of 349.3.

Voriconazole drug substance is a white or almost white powder.

Voriconazole for injection, is a white to off white lyophilized cake or powder containing nominally 200 mg voriconazole and 3200 mg hydroxypropyl ß-cyclodextrin (HPβCD) in a 30 mL Type I clear glass vial.

Voriconazole for injection is intended for administration by intravenous infusion. It is a single-dose, unpreserved product. Vials containing 200 mg lyophilized voriconazole are intended for reconstitution with Water for Injection to produce a solution containing 10 mg/mL Voriconazole for injection and 160 mg/mL of hydroxypropyl ß-cyclodextrin (HPβCD). The resultant solution is further diluted prior to administration as an intravenous infusion [see Dosage and Administration (2)].

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name		ADEQUATE
Dosage form and route of administration		ADEQUATE
Active moiety expression of strength with equivalence statement for salt (if applicable)		ADEQUATE
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.		ADEQUATE
Statement of being sterile (if applicable)		ADEQUATE
Pharmacological/ therapeutic class		ADEQUATE
Chemical name, structural formula, molecular weight		ADEQUATE
If radioactive, statement of important nuclear characteristics.		N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)		N/A

Conclusion: ADEQUATE

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

16.1 How Supplied

Powder for Solution for Injection

Voriconazole for injection is supplied in a single (b) (4) dose vial as a sterile white to off white lyophilized cake or powder equivalent to 200 mg voriconazole and 3200 mg hydroxypropyl ß-cyclodextrin (HPβCD).

Individually packaged vials of 200 mg Voriconazole for injection.

NDC (b) (4)

16.2 Storage

Voriconazole for injection unreconstituted vials should be stored at (b) (4) 20° – 25°C (68° – 77°F) [see USP Controlled Room Temperature]. Voriconazole for injection is a single dose unpreserved sterile lyophile. From a microbiological point of view, following reconstitution of the lyophile with Water for Injection, the reconstituted solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2° to 8°C (36° to 46°F). Chemical and physical in-use stability has been demonstrated for 24 hours at 2° to 8°C (36° to 46°F). Further diluted product (0.5 mg/mL and 5 mg/mL) should be used immediately after second step dilution. This medicinal product is for single (b) (4) dose only and any unused

solution should be discarded. Only clear solutions without particles should be used [see Dosage and Administration (2.1)].

Recommended revisions are highlighted.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form		ADEQUATE
Available units (e.g., bottles of 100 tablets)		ADEQUATE
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number		DEFICIENT
Special handling (e.g., protect from light, do not freeze)		ADEQUATE
Storage conditions		DEFICIENT

Manufacturer/distributor name listed at the end of PI, following Section #17

(b) (4)

Made in India

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)		ADEQUATE

Conclusion: DEFICIENT
Change from (b) (4) to "single dose"

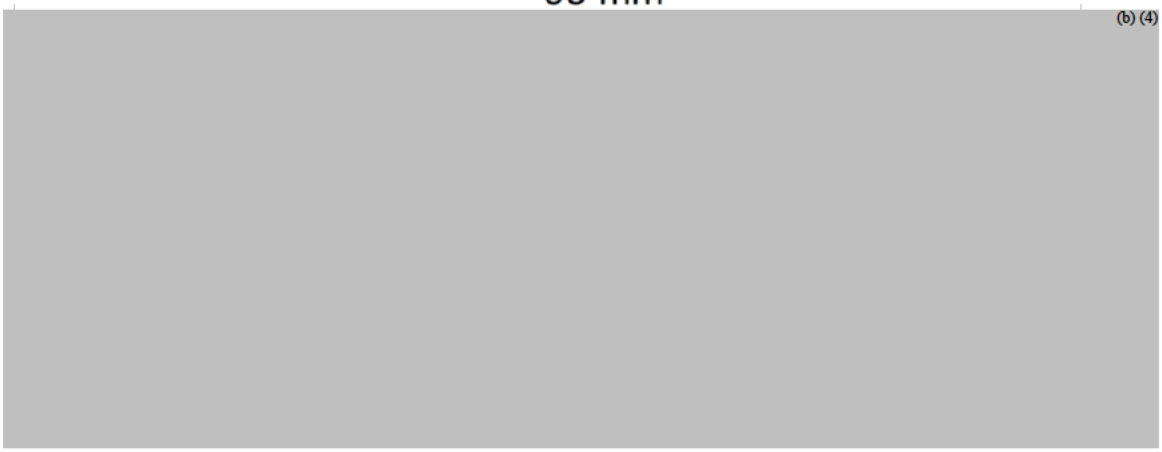
Statement on dosage form color needs to be added.

Storage condition should follow the USP controlled room temperature definition.

