CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216755Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	216755		
Applicant Name	Saptalis Pharmaceuticals, LLC		
Drug Product Name	LIKMEZ™ (metronidazole) Oral Suspension		
Dosage Form.	Suspension		
Proposed Strength(s)	500 mg/5 mL		
Route of Administration	Oral		
Maximum Daily Dose	4 grams		
Rx/OTC Dispensed	Rx		
Proposed Indication	Trichomoniasis, Amebiasis, and Anaerobic Bacterial Infections		
Drug Product Description	The proposed drug product is an aqueous oral suspension of metronidazole (500 mg per 5 mL), an antiprotozoal and antibacterial agent. In addition to metronidazole, the drug product formulation contains twelve (12) inactive ingredients, including excipients such as sucrose ((b) (4)%), glycerin ((b) (4)%), (b) (4)% magnesium aluminum silicate ((b) (4)), and strawberry and peppermint flavors, (b) (4) . Metronidazole oral suspension is described as a white to slightly brown suspension. The finished drug product is packaged in a 250 mL white HDPE bottle with a (b) (4) child-resistant cap, which contains a total volume of 200 mL suspension.		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	20°C to 25°C (68°F to 77°F)		
Review Team	**Discipline**	**Primary**	**Secondary**

	Drug Substance	Daniel Chan	Katherine Windsor
	Drug Product/ Labeling	Shrikant Pagay	David Claffey
	Manufacturing	Steven Hertz	Ying Zhang
	Biopharmaceutics	Min Kang	Elsbeth Chikhale
	Microbiology	Lauren Walling	Erika Pfeiler
	Other (specify):	N/A	
	RBPM	Anh-Thy Ly	
	ATL	Dorota Matecka	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

24 months at 20°C to 25°C (68°F to 77°F). Brief exposure to 15°C to 30°C (59°F to 86°F) permitted [see USP Controlled Room Temperature].

b. Additional Comments for Action

N/A

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed drug substance (metronidazole) and the drug product (metronidazole oral suspension). All comments and information requests identified by the review team and forwarded to the

Applicant regarding the drug product, including its microbiological quality, and manufacturing process have been addressed adequately. The CMC information regarding the metronidazole drug substance provided via a reference to a Type II DMF (b) (4) was also found acceptable (DMF (b) (4) was last reviewed and found adequate on February 8, 2021, in support of another application submitted to CDER). From the biopharmaceutics perspective, the Applicant conducted a comparative BA study to bridge the proposed drug product to the listed drug (LD). Since there were no changes to the drug product formulation, manufacturing site and/or process between the pivotal BE batch, registration batches, and the proposed commercial product, no additional bridging is needed. Furthermore, the proposed dissolution method and acceptance criteria were found acceptable based on information submitted in the original NDA and subsequent amendments submitted in response to the FDA questions and recommendations. In addition, all manufacturing and testing facilities have been found acceptable and an overall "Approve" recommendation was entered into Panorama by the Office of Pharmaceutical Manufacturing Assessment (OPMA) on July 7, 2023. Based on the individual subdiscipline assessments, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ).

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments: N/A
Comparability Protocols (PACMP): No
Comments: N/A
Additional Lifecycle Comments: N/A

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CHAPTER IV: LABELING

NDA 216755

1.0 PRESCRIBING INFORMATION

(b) (4)

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Adequate	
Route(s) of administration	Adequate	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	With the proposed changes
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	N/A	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

(b) (4)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting	Adequate	With the proposed changes

concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)		
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	N/A	
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	
For radioactive products, include radiation dosimetry for the patient and	N/A	

healthcare practitioner(s) who administer the drug		
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures"* with x numerical citation to "OSHA Hazardous Drugs".	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

(b) (4)

QUALITY ASSESSMENT

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	With the proposed changes
Strength(s) in metric system	Adequate	See above
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

Section 11 (DESCRIPTION)

(b) (4)

QUALITY ASSESSMENT

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	With the proposed changes
Dosage form(s) and route(s) of administration	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	N/A	
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	N/A	

Pharmacological/Therapeutic class	Adequate	
Chemical name, structural formula, molecular weight	Adequate	
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Adequate	

