CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205053Orig1s000

CHEMISTRY REVIEW(S)

NDA 205053

Noxafil™
(posaconazole)
Delayed-Release Tablets, 100 mg

Merck & Co.

Mark R. Seggel
ONDQA
Division of Pre-Marketing Assessment II

for the Division of Anti-Infective Products

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Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 205053

2. REVIEW #: 1

3. REVIEW DATE: 13-OCT-2013

4. REVIEWER: Mark R. Seggel

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Not Applicable	-

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed (eCTD)	Document Date
Original (0000)	25-JAN-2013
Amendment (0001); manufacturing site information and readiness	15-FEB-2013
Amendment (0003); acknowledge delayed-release dosage form, labeling	30-APR-2013
Amendment (0004); response to information request re: API	08-MAY-2013
Amendment (0006); primary stability data update	15-MAY-2013
Amendment (0009); in vitro alcohol dose dumping study	13-JUN-2013
Amendment (0010); response to information request	27-JUN-2013
Amendment (0012); updated Module 3	26-JUL-2013
Amendment (0015); dissolution test	10-SEP-2013
Amendment (0016); dissolution test acceptance criterion; manufacturing process	27-SEP-2013
Amendment (0017); revised container label	02-OCT-2013

7. NAME & ADDRESS OF APPLICANT:

Name:	Merck, Sharp & Dohme Corp. (Merck & Co.)
Address:	2015 Galloping Hill Road Kenilworth, NJ 07033
Representative(s):	Barbara Gunther, MA, MBA Associate Director and Liaison Global Regulatory Affairs

Chemistry Review Data Sheet

Telephone:	(908) 740-4892

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Noxafil™
   b) Non-Proprietary Name (USAN): Posaconazole
   c) Code Name/#: SCH-56592, MK-5592
   d) CAS Registry Number: 171228-49-2
   e) Chem. Type/Submission Priority:
      i. Chem. Type: 3
      ii. Submission Priority: S

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

10. PHARMACOL. CATEGORY: Antifungal, systemic

11. DOSAGE FORM: Tablets, delayed-release

12. STRENGTH/POTENCY: 100 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)
_____SPOTS product – Form Completed

___X__Not a SPOTS product

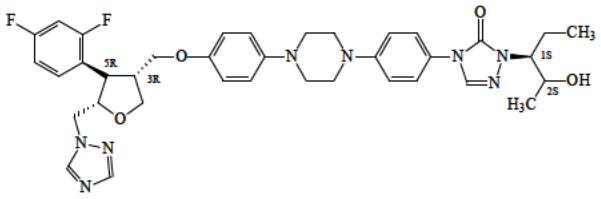
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT

IUPAC Name: 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-hydroxy-propyl]-2,4-dihydro-3H-1,2,4-triazol-3-one

IUPAC Name (Alternate): 4-4-[4-(4-[(3R,5R)-5-(2,4-difluorophenyl)-5-(1H-1,2,4 triazol-1-yl-methyl)tetrahydro-3-furanyl]methoxyphenyl)piperazino]phenyl-1-[(1S,2S)-1-ethyl-2- hydroxyl-propyl]-4,5-dihydro-1H-1,2,4-triazol-5-one

Chemistry Review Data Sheet

CAS Index Name: D-threo-pentitol, 2,5-anhydro-1,3,4-trideoxy-2-C-(2,4-difluorophenyl)-4-[[4-[4-[4-[1-[(1S,2S)-1-ethyl-2-hydroxypropyl]-1,5-dihydro-5-oxo-4H-1,2,4-triazol-4-yl]phenyl]-1-piperazinyl]phenoxy]methyl]-1-(1H-1,2,4-triazol-1-yl)



Molecular Formula: $C_{37}H_{42}F_2N_8O_4$
Molecular Weight: 700.78
CAS: 171228-49-2
WHO Number: 7713

17. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

[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 Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Original IND	IND (b) (4)	Posaconazole (b) (4) Tablets

Chemistry Review Data Sheet

Original IND	IND (b) (4)	Posaconazole Oral Suspension and Tablets
Original IND	IND (b) (4)	(b) (4)
Original NDA	NDA (b) (4)	(b) (4)
Original NDA	NDA 22-003	Noxafil (posaconazole) Oral Suspension, 40 mg/mL. Submitted 21-DEC-2005; for the prophylaxis of invasive fungal infections; AP 15-SEP-2006.
Original NDA	NDA 22-027	Noxafil (posaconazole) Oral Suspension, 40 mg/mL. Administratively split from NDA 22-003; indicated for the treatment of oropharyngeal candidiasis (OPC) and refractory OPC; AP 20-OCT-2006.

