CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209363Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: ***Approval***

NDA 209363
Review # 1

Drug Name/Dosage Form	SOLOSEC (secnidazole) Oral Granules
Strength	2 g
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Symbiomix Therapeutics, LLC
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	January 17, 2017	All
Amendment (eCTD 003)	February 17, 2017	Drug Product
Amendment (eCTD 010)	May 9, 2017	Drug Substance, Drug Product, Biopharmaceutics
Amendment (eCTD 014)	June 16, 2017	Process
Amendment (eCTD 015)	June 23, 2017	Biopharmaceutics
Amendment (eCTD 016)	June 30, 2017	Process
Amendment (eCTD 017)	July 7, 2017	Process
Amendment (eCTD 018)	July 27, 2017	Process

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Sithamalli Chandramouli	Benjamin Stevens
Drug Product	George Lunn	Balajee Shanmugam
Process	Sateesh Kumar Sathigari	Steven Frisbee
Microbiology*	Sateesh Kumar Sathigari	Steven Frisbee
Facilities	Daniel DeCiero	Derek Smith
Biopharmaceutics	Banu Zolnik	Elsbeth Chikhale
Regulatory Business Process Manager	Luz Rivera	N/A
Environmental Assessment**	Jim Laurenson	N/A
Application Technical Lead	Dorota Matecka	N/A

** The microbiology aspects of the drug product are assessed in the Process Chapter*
*** EA is covered in the Drug Product Chapter*

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II		(b) (4)	Adequate	6/30/2017 (Panorama)	Review by Mouli Sithamalli
	III			Adequate	4/17/17 (Panorama)	Review by George Lunn

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	117811	Pre-NDA meeting on September 30, 2016 (meeting minutes dated October 28, 2016 in DARRTS)

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	Complete	Acceptable	8/24/2017 (email)	Dr. Owen McMaster
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The NDA, as amended, has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed drug product, secnidazole oral granules. All information requests and review issues have been addressed and there are no pending approvability issues. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall "Approve" recommendation was entered into Panorama by the Office of Process and Facilities (OPF) on September 5, 2017. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ).

II. Summary of Quality Assessments

A. Product Overview

Secnidazole is an antimicrobial agent for treatment of bacterial vaginosis (BV). Secnidazole belongs to the 5-nitroimidazole class of antimicrobials.

This NDA provides for an oral formulation of secnidazole, secnidazole oral granules, supplied in packets containing 2 grams of secnidazole per dose.

Proposed Indication(s) including Intended Patient Population	Treatment of bacterial vaginosis in adult women
Duration of Treatment	One-time treatment (a single 2-gram packet to be taken once orally)
Maximum Daily Dose	As above
Methods of Administration	SOLOSEC can be administered at any time with or without a meal. The entire contents of one packet should be consumed at one time without chewing or crunching the granules. SOLOSEC is to be sprinkled onto soft food (applesauce, yogurt or pudding) prior to administration. The granules will not dissolve. The entire contents of the mixture of SOLOSEC and soft food should be consumed within 30 minutes. SOLOSEC granules are not intended to be dissolved in any liquid. However, a glass of water may be taken subsequent to administration of SOLOSEC granules to aid in swallowing.

B. Quality Assessment Overview

Secnidazole is considered a new molecular entity and belongs to the 5-nitroimidazole class of antimicrobials. The chemistry manufacturing and controls information for secnidazole drug substance has been provided via a reference to DMF Type II (b) (4) held by (b) (4) DMF (b) (4) was reviewed in support of this NDA and was found to be acceptable. The drug substance (secnidazole (b) (4) specification includes a number of relevant quality attributes such as appearance, identification, water content, melting range, assay, impurities, clarity of solution, transmittance, (b) (4) content, residue on ignition, and particle size. During the NDA review, an acceptance criterion for one of the process impurities, (b) (4), was tightened based on the recommendation received from the pharmacology/toxicology reviewer. The drug substance specification, as revised, was found acceptable. Based on the stability information provided by the DMF holder a retest period of (b) (4) months was established for secnidazole drug substance stored at (b) (4).

The drug product, secnidazole oral granules, consists of white to slightly yellowish granules (in size range of (b) (4) µm) to be administered with soft foods such as applesauce, yogurt or pudding. The granules are supplied in unit-dose packets containing 4.76 g granules, which supply a 2 g dose of secnidazole. The inactive ingredients include sugar spheres ((b) (4)), povidone, PEG 4000, Eudragit NE30D, (b) (4) . All the excipients used in the manufacture of secnidazole oral granules, are stated to meet the USP/NF specifications. However, a number of comments and recommendations regarding the critical quality attributes for several essential excipients, such as Eudragit, were conveyed to and addressed by the Applicant during the NDA review. In addition, Certificates of Analysis for all excipients were submitted to the NDA at the FDA request.

The drug product specification includes tests and acceptance criteria for appearance, identity, uniformity of dosage units (by weight), assay, impurities, dissolution, (b) (4) , microbial limits, (b) (4) leak testing and particle size. During the review, several revisions to the proposed drug product specification were recommended by reviewers such as a revision of the proposed acceptance criterion for dissolution (as discussed below). In addition, based on the review of the batch analysis data, the proposed limits for (b) (4) were lowered at the FDA recommendation. The drug product specification, as revised, was found acceptable. That includes microbiological controls proposed in the drug product specification, which were assessed as part of the manufacturing process review.

