

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205596Orig1s000

CHEMISTRY REVIEW(S)

M E M O R A N D U M

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

DATE: March 13, 2014
FROM: Xuhong Li, Ph.D., Review Chemist, Branch VI, DNDQA II/ONDQA
THROUGH: Dorota Matecka, Ph.D., CMC Lead, DNDQA II/ONDQA
Rapti Madurawe, Ph.D., Branch Chief, DNDQA II/ONDQA
Sarah Pope Miksinski, Ph.D., Division Director, DNDQA II/ONDQA
TO: NDA 205-596
SUBJECT: Addendum to CMC Review #1 for NDA 205-596

Overall Summary and Recommendation:

Data provided in the NDA shows that Noxafil infusion solutions prepared in the recommended diluents, 5% dextrose (D5W) and 0.9% sodium chloride (NS), frequently exceeded USP<788> limits for particulate matter in large volume injections. Particulate matter in an injection solution is a safety concern. Clinical studies to establish the safety of Noxafil injection were conducted with the use of a 0.22 µm in-line filter, indicating the applicant took precautionary measures to mitigate the risk of particulate matter. In response to FDA questions on particulate matter, the applicant submitted new data showing some batches (lots not identified) passed USP<788> and attributed the failed results reported in the NDA to improper sampling handling. The information provided is not sufficient to rule out particulate formation in Noxafil infusion solutions. Particulate matter in Noxafil infusion solutions remains a potential risk. However, data show that when Noxafil infusion solutions in D5W and NS are passed through an in-line polyethersulfone (PES) of 0.22 µm or 5µm pore size, post-catheter solutions met USP<788> requirements for large volume parenteral with no potency loss. This data indicate that appropriate use of an in-line filter can mitigate the potential risk to the patient caused by particulate matter. ONDQA recommends that Noxafil injection must be used with an in-line filter, the package insert and carton include prominent wording to indicate the requirement for filter usage, and to further enhance compliance of using an on-line filter during administration, co-package Noxafil injection with the intended in-line filter. The recommended filters are 0.22 µm pore-size polyethersulfone (PES) or polyvinylidene difluoride (PVDF) filters. In addition, to further evaluate the particulate matter potential and determine if further risk mitigation strategies are needed, the applicant should conduct the following studies under a post-marketing commitment and report the results to the Agency.

PMC 1: Provide USP <788> test results using both Method 1 and Method 2 for the diluted infusion solutions of posaconazole injection in D5W and Normal Saline at drug product release and at annual stability test time points for 10 commercial batches of the drug product, Noxafil Injection, 300 mg.

PMC 2: Conduct and provide the results of a detailed root-cause analysis of the particulate formation reported in Section 3.2.P.2.6 of the NDA for infusion solutions of

posaconazole in 5% Dextrose and Normal Saline. This analysis should include evaluation of conditions under which particulates can be formed, the potential causes for the observed precipitation, an evaluation of whether particulate matter is more likely to appear in infusions solutions of newly manufactured batches of posaconazole injection, and if “batch aging” is likely to reduce particulates. Use both USP<788> Method 1 and Method 2 in your analysis. For particulates observed, identify the particulate matter.

Review Notes

CMC Review #1 dated 20 Feb 2014 did not recommend approval of NDA 205596 and was finalized with the comments, “EES recommendation is pending. Also, the labels and labeling need to be finalized, and the use of in-line filter and particulate matter issues need to be further evaluated” in the signature block. In addition, the review listed the following pending issues:

1. The final recommendation from the Office of Compliance was pending.
2. An official submission of a revised drug product specification to include a pH tests had not been submitted to the NDA.
3. Label and labeling issues were not satisfactorily resolved.

The following issues have been resolved since the filing of CMC review # 1 in DARRTS:

1. An overall “Acceptable” recommendation was issued by the Office of Compliance on 02/27/2014 (See Attachment I for EER summary).
2. The applicant officially amended the NDA to include the pH test in both release and stability testing on 02/25/2014. Updated drug product specification (Attachment II) and stability protocol (Attachment III) are provided.
3. The following deficiencies pertinent to the particulate matter, in-line filter use and other general labeling issues have been addressed as described below:
 - a. Updated Carton and container labels contain required changes (see Attachment IV)
 - b. Package Insert:
 - 1) Drug product name changed from “NOXAFIL® (Posaconazole) Intravenous Solution” to “NOXAFIL® (Posaconazole) Injections” throughout the entire content of the package insert.
 - 2) As recommended, “concentrated solution for dilution before IV administration” is added for clarification purpose in the description section of the package insert.
 - 3) As recommended, statement of being sterile is added in the description section of the package insert.
 - 4) Per CFR 201.100 (b) (5) (iii), the applicant should include the information of quantity or proportion of all inactive ingredients.

In addition to the above recommended changes that have been conveyed to the applicant, the instructions to use an in-line filter for administration raised concern during the labeling review due to the potential for particulate matter.

In the original submission, the applicant provided compatibility studies results of posaconazole infusion solutions with IV bags, infusion sets, in-line filter and catheter. Admixture concentration of 1 mg/mL and 3 mg/mL posaconazole were studied which bracketed the proposed labeled admixture concentration of 1.8 mg/mL. It was observed that, with a 0.22 µm or a (b) (4) in-line filter, the post-catheter particulate matters counts

comply with USP<788> requirements and there is no posaconazole potency loss due to either of the in-line filters. However, some particulate counts results (b) (4) for the infusion solution in the container showed elevated counts for particle matters (b) (4) (b) (4) thus an in-line PES filter rated at (b) (4) or smaller was recommended to reduce the particulate level.

To understand the origin and risk of the elevated particulate counts observed in the infusion solutions of posaconazole and to obtain more information on the compatibility studies, an information request was sent to the applicant on February 25, 2014. The applicant's response was received on February 27, 2014:

- 1. Section 3.2.P.2.6 of the NDA shows that the admixtures with the proposed diluents, 5% dextrose (D5W) and 0.9% sodium chloride (NS), frequently exceeded USP<788> recommended particulate matter limits for large volume injections. What is the nature of the particulate matters formed in the admixture solutions and the probable cause(s) for particulate formation, if known?***

Response: The applicant claimed that the observations of higher particulate counts (b) (4) in the IV-container were likely due to sampling preparation variability and this sample preparation variability has been minimized over time, as shown by the more consistent data from the IV containers in subsequent studies. According to the applicant, a compatibility study to support end-of-shelf life 'in-use' stability was executed under comparable conditions as those used in two of the initial studies where elevated particulate counts in IV-container are observed (see Attachment V for the referenced data tables submitted in the original submission). In the new study, all results, including those from the pre-catheter admixture in container, met the USP <788> requirements (see Attachment VI for the new data tables).

