CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208562Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	(electronic stamp)
From	Dorota Matecka, Ph.D.
Subject	Cross-Discipline Team Leader (CDTL) Review
NDA #	208562
Applicant	Xellia Pharmaceuticals ApS
Date of Submission	January 9, 2017 (*Class 1 NDA Resubmission*)
PDUFA Goal Date	March 9, 2017
Proprietary Name / Established (USAN) names	Voriconazole for Injection* (voriconazole)
Dosage forms/Strength	Powder for injection, 200 mg/vial
Proposed Indication(s)	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
Recommended:	***Approval***

** No proprietary/trade name was proposed for the drug product*

1. Introduction

This 505(b)(2) NDA submitted by Xellia Pharmaceuticals ApS provides for a new injectable formulation of voriconazole. The listed drugs for this 505(b)(2) NDA are VFEND® (voriconazole) for Injection, 200 mg/vial (approved in 2002 via NDA 21267) and SPORANOX® (itraconazole) Injection, 10 mg/mL (approved via NDA 20966 in 1999 and withdrawn from the market in 2011 due to commercial reasons).

The drug product proposed by Xellia Pharmaceuticals ApS, Voriconazole for Injection, 200 mg/vial, is a new formulation of voriconazole lyophilized powder for injection, and differs from VFEND® (voriconazole) for Injection in the excipients used in the formulation; specifically, it contains (b) (4) hydroxypropyl β-cyclodextrin (hydroxypropylbetadex, HPβCD) instead of sulfobutylether β-cyclodextrin (SBEβCD). No clinical data have been submitted in this NDA as the Applicant is relying on previous findings of efficacy and safety for VFEND® for approval of the proposed drug product. In addition, to support the change in excipient, the Applicant is also relying on the Agency's finding of safety for SPORANOX® (itraconazole) Injection, 10 mg/mL, an injectable formulation of itraconazole that contains HPβCD as a solubilizing agent (400 mg/mL).

This NDA, originally submitted on July 24, 2015, was issued a Tentative Approval letter on May 24, 2016 due to the pending patent issues; no other deficiencies were identified. All of the reviewers found this NDA acceptable in the first review cycle, as described in their respective

reviews of the original NDA and the previous CDTL review. The current (Class 1) NDA resubmission contains only minor updates to the CMC section and labeling.

2. Background

Voriconazole is a broad spectrum triazole antifungal drug. The primary mode of action of voriconazole is the inhibition of fungal cytochrome P-450-mediated 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell wall and may be responsible for the antifungal activity of voriconazole.

Voriconazole is a lipophilic, poorly water soluble, drug characterized by nonlinear pharmacokinetics, high inter-individual pharmacokinetics, and hepatic elimination. The listed drug, VFEND® (voriconazole) for Injection, 200 mg, contains 3200 mg of (b) (4) SBEβCD, which upon reconstitution amounts to 10 mg/mL of voriconazole and 160 mg/mL of SBEβCD. The currently proposed drug product, Voriconazole for Injection, 200 mg, contains 3200 mg of HPβCD and upon reconstitution amounts to 10 mg/mL of voriconazole and 160 mg/mL of HPβCD.

There are two other generic IV formulations (i.e., powders for injection) and several oral formulations (i.e., tablets and powders for suspension) of voriconazole approved in the U.S. at this time. As discussed above, the drug product proposed by Xellia Pharmaceuticals ApS, has the same drug substance, dosage form, concentration, route of administration, (b) (4) as VFEND® (voriconazole) for Injection. Due to the difference in the formulation (i.e., a change in the excipients not permitted per 314.94(a)(9)(iii)), this application was submitted as 505(b)(2) application and not as a 505(j) application.

3. Product Quality

This NDA resubmission was reviewed by the following OPQ Reviewers: Dr. Yushi Feng (Drug Product), Dr. Steve Rhieu (Process) and Dr. Christina Capacci-Daniel (Facilities).

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. In addition, the status of the proposed manufacturing facilities was assessed by Dr. Christina Capacci-Daniel who found them acceptable in support of this NDA. The overall recommendation of "Approve" was entered by the Office of Process and Facilities (OPF) into Panorama on March 6, 2017. In addition, several minor revisions in the package insert and the container labels were found acceptable. Therefore, this NDA is recommended for approval from the Product Quality perspective (refer to the OPQ Review # 3 entered into Panorama on March 7, 2017 by Dorota Matecka on behalf of the OPQ team).