2. Container and Carton Labeling

1) Immediate Container Label

Zoom Size 200%
95 mm



Reviewer's Assessment:

- Change from (b) (4) to "Not made with natural rubber latex". Refer to final guidance: *Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex - Guidance for Industry and Food and Drug Administration Staff*.
- Change from "Sterile Single (b) (4) Vial" to "Sterile Single Dose Vial".
- Update storage condition to "Store at 20°C to 25°C (68°F to 77°F)"
- Change from (b) (4) to "each vial contains 200 mg voriconazole and 3200 mg hydroxypropyl β-cyclodextrin (HPβCD)".

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))		ADEQUATE
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))		ADEQUATE
Route of administration 21.CFR 201.100(b)(3))		ADEQUATE
Net contents* (21 CFR 201.51(a))		ADEQUATE
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**		DEFICIENT
Lot number per 21 CFR 201.18		ADEQUATE
Expiration date per 21 CFR 201.17		ADEQUATE
"Rx only" statement per 21 CFR 201.100(b)(1)		ADEQUATE
Storage (not required)		DEFICIENT
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		ADEQUATE
Bar Code per 21 CFR 201.25(c)(2)***		ADEQUATE
Name of manufacturer/distributor (21 CFR 201.1)		ADEQUATE
Others		

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.

**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label

**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: DEFICIENT

- Change from (b) (4) to "Not made with natural rubber latex". Refer to final guidance: *Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex - Guidance for Industry and Food and Drug Administration Staff.*
- Change from "Sterile Single (b) (4) Vial" to "Sterile Single Dose Vial".
- Update storage condition to "Store at 20°C to 25°C (68°F to 77°F)"
- Change from (b) (4) to "each vial contains 200 mg voriconazole and 3200 mg hydroxypropyl β-cyclodextrin (HPβCD)".

2) Carton Labeling

(b) (4)

Reviewer's Assessment:

- Change from (b) (4) to "Not made with natural rubber latex". Refer to final guidance: *Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex - Guidance for Industry and Food and Drug Administration Staff*.
- Change from "Sterile Single (b) (4) Vial" to "Sterile Single Dose Vial".
- Update storage condition to "Store at 20°C to 25°C (68°F to 77°F)"
- Change from (b) (4) to "each vial contains 200 mg voriconazole and 3200 mg hydroxypropyl β-cyclodextrin (HPβCD)".

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))		ADEQUATE
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))		ADEQUATE
Net contents (21 CFR 201.51(a))		ADEQUATE
Lot number per 21 CFR 201.18		ADEQUATE
Expiration date per 21 CFR 201.17		ADEQUATE
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]		DEFICIENT
Sterility Information (if applicable)		ADEQUATE
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)		ADEQUATE
Storage Conditions		DEFICIENT
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		ADEQUATE
Bar Code per 21 CFR 201.25(c)(2)**		ADEQUATE
Name of manufacturer/distributor		ADEQUATE
"See package insert for dosage information" (21 CFR 201.55)	Proposed label reads: refer to prescribing information Recommend to change to: See package insert for dosage information	DEFICIENT
"Keep out of reach of children" (optional for Rx, required for OTC)	Statement not included Statement is optional for Rx products. This product is proposed to be Rx.	ADEQUATE

Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))		ADEQUATE

Conclusion: DEFICIENT

- Change from [(b) (4)] to "Not made with natural rubber latex". Refer to final guidance: *Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex - Guidance for Industry and Food and Drug Administration Staff.*
- Change from "Sterile Single [(b) (4)] Vial" to "Sterile Single Dose Vial".
- Update storage condition to "Store at 20°C to 25°C (68°F to 77°F)"
- Change from "[(b) (4)] to "each vial contains 200 mg voriconazole and 3200 mg hydroxypropyl β-cyclodextrin (HPβCD)".
- Change from [(b) (4)] to "See package insert for dosage information"

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature: DEFICIENT
Revisions to the labeling are needed.
Yushi Feng, Ph.D.; Staff Fellow; Branch 3; Division of New Drug Product I.
Apr 29, 2016.

Secondary Review Comments and Concurrence:

II. List of Deficiencies To Be Communicated

Label/Labeling Revisions (recommendations to be conveyed to the applicant and finalized in Review # 2)

III. Attachments

A. Lifecycle Knowledge Management

a) Drug Product

From Initial Risk Identification			Review 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 of Voriconazole	Quality of the incoming API; analytical method	L	The DMF was found adequate.	Acceptable	
Impurities/ Degradation Products	Quality of the API, and excipient	L	The DMF of DS and excipient were both adequate.	Acceptable	
Particulate matter (reconstituted solution)	Quality of the API, excipient, and container closure	M	The DMF of DS and excipient were both adequate.	Acceptable	
Leachables/ extractables	Quality of the API, excipient, and container closure	L	The DMF of DS, excipient and container closure were adequate.	Acceptable	
Sterility	Starting materials, manufacturing process, and container/ closure integrity.	H	Evaluate (b) (4)	Acceptable	
Endotoxins	Starting materials and processing of container closure components	M	Evaluate depyrogenation of container closure components and final product specification.	Acceptable	