In addition, the applicant also generated data intended to support the IV administration without filter, i.e., compatibility study executed using an IV set without in-line filter. The particulate counts comply with USP<788>:



Reviewer's Comment: *The applicant claims that the elevated particulate counts observed in the earlier studies were due to sampling preparation variability. In a teleconference (dated 10 Mar 2014) held between the Agency and the applicant, the applicant further explained that the elevated particulate counts is believed to be caused by air bubble generated during sample preparation, and the issue has been resolved by letting the sample sit and dissipate the air bubbles before testing. Although, air bubble is a common cause of false alarm associated with USP<788> method 1, and it may be a valid hypothesis for the root cause of the earlier observed elevated particulate counts, thorough studies are needed to confirm this hypothesis. At present, the body of new data submitted in the February 27, 2013 amendment is not sufficient to address the identity and causes of the possible particulate formation during dilution.*

- 2. We note that no particulate matter failures were observed in the compatibility study of an aged drug product (30-month old). Also, it appears the particulate matter levels were much higher at the 3-month time point versus later time points (including a 24-month time point) for several primary stability batches of the drug product. Is there any explanation for these observations?***

Response: The applicant confirms that no particulate matter failures were observed in the admixture compatibility study of aged drug product, including both the data at 30 months referenced above, as well as additional data generated at end-expiry.

The applicant explains that, the 3 months data for the levels of (b) (4) particulate matter in the drug product are higher than values observed for other time points, however, since this data was within the stability specifications (USP<788> Method 1 small volume injectable limits), further investigation was not deemed necessary at the time of testing. The applicant argued that the elevated particulate counts are likely a result of sampling preparation variability, specific to the testing performed at the 3 month time point. The applicant believes that this conclusion is supported by the lack of trending associated with particulate counts on stability for these batches.

- 3. In addition to D5W and NS, were other diluents evaluated in the compatibility studies? Also, were different brands of D5W and NS evaluated in the compatibility studies? Please submit the data, if available.***

Response: Additional common diluents, as listed below, were evaluated as admixtures at the intended commercial dose of 300 mg and included sampling from the admixture container (IV bag) as well as post-catheter samples (with in-line filter included).

Diluent	Sample Types	Compatible	Storage Conditions	Time Points	Data Location
(b) (4)	Admixture container and Post-catheter	Yes	RT, 2-8°C	Initial and 24 hr	Table 5
(b) (4)	Admixture container and Post-catheter	Yes	RT, 2-8°C	Initial and 24 hr	Table 6
5% Dextrose and 0.9% NaCl	Admixture container and Post-catheter	Yes	RT, 2-8°C	Initial and 24 hr	Table 7
(b) (4)	Admixture container and Post-catheter	Yes	RT, 2-8°C	Initial and 24 hr	Table 8
(b) (4)	Admixture container and Post-catheter	No	n/a	Initial	Table 9
(b) (4)	Admixture container and Post-catheter	No			
(b) (4)	Admixture Container	No			

*Data not available at time of filing

The particulate matters results met USP<788> requirement for a large volume parenteral, both pre-catheter and post-catheter, for (b) (4), 5% Dextrose and 0.9% NaCl and (b) (4). However, (b) (4)

Total Dose [mg]	Diluent	Sample Name	Visual Description
300	(b) (4)	(b) (4)	(b) (4)
300	(b) (4)	(b) (4)	(b) (4)
300	(b) (4)	(b) (4)	(b) (4)

Reviewer's Comment: *The pore size for the filter used in these studies is not specified. However, it is likely to be no more than 5 µm because these data were generated by the applicant to support the labeling that included the in-line filter use.* (b) (4)

(b) (4)

it should be emphasized in the package insert that the use of the drug product with only two diluents: normal saline or 5% dextrose solutions should be strictly followed.

4. ***Did you evaluate the admixture compatibility with other types of in-line filters (i.e., other than the PES filter reported)? Please submit the data, if available.***

Response: The applicant reported that additional filter types beyond PES were not evaluated as part of admixture compatibility. The applicant propose (b) (4)

particulate matters results met the USP<788> requirement for large volume parenteral.

Reviewer's Comment: *On 13 Mar 2014, during the teleconference held between the Agency and the applicant, the applicant proposed* (b) (4)

Overall Evaluation: *Information available is not sufficient to rule out the potential particulate formation during posaconazole infusion preparation. However, data show that all post catheter samples with an in-line PES filter (5µm or less) used, met USP<788> requirements for a large volume parenteral with no posaconazole potency loss. That indicates that the appropriate use of an in-line PES filter (5µm or less) can mitigate the potential risk to the patient caused by particulate matters. In addition, to further enhance compliance of using an on-line filter during administration, ONDQA precedence committee recommended that the applicant co-package the drug product with the intended in-line filter. In addition, it should be specified in the package insert that the in-line filter must be used and both Noxafil injection and the co-administered drug products should only be administered with D5W or Normal Saline. It should also emphasize that use of other infusion solutions may result in particulate formation.*

Attachment I

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application:	NDA 205596/000	Sponsor:	MERCK SHARP DOHME
Org. Code:	520		351 NORTH SUMNEYTOWN PIKE LG 2CD 68
Priority:	3		NORTH WALES, PA 194542505
Stamp Date:	13-SEP-2013	Brand Name:	NOXAFIL
PDUFA Date:	13-MAR-2014	Estab. Name:	
Action Goal:		Generic Name:	
District Goal:	12-JAN-2014	Product Number; Dosage Form; Ingredient; Strengths	001; SOLUTION, INJECTION; POSACONAZOLE; 18MG/ML

FDA Contacts:	X. LI	Prod Qual Reviewer	3017964987
	N. BHANDARI	Product Quality PM	2404023815
	A. RODGERS	Regulatory Project Mgr	(HFD-520) 3017960797

Overall Recommendation:	ACCEPTABLE	on 27-FEB-2014	by J. WILLIAMS	()	3017964196
	PENDING	on 04-OCT-2013	by EES_PROD		

Establishment:	CFN: 9612726	FEI: 1000288672		
	SCHERING PLOUGH (AVONDALE) LARAGH ROAD AVONDALE, COUNTY WICKLOW, RATHDRUM, IRELAND			
DMF No:		AADA:		
Responsibilities:	DRUG SUBSTANCE MANUFACTURER DRUG SUBSTANCE RELEASE TESTER DRUG SUBSTANCE STABILITY TESTER			
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	OAI Status:	NONE	
Last Milestone:	OC RECOMMENDATION			
Milestone Date:	07-OCT-2013			
Decision:	ACCEPTABLE			
Reason:	BASED ON PROFILE			

Establishment:	CFN: 9611641	FEI: 3003974846		
	SCHERING PLOUGH LABO NV INDUSTRIEPARK 30 3100 HEIST-OP-DEN-BERG, ANTWERPEN, BELGIUM			
DMF No:		AADA:		
Responsibilities:	FINISHED DOSAGE PACKAGER			
Profile:	STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS	OAI Status:	NONE	
Last Milestone:	OC RECOMMENDATION			
Milestone Date:	04-NOV-2013			
Decision:	ACCEPTABLE			
Reason:	DISTRICT RECOMMENDATION			

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: 9616653 FEI: 3002808087
SCHERING-PLOUGH (BRINNY) CO
INNESHANNON
COUNTY BRIDGE, , IRELAND

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER

Profile: STERILE-FILLED SMALL VOLUME PARENTERAL OAI Status: NONE
DRUGS

Last Milestone: OC RECOMMENDATION

Milestone Date: 27-FEB-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Attachment II