4. Nonclinical Pharmacology/Toxicology

Dr. Owen McMaster was the Pharmacology/Toxicology Reviewer for this application who found this NDA approvable in the first cycle (refer to the review dated March 28, 2016 in DARRTS). The same recommendation was made by Dr. McMaster in his review of the NDA resubmission (via review dated February 14, 2017, in DARRTS).

5. Clinical Pharmacology

The Clinical Pharmacology Reviewer, Dr. Zhixia (Grace) Yan, recommended this NDA for approval in the first review cycle with a number of labeling revisions (refer to the review dated May 3, 2016, in DARRTS). No new clinical pharmacology information was submitted in the current resubmission; therefore, the Clinical Pharmacology review team continues recommending this NDA for approval, provided the labeling revisions are adequately addressed by the Applicant (review dated February 24, 2017, in DARRTS).

6. Clinical Microbiology

Shukal Bala, Ph.D., was the Clinical Microbiology Reviewer for this application.

No new clinical microbiology information was submitted in this resubmission. Dr. Bala continues recommending approval of this application from the microbiology standpoint with several minor revisions in the product package insert (refer to the review dated February 17, 2017, in DARRTS).

7. Clinical/Statistical – Safety and Efficacy

Caroline Jjingo, MD, MPH, was the Clinical Reviewer, and Cheryl Dixon, Ph.D., was the Statistical Reviewer for this NDA.

No new clinical information was submitted in this resubmission. Dr. Jjingo recommended this application for approval in her review of the original NDA submission (review and Addendum dated April 28 and May 24, 2016, respectively, and Addendum II filed for the current resubmission dated March 6, 2017, in DARRTS).

The only recommended change in the labeling by Dr. Dixon included the removal of reference to the [redacted] (b) (4) in the Clinical Studies section (review dated May 10, 2016, in DARRTS). Dr. Dixon did not have any additional recommendations for this resubmission (review dated February 3, 2017, in DARRTS).

8. Advisory Committee Meeting

There was no Advisory Committee Meeting for this application.

9. Pediatrics

The drug product proposed via this 505(b)(2) NDA does not contain a new active ingredient and is not a new dosage form. No new indication is proposed and no new dosing regimen is proposed. There is no new route of administration associated with the new product. For these reasons, the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), does not apply to this application. No pediatric studies will be required as a condition of approval.

10. Other Relevant Regulatory Issues

No clinical studies/trials were conducted in support of this NDA. Therefore, no inspection request was sent to the Office of Scientific Investigations (OSI).

One of the listed drugs, VFEND ® (voriconazole) for Injection, 200 mg/vial (NDA 21267), has the following unexpired patent listed in the Orange Book:

- US Patent No. 6,632,803 - Expiry Date: June 2, 2018

The Applicant of the current NDA included in their original NDA submission Paragraph IV Certification regarding the above patent and certified via a subsequent NDA amendment that notices regarding the Paragraph IV certification were delivered to the holders of the patent and the NDA (Pfizer Inc. and PF Prism C.V.); however, no lawsuit has been filed.

The second listed drug, SPORANOX® (itraconazole) Injection, 10 mg/mL (NDA 20966 held by Janssen), has the following unexpired patent listed in the Orange Book:

- US Patent No. 6,407,079 - Expiry Date: June 18, 2019

The Applicant of the current NDA also submitted Paragraph IV Certification for the above patent. On June 29, 2016, Janssen filed suit against Xellia in the U.S. District Court for the District of Delaware alleging infringement of U.S. Patent No. 6,407,079 and resulting in a 30-month stay of approval under FDCA 505(c)(3)(C). However, the Janssen's lawsuit against Xellia was dismissed by the Court on December 22, 2016, thus terminating the 30-month stay of approval for the current NDA.

11. Labeling

The proposed labeling and labels for Voriconazole for Injection, 200 mg/vial, were submitted in the NDA. No trade name was proposed for the drug product.