Section 11 (DESCRIPTION) Continued

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

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QUALITY ASSESSMENT

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

(b) (4)

QUALITY ASSESSMENT

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	With the proposed changes
Strength(s) in metric system	Adequate	
Available units (e.g., bottles of 100 tablets)	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures" with x numerical citation to "OSHA Hazardous Drugs."	Adequate	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	N/A	
Include information about child-resistant packaging	Adequate	

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenteral, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug review division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	

2.0 PATIENT LABELING

(b) (4)

(b) (4)

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):

QUALITY ASSESSMENT

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2]	Adequate	
Special preparation instructions (If applicable)	N/A	
Storage and handling information (If applicable)	Adequate	
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	N/A	
Active ingredient(s) (if applicable)	Adequate	
Alphabetical listing of inactive ingredients (if applicable)	Adequate	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

[2] Established name = [Drug] [Route of Administration] [Dosage Form]

3.0 CONTAINER AND CARTON LABELING

(b) (4)

QUALITY ASSESSMENT

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[3], (font size and prominence)	Adequate	
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	
Net contents (e.g., tablet count, volume of liquid)	Adequate	
"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	
Lot number and expiration date	Adequate	Space provided
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Inadequate	Include the following statement on the container label: **Discard the contents ten days after first opening the bottle.**
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement.	N/A	

[3] Established name = [Drug] [Route of Administration] [Dosage Form]

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QUALITY ASSESSMENT

For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	

QUALITY ASSESSMENT

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	

Assessment of Carton and Container Labeling: ***{Adequate/Inadequate}***

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

ITEMS FOR ADDITIONAL ASSESSMENT

Assess consistency of product-quality information in prescription drug labeling (PI, c/c labeling, and FDA-approved patient labeling). See Carton/Container Labeling Specific Resources for a presentation about inappropriate inconsistencies of product quality information between labeling.

QUALITY ASSESSMENT

If there are inappropriate inconsistencies between the labeling (e.g., established name, strength(s), package type term, discard statement, identifying characteristics, storage, reconstitution/dilution instructions), please list these as deficiencies in this section.

Overall Assessment and Recommendation: Adequate

The proposed changes in the package insert, patient labeling and the container label should be communicated to the applicant.

Primary Labeling Assessor Name and Date:

Secondary Assessor Name and Date (and Secondary Summary, as needed):

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Shrikant Pagay

Digitally signed by Shrikant Pagay
Date: 7/18/2023 05:23:03PM
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David Claffey

Digitally signed by David Claffey
Date: 7/19/2023 09:08:38AM
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CHAPTER VI: BIOPHARMACEUTICS

NDA Number	NDA 216755—505(b)(2)
Submission History	11/23/2022: Original Submission 3/30/23 (SDN-10): Response to the Biopharmaceutics IR #1 5/13/23 (SDN-13): Response to the Biopharmaceutics IR #2
Drug Product Name/ Strength	Metronidazole Oral Suspension, 500 mg/ 5mL
Route of Administration	Oral
Listed Drug	FLAGYL® (metronidazole) Tablets, 250 mg and 500 mg, NDA 012623, Pfizer Inc.
Applicant Name	Saptalis Pharmaceuticals LLC
OND Division / Proposed Indication	DAI/ Treatment of symptomatic and asymptomatic trichomoniasis, asymptomatic sexual partners, amebiasis, anaerobic bacterial infections (e.g., intra-abdominal infections, skin and skin structure infections, gynecologic infection, bacterial septicemia, bone and joint infections, central nervous system infections, lower respiratory tract infection, endocarditis).
Primary Reviewer	Min Kang, PharmD, MS
Secondary Reviewer	Elsbeth Chikhale, PhD
Assessment Recommendation	**Adequate**

EXECUTIVE SUMMARY:

The Applicant submitted 505(b)(2) NDA 216755-ORIG-1 for Metronidazole Oral Suspension, 500 mg/ 5mL, indicated for treatment of symptomatic and asymptomatic trichomoniasis, asymptomatic sexual partners, amebiasis, anaerobic bacterial infections (e.g., intra-abdominal infections, skin and skin structure infections, gynecologic infection, bacterial septicemia, bone and joint infections, central nervous system infections, lower respiratory tract infection, endocarditis).