Test	Acceptance Criteria	Method
Description	Release and Shelf Life Clear colorless to yellow liquid essentially free of foreign matter	Visual
Color	Release (b) (4)	Visual
	Shelf Life (b) (4)	
Identification	Release The relative retention time ratio of the analyte peak in the sample and in the reference standard is (b) (4)	HPLC
Identification	Release UV Maximum is (b) (4) nm	UV-Vis
Assay	Release and Shelf Life (b) (4) Label Strength	HPLC
Degradation Products	Release and Shelf Life Individual Unspecified (b) (4) Total (b) (4)	HPLC
pH	Release and Shelf Life (b) (4)	USP <791> Ph. Eur. 2.2.3
Particulate Matter	Release and Shelf Life NMT (b) (4) NMT (b) (4)	USP <788> Ph. Eur. 2.9.19
Volume of Injection in Container	Release (b) (4)	USP <1> Ph. Eur. 2.9.17
Bacterial Endotoxins	Release and Shelf Life NMT (b) (4)	USP <85> Ph. Eur. 2.6.14
Sterility	Release and Shelf Life Meets Requirements	USP <71> Ph. Eur. 2.6.1

Attachment III

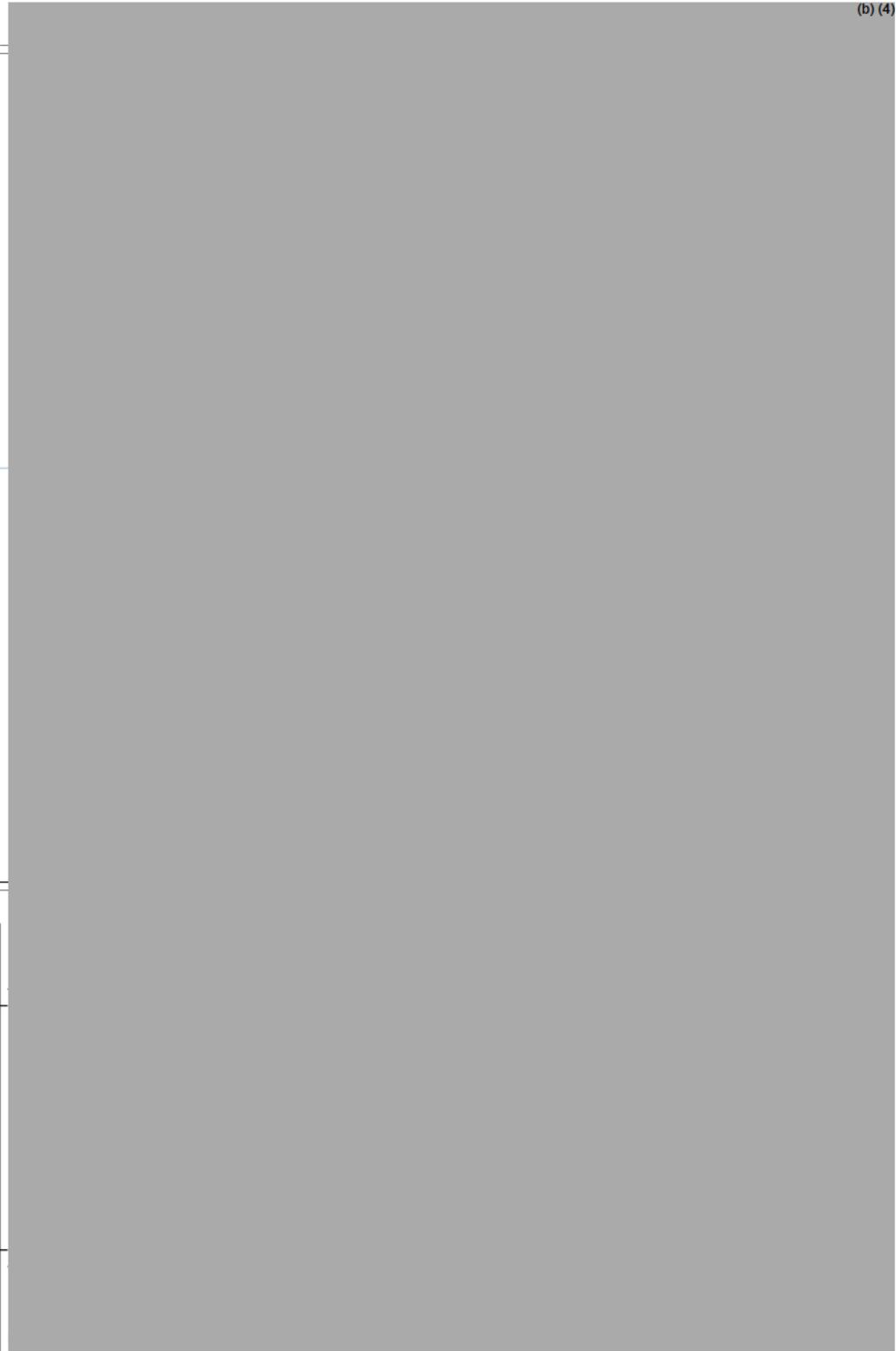
Table 1 Initial Long Term Stability Protocol for Posaconazole Injection, 18 mg/mL								
Storage Condition	Packages							
5°C ± 3°C/Ambient RH	Type 1 ^{(b) (4)} glass vials with Bromobutyl stoppers and flip-off seals							
Test	Stability Interval in Months							
	0	3	6	9	12	18	24	36
Description	X	X	X	X	X	X	X	X
Assay: Posaconazole	X	X	X	X	X	X	X	X
Degradation Products: Posaconazole	X	X	X	X	X	X	X	X
Particulate Matter	X	X	X	X	X	X	X	X
Color	X	X	X	X	X	X	X	X
pH	X	X	X	X	X	X	X	X
Bacterial Endotoxin	X							X
Sterility	X							X

Table 2 Accelerated Stability Protocol for Posaconazole Injection, 18 mg/mL			
Storage Condition	Packages		
30 ± 2°C / 65 ± 5% RH	Type 1 ^{(b) (4)} glass vials with Bromobutyl stoppers and flip-off seals		
Test	Sample Age in Months		
	0	3	6
Description	X	X	X
Assay: Posaconazole	X	X	X
Degradation Products: Posaconazole	X	X	X
Particulate Matter	X	X	X
Color	X	X	X
pH	X	X	X

Table 3 Ongoing Long Term Stability Protocol for Posaconazole Injection, 18 mg/mL				
Storage Condition		Packages		
5°C ± 3°C/Ambient RH		Type 1 ^{(b) (4)} glass vials with Bromobutyl stoppers and flip-off seals		
Test	Stability Interval in Months			
	0	12	24	36
Description	X	X	X	X
Assay: Posaconazole	X	X	X	X
Degradation Products: Posaconazole	X	X	X	X
Particulate Matter	X	X	X	X
Color	X	X	X	X
pH	X	X	X	X
Bacterial Endotoxin	X			X
Sterility	X			X

Attachment IV

1) Carton and container labels



(b) (4)

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

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

/s/

XUHONG LI
03/13/2014

DOROTA M MATECKA
03/13/2014

RAPTI D MADURawe
03/13/2014

SARAH P MIKSINSKI
03/13/2014

NDA 205-596

NOXAFIL[®]
(posaconazole)
Injection , 18 mg/mL

Merck Sharp & Dohme Corp.