Labeling revisions and recommendations were provided from all disciplines (including OPDP and DMEPA) during the review of the original NDA submission and the current resubmission. All recommended labeling revisions were incorporated in the package insert and vial and carton labels.

12. Recommendations/Risk Benefit Assessment

I concur with the assessments made by the review team and recommend that this NDA be approved. The drug product proposed via this 505(b)(2) NDA, Voriconazole for Injection, 200 mg/vial, would provide an alternative injectable product that would have the risk-benefit profile similar to the listed drug (VFEND ®). There are no unresolved issues or deficiencies that need to be conveyed to the Applicant. No PMRs, PMCs, or pediatric studies need to be requested.

Dorota M. Matecka -S

Cross-Discipline Team Leader Review

Date	(electronic stamp)
From	Dorota Matecka, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA #	208562
Applicant	Xellia Pharmaceuticals ApS
Date of Submission	July 24, 2015
PDUFA Goal Date	May 24, 2016
Proprietary Name / Established (USAN) names	Voriconazole for Injection* (voriconazole)
Dosage forms/Strength	Powder for injection, 200 mg/vial
Proposed Indication(s)	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
Recommended:	***Tentative Approval***

** No proprietary/trade name was proposed for the drug product*

1. Introduction

This 505(b)(2) NDA submitted by Xellia Pharmaceuticals ApS provides for a new injectable formulation of voriconazole. The listed drugs for this 505(b)(2) NDA (as identified on an updated Form 356h submitted via the May 23, 2016 amendment) are VFEND® (voriconazole) for Injection, 200 mg/vial (approved in 2002 via NDA 21267) and SPORANOX® (itraconazole) Injection, 10 mg/mL (approved via NDA 20966 in 1999 and withdrawn from the market in 2011 due to commercial reasons).

The drug product proposed by Xellia Pharmaceuticals ApS, Voriconazole for Injection, 200 mg/vial, is a new formulation of voriconazole lyophilized powder for injection, and differs from VFEND® (voriconazole) for Injection in the excipients used in the formulation; specifically, it contains [redacted] (b) (4) hydroxypropyl β-cyclodextrin (HPβCD) instead of sulfobutylether β-cyclodextrin (SBEβCD). No clinical data have been submitted in this NDA as the Applicant is relying on previous findings of efficacy and safety for VFEND® for approval of the proposed drug product. In addition, to support the change in excipient, the Applicant is also relying on the Agency's finding of safety for SPORANOX® (itraconazole) Injection, 10 mg/mL, an injectable formulation of itraconazole that contains HPβCD as a solubilizing agent (400 mg/mL).

The majority of the information submitted in the NDA relates to the chemistry, manufacturing and controls used in the manufacture of the proposed voriconazole drug product. In view of the

similarities between the proposed and listed drugs, a biowaiver for conducting in-vivo bioequivalence studies was requested by the Applicant.

It should be noted that the original NDA submission included a reference (b) (4) via the NDA amendment dated May 23, 2016, in which the Applicant has also clarified that the scientific "bridge" between their product, Voriconazole for Injection and VFEND® relies only upon *in vitro* studies conducted by the Applicant and other *in vitro* and *in vivo* studies available in the published literature. Subsequently, several reviews of this NDA (i.e., Product Quality, Clinical Pharmacology, and Clinical reviews), (b) (4) accordingly to reflect this revision submitted in the May 23, 2016 amendment.

2. Background

Voriconazole is a broad spectrum triazole antifungal drug. The primary mode of action of voriconazole is the inhibition of fungal cytochrome P-450-mediated 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell wall and may be responsible for the antifungal activity of voriconazole.

Voriconazole is a lipophilic, poorly water soluble, drug characterized by nonlinear pharmacokinetics, high inter-individual pharmacokinetics, and hepatic elimination. The listed drug, VFEND® (voriconazole) for Injection, 200 mg, contains 3200 mg of (b) (4) SBEβCD, which upon reconstitution amounts to 10 mg/mL of voriconazole and 160 mg/mL of SBEβCD. The currently proposed drug product, Voriconazole for Injection, 200 mg, contains 3200 mg of HPβCD and upon reconstitution amounts to 10 mg/mL of voriconazole and 160 mg/mL of HPβCD.