Note: Posaconazole drug substance and oral suspension CMC were originally submitted and reviewed under NDA (b) (4) therefore drug substance CMC is now by cross-reference to NDA 22-003.

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not applicable		
EES	Acceptable	04-OCT-2013	T.Sharp, OC/OMPQ
Pharm/Tox	Approval	09-OCT-2013	O. McMaster, DAIP
Methods Validation	Not applicable		
DMEPA	Labeling revisions recommended.	27-SEP-2013	Alek Winiarski, DMEPA
EA	Adequate per this review		
Product Quality Microbiology	Not applicable		
ONDQA Biopharmaceutics	Recommends Approval based on revised dissolution test meth and acceptance criteria	30-SEP-2013	M. Seggel

19.GOAL DATES

GRMP Goal: 28-OCT-2013
PDUFA Goal: 25-NOV-2013

Executive Summary Section

The Chemistry Review for NDA 205053

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

As amended, this new drug application for posaconazole delayed-release tablets, contains chemistry, manufacturing and controls (CMC) data and information in sufficient detail to assure the identity, strength, purity, and quality of the drug product. Drug substance CMC is up-to-date, and is adequately documented in NDA 22-003.

The dissolution test and acceptance criteria for the delayed-release product have been revised, and are suitable for assuring the requisite product performance (see ONDQA Biopharmaceutics Review dated September 30, 2013).

The package insert and container label have been revised to reflect the correct dosage form, delayed-release tablets. The product description and storage statements, and other CMC-related information, are factually correct and complete. The Office of Compliance has issued an overall recommendation of Acceptable for this application on October 4, 2013.

Therefore, from the CMC perspective, NDA 205053 for posaconazole delayed-release tablets is recommended for approval.

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

There are no special post-marketing commitments or agreements related to posaconazole delayed-release tablets CMC.

II. Summary of Chemistry Assessments

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

Posaconazole is a synthetic, small molecule inhibitor of the fungal enzyme lanosterol 14α-demethylase. Posaconazole is a weakly basic compound and has extremely low solubility (b) (4) (b) in an aqueous solution with pH higher than 4, but is relatively soluble (b) (4) in an

Executive Summary Section

aqueous solution with pH (b) (4) In pH (b) (4) phosphate buffer with (b) (4) polysorbate the solubility of amorphous posaconazole is approximately (b) (4). (b) (4) Thus, posaconazole is considered a BCS Class 2 (low solubility-high permeability) compound.

Drug substance chemistry, manufacturing and controls are currently filed under NDA 22-003 (posaconazole oral suspension, 40 mg/mL). The synthesis and characterization of posaconazole are documented therein. The specification for posaconazole, which assures the identity, strength, quality, and purity of the drug substance used in the manufacture of the oral suspension is also suitable for posaconazole used in the manufacture of posaconazole delayed-release tablets.

The drug product, posaconazole delayed-release tablets, 100 mg, was developed to overcome the limitations of posaconazole oral suspension (i.e., low and variable absorption, the need to administer the oral suspension "with a full meal or with a liquid nutritional supplement or an acidic carbonated beverage (e.g., ginger ale) in patients who cannot eat a full meal"). The tablet consists of a (b) (4), along with other tableting and stabilizing excipients, and a non-functional film coating. By limiting the dissolution of posaconazole in the acidic stomach environment, the uncontrolled precipitation in the small intestine is eliminated. Solubility in the near neutral pH environment of the intestine is enhanced by dissolution of amorphous posaconazole to form a supersaturated solution. Thus, the quality target product profile (QTPP) includes a pharmacokinetic profile consisting of a reduced food effect and enhanced bioavailability. Accordingly, one of the critical quality attributes (CQAs) of the drug product is its dissolution profile. The QTPP includes other requirements such as control of impurities and degradants below ICH qualified levels and a shelf-life of at least 24 months at room temperature in an HDPE bottle. Other CQAs derived from the QTPP include assay, dose uniformity, degradants, and pharmaceutical elegance.