The listed drug (LD), Flagyl® (metronidazole) Tablet, has been on the market in the United States since its original approval by FDA in July 1963 (NDA 012623). However, to address the need for improved palatability, this application seeks to provide a new taste-masked oral suspension dosage form of metronidazole. A bridge between the proposed drug product and the LD is established based on a comparative Bioavailability (BA) study that was designed to compare the bioavailability of the proposed metronidazole oral suspension with that of Flagyl tablets administered at the recommended dose, under both fasting and fed conditions (Study#: 21-VIN-0347, 21-VIN-0348). It is noted that the Applicant plans to further study this oral suspension dosage form in a pediatric population after the initial approval of this NDA, to meet the obligations outlined in the Pediatric Study Plan agreed with the FDA on 4/9/2022.

Assessment Summary:

This Biopharmaceutics Review focuses on evaluating (1) the in vitro dissolution method and acceptance criterion as a quality control (QC) test, and (2) the bridging between the LD and the proposed to-be-marketed drug product and the need for bridging between the drug product used in the comparative BA study and the proposed to-be-marketed drug product.

- **In Vitro Dissolution Method and Acceptance Criterion:**

The Applicant developed a dissolution method and submitted a Dissolution Method Development Report investigating the selection of each parameter. Based on the dissolution data and information submitted, the following originally proposed dissolution method and acceptance criterion are found acceptable for the Quality Control (QC) test of Metronidazole Oral Suspension, 500 mg/ 5mL, at batch release and on stability:

Approved Dissolution Method and Acceptance Criterion for Metronidazole Oral Suspension, 500 mg/ 5mL				
Apparatus	**Speed**	**Volume/ Temp**	**Medium**	**Acceptance Criterion**
USP II (Paddle)	50 rpm	500 mL/ 37 °C	0.1 N HCl (pH 1.2)	Q = (b) (4) % in 30 minutes

- **Risk Assessment:**

CQAs	**Initial Risk Ranking**	**Comments**	**Updated Risk Ranking after Assessment**	**Comments**
Dissolution	Low	Metronidazole drug substance exhibits high soluble across the physiologic pH (pH 1-6.8) with highest solubility at pH 1.2	Very Low	(1) The Applicant's proposed Dissolution Method is consistent with that of the FDA's Guidance recommendation for DP containing highly soluble DS (2) Tightening of dissolution acceptance criterion was not considered based on the Tmax ~0.75 hour[1] of the proposed DP.

[1] Tmax ~0.75 hr (45 min) for the proposed oral suspension dosage form, vs Tmax ~1 hr for the Tablet dosage form (RLD).

- **Product Bridging:**

  The Applicant conducted a comparative BA study under fed and fasted conditions, to bridge the proposed drug product to the LD. Since there were no changes to the drug product formulation, manufacturing site and/or process between the pivotal BE batch, registration batches, and To-Be-Marketed (TBM) products, no additional bridging is needed.

List of Submissions Being Assessed:

IND/NDA	eCTD sequence #	Date of response	Document
NDA	0001	11/23/2022	2/28/2023: Original Submission
NDA	0010	3/30/2023	Response to the Biopharmaceutics IR #1[2]
NDA	0013	5/13/2023	Response to the Biopharmaceutics IR #2[3]

Concise Description of Outstanding Issues *(list bullet points with key information and update as needed*):

None.

Overall Biopharmaceutics Recommendation:

From the Biopharmaceutics perspective, NDA 216755-ORIG-1 for Metronidazole Oral Suspension, 500 mg/ 5mL*, is* ***Adequate*** *and recommended for Approval.*

[2] SDN-9 (M.1.11.1): \\CDSESUB1\EVSPROD\nda216755\0010\m1\us\cover-letter-216755-0010.pdf
[3] SDN-13 (M.1.11.1): \\CDSESUB1\EVSPROD\nda216755\0013\m1\us\cover-letter-216755-0013.pdf

BIOPHARMACEUTICS ASSESSMENT

B.1 BCS DESIGNATION

Assessment: N/A.