Xuhong Li

DPA II/Branch VI

Office of New Drug Quality Assessment
for the Division of Anti-Infective Products

Table of Contents

The Executive Summary	8
I. Recommendations	8
A. Recommendation and Conclusion on Approvability	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable	8
II. Summary of Chemistry Assessments.....	8
A. Description of the Drug Product(s) and Drug Substance(s).....	8
B. Description of How the Drug Product is Intended to be Used.....	9
C. Basis for Approvability or Not-Approval Recommendation.....	10
III. Administrative.....	10
A. Reviewer’s Signature	10
B. Endorsement Block.....	10
C. CC Block.....	10
Chemistry Assessment.....	11
I. Review Of Common Technical Document-Quality (Ctd-Q) Module	11
3.2: Body Of Data.....	11
S DRUG SUBSTANCE [Posaconazole, Schering-Plough (Avondale)]	11
S.1 General Information.....	11
S.2 Manufacture.....	12
S.3 Characterization.....	12
S.4 Control of Drug Substance.....	13
S.5 Reference Standards or Materials.....	16
S.6 Container Closure System.....	16
S.7 Stability	16
P DRUG PRODUCT [Posaconazole Injection, 18 mg/mL].....	18
P.1 Description and Composition of the Drug Product	18
P.2 Pharmaceutical Development	19
P.2.1 Components	20
P.2.2 Formulation development.....	21
P.2.3 Manufacturing Processes Development.....	26
P.2.4 Container Closure System.....	31

P.2.5 Microbiological Attributes 36

P.2.6 Compatibility 36

P.3 Manufacture 38

 P.3.1 Manufacturers 38

 P.3.2. Batch Formula 38

 P.3.3 Description of Manufacturing Process and Process Controls 39

 P.3.4 Controls of Critical Steps and Intermediates 40

 P.3.5 Process Validation and/or Evaluation 41

P.4 Control of Excipients 41

P.5 Control of Drug Product 41

 P.5.1 Specifications 42

 P.5.2 Analytical Procedures 43

 P.5.3 Validation of Analytical Procedures 44

 P.5.4 Batch Analysis 48

 P.5.5 Characterization of impurities 48

 P.5.6 Justification of Specifications 50

P.6 Reference Standards and Materials 54

P.7 Container Closure System: 58

P.8 Stability 60

 P.8.1 Stability Summary and Conclusions 60

 P.8.2 Post Approval Stability Protocol and Stability Commitment 70

 P.8.3 Stability Data 71

A APPENDICES 71

R REGIONAL INFORMATION 71

 R.1.P Executed Batch Records 71

 R.2.P Comparability Protocols 72

 R.3.P Method Validation Package 75

II. Review of Common Technical Document – Quality (CTD-Q) Module 1 ... 75

 A. Labeling & Package Insert 75

 B. Environmental Assessment Or Claim Of Categorical Exclusion 82

III. List of Deficiencies Communicated 83

Chemistry Review Data Sheet

1. NDA 205596
2. REVIEW #: 1.0
3. REVIEW DATE: 28-Dec-2013
4. REVIEWER: Xuhong Li, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
IND 75061: COR-MEET-09 (Final Written Response)	18-Apr-2013

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
SDN 000 New/NDA	12-Sep-2013
SDN 001 Quality Response to Information Request	14-Oct--2013

7. NAME & ADDRESS OF APPLICANT:

Name:	Merck Sharp & Dohme Corp.
Address:	351 North Sumneytown Pike, PO Box 1000 North Wales, PA 19454-2505 USA
Telephone:	267-305-6679

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: NOXAFIL®
- b) Non-Proprietary Name (USAN): Posaconazole
- c) Code Name/#: MK-5592/ SCH-56592

- d) Chem. Type/Submission Priority:
- Chem. Type: Type 3 (New Dosage Form)
 - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOLOGICAL CATEGORY: Antifungal

11. DOSAGE FORM: Injectable solution

12. STRENGTH/POTENCY: 18 mg/mL

13. ROUTE OF ADMINISTRATION: IV

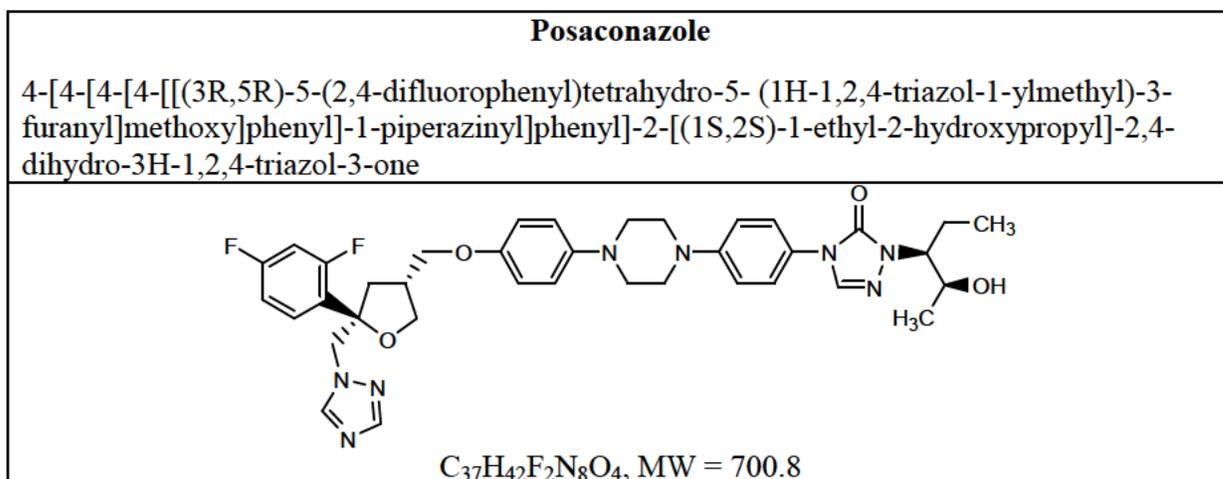
14. Rx/OTC DISPENSED: X Rx ___ OTC

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

___ SPOTS product – Form Completed

X Not a SPOTS product

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



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	REVIEW DATE	COMMENT
(b) (4)	III		(b) (4)	1	Adequate	06 Feb 2014	LoA confirmed, 02-Apr- 2013
	III			1	Adequate	25-Jan-2013, by Dr. Joseph Leginus	LoA confirmed. 05-Apr-2013

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Product Quality Reviews:

REVIEW	RECOMMENDATION	DATE	REVIEWER
Quality Micro	Acceptable	14 Feb 2014	Dr. Vinayak Pawar

C. Consults or Outside CMC Review Team input:

CONSULTS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
Pharm/Tox	Acceptable	23 Jan 2014	Dr. Owen McMaster
Pharm/Tox	Acceptable	13 Feb 2014	Dr. Owen McMaster

D. Other Applications or Submissions Referenced:

DOCUMENT Referenced	APPLICATION NUMBER	DESCRIPTION
IND	51,316	Posaconazole Capsules/Tablets
IND	51,662	Posaconazole Oral Suspension
IND	75, 061	Posaconazole IV solution

NDA	22-003	Noxafil® (posaconazole) Oral Suspension, 40 mg/mL
NDA	22-027	Noxafil® (posaconazole) Oral Suspension, 40 mg/mL
(b) (4)		
NDA	205-053	Noxafil® Delayed-Release Tablets,

The Chemistry Review for NDA 205596

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has generally provided satisfactory information to assure identity, strength, purity, and quality of the drug product, posaconazole injection, 18 mg/mL.

However, the labeling issues are still pending and a site recommendation from the Office of Compliance has not been made as of the date of this review.