The container closure system to be used for the commercial drug product, secnidazole granules, is a white, ink-printed foil packet with a child-resistant opening notch. The foil material is a white (b) (4)-lined aluminum. Each packet is individually placed in a cardboard carton. Display boxes containing twelve individual cartons will be used for product distribution. Based on the review of the overall information provided in the NDA and in a referenced DMF Type III (DMF (b) (4) which

was reviewed in support of this NDA), the proposed container closure system was found safe and suitable for the proposed commercial drug product.

The drug product stability information provided in the NDA includes 18-month long term (25°C/60% RH), 12-month of intermediate (30°C/65% RH), and 6-month of accelerated (40°C/75% RH) stability data for three registration batches of the proposed drug product, secnidazole oral granules, 2 g, packaged in the proposed commercial container closure system. Based on the review of the overall information submitted in the NDA (which did not indicate any failures or obvious stability trends), the proposed expiry dating of 30 months for the drug product to be stored at room temperature, has been found acceptable.

The manufacturing process for the drug product, secnidazole oral granules, includes the (b) (4) . The commercial batch formula and process are same as that of the formula and process used for registration batches. The proposed commercial batch size may vary from (b) (4) kg ((b) (4)) to (b) (4) kg (b) (4) packets); the maximum proposed commercial batch size is around (b) (4) times larger than the registration batch size, which is acceptable. During the NDA review, additional information regarding different unit operations, including the proposed (b) (4) and various in-process controls and process ranges for the critical process parameters, was requested and provided by the Applicant. Overall, information regarding the drug product manufacturing process provided in the original NDA submission and subsequent amendments has been found acceptable.

The Biopharmaceutics assessment focused on the dissolution method and acceptance criteria proposed for the finished drug product, secnidazole oral granules. The proposed dissolution method was found acceptable. The dissolution acceptance criteria proposed for the drug product in the initial NDA submission were revised based on FDA's recommendation to the following: 30 minutes: NMT (b) (4) %, 2 hours: NLT (b) (4) %, and 3 hours: NLT (b) (4) %. In addition, the comparative in vitro dissolution data provided in support of the minor formulation difference between the formulations used in clinical studies and the commercial formulation were found acceptable.

The Applicant's claim of categorical exclusion from the Environmental Assessment per 21 CFR 25.31(b), as revised and amended during the NDA review, has been found acceptable. In addition, the Comparability Protocol submitted in the NDA for the change in the container closure system (specifically, proposing a slight increase in the size of the foil packet with no change to the materials) was reviewed and found acceptable.

During the labeling review a number of revisions were recommended from the product quality perspective in the package insert and in the container labels, such as a revision to the weight of granules expressed in the labeling, listing of excipients in alphabetical

order, description of the container, and several other minor revisions. The labels and package insert, as revised, were found acceptable from the product quality perspective.

The secnidazole drug substance manufacturer is (b) (4) and the drug product manufacturer is Catalent Pharma Solutions, USA. In addition, the packaging of the drug product is performed at (b) (4). Based on the review of the application and inspectional history for all manufacturing sites listed in this NDA, it has been determined that there are no significant outstanding issues with the facilities involved in the manufacturing of the proposed product. Therefore, the overall recommendation of "Approve" was entered into Panorama for this NDA by OPF on September 5, 2017.

C. Special Product Quality Labeling Recommendations (see table above**)**

D. Final Risk Assessment (see Attachment I**)**

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BIOPHARMACEUTICS

Product Background:

NDA: 209363

Drug Product Name / Strength: Solosec® (Secnidazole) granules, 2 gram

Route of Administration: Oral

Applicant Name: Symbiomix Therapeutics, LLC

Review Summary:

Dissolution Method and Acceptance Criteria

The final dissolution method and acceptance criteria for the drug product are acceptable and are shown below.

USP Apparatus	Rotation	Volume	Temperature	Medium	Final Acceptance Criteria
USP I (basket)	50 rpm	900 mL	37°C ± 0.5°C	pH 6.8 Phosphate Buffer	30 min: NMT (b) (4) % 2 hr: NLT (b) (4) % 3 hr: NLT %

Bridging Formulations and Manufacturing Site

Three formulations have been used in clinical trials during the development of SYM-1219 granules, one manufactured at (b) (4) (Formulation F1) and two manufactured at Catalent (Formulations F2 and F3). The Applicant conducted a comparative PK study between F1 and F2 formulations. This study is reviewed by OCP. Bridging between Formulation 2 and Formulation 3 is supported by an in vitro dissolution study. Drug release profiles between Formulation 2 and 3 are similar indicating minor formulation difference did not impact dissolution.

Recommendation

From a Biopharmaceutics perspective, NDA 209363 for Secnidazole granules, 2 gram is recommended for **Approval**.

List of Submissions being reviewed:

Original dated 1/17/2017

Seq. 0010 (SDN 11) dated 05/09/2017

Seq.0014 (SDN 15) dated 06/16/2017

Seq.0015 (SDN 16) dated 06/23/2017

Drug Product

Secnidazole oral granules is an antimicrobial agent for treatment of bacterial vaginosis. Secnidazole belongs to the 5-nitroimidazole class of antimicrobials.

