CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215888Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☐ Approval
☒ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 215888
Assessment # 1

Drug Product Name	VIVJOA* (oteseconazole capsules)
Dosage Form	Capsules
Strength	150 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Mycovia Pharmaceuticals, Inc.
US agent, if applicable	N/A

**Proposed trade name – under review*

Submission(s) Assessed	Document Date	Discipline(s) Affected
0000	May 27, 2021	All
0010	July 19, 2021	Environmental Analysis
0021	August 19, 2021	Drug Substance
0023	September 3, 2021	Process, Environmental Analysis
0032	October 1, 2021	Drug Product, Biopharmaceutics
0033	October 7, 2021	Biopharmaceutics
0036	October 12, 2021	Environmental Analysis

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Soumya Mitra	Paresma Patel
Drug Product	Hailing (Sheena) Wang	David Claffey
Manufacturing	Iwona Weidlich	Steven Frisbee
Microbiology	Iwona Weidlich	Steven Frisbee
Biopharmaceutics	Kevin Wei	Elsbeth Chikhale
Environmental Analysis	James Laurenson (*refer to Drug Product Review*)	
Laboratory (OTR)	N/A	
Regulatory Business Process Manager	Anh-Thy Ly	
Application Technical Lead	Dorota Matecka	

QUALITY ASSESSMENT DATA SHEET

IQA NDA Assessment Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs*:

DMF #	Type	Holder	Item Referenced	Status*	Date Assessment Completed*	Comments*
(b) (4)	III		(b) (4)			
	III					
	IV					

**Sufficient information provided in the NDA – refer to the Drug Product Chapter*

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	111675	*Development of oteseconazole capsules*

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/ Toxicology	Complete	Adequate (acceptance criteria for impurities)	*Refer to Drug Substance review*	Dr. Owen McMaster
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			
Other	N/A			

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

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, oteseconazole capsules. The manufacturing and testing facilities have been found acceptable and the Overall Manufacturing Inspection Recommendation (OMIR) of "Approve" was entered into Panorama by the Office of Pharmaceutical Manufacturing Assessment (OPMA) on October 5, 2021. Therefore, this NDA is recommended for **approval** by the Office of Pharmaceutical Quality (OPQ).

The following Post-Marketing Commitment (PMC) should be included in the action letter (refer to the Drug Product Review, below):

PMC Study
Submit the final reports and summaries of the currently ongoing ecotoxicity studies to support the categorical exclusion from an environmental assessment.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Oteseconazole is an azole antifungal that has been under development (b) (4) Oteseconazole is an azole metalloenzyme inhibitor targeting the fungal sterol, 14α demethylase (CYP51), which mediates membrane permeability and fluidity by demethylating the 14α position of lanosterol.

Oteseconazole has been formulated as an immediate-release, capsules, each containing 150 mg of oteseconazole drug substance. Oteseconazole capsules) are lavender, hard gelatin, size 2 capsules printed with OTE 150 mg using black ink, proposed to be packaged in (b) (4) 18-count blister packages* within a child-resistant carton.

The proposed drug product, oteseconazole capsules, received Qualified Infectious Disease Product (QIDP) and Fast Track (FT) designations on September 27, 2016 [for the treatment of vulvovaginal candidiasis (VVC) and recurrent vulvovaginal candidiasis (RVVC)].

**The proposed indications and packaging presentations is currently under discussion by the NDA review team*

Proposed Indication(s) including Intended Patient Population	(b) (4)
Duration of Treatment	
Maximum Daily Dose	600 mg
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

The CMC information for the oteseconazole drug substance has been provided in Module 3 of the NDA.

Oteseconazole is an off-white crystalline powder, which is practically insoluble in water within a pH range of 1 to (b) (4) It is soluble in acetone and acetonitrile, and partially soluble in methanol, ethanol and isopropanol. The chemical structure of oteseconazole was unequivocally confirmed using 1D and 2D NMR, mass spectrometry, UV and IR techniques. Single crystal X-Ray structure and XRPD data confirmed the proposed stereochemistry and the polymorphic form of the API. The oteseconazole drug substance is manufactured as a single enantiomer with an absolute "R" configuration.