Therefore, from the CMC perspective, this NDA is not recommended for approval at this time until an acceptable recommendation for all manufacturing facilities is received from the Office of Compliance (EES) and the labeling and labels are found acceptable.

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

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product

Posaconazole Injection, also known as Posaconazole Concentrate for Solution for Infusion, contains 18 mg posaconazole per mL. The drug product is a single-dose unpreserved sterile solution that is formulated with Betadex Sulfobutyl Ether Sodium (SBECD) as (b) (4) Disodium Edetate (EDTA) as (b) (4) and hydrochloric acid/sodium hydroxide for pH adjustment. The challenges in the drug product formulation and process development including the (b) (4) of the drug substance and a (b) (4) of the drug substance. The drug product manufacturing process involves (b) (4)

(b) (4) The drug product is sterilized by (b) (4) filled in a 20 mL Type I glass vial and closed with bromobutyl rubber stopper and aluminum seal. The target deliverable volume (label claim) is 16.7 mL, corresponding to 300 mg/vial. The target fill volume is controlled at (b) (4) which contains (b) (4) to ensure that there is enough drug product solution available for withdrawal from the vial for delivery. The drug product is to be diluted in 0.9 % saline or 5% dextrose solution prior to administration by IV infusion.

The drug product specification includes the following attributes: description, color, identification, assay, degradation products, pH, particulate matter, volume of injection in container, bacterial endotoxins and sterility. Several tests, including a pH test, have not been proposed to be included in the drug product shelf life specification. However, the proposed drug product is an intravenous solution and pH is one of the important quality attributes for this dosage form. Therefore, it was recommended to the applicant that the pH test should be part of both release and shelf life specification for the drug product. A response to this recommendation was received by email to the Project Manager dated February 20, 2014. The applicant agreed to include the pH test in both release and stability specifications, and stated that the revised documents (the drug product specification and stability protocols) will be submitted to the NDA by February 25, 2014. The revised specification will be documented in DARRTS along with the EES recommendation for this NDA (once received from the Office of Compliance) via an addendum to this review.

The proposed 36 months shelf life for the drug product when stored under refrigerated condition ($5^{\circ}\text{C} \pm 3^{\circ}\text{C}$) is supported by stability data provided. The drug product is stable when exposed to light for up to 30 days at ambient conditions and the secondary container box is able to protect the product from the light under storage condition. In addition, in use compatibility studies showed that the posaconazole injection admixtures are stable for up to 120 minutes of infusion after 24 hour storage in admixture containers at room temperature and 5°C .

Drug Substance

Posaconazole drug substance is a triazole broad-spectrum antifungal compound which has been approved for posaconazole oral suspension ((b) (4)), NDA 22-003 and NDA22-027). The applicant uses the same drug substance approved for posaconazole oral suspension for the posaconazole injection, with bacterial endotoxins and microbiological examination added to control the drug substance as parenteral grade. Majority of the drug substance information was referenced to the approved NDAs for Noxafil® Oral Suspension. However, the drug substance specification, the justification for the proposed acceptance criteria for Microbiological Examination and Bacterial Endotoxins tests, as well as the microbiological stability data are provided in this submission for evaluation. Posaconazole drug substance has a low aqueous solubility (no more than $1\mu\text{g}/\text{mL}$ in an aqueous media with pH higher than pH 5) and two pKa values (b) (4). The (b) (4) of the drug substance presented a challenge for the posaconazole injection formulation development that was overcome by (b) (4). Posaconazole drug substance in its powder form has good stability and degrades only under stress conditions. The drug substance is to be stored at controlled room temperature. The proposed retest period for the drug substance, (b) (4), is supported by the stability data.

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

Noxafil (posaconazole) Injection is indicated for prophylaxis of invasive *Aspergillus* and *Candida* infections. The drug product is supplied in a glass vial as a concentrated solution

(label claim of 300 mg/16.7 mL) and is to be diluted in 0.9 % saline or 5 % dextrose solution prior to administration by IV infusion. It is not intended for IV bolus administration.

Posaconazole injection, 18 mg/mL, will be labeled for storage under refrigerated condition 2°-8°C (36°-46°F). In addition, the diluted solutions can be stored up to 24 hours under refrigerated conditions 2°-8°C (36°-46°F).

C. Basis for Approvability or Not-Approval Recommendation

This NDA has generally provided sufficient information on raw material controls, manufacturing processes and process controls, test methods, specifications, batch data and stability data for assuring consistent product quality of the drug substance and drug product over the storage period. In addition, the product quality microbiology review (dated February 14, 2014, in DARRTS) has recommended approval of this NDA from the quality microbiology viewpoint. However, the labeling issues are still pending and a site recommendation from the Office of Compliance has not been made as of the date of this review. Therefore, from the CMC perspective, this NDA is not recommended for approval at this time until an acceptable recommendation for all manufacturing facilities is received from the Office of Compliance.

III. Administrative

A. Reviewer's Signature

(See appended electronic signature page)

Xuhong Li

B. Endorsement Block

(See appended electronic signature page)

Dorota Matecka, CMC Lead
Rapti, Madurawe, Ph.D., Branch Chief

C. CC Block

{see DARRTS}

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

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

/s/

XUHONG LI
02/20/2014

DOROTA M MATECKA
02/20/2014

I concur.
EES recommendation is pending. Also, the labels and labeling need to be finalized, and the use of in-line filter and particulate matter issues need to be further evaluated.

RAPTI D MADURawe
02/20/2014
The pending issues need to be resolved for NDA approval.

ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: **205596**

2. DATES AND GOALS:

Letter Date: September 13, 2013	Submission Received Date : September 13, 2013
PDUFA Goal Date: March 13, 2013	

3. PRODUCT PROPERTIES:

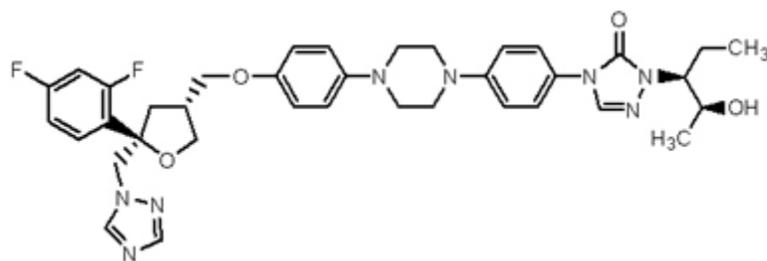
Trade or Proprietary Name:	Noxafil®
Established or Non-Proprietary Name (USAN):	posaconazole
Dosage Form:	IV solution
Route of Administration:	Intravenous
Strength/Potency:	18 mg/mL (300 mg/vial)
Rx/OTC Dispensed:	Rx

4. INDICATION:

Prophylaxis of invasive Aspergillus and Candida infections

5. DRUG SUBSTANCE STRUCTURAL FORMULA:

Posaconazole: 4-[4-[4-[4-[[(3R,5R)-5- (2,4-difluorophenyl)tetrahydro-5- (1H-1,2,4-triazol-1-ylmethyl)-3-furanyl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-[(1S,2S)-1-ethyl-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one



$C_{37}H_{42}F_2N_8O_4$
MW = 700.8

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

6. NAME OF APPLICANT (as indicated on Form 356h):

Merck Sharp & Dohme Corp.