Secnidazole granules are supplied in single-dose packets which will be administered as a single dose (once only treatment), with soft foods such as apple sauce, yogurt, or pudding as per the proposed label.

The composition of the proposed commercial formulation is shown below in Table 1.

Secnidazole Oral Granules are manufactured b (b) (4) .

Table 1 Composition of Secnidazole Granules

Table 1 Composition of Secnidazole Oral Granules

Component	Function	Quality Standard	Quantity, mg/2g Dose (mg/packet)	% w/w
Secnidazole, (b) (4)	Active Ingredient	Manufacturer's specifications	2000.00	42.017
Sugar Spheres (b) (4)	(b) (4)	NF		(b) (4)
Povidone		USP		
Polyethylene Glycol 4000		NF		
Eudragit NE30D (Ethyl Acrylate, Methyl Methacrylate Copolymer (b) (4)		NF		
(b) (4)		USP		
		USP		
Talc		USP		
Total			4760.00	100.00

(b) (4)

BCS Designation

The Applicant stated that secnidazole belongs to BCS class 1; however the Applicant did not submit an official BCS class 1 designation request to the Agency's BCS Committee.

Dissolution Method and Acceptance Criteria

The Applicant proposed the dissolution method below as a quality control tool for the drug product.

USP Apparatus	Rotation	Volume	Temperature	Medium	Proposed Acceptance Criteria
USP I (basket)	50 rpm	900 mL	37°C ± 0.5°C	pH 6.8 Phosphate Buffer	(b) (4)

Secnidazole has an aqueous solubility of approximately 40 mg/mL which is slightly increased at low pH. The solubility of secnidazole is 18 times the concentration of 2 gram secnidazole in 900 mL, therefore sink conditions are maintained.

Dissolution Method Development:

(b) (4)

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(b) (4)

Discriminating Ability of the Method:

As stated above, the dissolution method is able to discriminate batches with (b) (4) rate between (b) (4) compared to the target batches with (b) (4) rated between (b) (4) as shown in Figure 3.

IN VITRO ALCOHOL INDUCED DOSE DUMPING

Although the proposed drug product is considered an immediate release product, (b) (4) the below comment was conveyed to the Applicant to gain further understanding of the product's performance in the presence of alcohol.

IR Comment Conveyed to the Applicant in an IR letter dated June 6, 2017

Provide the in vitro alcohol- induced dose dumping study of your product. The following points should be considered during the evaluation of the in vitro alcohol induced dose dumping of your proposed drug product:

Dissolution data should be generated from 12 dosage units (n=12) at multiple time points to obtain a complete dissolution profile.

The following alcohol concentrations are recommended for the in vitro dissolution studies: 0 %, 5 %, 10 %, 20 %, and 40 % in 0.1N HCl and in the proposed dissolution medium.

The f2 values assessing the similarity (or lack thereof) between the dissolution profiles should be calculated (using 0% alcohol as the reference).

Provide 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.

The Reviewer's Assessment of the Applicant's Response dated June 16, 2017

ADEQUATE

The Applicant provided the requested data in an amendment dated June 16, 2017. Figures 4 and 5 show that drug dissolution increased in the presence of alcohol in pH 6.8 and 0.1 N HCl, respectively.

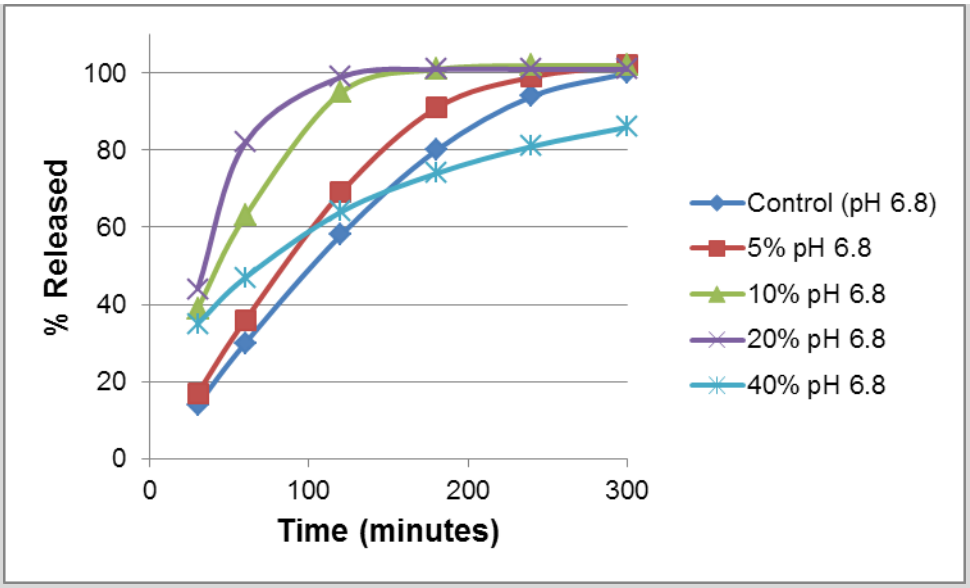


Figure 4. Dissolution Profiles for the proposed drug product in different amount of alcohol in pH 6.8 (Plotted by the Reviewer)