Oteseconazole drug substance is manufactured (b) (4)

The drug substance specification includes essential quality attributes such as appearance, identification, assay, related substances (impurities), chiral purity, elemental impurities, residue on ignition, water content, residual solvents, particle size distribution, and crystalline form. All tests except the particle size distribution and the X-ray diffraction are performed on the drug substance (b) (4) All tests are performed (b) (4) (b) (4) Satisfactory API batch release data (b) (4) (b) (4) have been provided in the NDA. All batches were found to be of consistent and comparable quality with no change in the polymorphic form. All the process impurities are controlled within the ICH Q3A limits. Control for potentially mutagenic impurities have been adequately justified as per ICH M7. Nonclinical safety of oteseconazole was evaluated in pharmacology and toxicology studies to support chronic administration of oteseconazole (this information was consulted with the Pharmacology/Toxicology Reviewer). The registration batch stability data include 6 months accelerated and 12 months long-term stability results. A retest date of (b) (4) months (when stored at (b) (4)) requested by the Applicant and overall CMC information submitted for the drug substance in the NDA was found acceptable by the Drug Substance Reviewer.

For further details refer to the Drug Substance Review, below.

Drug Product: Adequate

The drug product has been developed as an immediate release capsule proposed to be used for (b) (4) recurrent vulvovaginal candidiasis. Oteseconazole capsules are lavender, hard gelatin, size 2 capsules printed with OTE 150 mg using black ink.

Oteseconazole is a BCS Class II c drug with poor water solubility.

(b) (4)

The drug product specification includes relevant quality attributes such as: appearance, identification, assay, related substances, dissolution, (b) (4) (b) (4) uniformity of dosage units, and microbial limits. Oteseconazole

drug substance used in the manufacture of the drug product is the (b) (4)

NDA includes XRPD data along with the dissolution data under the accelerated storage condition to support the physical stability of the drug substance after manufacturing and upon long term storage.

The proposed commercial drug product packaging configurations include (b) (4) 18-count (b) (4) blister cards made of a clear film and aluminum lidding contained within a child-resistant carton. Overall information provided for the container closure system was found acceptable by the Drug Product Reviewer; however, the proposed packaging presentations are closely related to the proposed indications and duration of administration, *which are currently under discussion with the clinical team*.

The stability information submitted for the drug product in the NDA includes 18 months long term (25°C/60% RH) and 6 months accelerated (40°C/75% RH) stability data for the three primary stability batches ((b) (4) (b) (4) kg scale). All stability testing results conform to the acceptance criteria set in the proposed drug product specification. Oteseconazole is chemically very stable; individual unspecified related substance impurities are controlled at 0.2%, in line with ICH Q3B requirements for the maximum daily dose (MDD) of 600 mg. Therefore, the proposed 24 months expiry dating for this product is granted and controlled room temperature storage recommendation has been found acceptable by the Drug Product Reviewer. To further mitigate the risk of any potential changes in appearance of the capsules, an outer carton is used in conjunction with a "protect from light" statement on the carton.

Environmental Assessment (*reviewed by James Laurenson, EA Team*):

The applicant submitted a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR 25.31(b), which is for substances that increase in use but result in an expected introduction concentration (EIC) of < 1 ppb. The estimated use amount has been consistent with the claim. The required statement of no extraordinary circumstances was provided, in accordance with 21 CFR 25.15. The EA Team reviewed the exclusion claim and noted that oteseconazole appears to have the potential to interact with the endocrine system. Therefore, the EA Team requested data and analysis to support the categorical exclusion. The applicant submitted relevant data, as well as a schedule for finalization of a series of ecotoxicity studies that are being conducted. The EA Team reviewed the submitted data and concluded that approval of this application likely would have no significant environmental impact, and therefore the claim for an exclusion from an EA would likely be acceptable. However, due to some uncertainties, such as potential endocrine activity and cumulative risk from other substances

with a similar mechanism of action, the results of the studies are being requested via a post marketing commitment (PMC).