Each capsule-shaped (oblong) posaconazole delayed-release tablet contains (b) (4) 100 mg posaconazole (b) (4) Other excipients in the tablet include (b) (4) microcrystalline cellulose (b) (4), hydroxypropyl cellulose (b) (4), croscarmellose sodium (b) (4) silicon dioxide (b) (4) and magnesium stearate (b) (4). The tablets are debossed on one side with "100", and have a non-functional Opadry II yellow film coating. Tablets are packaged in 60-count HDPE bottles with child-resistant closures.

(b) (4) . In posaconazole delayed-release tablets, it serves to stabilize posaconazole in an amorphous state and to provide pH-controlled delayed-release. (b) (4)

Executive Summary Section

(b) (4)

(b) (4)

Merck considers this a 'traditional' application from the QbD perspective since it does not provide for flexible regulatory approaches (e.g., design space or real time release testing). However, "enhanced approaches" (e.g., risk assessment, process-understanding) were applied to product and process development. The result is a robust process, with control strategies in place at each stage (unit operation).

(b) (4)

Executive Summary Section

Overall, the defined product manufacturing processes and controls provide assurance of consistent batch-to-batch quality.

The drug product specification provides additional assurance that the finished product has the requisite identity, strength, quality, purity, potency, and bioavailability. The regulatory specification includes two complementary tests for identification, and tests for appearance, assay, individual and total degradation products, content uniformity, and moisture content. A dissolution test appropriate for a delayed-release dosage forms ensures the desired product performance (see ONDQA Biopharmaceutics review). While the specification does not include a test for solid state form of the active ingredient (b) (4) sufficient information has been provided to demonstrate that (b) (4) of posaconazole during manufacturing and on stability is low risk. However, the applicant has agreed to perform (b) (4) testing on process validation batches at release and on stability.

Overall, the control manufacturing process and the drug product specification will ensure that the drug product has the overall quality necessary for safe and effective treatment of patients.

The stability of the drug product under long term (25°C/60% RH) and accelerated (40°C/75% RH). Twelve-month long term data on three primary stability batches and 24-36 month long term data from supporting stability batches shows very little change in drug product quality. No significant changes were observed under accelerated conditions. Overall, the data support a 24-month expiration dating period. This will be confirmed during on-going stability studies.

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

Noxafil (posaconazole) delayed-release tablets and oral suspension are 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.

The proposed dose and administration for posaconazole delayed-release tablets includes a loading dose of 300 mg (three 100 mg tablets) twice a day on the first day, followed by 300 mg (three 100 mg tablets) once daily thereafter for the duration of therapy (based on recovery from neutropenia or immunosuppression). Each 60-count bottle can supply a 19-day treatment course at the recommended dose.

(b) (4)

Executive Summary Section

(b) (4)

Posaconazole delayed-release tablets will be labeled for storage at 20-25°C (68-77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. An expiration dating period of 24 months at 20-25°C has been established.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA has also provided sufficient stability information on the drug product to assure strength, quality, purity, potency, and bioavailability of the drug product throughout the expiration dating period of 24 months.

All facilities have acceptable site recommendations (see attached EES report).

All labels have the required information.

III. Administrative

A. Reviewer's Signature

{see electronic signature page}
Mark R. Seggel, Chemistry Reviewer

B. Endorsement Block

{see electronic signature page}
Dorota Matecka, Ph.D., CMC Lead and Secondary Reviewer

{see electronic signature page}
Rapti Madurawe, Ph.D., Branch Chief

C. CC Block

{see DARRTS}

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/s/

MARK R SEGGEL
10/25/2013

DOROTA M MATECKA
10/25/2013

RAPTI D MADURAWE
10/25/2013

Initial Quality Assessment (IQA) and Filing Review for Pre-Marketing Applications

Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: **205053**
   Submission Date: January 25, 2013
   GRMP Goal Date: October 28, 2013
   PDUFA Goal Date: November 25, 2013

2. PRODUCT PROPERTIES:

Trade or Proprietary Name:	NOXAFIL®
Established or Non-Proprietary Name (USAN) and strength:	Posaconazole tablets, 100 mg

3. NAME:

Name:	Merck Sharp & Dohme Corp.