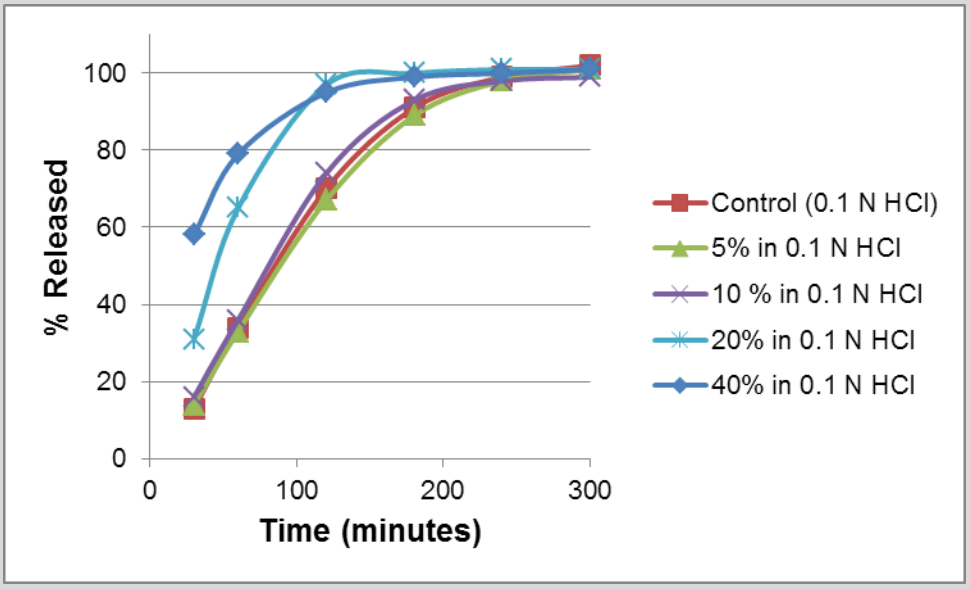


Figure 5. Dissolution Profiles for the proposed drug product in different amount of alcohol in 0.1 N HCl (Plotted by the Reviewer)

The in vitro alcohol induced increase in dissolution finding was communicated to the Reviewers in the Office of Clinical Pharmacology and the Clinical Reviewer.

Dissolution method acceptance criteria

The acceptance criteria proposed by the Applicant are permissive and not acceptable. The below IR comment was conveyed to the Applicant to revise the acceptance criteria.

IR Comment Conveyed to the Applicant in an IR letter dated June 15, 2017

Based on the evaluation of the submitted dissolution data, your proposed dissolution acceptance criteria of (b) (4) *are not acceptable and the following recommended dissolution acceptance criteria should be implemented:*

30 min: NMT (b) (4) *%*

2 hr: NLT (b) (4) *%*

3 hr: NLT (b) (4) *%*

Note that the setting of the dissolution acceptance criteria is based on mean values and therefore, it must be recognized that some batches may require Stage 2 and, occasionally, Stage 3 testing. Revise your drug product specifications and stability protocol accordingly and submit a copy of the updated drug product specifications table.

The Reviewer's Assessment of the Applicant's Response dated June 23, 2017
ADEQUATE

The Applicant accepted the above FDA recommended dissolution acceptance criteria.

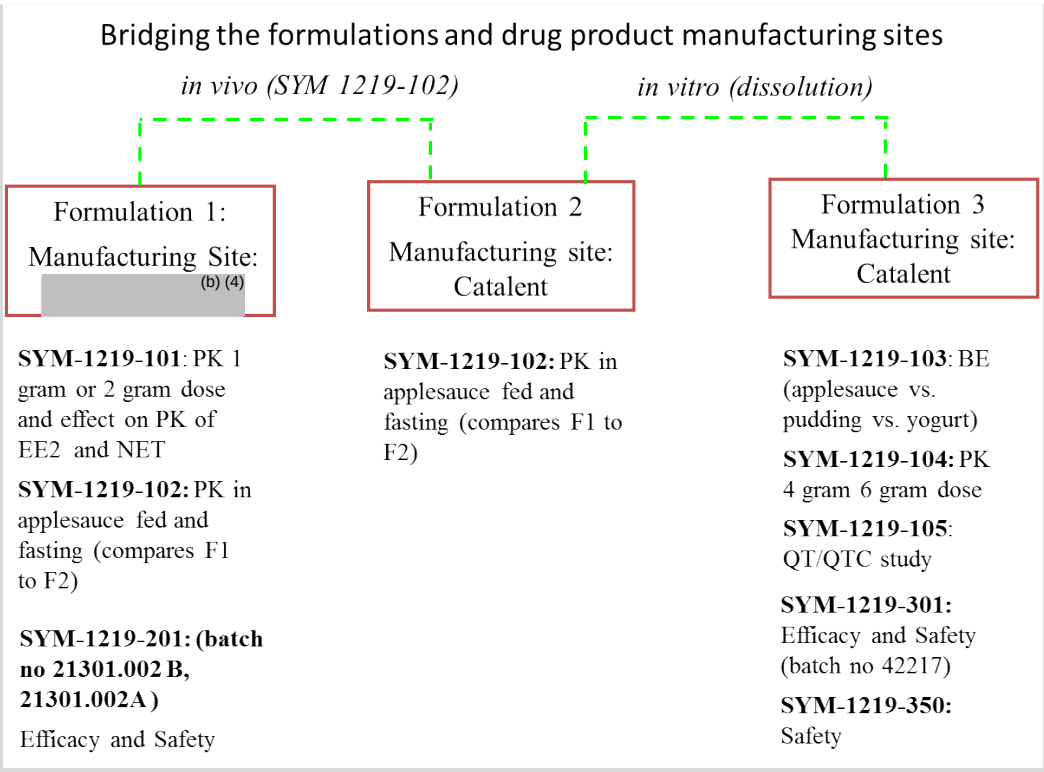
Bridging of Formulations and Drug Manufacturing Sites