7. SUBMISSION PROPERTIES:

Review Priority:	Expedited Review Granted
Submission Classification (Chemical Classification Code):	3
Application Type:	505(b)(1)
Breakthrough Therapy	No
Responsible Organization (Clinical Division):	DAIP

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		x	
Clinical Pharmacology		x	
Establishment Evaluation Request (EER)	x		
Pharmacology/Toxicology			TBD
Methods Validation			TBD
Environmental Assessment		x	
CDRH		x	
Other			N/A

ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective? Yes
CMC Filing Issues:
None

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter? Yes
CMC Comments for 74-Day Letter: We acknowledge that you cross-reference NDA 22003 for posaconazole drug substance information. However, to facilitate our review please provide the following: a. A summary of each change made to the manufacture of the posaconazole drug substance since the original approval of NDA 22003 (including a list of approved and pending supplements), and b. Location (e.g., section number, page number, submission date, etc., as appropriate) of the change information as given above.

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective?
Biopharmaceutics Filing Issues:
Not Applicable. There is no information in the NDA under Biopharmaceutics review purview.

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter?
Biopharmaceutics Comments for 74-Day Letter:
Not Applicable.

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective? Yes
Microbiology Filing Issues:
See Microbiology Filing Review for details and for any potential Microbiology review issues.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

Summary of Initial Quality Assessment

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain
	x		

Is a team review recommended?	Yes	No
Suggested expertise for team:		

Summary of Critical Issues and Complexities
The assessment below describes the important issues for this NDA.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

Initial Quality Assessment

Posaconazole (also known as, SCH 056592, and MK-5592, also referred to as POS throughout the NDA) is a broad-spectrum systemic triazole antifungal.

In the US, POS oral suspension (Noxafil®) is indicated for prophylaxis of invasive *Aspergillus* and *Candida* infections in patients, 13 years of age and older, who are at high risk of developing these infections due to being severely immunocompromised, or those with hematologic malignancies with prolonged neutropenia from chemotherapy (indication approved via NDA 22003). POS Oral Suspension is also approved in the US for the treatment of oropharyngeal candidiasis, including oropharyngeal candidiasis refractory to itraconazole and/or fluconazole (indication approved via NDA 22027). In addition, a new NDA for a solid oral tablet formulation, which allows for once daily administration and is proposed to be indicated for the same approved prophylaxis indication as POS oral suspension, is currently under review in DAIP (NDA 205053).

POS IV solution has been developed under IND 75,061 for the same prophylaxis indication approved for POS oral suspension. A Type C meeting (teleconference) was held on February 11, 2009 between the applicant (Merck) and the FDA to discuss the proposed clinical development program for POS IV solution, specifically use of a PK bridging strategy to register the POS IV solution. Also, a Type C CMC guidance teleconference took place on September 9, 2010 and included discussing issues such as drug product stability program and sterilization procedures. In addition, comments and recommendations regarding the NDA stability data package and bridging strategy proposed by the applicant in the meeting request dated February 26, 2013 were conveyed to the applicant via a correspondence (Written Responses) dated April 18, 2013.

Drug Substance

The applicant stated that the posaconazole drug substance for the proposed injection formulation will be the same as the one used for Posaconazole Oral Suspension. No changes were made to the drug substance manufacturing or packaging processes. The proposed specification for posaconazole drug substance to be used in the IV formulation includes all the tests listed in the specification of posaconazole drug substance approved for the POS oral suspension along with two additional tests appropriate for a drug substance to be used for parenteral route of administration, bacterial endotoxins and microbiological limits (refer to Attachment 1 of this review).

The Module 3 of the submission contains a specification for the proposed parenteral drug substance, batch analysis data for several batches, and stability data (up to 24 months) for the two additional microbiological tests, bacterial endotoxins and microbiological limits. For information on the other stability attributes, a reference is made to the NDA for posaconazole oral suspension.

Comment: For majority of CMC information for the drug substance a cross reference is made to the approved application for Posaconazole Oral Suspension (NDA 22003). As mentioned above, the drug substance section in Module 3 of the current NDA contains a specification, batch

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

analysis data and stability results for microbiological attributes. Some discussion of the physico-chemical properties of posaconazole has been included in Pharmaceutical Development section of this NDA; however, a separate section S.1 (General Information) was not included in the current NDA. In addition, it would be helpful to have a list of all changes made in the manufacture of the posaconazole drug substance since its original approval via NDA 22003. A comment regarding this should be included in the 74-day letter.

Drug Product

The drug product, Posaconazole Injection, containing 18 mg posaconazole per mL, also known as Posaconazole Concentrate for Solution for Infusion, is an intravenous (IV) formulation that has been developed as an additional dosage form to the approved oral suspension formulation. Posaconazole Injection is a clear solution formulated with Betadex Sulfbutyl Ether Sodium (SBECD) to (b) (4) the drug substance, and hydrochloric acid and sodium hydroxide to adjust pH of the solution. The composition of Posaconazole Injection, 18 mg/mL, is attached in Attachment 2 (below). All excipients are of compendial grade (USP/NF).

The intended commercial presentation of the drug product is a 20 mL Type I glass vial with a label fill volume of 16.7 mL, the equivalent of 300 mg dose strength. The drug product is to be diluted in 0.9 % saline or 5 % dextrose solution prior to administration by IV infusion. The application does include data on compatibility of the drug product with the proposed diluents, bags, catheters and infusions sets. This data is provided in the Pharmaceutical Development section. *Comment: This data should be evaluated along with the storage statements included in the labeling for the proposed drug product. In addition, evaluation from the product quality microbiology stand point will also be needed.*

It is stated that the label fill for Posaconazole Injection is 16.7 mL, which equates to an (b) (4). This excess volume corresponds to (b) (4) of the label fill. Therefore, the applicant stated that a volume of at least (b) (4) is needed to ensure delivery of the label volume from the vial.

Posaconazole injection will be manufactured at Schering-Plough (Brinny) Co. Brinny, Ireland.

As stated in the QOS, the formulation of Posaconazole Injection has remained unchanged from clinical to commercial product. In addition, the manufacturing process (b) (4)

The Pharmaceutical Development section includes a discussion of QTPPs and CQAs for the drug product, and risk assessment and control strategy (including PARs) for each unit operation. The applicant stated that this NDA is considered a traditional submission from a Quality by Design (QbD) perspective, and it does not contain flexible regulatory approaches, such as design spaces or real time release testing. (b) (4)

(b) (4) was utilized in the drug product formulation

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

and manufacturing process development. *Comment: These aspects of the manufacture and process development will need to be reviewed in detail (e.g., how were the proposed ranges in process parameters studied and established?)*

The manufacturing process for the drug product includes (b) (4)

(b) (4) A flow chart and narrative description are provided in section 3.2.P.3.3 and the process parameters and in-process controls discussed in section 3.2.P.3.4. *Comment: A detailed review of these sections will need to be performed to decide if sufficient details are provided (or if a master batch record should be submitted). It should be noted that executed batch records have been provided in section 3.2.R.*