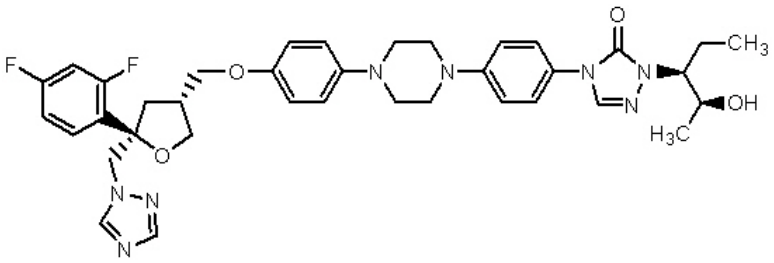
4. SUBMISSION PROPERTIES:

Review Priority :	PRIORITY
Property (Legal Basis):	505 (b)(1)
Responsible Organization:	DAIP

Review Information

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

Posaconazole: 4-[4-[4-[4-[[(3*R*,5*R*)-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-3*H*-1,2,4-triazol-3-one



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

2. INDICATION: (b) (4)

3. ROUTE OF ADMINISTRATION: Oral

4. STRENGTH/POTENCY: 100 mg

5. Rx/OTC DISPENSED: ☒Rx ☐OTC

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

Is this a SPOTS product? ☐Yes ☒No ☐ Not evaluated at time of IQA.

7. RELATED REVIEW DOCUMENTS:

a. Drug Master Files listed on 356h form:

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	III		(b) (4)	April 7, 2011	
	III			May 13, 2010	
	III			April 1, 2010	
	III			April 1, 2010	
	III			May 18, 2012	

b. Consults Recommended by CMC and Biopharmaceutics

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics	☐	☒	
Clin Pharm	☐	☐	
EES	☒	☐	Submitted (February 19, 2013)
Pharm/Tox	☒	☐	TBD (*if needed*)
Methods Validation	☒	☐	
EA	☐	☒	Categorical exclusion claim
New Drug Micro	☐	☐	TBD (*if needed*)
CDRH	☐	☐	
Other ( )	☐	☐	

c. Other Applications or Submissions to note (if any):

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
IND	8/20/1996	(b) (4)	Active
NDA	9/15/2006	22003	Approved

d. Previous Communications with the Applicant to note (if any):

DOCUMENT NAME	Document DATE	APPLICATION NUMBER	DESCRIPTION
CMC meeting preliminary responses	11/17/2012 in DARRTS	IND (b) (4)	Preliminary responses for a meeting dated 11/21/2012
CMC meeting minutes	12/21/2012 in DARRTS	IND (b) (4)	Minutes of meeting dated 11/21/2012

Overall Conclusions and Recommendations

Is the Product Quality Section of the application fileable from a CMC perspective?		
Yes	No	CMC Filing Issues
☒	☐	

Are there potential CMC review issues to be forward to the applicant with the 74 day letter?		
Yes	No	CMC Comment 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 tabulation of the current drug substance specification, b. 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 c. Location (e.g., section number, page number, submission date, etc., as appropriate) of the change information as given above.

Is the Product Quality Section of the application fileable from a biopharmaceutics perspective?		
Yes	No	Biopharmaceutics Filing Issues
☒	☐	

Are there potential biopharmaceutics review issues to be forward to the applicant with the 74 day letter?		
Yes	No	Biopharmaceutics Comments for 74 Day Letter
☒	☐	1. The proposed regulatory dissolution test is not acceptable. Posaconazole delayed-release tablets should be tested in accordance with USP<711>, Dissolution, Delayed-Release Dosage Forms. Please note that the acid stage is 2 hours long. Buffer should be added immediately after removal of the sample aliquots. (b) (4) [redacted] Please develop a discriminatory dissolution method in accordance with the USP dissolution monograph. Deviations from the USP method should be justified with supporting data. The dissolution report should include individual (n=12) and mean data, %RSDs, and profiles. 2. As a delayed-release product, the potential impact of alcohol induced dose

		dumping should be evaluated. Please conduct an in vitro alcohol dose dumping study in 0.1 N HCl dissolution media containing 0%, 5%, 10%, 20% and 40% alcohol. Dissolution data should be generated from 12 dosage units (n=12) at multiple time points to obtain a complete dissolution profile. The shape of the dissolution profiles should be compared to determine if the delayed release characteristics are maintained. The f2 values assessing the similarity (or lack thereof) between the dissolution profiles should be estimated (using 0% alcohol as the reference). The report with the complete data (i.e., individual, mean, SD, comparison plots, f2 values, etc.) collected during the evaluation of the in vitro alcohol induced dose dumping study should be provided to FDA for review and comments. 3. Please note, that as a delayed-release product, the correct established name for the drug product is, 'posaconazole delayed-release tablets'. This should be reflected in all product labeling. 4. Please confirm that the dissolution data reported in P.2.3 Manufacturing Process Development were obtained using the originally proposed regulatory method. If not, the specific methods should be indicated. Where only mean values (or plots of mean values) are reported, please provide individual values and %RSD along with the mean results.