Three formulations have been used in clinical trials during the development of SYM-1219 granules, one manufactured at (b) (4) (Formulation F1) and two manufactured at Catalent (Formulations F2 and F3).

Table 6 Composition of Three Formulations of SYM-1219 Used in Clinical Trials

	Formulation F1 (b) (4)			Formulation F2 (Catalent)			Formulation F3 (Catalent)		
Purpose and Use	SYM-1219-101, SYM-1219-102, SYM-1219-201			SYM-1219-102			SYM-1219-103, SYM-1219-104, SYM-1219-105; SYM-1219-301, SYM-1219-350, Registration Batches, Commercial Production		
Ingredient	**Quantity (mg/dose)**	**% w/w**	**Theoretical Batch (kg)**	**Quantity (mg/dose)**	**% w/w**	**Theoretical Batch (kg)**	**Quantity (mg/dose)**	**% w/w**	**Theoretical Batch (kg)**
(b) (4)									

	Formulation F1 (b) (4)	Formulation F2 (Catalent)	Formulation F3 (Catalent)
Purpose and Use	SYM-1219-101, SYM-1219-102, SYM-1219-201	SYM-1219-102	SYM-1219-103, SYM-1219-104, SYM-1219-105; SYM-1219-301, SYM-1219-350, Registration Batches, Commercial Production
(b) (4)			



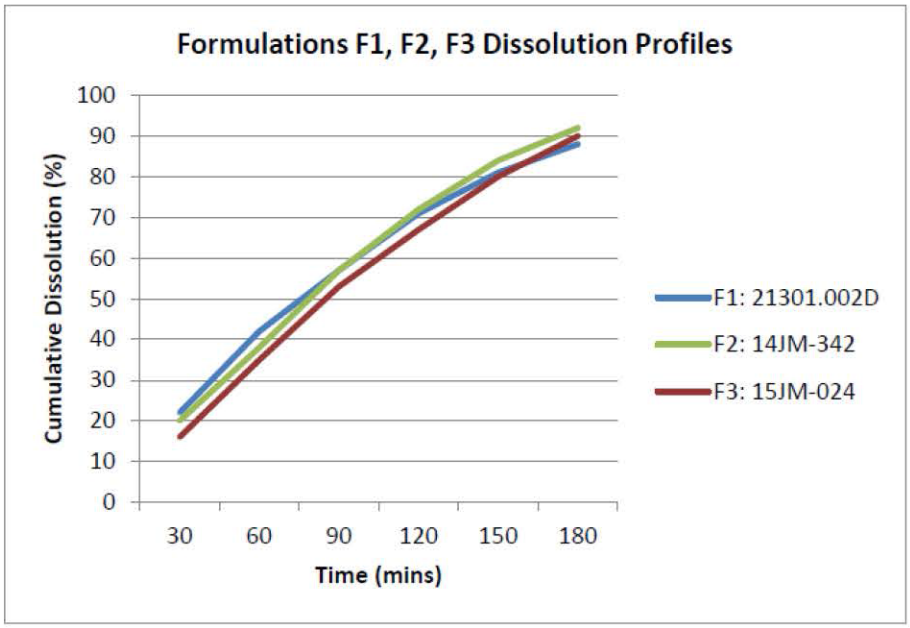
Formulation 1 (b) (4) was used in clinical studies SYM-1219-101, SYM-1219-102 and SYM-1219-201. The Applicant stated that (b) (4) . The Applicant concluded that (b) (4) . Consequently, the Applicant changed the formulation. The Applicant conducted a PK study (SYM 1219-102) comparing the Formulation 1 (b) (4) and Formulation 2 (Catalent). The study is reviewed by OCP. The difference between Formulation 2(Catalent) and Formulation 3 (Catalent) is considered minor and the below comparative dissolution data support the in vitro bridging between these two formulations. Formulation F3 has been used in clinical studies SYM-1219-103, SYM-1219-104, SYM-1219-105; SYM-1219-301 and SYM-1219-350 (refer to schematic above for all the formulations used in the clinical studies). Comparative dissolution studies between F1, F2 and F3 are shown below.

2.1.4.5 Equivalency of Clinical Formulations

Table 7 Dissolution Data for Formulation F1, F2 and F3 Batches Used in Clinical Trials.