Solubility: The Applicant has submitted the solubility of Metronidazole, USP ((b) (4)) as shown in Table 1 below.

Table 1: Solubility (mg/mL) of Metronidazole, USP ((b) (4)) at 37°C

Theoretical pH	Individual pH measurement	Final pH before correction	Adjusted with HCl (g)	Final pH corrected	Metronidazole weight (g)	Buffer Volume (mL)	Final pH	Metronidazole equilibrium concentration (mg/g)	Specific Gravity	Metronidazole equilibrium concentration (mg/mL)	Metronidazole equilibrium concentration mean (mg/mL)
pH 1.2	1.18	2.38	3.6802	1.18	8.0157	22.4	1.3	213.4	1.0900	195.8	195.8
	1.18	2.41	3.6858	1.17	8.0048	22.4	1.3	212.1	1.0897	194.6	
	1.18	2.40	3.6949	1.17	8.0073	22.4	1.3	214.8	1.0898	197.1	
pH 2.6	2.61	3.79	0.12	2.61	2.1011	50.0	2.7	21.4	1.0084	21.2	21.1
	2.61	3.84	0.14	2.61	2.1016	50.0	2.7	21.4	1.0082	21.2	
	2.61	3.84	0.12	2.61	2.1013	50.0	2.7	21.0	1.0081	20.8	
pH 4.5	4.53	4.57	0.04	4.52	1.1038	50.0	4.6	14.9	1.0052	14.8	14.9
	4.53	4.57	0.04	4.52	1.1006	50.0	4.6	14.9	1.0052	14.8	
	4.53	4.57	0.04	4.51	1.1046	50.0	4.5	15.0	1.0052	14.9	
pH 6.8	6.80	6.89	0.06	6.80	1.1040	50.0	6.8	14.4	1.0087	14.3	14.2
	6.80	6.91	0.06	6.78	1.1023	50.0	6.8	14.4	1.0087	14.3	
	6.80	6.89	0.04	6.81	1.1026	50.0	6.8	14.2	1.0087	14.1	

Reference: 0543/138

Reviewer's comments:

A BCS designation is not requested by the Applicant, nor required by the FDA. Permeability data are not submitted nor required. Based on the submitted solubility data which demonstrates a high solubility across the physiologic pH (≥ 2 mg/mL), this Reviewer considers metronidazole to be a high solubility drug substance. *The proposed drug product is an immediate release (IR) oral suspension* (b) (4) *. Therefore, the risk of drug release and bioavailability from this IR product at gastric pH is considered very low especially given its high solubility at low pH (pH 1.2).*