There are two other generic IV formulations (i.e., powders for injection) and several oral formulations (i.e., tablets and powders for suspension) of voriconazole approved in the U.S. at this time. As discussed above, the drug product proposed by Xellia Pharmaceuticals ApS, has the same drug substance, dosage form, concentration, route of administration, (b) (4) as VFEND® (voriconazole) for Injection. Due to the difference in the formulation (i.e., a change in the excipients not permitted per 314.94(a)(9)(iii)), this application was submitted as 505(b)(2) application and not as a 505(j) application.

3. Product Quality

The Product Quality Team from the Office of Pharmaceutical Quality (OPQ) included the following individuals:

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

The chemistry manufacturing and controls information for voriconazole drug substance has been provided via a reference to DMF Type II (b) (4) held by (b) (4). Dr. Yushi Feng, the Drug Substance Reviewer stated that DMF (b) (4) has been found to be adequate via a chemistry review dated January 8th, 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).

The 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) (SBEβCD) in VFEND® has been replaced with the same amount of (b) (4) (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, claiming that the proposed change in the (b) (4) will have no impact on the BA/BE of voriconazole. The Biopharmaceutics Reviewer, Dr. Gieser, noted the pH range of the Applicant's proposed voriconazole drug product upon reconstitution, the osmolality/osmolarity of the infusion solution upon reconstitution and dilution, and the in vitro antifungal activity are comparable to those of the listed drug, VFEND®. In addition, per the proposed labeling of the Applicant's Voriconazole for Injection, the (b) (4) and the labeling instructions for reconstitution and further dilution are the same as that in the approved VFEND® labeling. Therefore, Dr. Gieser concluded that the overall information provided in the NDA supports the biowaiver request, and the biowaiver request is granted, under 21 CFR 320.24(b)(5).

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 by the Drug Product Reviewer, Dr. Feng. The proposed drug product is supplied in a glass vial with a rubber stopper. The overall information provided for the proposed container closure system that includes compliance with the USP 381> and <87> was found acceptable by the same Reviewer. 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 for three batches of the proposed drug product [24 months at 25°C ± 2°C/60% RH ± 5%RH, 12 months at 30°C ± 2°C/75% RH ± 5%RH, and 6 months at 40°C ± 2°C/75% RH ± 5%RH (samples placed in inverted and upright orientations)] was found acceptable by Dr. Feng. 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].

The manufacturing process for the proposed drug product includes: (b) (4) The information on the manufacturing process provided in the original NDA submission, along with additional information regarding a sampling plan for commercial batches and (b) (4) (submitted via a subsequent NDA amendment) was found acceptable by the Process Reviewer, Dr. Steve Rhieu.

Information provided for the proposed drug product from the product quality microbiology perspective (i.e., sterility assurance in the manufacturing process, container closure system, drug product specification and stability) was found acceptable by Dr. Lisa Shelton who recommended several revisions to the proposed in the package insert storage time and conditions for the reconstituted and further diluted solutions of the proposed drug product.

The drug substance manufacturing sites are (b) (4) and (b) (4) The drug product facilities include (b) (4) (a drug product manufacturer) and (b) (4) (excipient testing facility). 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.

In addition, several revisions in the package insert and the container labels were recommended by the Drug Product and the Product Quality Microbiology Reviewers (e.g., a change from the (b) (4) to the "single dose vial" statement in all parts of the product labeling). Therefore, the recommendation in the Product Quality Review # 1 (entered into Panorama on April 30, 2016) was "Approval pending labeling revisions". Since all labeling revisions recommended by the Product Quality Team were accepted by the Applicant, the overall recommendation from the Product Quality perspective is now "Approval" (refer to the final Product Quality Review # 2 entered into Panorama on May 24, 2016 by Dorota Matecka).

4. Nonclinical Pharmacology/Toxicology

Dr. Owen McMaster was the Pharmacology/Toxicology Reviewer for this application. No nonclinical toxicology studies were conducted to support this NDA as the Applicant is relying on FDA's prior finding of the safety and effectiveness of the reference listed drug. In addition, Dr. McMaster stated that there no safety concerns regarding the substitution of SBEβCD with

HPβCD as HPβCD has been approved for use in the US in drugs such as Sporanox (itraconazole) Injection and Vibativ (telavancin for injection). Therefore, Dr. McMaster recommends approval of this NDA from the pharmacology/toxicology perspective with several (for details refer to the review dated March 28, 2016 in DARRTS).