As stated above, POS IV solution is (b) (4) filled product. Justification for utilizing the (b) (4) process has been incorporated in the NDA. Filling is conducted in an (b) (4) with controlled environment and under Grade A and Grade B conditions. *Comment: The proposed sterilization process, including validation and other microbiological quality aspects of the proposed drug substance and drug product, should be evaluated by the Product Quality Microbiology Reviewer (note previously mentioned discussions regarding the sterilization method that took place during the teleconference on September 9, 2010). It should be noted that Dr. Vinayak Pawar found the current application fillable from the product quality microbiology perspective (filing review dated October 23, 2013 in DARRTS).*

The applicant stated that the commercial process has been demonstrated and validated at the (b) (4) batch size, producing approximately (b) (4) vials per batch. (b) (4)

(b) (4) A comparability protocol based on the draft FDA Guidance for Industry: Comparability Protocols – Chemistry, Manufacturing, and Controls Information, February 2003 is provided in Module 3, Regional Section, 3.2.R.2.P “Comparability Protocol for Batch Size Increase.” The comparability protocol provides a detailed description of all proposed changes, studies to be performed, as well as the proposed reduced reporting category. *Comment: Evaluation of this comparability protocol will need a Product Quality Microbiology Reviewer’s input.*

The commercial container closure system for the proposed drug product, Posaconazole Injection, includes 20 mL Type I tubing glass vials sealed with a bromobutyl rubber stopper and capped with a flip-off seal. The physical description, specifications, and drawings for each component of the container closure system are provided in section 3.2.P.7. Information and data regarding suitability of the container closure system for Posaconazole Injection are provided in section 3.2.P.2.4. That includes evaluation and comparison of the 15 and 20 mL glass vials used for the clinical and commercial presentations, respectively, in terms of glass contact surface area, headspace, weight loss and container closure seal integrity. Information on extractables and leachables from the stopper is also included in this section. *Comment: This information, including stability data for leachables, will need to be evaluated in detail and consulted with the pharm/tox reviewer.*

ONDQA Initial Quality Assessment (IQA) and Filing Review For Pre-Marking Applications

The applicant has outlined the stability data submitted in support of the proposed the shelf life, as follows:

- Six primary stability batches (100 mg/5.6 mL and 200 mg/11.2 mL per 15 mL vial)
- One pilot scale final market image stability batch (300 mg/ 16.7 mL per 20 mL vial)
- Two full scale final market image and site specific stability batches (300 mg/ 16.7 mL per 20 mL vial)
- Three full scale final market image and process validation stability batches (300 mg/16.7 mL per 20 mL vial)
- Four supportive stability batches (100 mg/5.6 mL per 5 mL vial and 200 mg/11.2 mL per 20 mL vial)

The applicant has provided the following justifications for use of the stability data from batches that have different fill volumes and vial size from the final market image to support the final market image stability and shelf life:

- All batches contain identical formulation.
- Compounding processes for primary stability batches and final market image stability batches are the same. Processes for the final market image pilot scale batch and supportive stability batches are representative of the final commercial process.
- For all batches used throughout development and clinical studies, the packaging materials in contact with the drug product solutions are of the same type. Additionally, the 100 mg/5.6 mL per 15 mL vial image from the primary stability batches represents the worst case scenario for glass contact surface area and headspace in vials.
- Stability of the drug product has been shown to be independent from the fill volume and vial size.
- Available bridging stability data between the primary stability batches and the final market image confirm their stability profiles are comparable.

It should be noted that per FDA recommendation (dated April 18, 2013) the applicant did provide an additional 3-months of long-term stability data for the batches of the commercial presentation. In addition, the applicant has also provided 3 months of stability data on three process validation batches.

The shelf life of 36 months is proposed for a product when stored under refrigerated condition ($5^{\circ}\text{C} \pm 3^{\circ}\text{C}$). The admixture solutions are to be stored up to 24 hours storage under refrigerated and at room temperature. *Comment: The proposed expiration and in-use periods should be evaluated by both, the CMC and the Product Quality Microbiology Reviewers.*

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	x		CMC information submitted per CTD (Modules 2 and 3).
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		

B. FACILITIES*				
* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a <i>potential</i> filing issue or a <i>potential</i> review issue.				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		Amendment dated October 15, 2013.
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			N/A

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

	Parameter	Yes	No	Comment
7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

	Parameter	Yes	No	Comment
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		

C. ENVIRONMENTAL ASSESMENT

	Parameter	Yes	No	Comment
11.	Has an environmental assessment or claim of categorical exclusion been provided?	x		Categorical exclusion

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?			N/A (cross reference to NDA 22003)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?			N/A (cross reference to NDA 22003)
14.	Does the section contain information regarding the characterization of the DS?			N/A (cross reference to NDA 22003)
15.	Does the section contain controls for the DS?			N/A (cross reference to NDA 22003)
16.	Has stability data and analysis been provided for the drug substance?			N/A (cross reference to NDA 22003); microbiological stability testing data provided in Module 3
17.	Does the application contain Quality by Design (QbD) information regarding the DS?			N/A
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?			N/A

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
21.	Is there a batch production record and a proposed master batch record?	x		Executed batch records for two stability batches and one clinical batch are provided in section 3.2.R.
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?			N/A (formulation used in clinical studies is identical to the proposed commercial formulation)
23.	Have any biowaivers been requested?			N/A
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	x		
25.	Does the section contain controls of the final drug product?	x		
26.	Has stability data and analysis been provided to support the requested expiration date?	x		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?	x		QbD elements (CQAs, PAR, risk assessment analysis)
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?			<i>Not obvious</i>

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	x		

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product	x		

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	III		(b) (4)	April 2, 2013	
	III			April 5, 2013	

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	x		
33.	Have the immediate container and carton labels been provided?	x		

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

BIOPHARMACEUTICS FILING REVIEW

NDA Number	NDA 205596
Submission Date	13 September 2013
Product name, generic name of the active	Noxafil (posaconazole MK-5592)
Dosage form and strength	Injectable (IV)
Applicant	Merck Sharp & Dohme Corp.
Clinical Division	Division of Antimicrobial Products
Type of Submission	505(b)(1) original NDA
Primary Biopharmaceutics Reviewer	Minerva Hughes, Ph.D.
Biopharmaceutics Team Leader	Angelica Dorantes, Ph.D.
Assignment Date	19 September 2013
Filing Date	12 November 2013
Filing Review Date	23 October 2013

SUBMISSION OVERVIEW

This new drug application (NDA) is for an intravenous formulation of posaconazole (POS IV solution). POS IV is an aqueous solution of posaconazole containing the (b) (4) Betadex Sulfobutyl Ether Sodium (SBECD) (b) (4)

Posaconazole (also known as, SCH 056592, and MK-5592; hereafter referred to as POS) is a broad-spectrum systemic triazole antifungal. In the US, POS oral suspension (Noxafil®) is indicated for prophylaxis of invasive *Aspergillus* and *Candida* infections in patients, 13 years of age and older, who are at high risk of developing these infections due to being severely immunocompromised, such as hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy (NDA 022-003). POS Oral Suspension is also approved in the US for the treatment of oropharyngeal candidiasis, including oropharyngeal candidiasis refractory to itraconazole and/or fluconazole (NDA 022-027).

The NDA contains clinical data to support the use of POS IV solution in adults (18 years of age and older) for the same prophylaxis indication as currently approved for POS oral suspension in the US, i.e., prophylaxis of invasive *Aspergillus* and *Candida* infections in patients who are at high risk of developing these infections due to being severely immunocompromised, such as hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy.