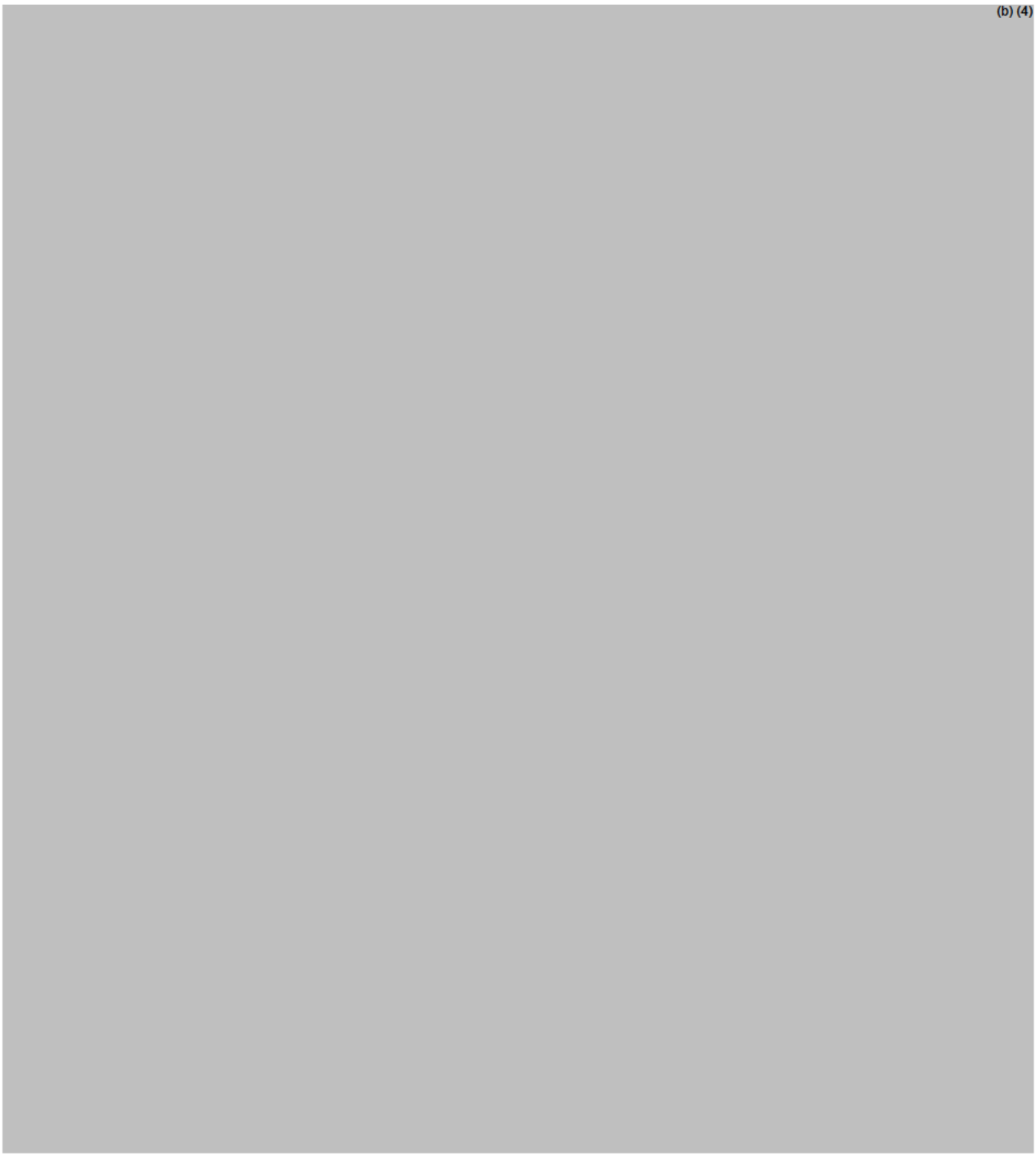
B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERION

Assessment: Adequate

Table 2: The Applicant's proposed dissolution method and the acceptance criterion for Metronidazole Oral Suspension, 500 mg/ 5mL

Apparatus	Speed	Volume/Temp	Medium	Acceptance Criterion
USP II (Paddle)	50 rpm	500 mL/ 37 °C	0.1N HCl	Q = (b) (4)% in 30 minutes

(b) (4)



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(b) (4)

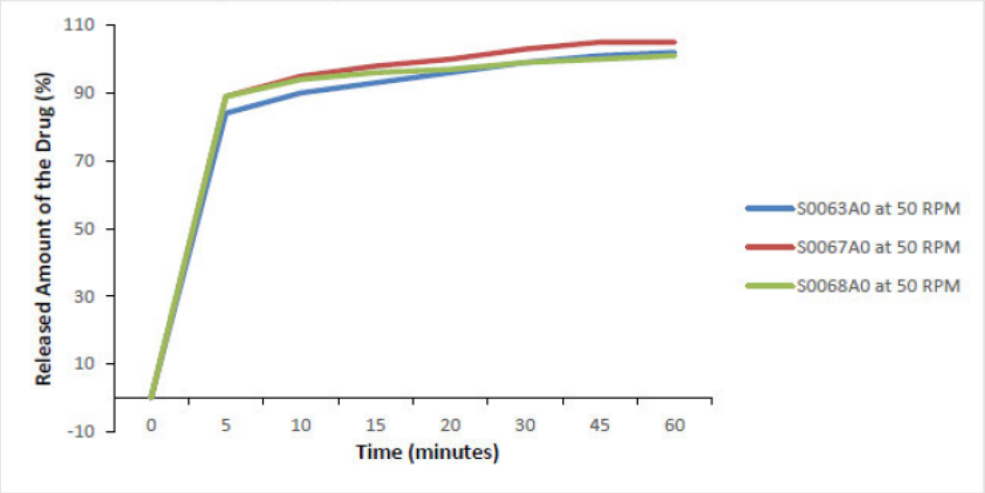
Since the proposed drug product contains a high solubility drug substance for which a deemed risk is low from a Biopharmaceutics perspective, an evaluation of the discriminating ability of the proposed dissolution method was not needed. Moreover, the proposed drug product is an immediate release (IR) oral suspension (b) (4) . Therefore, the risk of issues with drug release and bioavailability from this IR product at gastric pH is considered very low especially given its significantly increased solubility at low pH (pH 1.2). Based on the totality of the submitted information and data, the Applicant proposed dissolution method is deemed acceptable for QC at batch release and on stability.