Time (mins.)	Formulation F1: (b) (4) Batch 21301.002D	Formulation F2: Catalent Batch 14JM-342	Formulation F3: Catalent Batch 15JM-024
	Cumulative % Dissolved (%RSD)		
30	22(2)	20(2)	16(3)
60	42(1)	38(2)	35(1)
90	57(2)	57(1)	53(2)
120	71(1)	72(2)	67(1)
150	81(1)	84(2)	80(1)
180	88(1)	92(2)	90(1)

Figure 3 Dissolution Profiles of Formulation F1, F2, and F3 Batches Used in Clinical Trials



Reviewer's Assessment of the Bridging of the Formulations and Drug Product Manufacturing Sites

The Applicant conducted a comparative PK study between F1 and F2 formulation. This study is reviewed by OCP. Bridging between Formulation 2 and Formulation 3 is supported by the in vitro dissolution study. Drug release profiles between Formulation 2 and 3 are similar indicating minor formulation difference did not impact dissolution. The in vitro component of the bridging is found acceptable based on the provided dissolution data.

RECOMMENDATION

From Biopharmaceutics perspective, NDA 209363 for Secnidazole granules, 2 gram is recommended for Approval.

Below are the final acceptable dissolution method and acceptance criteria for the proposed drug product.

USP Apparatus	Rotation	Volume	Temperature	Medium	Final Acceptance Criteria
USP I (basket)	50 rpm	900 mL	37°C ± 0.5°C	pH 6.8 Phosphate Buffer	30 min: NMT (b) (4) % 2 hr: NLT (b) (4) % 3 hr: NLT %

Primary Biopharmaceutics Reviewer Name and Date:

Banu S. Zolnik, PhD, 7/20/2017

Secondary Reviewer Name and Date

I concur with Dr. Zolnik's assessment and recommendation.

Elsbeth Chikhale, PhD, 07/20/2017

Banu Zolnik

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Elsbeth Chikhale

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I. Review of Common Technical Document-Quality (Ctd-Q) Module 1 Labeling & Package Insert

1. Package Insert

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

----------DOSAGE FORMS AND STRENGTHS----------

[TRADENAME] (secnidazole) Oral Granules

Oral granules 2 g secnidazole, in a (b) (4) child-resistant foil packet.

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	TRADENAME, secnidazole	Adequate
Dosage form, route of administration	Oral granules	It was previously decided (WRO of 7/5/16 to applicant) that "oral granules" is acceptable(vs. "granules").
Controlled drug substance symbol (if applicable)	NA	
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	2 g oral granules	Adequate

(b) "Full Prescribing Information" Section

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

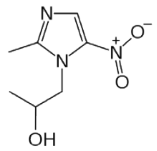
(b) (4) Oral Granules, 2 g, (b) (4) off-white to slightly yellowish granules with (b) (4) g net weight, packed in a (b) (4) child-resistant foil packet.

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	2 g oral granules	Adequate
Strengths: in metric system	2 g oral granules with net weight (b) (4) g	Net weight is 4.76 g so this should be 4.8 g
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	off-white to slightly yellowish granules, packed in a (b) (4) child-resistant foil packet	Adequate

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

The active ingredient in [TRADENAME] Oral Granules is secnidazole (also named 1-(2-hydroxypropyl)-2-methyl-5-nitroimidazole and 1-(2-methyl-5-nitro-1*H*-imidazol-1-yl) propan-2-ol).

The molecular formula of secnidazole is $C_7H_{11}N_3O_3$, the molecular weight is 185.18 and the chemical structure is



Each packet of [TRADENAME] contains (b) (4) g of off-white to slightly yellowish granules, which contain 2 g of secnidazole and the following inactive ingredients: sugar spheres, povidone, polyethylene glycol 4000, Eudragit NE30D (ethyl acrylate methyl methacrylate copolymer), and (b) (4).

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	TRADENAME, secnidazole	Adequate
Dosage form and route of administration	Oral granules	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	2 g active moiety, (b) (4) g total weight	Adequate, should be 4.8 g total weight
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Sugar spheres, povidone, polyethylene glycol 4000, Eudragit NE30D (ethyl acrylate methyl methacrylate copolymer), and (b) (4)	Generally adequate. Suggest that the inactive ingredients be in alphabetical order. The USAN and USP name "talc" should be used rather than (b) (4)
Statement of being sterile (if applicable)	NA	
Pharmacological/ therapeutic class	Not present	Should be added
Chemical name, structural formula, molecular weight	Molecular formula $C_7H_{11}N_3O_3$, molecular weight 185.18, chemical structure present	Adequate
If radioactive, statement of important nuclear characteristics.	NA	
Other important chemical or physical properties (such as pKa, solubility, or pH)	NA	

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

[TRADEMARK] (secnidazole) Oral Granules, 2 g, consists of off-white to slightly yellowish granules containing secnidazole. [TRADEMARK] is supplied in (b) (4) packages containing one packet of granules in an individual carton. Each packet contains (b) (4) g of granules containing 2 g secnidazole. [TRADEMARK] is supplied as follows:

NDC 71000-102-01 (b) (4) 2 g packet

Store at 20-25°C; excursions permitted to 15-30ºC (59-86ºF). [See USP Controlled Room temperature]

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	2 g	Adequate. Total weight should be 4.8 g
Available units (e.g., bottles of 100 tablets)	(b) (4) packages containing one packet of granules in an individual carton.	Adequate but the NDA describes a carton of 12 single dose packets which is not mentioned in the PI. Add the carton of 12 to the PI.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	off-white to slightly yellowish granules	Adequate
Special handling (e.g., protect from light, do not freeze)	NA	
Storage conditions	Store at 20-25°C; excursions permitted to 15-30ºC (59-86ºF). [See USP Controlled Room temperature]	Adequate