5. Clinical Pharmacology

The Clinical Pharmacology Reviewer, Dr. Zhixia (Grace) Yan, stated in her review (dated May 3, 2016) that this application did not provide any new clinical pharmacology studies. However, due to the formulation change in the proposed drug product as compared to the listed drug, the clinical pharmacology review focused on the available PK information for HPβCD and SBEβCD and comparison of the PK information for voriconazole formulations containing HPβCD and SBECD. Following the Applicant's amendment dated May 23, 2016, a Clinical Pharmacology Addendum was filed in DARRTS stating that the information from the (b) (4) were not considered in the recommendation to approve this NDA (refer to the Addendum by Dr. Philip Colangelo dated May 24, 2016 in DARRTS).

Dr. Yan has recommended several revisions in the proposed drug product labeling related to the replacement of SBEβCD with HPβCD stating that the same warning in patients with moderate to severe impairment as that found in the listed drug VFEND®'s labeling should be used for the current product. In conclusion, the Clinical Pharmacology review team has recommended approval of this NDA, provided the labeling recommendations are adequately addressed by the Applicant.

6. Clinical Microbiology

Shukal Bala, Ph.D., was the Clinical Microbiology Reviewer for this application.

No new clinical microbiology information was submitted with this application other than a study report of in vitro studies against quality control strains of three Candida species to assess if the new formulation had any impact on the antifungal activity of voriconazole, which, as assessed by Dr. Bala, did not show any impact on the activity of voriconazole. Dr. Bala recommended approval of this application from the microbiology standpoint with several minor changes in the product package insert (refer to the review dated February 25, 2016 in DARRTS).

7. Clinical/Statistical – Safety and Efficacy

Caroline Jjingo, MD, MPH, was the Clinical Reviewer, and Cheryl Dixon, Ph.D., was the Statistical Reviewer for this NDA.

Dr. Jjingo states in her review that this 505(b)(2) NDA, which provides for a new IV formulation of voriconazole, does not contain any clinical studies as the Applicant of the current 505(b)(2) NDA is relying on the previous findings of safety and efficacy for the listed drug, VFEND® (voriconazole) for Injection, 200 mg.

As requested by the Agency, the Applicant conducted a review of the literature and FDA Adverse Events Reporting System (AERS) and concluded that no new safety signals, which would warrant a modification to the pre-existing approved VFEND® labeling, were identified. Dr. Jjingo conducted a PubMed/MeSH search yielding a total of 41 publications, which was further narrowed to 25 publications using the publication date restriction of October 1, 2014 to March 31, 2016. The two most commonly safety related topics cited in these 25 publications included voriconazole-induced periostitis (6 publications) and voriconazole-induced squamous cell carcinomas (5 publications). There was one article addressing voriconazole associated alopecia and nail changes. Other publications pertained to drug-drug interactions, such as those between voriconazole and sirolimus, and voriconazole and everolimus. Four publications that included clinical trials results were reviewed for adverse events (AEs); however, no new safety AE was identified. Dr. Jjingo also noted that no new articles with concerning safety signals were identified via PubMed Alerts. Additionally, it is noted in the review that Dr. Kelly Cao from OSE/DPVII confirmed that as of February 18, 2016, OSE was not aware of any new signals with voriconazole that require regulatory action.

Regarding the use of the new excipient, HPβCD, Dr. Jjingo states that he Applicant relies on safety data from several other previously FDA-approved products containing the excipient HPβCD, such as intravenous itraconazole (SPORANOX® approved via NDA 20966). Dr. Jjingo notes that the primary route of elimination for both HPβCD and SBEβCD is through renal excretion via glomerular filtration and renal impairment may cause cyclodextrin accumulation and increase elimination half-life regardless of which drug vehicle (HPβCD or SBEβCD) is used. Therefore, Dr. Jjingo agrees with the clinical pharmacology review team that the Applicant should include the same warning in patients with moderate to severe impairment as that found in the listed drug VFEND®'s package insert.