B.2.4. Dissolution Data and Acceptance Criterion:

Table 3: Registration/ Primary Stability Batches of Metronidazole Oral Suspension, 500 mg/ 5mL

Exhibit Batch#	S0063A0	S0067A0	S0068A0
API Lot Numbers	20IC052	20IC052 20IC053	20IC054
Manufacturing Dates	04/02/2021	07/09/2021	07/15/2021

Figure 5: Dissolution Profile of Metronidazole Oral Suspension, 500 mg/ 5 mL, using the proposed dissolution method (Testing date: 4/25/23)



Reviewer's Comments:

The Applicant has proposed a dissolution acceptance criterion of "Q = (b) (4) % in 30 minutes". Initially, tightening of dissolution acceptance criterion was considered; however, (i) based on the deemed low risk of the proposed drug product as discussed

above, (ii) the fact that the Tmax of the proposed oral suspension is about 0.75 hrs[5] (45 minutes), and (iii) stability data has been collected only at 30 minutes time points thus far, "Q= (b)(4)% in 30 min" which is consistent with that of the FDA's Guidance for drug products containing high solubility drug substances recommendation was deemed acceptable as is.

With regards to the samples used for the dissolution testing, the Applicant was requested to clarify whether the drug product samples for dissolution testing were obtained from a single bottle or from multiple bottles (i.e., 12 separate bottles for 12 samples) via Information Request #1 dated 3/13/23, and in response the Applicant clarified that they used 12 separate bottles for the comparative in vitro dissolution testing of Reference vs Test Product, whereas a single bottle had been used for the stability testing up until this point (i.e., 3, 6, 9 months). Then, the Applicant committed that they will use 6 separate bottles for future stability samples (i.e., 12, 24, 36 months)[6], and have revised the dissolution release and stability protocols accordingly.

B.3. PRODUCT BRIDGING

Assessment: Adequate

The Applicant conducted a comparative BA study under fed and fasted conditions, to bridge the proposed drug product to the LD. Since there were no changes to the drug product formulation, manufacturing site and/or process between the pivotal BE batch, registration batches, and To-Be-Marketed (TBM) products, no additional bridging is needed.

B.4. BIOWAIVER REQUEST

Assessment: Not Applicable

The biowaiver is not requested nor required for this NDA.

BIOPHARMACEUTICS DEFICIENCIES PENDING:

None

[5]Tmax ~0.75 hr (45 min) for the proposed oral suspension dosage form, vs Tmax ~1 hr for the Tablet dosage form (RLD).

[6] Applicant also noted that they will include the 1 bottle sample data at 18 month stability time point, so that the dissolution trends using a single bottle (3, 6, 9 month data) can be compared to the multiple bottles data (12 ,24, 36 months).

Appendix. I: Biopharmaceutics Information Requests

Biopharmaceutics Information Request #1 conveyed to the Applicant on 3/13/2023

1. (b) (4)

2. It is unclear whether the drug product samples for dissolution testing were obtained from a single bottle or from multiple bottles. For example, for dissolution testing of twelve (12) unit samples, twelve (12) different bottles should be used for each sample. Clarify how your samples have been obtained. Update the Analytical Procedure (M.3.2.P.5.2) to clearly indicate that suspension samples for dissolution testing should be taken from separate bottles, e.g. "*use a separate single bottle for each sample unit*" for batch release and stability dissolution testing.