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

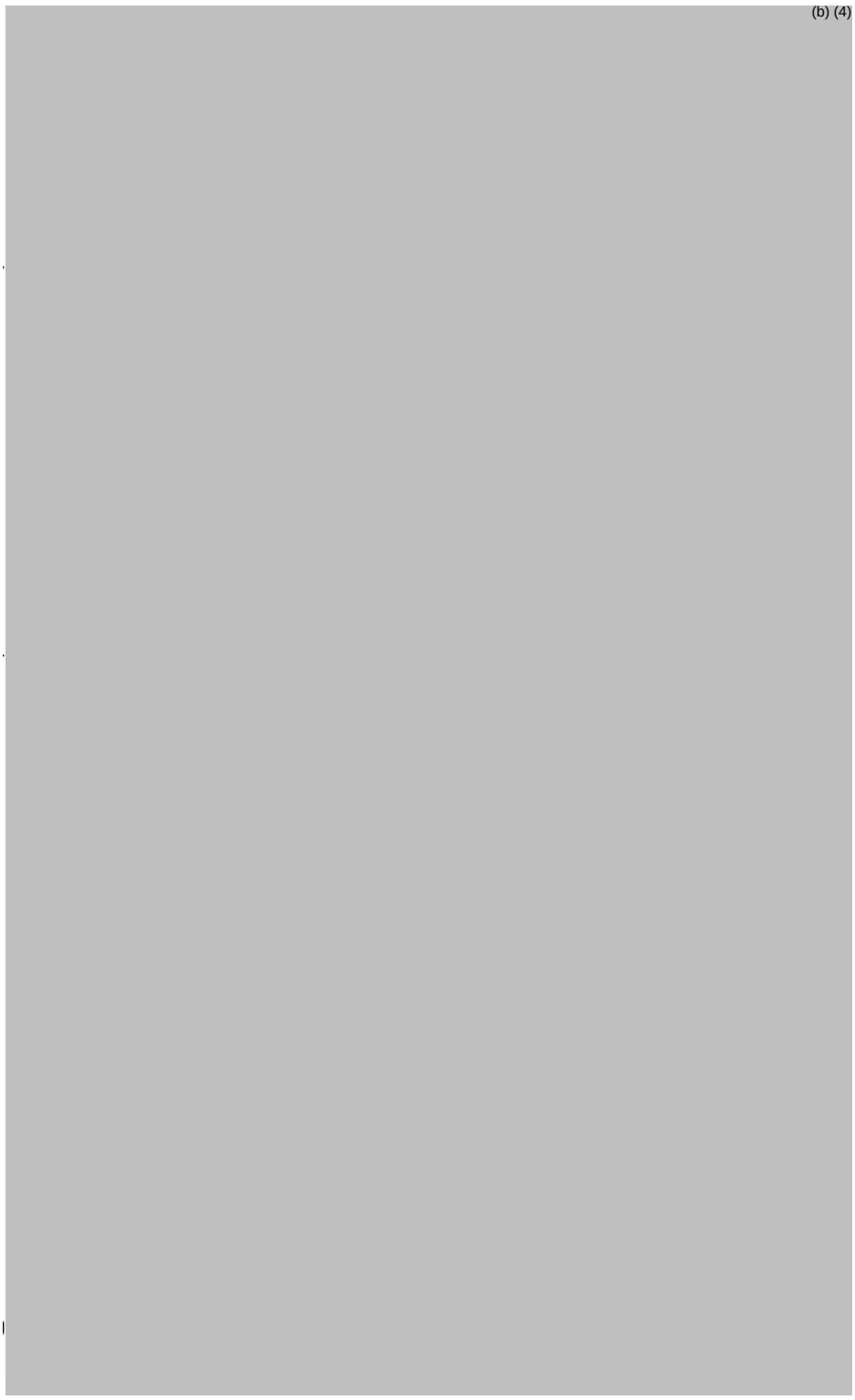
Distributed by:
Symbiomix Therapeutics LLC
Newark, NJ 07103

Manufactured by:
Catalent Pharma Solutions
Somerset, NJ 08873

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

2. Container and Carton Labeling

1) Immediate Container Label



Text as follows:

USUAL DOSAGE: One packet.

Solosec® granules should be administered as follows:

• Consume the contents of one packet without chewing or crunching the granules.

• May be taken at any time with [redacted].

• [redacted] The granules will not dissolve. Consume all of the granules within 30 minutes.

• A glass of water [redacted] may be taken to aid in swallowing.

Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F). (See USP Controlled Room Temperature).