For further details refer to the Drug Product Review, below.

Labeling: Adequate

The proposed prescribing information (PI), container labels, and the carton labeling were found to generally include the necessary information. Several revisions and additions have been recommended in the applicable to the product quality sections of the PI (Sections 3, 11 and 16); also, for the container/blister label and carton labeling (for details refer to the Labeling Review, below). Labeling recommendations have been communicated to OND PM. The labeling review by the NDA review team is currently pending.

It should also be noted that the indications and dosage regimen proposed in the original NDA are currently under discussions by the NDA review team. These discussions may result in potential changes to the proposed commercial product presentations and product labeling. Any significant changes will be addressed in an Addendum to this IQA, if necessary.

Manufacturing: Adequate

Oteseconazole capsules are manufactured (b) (4) During the NDA review, several minor information requests (IRs) were sent to the Applicant (b) (4) These IRs were addressed adequately. In addition, the proposed microbiological controls were reviewed and deemed acceptable. The overall information provided in the initial NDA submission and the subsequent amendments regarding the proposed manufacturing process and controls have been found adequate by the Process Reviewer.

The drug product for commercial use will be manufactured by Patheon, Inc. located in Canada, which is a known manufacturer of the proposed dosage form and packaged at the (b) (4) The drug substance, oteseconazole, will be manufactured for commercial use (b) (4) In addition, there are several facilities listed in the NDA, which are involved in the drug substance and drug product testing.

All manufacturing facilities have been found acceptable by OPMA based on the review of their previous inspectional history. The overall "Approve" recommendation for manufacturing facilities was entered into Panorama on October 5, 2021 (for details refer to the Manufacturing Integrated Assessment, below).

Biopharmaceutics: Adequate

The Biopharmaceutics review focused on the assessment of the proposed dissolution test (analytical procedure and acceptance criterion), to be used for release and stability testing of oteseconazole capsules and the need for bridging between the clinical and To-Be-Marketed (TBM) drug products.

Dissolution:
The proposed 2-step Tier 1 and Tier 2 (enzymatic) dissolution methods were found acceptable. However, the acceptance criterion of Q= (b)(4)% in (b)(4) minutes originally proposed by the Applicant was found too permissive and the Biopharmaceutics Team recommended to tighten the acceptance criterion to Q= (b)(4)% in 45 minutes. The Applicant accepted the FDA's recommendations and revised the dissolution acceptance criterion to Q= (b)(4)% in 45 minutes for both Tier 1 and 2 dissolution tests.

Bridging of formulations:
Bridging of formulations was also part of the biopharmaceutics assessment. The capsule product used in the pivotal clinical studies differs from the registration batches and the to-be-marketed (TBM) product in terms of capsule shell color and printing. In addition, although the Phase 3 clinical batch and registration batches were manufactured at the same manufacturing site with a similar manufacturing process, the batch sizes for registration batches are (b)(4) larger than that used for the Phase 3 clinical batch. The comparative dissolution data submitted in the NDA were found adequate to support the bridging between the clinical product and the TBM drug product with respect to the changes in capsule color, printing, and drug product batch size.

For further details refer to the Biopharmaceutics Review, below.

Microbiology: Adequate

The drug product (oteseconazole capsules) is an oral dosage form; therefore, a separate microbiology review was not needed. The microbiological controls proposed for the drug product were found adequate by the Process Reviewer (refer to the Manufacturing Integrated Assessment, below).