Provide your response by COB 3/30/2023

Response received on 3/30/2023 (SDN-10) and assessment included throughout this review document.

Biopharmaceutics Information Request #2 conveyed to the Applicant on 4/17/2023

We acknowledge that you have provided the full in vitro dissolution profile data for your pivotal/clinical batch (S0068A0); however, you have not provided the full dissolution profile data of your other two registration/commercial batches (S0063A0 and SS0067A0) using the proposed dissolution method. Provide the complete dissolution profile data [individual (n=12), mean, range, %RSD at each time point (5, 10, 15, 20, 30, 45, 60 min and/or until complete dissolution)] for the two registration batches S0063A0

and SS0067A0 at the current stability time point. Report the dissolution data as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim). The individual dissolution data of these batches should also be presented in tabular and graphical formats. Provide detailed information for the batches of drug product tested using the proposed dissolution method (i.e., USP Apparatus II [paddle] in 500 mL of 0.1 N HCl at 50 rpm, batch/lot no., manufacturing date, manufacturing site, testing date, batch size, age of drug product at the time of dissolution testing, etc.).

Response received on 5/3/2023 (SDN-13) and assessment included throughout this review document.

Min (Sammie) Kang

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Elsbeth Chikhale

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	216755
Assessment Cycle Number	1
Drug Product Name/ Strength	LIKMEZ (Metronidazole Oral Suspension), 500 mg/5 mL
Route of Administration	Oral
Applicant Name	Saptalis Pharmaceuticals, LLC
Therapeutic Classification/ OND Division	CDER/OND/OID/DAI
Manufacturing Site	Saptalis Pharmaceuticals, LLC 20 Davids Drive Hauppauge, NY 11788 USA
Method of Sterilization	N/A; non-sterile

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions being assessed (table):

Document(s) Assessed	Date Received
ORIG-1 / SN 0001	11/23/2022
IR response / SN 0008	2/7/2023

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: The drug product is a non-sterile white/slightly brown liquid oral suspension indicated for treating symptomatic trichomoniasis, asymptomatic trichomoniasis, treatment of asymptomatic sexual partners, amebiasis, and anaerobic bacterial infections. Metronidazole Oral Suspension is a multi-dose, (b) (4) product that comes in a 200 mL bottle.

Concise Description of Outstanding Issues: N/A

Supporting Documents: N/A

S DRUG SUBSTANCE

The drug substance is not provided sterile. Therefore, a product quality microbiology review of the drug substance is not reviewed.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –** Section 3.2.P.1, p. 2 of 7
  Metronidazole Oral Suspension is a non-sterile, white to slightly brown liquid oral suspension, provided in a multi-dose 200 mL bottle.

- **Drug product composition –** Section 3.2.P.1, p. 3-4 of 7

Ingredient	Quantity per mL	Function
Metronidazole, USP	100 mg	API
Magnesium Aluminum Silicate – (b) (4), NF	(b) (4)	(b) (4)
Microcrystalline Cellulose ((b) (4)), NF		
Methylparaben, NF		
Propylparaben, NF		
Glycerin, USP		
Sodium Phase Dibasic ((b) (4)), USP		
Sodium Phosphate Monobasic (b) (4), USP		
Sucrose, NF		
Sucralose, NF		
Strawberry Flavor, Natural (b) (4)		Flavoring Agent
Natural Peppermint Flavor ((b) (4)		Flavoring Agent
Purified Water, USP		(b) (4)

- **Description of container closure system –** Section 3.2.P.7, p. 2-3 of 6

Component	Description	Manufacturer
Bottle	250 mL (b) (4) Round (b) (4) White	(b) (4)
Cap	(b) (4) CRC Cap with (b) (4) Liner	

Assessment: *Adequate*
The applicant provided an adequate description of the drug product composition and the container closure system.

P.2 PHARMACEUTICAL DEVELOPMENT

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Lauren Walling

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Erika Pfeiler

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/s/

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