BIOPHARMACEUTICS SUMMARY

There are no review topics for CDER-ONDQA Biopharmaceutics to evaluate in this NDA. The clinical development program for the POS IV solution was designed to bridge to the prior POS

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

oral suspension clinical program, which will be reviewed by the Clinical Division. The pharmacokinetics of the IV solution was characterized as part of the clinical program, which is sufficient to satisfy the bioavailability data requirement under CFR 320.21. The same formulation used throughout clinical development was used for the registration stability program and is the proposed commercial formulation. As such, a BA/BE waiver is not needed for this NDA.

Accordingly, a Biopharmaceutics review is not needed for this NDA, and no further action is warranted from the ONDQA-Biopharmaceutics.

FILING REVIEW CHECKLIST

The following parameters for the ONDQA’s Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-Biopharmaceutics				
A. Initial overview of the NDA application for filing				
	Parameter	Yes	No	Comment
34.	Does the application contain dissolution data?		x	
35.	Is the dissolution test part of the DP specifications?		x	
36.	Does the application contain the dissolution method development report?		x	
37.	Is there a validation package for the analytical method and dissolution methodology?		x	
38.	Does the application include a biowaiver request?		x	
39.	Does the application include a IVIVC model?		x	
40.	Is information such as BCS classification mentioned, and supportive data provided?		x	
41.	Is information on mixing the product with foods or liquids included?		x	

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

ONDQA-Biopharmaceutics				
A. Initial overview of the NDA application for filing				
	Parameter	Yes	No	Comment
42.	Is there any <i>in vivo</i> BA or BE information in the submission?	x		Several Phase 1 PK studies were completed to support the POS IV solution. A parallel BA study using the tablet formulation was also included to compare relative BA. These data will be reviewed by the Office of Clinical Pharmacology.
43.	Are any of the BE studies for formulation/product quality issues? If yes, list the studies and verify the following: (a) Analysis datasets available in sas format? (b) Bioanalytical method validation report submitted?		x	
44.	For a 505(b)2 NDA with only BE study data, are there any changes to approved labeling for the referenced listed drug (e.g., dosing regimen, dosage form, etc.)? If yes, were data submitted to support the proposed labeling changes?		N/A	This is a 505(b)1 NDA.
45.	Is there a modified-release claim? If yes, address the following: a.) Is there information submitted to support the claim in accordance with 320.25(f)? b.) Is there information on the potential for alcohol-induced dose dumping? c.) Is there a site comparability protocol?		x	

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

[See appended electronic signature page](#)

Dorota Matecka, Ph.D.

CMC-Lead

Division II

Office of New Drug Quality Assessment

[See appended electronic signature page](#)

Minerva Hughes, Ph.D.

Biopharmaceutics Reviewer

Office of New Drug Quality Assessment

[See appended electronic signature page](#)

Sandra Suarez, Ph.D.

Acting Biopharmaceutics Team Leader

Office of New Drug Quality Assessment

[See appended electronic signature page](#)

Rapti Madurawe, Ph.D.

Branch Chief

Division II

Office of New Drug Quality Assessment

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

Attachment 1. DS Specification

Posaconazole Drug Substance, Parenteral Grade		
Page 1 of 2		
Test	Acceptance Criteria	Method Number
Description	Release and Retest (Recertification) White powder free from foreign matter	056592-501A-006-01
Identification	Release and Retest (Recertification)	
Infrared Spectrum ^a (Posaconazole)	(b) (4)	USP <197K> Ph. Eur. (2.2.24) KBr Dispersion
Chiral HPLC (b) (4)	Release Only The ratio of the retention time of the sample and standard peak is between (b) (4)	056592-501A-001-02
Specific Rotation ^a (b) (4)	(b) (4)	USP <781S> Ph. Eur. (2.2.7)
Moisture Content (Karl Fischer) (b) (4)	(b) (4)	056592-501A-005-01
		USP <231>, Method II Ph. Eur. (2.4.8, Method C)
		Ph. Eur. (2.4.14)
Assay (Chiral HPLC)		056592-501A-001-02
Related Compounds	Release and Retest (Recertification) (b) (4)	056592-501A-001-02
	(b) (4)	

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

Posaconazole Drug Substance, Parenteral Grade

Page 2 of 2

Test	Acceptance Criteria	Method Number
Related Compounds	Release and Retest (Recertification) (b) (4)	056592-501A-002-03
Residual Solvent	Release Only (b) (4)	056592-501A-004-02
Particle Size	Release Only (b) (4)	056592-501A-003-01
Microbiological Examination:	Release and Retest (Recertification) (b) (4)	USP <61> Ph. Eur (2.6.12)
Bacterial Endotoxins	Release and Retest (Recertification) (b) (4)	USP <85> Ph. Eur (2.6.14)

^a Region Specific Note: Drug substance for product marketed in the US is evaluated according to USP. Drug substance for product marketed in all other countries is evaluated according to Ph. Eur.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

Attachment 2. DP Composition

Table 1 Unit Composition of Posaconazole Injection, 18 mg/mL			
Component	Grade	Concentration (mg/mL)	Function
Posaconazole	In-house (Parenteral)	18	Active
Betadex Sulfobutyl Ether Sodium (SBECD) ^d	NF	(b) (4)	(b) (4)
Edetate Disodium	USP, Ph. Eur.		
Hydrochloric acid ^a	NF, Ph. Eur.		
Sodium Hydroxide ^b	NF, Ph. Eur.		
Water for Injection	USP, Ph. Eur.		
		(b) (4)	

Table 1 Batch Formula for Posaconazole Injection, 18 mg/mL			
Ingredients	Grade	Amount (g / 200L)	Amount (g/vial)
Posaconazole	In-house (Parenteral)	3,600	0.30
Betadex Sulfobutyl Ether Sodium (SBECD)	NF		(b) (4)
Edetate Disodium (EDTA)	USP, Ph. Eur.		
Hydrochloric acid ^a	NF, Ph. Eur.		
Sodium hydroxide ^b	NF, Ph. Eur.		
Water for Injection	USP, Ph. Eur.		
		(b) (4)	

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

Attachment 3. DP proposed specification

Test	Acceptance Criteria	Method
Description	Release and Shelf Life Clear colorless to yellow liquid essentially free of foreign matter	Visual
Color	Release (b) (4)	Visual
	Shelf Life (b) (4)	
Identification	Release The relative retention time ratio of the analyte peak in the sample and in the reference standard is (b) (4)	HPLC
Identification	Release UV Maximum is (b) (4) nm	UV-Vis
Assay	Release and Shelf Life (b) (4) Label Strength	HPLC
Degradation Products	Release and Shelf Life (b) (4)	HPLC
pH	Release (b) (4)	USP <791> Ph. Eur. 2.2.3
Particulate Matter	Release and Shelf Life (b) (4)	USP <788> Ph. Eur. 2.9.19
Volume of Injection in Container	Release (b) (4)	USP <1> Ph. Eur. 2.9.17
Bacterial Endotoxins	Release and Shelf Life (b) (4)	USP <85> Ph. Eur. 2.6.14
Sterility	Release and Shelf Life	USP <71> Ph. Eur. 2.6.1
	Meets Requirements	

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

/s/

DOROTA M MATECKA
11/13/2013

MINERVA HUGHES
11/13/2013

SANDRA SUAREZ
11/13/2013

RAPTI D MADURAWA
11/13/2013