Mfd for: Symbiomix Therapeutics, LLC, Newark, NJ 07103
By: Catalent Pharma Solutions, Somerset, NJ 08873

Product of USA
EXP XX XXXX
LOT XXXXXX

APPEARS THIS WAY ON ORIGINAL

Barcode Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Solosec, secnidazole	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	2 g	Adequate
Route of administration 21.CFR 201.100(b)(3))	Oral	Adequate
Net contents* (21 CFR 201.51(a))	Dosage of 2 g is present but not the total weight of (b) (4) g	Adequate
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Not present but acceptable given the small size of the packet	Adequate
Lot number per 21 CFR 201.18	Present	Adequate
Expiration date per 21 CFR 201.17	Present	Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)	Present	Adequate
Storage (not required)	Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F). (See USP Controlled Room Temperature).	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Present	Adequate
Bar Code per 21 CFR 201.25(c)(2)***	Present	Adequate
Name of manufacturer/distributor (21 CFR 201.1)	Both are present	Adequate
Others	Instructions for administration are present: **Solosec® granules should be administered as follows:** • Consume the contents of one packet without chewing or crunching the granules. • May be taken at any time with (b) (4). • (b) (4) The granules will not dissolve. Consume all of the granules within 30 minutes. • A glass of water (b) (4) may be taken to	Adequate

	aid in swallowing.	

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ‘‘sample’’, ‘‘physician’s sample’’, or a substantially similar statement and the contents of the package do not exceed 8 grams.
**For solid oral dosage forms, CDER policy provides for exclusion of “oral” from the container label

2) Carton Labeling

Single Dose Carton

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

12 Single Dose Packets Carton

Text for both cartons as follows:

USUAL DOSAGE: One packet.
Solosec® granules should be administered as follows:
• Consume the contents of one packet without chewing or crunching the granules.
• May be taken at any time with (b) (4).
• (b) (4) The granules will not dissolve. Consume all of the granules within 30 minutes.
• A glass of water (b) (4) may be taken to aid in swallowing.
Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F). (See USP Controlled Room Temperature).

Solosec® is a (b) (4) trademark of Symbiomix therapeutics, LLC.

Mfd for: Symbiomix Therapeutics, LLC, Newark, NJ 07103
By: Catalent Pharma Solutions, Somerset, NJ 08873

APPEARS THIS WAY ON ORIGINAL

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Solosec secnidazole	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	2 g	Adequate
Net contents (21 CFR 201.51(a))	Total weight is (b) (4) g, not present on carton	Adequate
Lot number per 21 CFR 201.18	Present	Adequate
Expiration date per 21 CFR 201.17	Present	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	Not present	Adequate
Sterility Information (if applicable)	NA	
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Present	Adequate
Storage Conditions	Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F). (See USP Controlled Room Temperature).	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Present	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	Present on carton of one, not on carton of 12	Adequate for carton of one, not for carton of 12
Name of manufacturer/distributor	Present	Adequate
"See package insert for dosage information" (21 CFR 201.55)	Dosing information provided on cartons. **Solosec® granules should be administered as follows:** • Consume the contents of one packet without chewing or crunching the granules. • May be taken at any time with (b) (4). • (b) (4)	Adequate

	(b) (4) The granules will not dissolve. Consume all of the granules within 30 minutes. • A glass of water (b) (4) may be taken to aid in swallowing.	
"Keep out of reach of children" (optional for Rx, required for OTC)	Not present	Adequate
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))	Oral	Adequate

Overall Comments: Generally acceptable. Note that the term "oral granules" was previously agreed (WRO to sponsor on 7/5/16). The following points were conveyed to clinical:

- Sections 3, 11, and 16 describe 2 g oral granules with net weight (b) (4) g. However actual net weight is 4.76 g so this should be 4.8 g.

- In Section 11 inactive ingredients are listed as "Sugar spheres, povidone, polyethylene glycol 4000, Eudragit NE30D (ethyl acrylate methyl methacrylate copolymer), and (b) (4) ". The inactive ingredients be in alphabetical order. The USAN and USP name "talc" should be used in place of (b) (4) .

- Pharmacological/therapeutic class is not present in Section 11.

- Section 16 generally adequate but the NDA describes a carton of 12 single dose packets which is not mentioned in the PI. The carton of 12 does not appear to have a barcode.

- For the foil packet the dosage of 2 g is present but not the total weight of (b) (4) g. Inactive ingredients are not present but acceptable given the small size of the packet.

George Lunn

Digitally signed by George Lunn
Date: 8/10/2017 09:27:53AM
GUID: 508da72000029f40833369b0a181e8b3

Balajee Shanmugam

Digitally signed by Balajee Shanmugam
Date: 8/10/2017 09:28:32AM
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ATTACHMENT I: Final Risk Assessment

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay, stability of secnidazole	Formulation Raw materials Process parameters Scale/equipment Site	L	Adequate specification for the drug substance, drug product, and excipients	Acceptable	
Content uniformity	Formulation Raw materials Process parameters Scale/equipment Site	L	Controlled by USP test <905> (uniformity of dosage units by weight)	Acceptable	
Physical stability	Formulation Raw materials Process parameters Scale/equipment Site	L	Only one polymorph	Acceptable	
Microbial limits	Formulation Raw materials Process parameters Scale/equipment Site	L	Microbial limits testing test is part at release and shelf life specification	Acceptable	
Dissolution	Formulation Raw materials Process parameters Scale/equipment Site	L	The dissolution method and the revised acceptance criterion for drug product release and stability testing were found adequate	Acceptable	

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

Dorota M. Matecka -S

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Date: 2017.09.08 07:47:40 04'00'

On behalf of OPQ Team

Dorota Matecka, Ph.D. ATL for NDA 209363