Dr. Jjjingo states that no new safety information was presented or identified that would alter the favorable risk/benefit assessment of voriconazole in the treatment of the labeled indications, such as invasive aspergillosis; candidemia (nonneutropenics) and disseminated candidiasis in skin, abdomen, kidney, bladder wall, and wounds; and serious infections caused by *Scedosporium apiospermum* and *Fusarium species* including *Fusarium solani*, in patients intolerant of, or refractory to other therapy. These indications do NOT include (b) (4) [redacted] In conclusion, Dr. Jingo recommends this application for approval (refer to the review dated April 28, 2016 in DARRTS). In addition, the Addendum filed into DARRTS on May 24, 2016 by Dr. Jjingo, states that the Applicant of this NDA is not relaying on (b) (4) [redacted] (per NDA amendment dated May 23, 2016).

Dr. Dixon stated that this submission did not require any statistical review since there were no clinical studies provided in the submission. The only recommended change in the labeling by Dr. Dixon includes the removal of reference to the [redacted] (b) (4) in the Clinical Studies section (review dated May 10, 2016 in DARRTS).

8. Advisory Committee Meeting

There was no Advisory Committee Meeting for this application.

9. Pediatrics

The drug product proposed via this 505(b)(2) NDA does not contain a new active ingredient and is not a new dosage form. No new indication is proposed and no new dosing regimen is proposed. There is no new route of administration associated with the new product. For these reasons, the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), does not apply to this application. No pediatric studies will be required as a condition of approval.

10. Other Relevant Regulatory Issues

No clinical studies/trials were conducted in support of this NDA. Therefore, no inspection request was sent to the Office of Scientific Investigations (OSI).

One of the listed drugs, VFEND ® (voriconazole) for Injection, 200 mg/vial (NDA 21267), has the following unexpired patents listed in the Orange Book:

- US Patent No. 5,567,817- Expiry Date: May 24, 2016
- US Patent No. 6,632,803 - Expiry Date: June 2, 2018

The Applicant of the current NDA, Xellia Pharmaceuticals ApS, included in the original NDA submission, Paragraph IV Certification [per 505(j)(2)(A)(vii)(IV) of the Act and 21 CFR 314.50(i)(1)(i)] regarding for the above patents stating that they are invalid, unenforceable, and/or will not be infringed by the manufacture, use, or sale of Voriconazole for Injection (200 mg/vial), for which the current 505(b)(2) NDA is submitted. Subsequently, the Applicant submitted the NDA amendment dated November 24, 2015 to certify that notices regarding the "Paragraph IV" certification were delivered to Pfizer Inc. and PF Prism C.V. ("Pfizer"), which are the holders of the patents and the NDA; however, no lawsuit has been filed.

The second listed drug, SPORANOX® (itraconazole) Injection, 10 mg/mL (NDA 20966), has the following unexpired patent listed in the Orange Book:

- US Patent No. 6,407,079 - Expiry Date: June 18, 2019

For the above patent, the Applicant has submitted Paragraph IV Certification via the NDA amendment dated May 23, 2016.

11. Labeling

The proposed labeling and labels for Voriconazole for Injection, 200 mg/vial, were submitted in the NDA. No trade name was proposed for the drug product.

Labeling revisions and recommendations were provided from all disciplines including OPDP (review by Adam George, Pharm.D. dated May 16, 2016 in DARRTS) and DMEPA (reviews by Sevan Kolejian, Pharm.D., dated March 23, 2016 and May 19, 2016). All recommended labeling revisions were incorporated in the package insert and vial and carton labels.

12. Recommendations/Risk Benefit Assessment

I concur with the assessments made by the review team and recommend that this NDA be approved. The drug product proposed via this 505(b)(2) NDA, Voriconazole for Injection, 200 mg/vial, would provide an alternative injectable product that would have the risk-benefit profile similar to the listed drug. There are no unresolved issues or deficiencies that need to be conveyed to the Applicant. No PMRs, PMCs, or pediatric studies need to be requested. However, due to the pending patent issues for Sporanox®, a tentative approval is recommended at the present time.

Dorota M. Matecka -S