CMC Summary: Critical Issues and Complexities

CMC Critical Issues or Complexities

Posaconazole (POS) (SCH 56592, MK-5592) is a potent broad-spectrum triazole antifungal that blocks the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of the enzyme lanosterol 14α-demethylase and accumulation of methylated sterol precursors. POS is active against a wide spectrum of pathogenic yeasts and moulds.

Posaconazole has been previously approved as Posaconazole Oral Suspension indicated for prophylaxis of invasive Aspergillus and Candida infections and for the treatment of oropharyngeal candidiasis, including oropharyngeal candidiasis refractory to itraconazole and/or fluconazole. The current NDA provides for a new formulation of posaconazole, Posaconazole Tablets, 100 mg, to be used for the same indications.

Important issues for this NDA are discussed in the Summary section, below.

Does the submission contain any of the following elements?

Nanotechnology	QbD Elements	PET	Other, please explain
☐	☒	☐	

Is a team review recommended?

Yes	No	Suggested expertise for team
☐	☐	

Review Team Assignments (if known)

Drug Substance	N/A
Drug Product	Mark Seggel
Biopharmaceutics	Mark Seggel
QbD	Mark Seggel
Product Quality Microbiology	TBD (*if needed*)
ONDQA PM	Althea Cuff

Summary or Highlights of the Application *(not already mentioned in other sections)*

Changes between Clinical DP and Proposed Commercial DP

Clinical Tablets	Commercial Tablets
Several prototype formulations of the drug product were developed (Tablet A, B, C and a Capsule). The formulation proposed for the commercial use is Tablet D (yellow), which was also used in one of the clinical studies and stability studies. Changes in the formulations are described below (in the Drug Product section).	

In addition, there are some differences (which do not appear major) between the process used in the manufacture of the Formal Stability Studies (FSS) batches and commercial processes (they are described below).

Drug Substance

Cross reference is made to the approved application for Posaconazole Oral Suspension (NDA 22003) for drug substance information. *Comment: No information on the drug substance has been provided in this NDA. Some discussion of physicochemical characteristics of posaconazole has been included in the Pharmaceutical Development section (P.2). However, a current specification for the drug substance should also be included. 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 will be included in the 74-day letter.*

Drug Product

Posaconazole Oral Suspension demonstrated that posaconazole has a significant food effect in absorption: its exposure in a high fat meal is about four times higher than that in a fasted condition. The current formulation was designed to create a tablet with limited posaconazole release at the low pH of the stomach. Therefore, the proposed tablet formulation contains (b) (4) that is highly soluble at the more neutral pH of the intestine (b) (4) releasing the amorphous posaconazole in the intestine, which may provide higher absorption and reduced food effect as compared to Posaconazole Oral Suspension.

The new formulation of posaconazole is a film coated (yellow) tablet containing 100 mg of posaconazole drug substance. The applicant stated that the product has been designated as a delayed release tablet in compliance with the USP/NF. The excipients used are all compendial except Opadry Yellow (the qualitative and quantitative composition has been attached below as Appendix 1). *Comment: The delayed-release tablet designation will be a review issue from both CMC and biopharmaceutics perspective.*

The Pharmaceutical Development section includes a discussion of QTPPs and CQAs for the drug product, risk assessment and control strategy (including PARs) for each unit operation. The applicant stated that this NDA does not contain flexible regulatory approaches, such as design spaces or real time release testing. However, the principle of "enhanced" approaches as described in ICH Q8 through ICH Q11, such as risk assessment (b) (4)

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ONDQA - CMC and Biopharmaceutics
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?	☒	☐	
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	☒	☐	CMC information submitted per CTD (Modules 2 and 3).
3.	Are all the pages in the CMC section legible?	☒	☐	
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	☒	☐	

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	☒	☐	Amendment dated February 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

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • 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)	☒	☐	
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • 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)	☒	☐	
9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • 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)	☒	☐	

10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	☒	☐	

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	☒	☐	

D. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
12.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	☐	☐	N/A (cross reference to NDA 22-003)

E. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
13.	Does the section contain a description of the DS manufacturing process?	☐	☐	N/A (cross reference to NDA 22-003)
14.	Does the section contain identification and controls of critical steps and intermediates of the DS in process parameters?	☐	☐	N/A (cross reference to NDA 22-003)
15.	Does the section contain information on impurities?	☐	☐	N/A (cross reference to NDA 22-003)
16.	Does the section contain information regarding the characterization of the DS?	☐	☐	N/A (cross reference to NDA 22-003)
17.	Does the section contain controls for the DS?	☐	☐	N/A (cross reference to NDA 22-003)
18.	Has stability data and analysis been provided for the drug substance?	☐	☐	N/A (cross reference to NDA 22-003)
19.	Does the application contain Quality by Design (QbD) information regarding the DS?	☐	☐	N/A (cross reference to NDA 22-003)
20.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?	☐	☐	N/A (cross reference to NDA 22-003)
21.	Does the section contain container and closure information?	☐	☐	N/A (cross reference to NDA 22-003)

F. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
22.	Does the section contain quality controls of excipients?	☒	☐	
23.	Does the section contain information on composition?	☒	☐	
24.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	☒	☐	
25.	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?	☒	☐	
26.	Is there a batch production record and a proposed master batch record?	☒	☐	Provided in section 3.2.R. Regional Information (executed batch record)
27.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	☒	☐	
28.	Have any Comparability Protocols been requested	☐	☐	
29.	Does the section contain description of to-be-marketed container/closure system and presentations?	☒	☐	120-ml HDPE bottle with a child resistance cap containing 60 tablets
30.	Does the section contain controls of the final drug product?	☒	☐	
31.	Has stability data and analysis been provided to support the requested expiration date?	☒	☐	Stability data submitted in section 3.2.P.8.3
32.	Does the application contain Quality by Design (QbD) information regarding the DP?	☒	☐	CQAs, PAR, risk assessment analysis
33.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	☐	☒	(b) (4) [redacted]

G. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
34.	Is there a methods validation package?	☒	☐	

H. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
35.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?	☐	☒	N/A (not a sterile product)

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
36.	Has the draft package insert been provided?	☒	☐	
37.	Have the immediate container and carton labels been provided?	☒	☐	Bottle label provided
38.	Does section contain trade name and established name?	☒	☐	

J. BIOPHARMACEUTICS				
	Parameter	**Yes**	**No**	**Comment**
39.	Does the application contain dissolution data?	X		
40.	Is the dissolution test part of the DP specifications?	X		Proposed: (b) (4)
41.	Does the application contain the dissolution method development report?	X		However, the proposed regulatory method does not appear to be appropriate.
42.	Is there a validation package for the analytical method and dissolution methodology?	X		
43.	Does the application include a biowaiver request?		X	
44.	Does the application include an IVIVC model?		X	
45.	Is information such as BCS classification mentioned, and supportive data provided?	X		(b) (4)

46.	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) Does the application include information/data on in vitro alcohol dose-dumping potential?			(b) (4) [redacted] Note that one of the pre-NDA questions asked by the applicant was if FDA agreed that the formulation is an immediate release dosage form. The answer was No. An in vitro alcohol dose dumping study was not reported.
47.	Is information on mixing the product with foods or liquids included?	X		The tablet formulation of POS was developed to eliminate the limitations of POS oral suspension; (b) (4) [redacted]
48.	Is there any in *vivo* BA or BE information in the submission?	X		The BA/BE information will be reviewed by the Office of Clinical Pharmacology.
49.	Is there any Biopharmaceutics requests/comments for the Applicant ?	X		See above.
FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
50.	**ARE THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	X		
51.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Fileable
52.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Fileable
53.	Are there any potential review issues identified?	X		See comments above.

REVIEW AND APPROVAL

See appended electronic signature page}
Dorota Matecka, Ph.D.
CMC Lead
Division of Pre-Marketing Assessment II, Branch V
Office of New Drug Quality Assessment

{See appended electronic signature page}
Mark Seggel, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

{See appended electronic signature page}
Sandra Suarez Sharp, Ph.D.
Biopharmaceutics Team Lead
Office of New Drug Quality Assessment

{See appended electronic signature page}
Rapti Madurawe, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment II, Branch V
Office of New Drug Quality Assessment

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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
03/25/2013

MARK R SEGGEL
03/25/2013

SANDRA SUAREZ
03/25/2013

RAPTI D MADURAWE
03/25/2013