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
		H, M, or L		Acceptable or Not Acceptable	
Assay, Stability	Formulation Raw materials Process parameters Scale/equipment Site	Low	(b) (4)	Acceptable	
Content uniformity	Formulation Raw materials Process parameters Scale/equipment Site	Low		Acceptable	
Physical stability	Formulation Raw materials Process parameters Scale/equipment Site	Medium		Acceptable	
Microbial limits	Formulation Raw materials Process parameters Scale/equipment Site	Low		Acceptable	
Dissolution	Formulation Raw materials Process parameters Scale/equipment Site	Medium		Acceptable	

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CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide

NDA 215888

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION (as in SD14 on 08/05/21)

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	**Recommended revision conveyed to OND:** From (b) (4) to "capsules"
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	**Recommended revision conveyed to OND:** From (b) (4) to "Capsules"
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	
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the	N/A	

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

active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).		

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

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 concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Adequate	
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	Adequate	
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	N/A	

section of the PI (e.g., Section 11).		
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]"* with x numerical citation to "OSHA Hazardous Drugs".	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

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	**Recommended revisions conveyed to OND:** From [redacted] (b) (4) to "Oteseconazole capsules"
Strength(s) in metric system	Adequate	
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	**Recommended revisions conveyed to OND:** From [redacted] (b) (4) to "lavender hard gelatin capsules"
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)

APPEARS THIS WAY ON ORIGINAL

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	
Dosage form(s) and route(s) of administration	Adequate	**Recommended addition/revision conveyed to OND:** From (b) (4) (b) (4) to "Each oteseconazole capsule, for oral use, contains…"
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	Inactive ingredients were not listed in alphabetical order. Capsule shell and print constituents were not provided. **Recommended revision conveyed to OND**: From (b) (4) (b) (4) To: "croscarmellose sodium, hydroxypropyl cellulose, lactose, magnesium stearate microcrystalline cellulose, and sodium lauryl sulfate." **Recommended addition conveyed to OND:** Capsule shell and print constituents: FD&C Blue #1, FD&C Red #3, gelatin, Opacode SW-9008/SW-9009 and titanium dioxide.

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	Confirmed P/T input
Chemical name, structural formula, molecular weight	Adequate	Chemical name and structural formula are consistent with information provided in section 3.2.S.1. **Recommended addition conveyed to OND:** The empirical formula is C23H16F7N5O2. The molecular weight is 527.39 g/mol
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Adequate	DS solubility properties is consistent with information provided in section 3.2.S.1.

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	N/A	

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).		

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

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	**Recommended revision conveyed to OND:** From [redacted] (b) (4) to "Oteseconazole capsules".
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	**Recommended revisions conveyed to OND:** From [redacted] (b) (4) to "…lavender hard gelatin capsules…" Recommended adding a placeholder for NDC numbers.
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	

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)
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.[x]" with x numerical citation to "OSHA Hazardous Drugs."	Adequate	Protect from light statement is provided in the PI, and on the wallet outer carton as well. This is adequate to mitigate the potential risk of color fading of the lavender capsule shell observed during photo stability study.
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	Proposed storage condition is supported by primary batch stability data.
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	Oteseconazole capsules are available in (b) (4) (b) (4) 18-count blister packaged within a child resistant wallet.

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 parenterals, 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

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

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	**Recommended addition of storage information conveyed to OND:** "excursions permitted to 59◦F to 86◦F (15◦C to 30◦C)" to be consistent with section 16 How Supplied/Storage and Handling.
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	**Recommended revision conveyed to OND:** listing of inactive ingredients should follow alphabetical order
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."

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels (taken from SD1 on 05/27/2021)

Blister label – (b) (4)

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

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 (21 CFR 201.10(g)(2))	Adequate	The font of the established name appears to be at least half as large as the letters comprising the proprietary name. The propriety name and established name appear to have same prominence. **Recommended revision conveyed to OND:** From (b) (4) to "(oteseconazole capsules), 150 mg".
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	**Recommend addition conveyed to OND:** "for oral use" to the wallet and carton labels.
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	
Net contents ((21 CFR 201.51(a) e.g., tablet count, volume of liquid)	Adequate	
"Rx only" displayed on the principal display	Adequate	Present on blister, wallet, and carton labels
NDC	Adequate	Present on carton label only
Lot number and expiration date	Adequate	Present on blister, wallet, and carton labels
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	Not present on blister label but present on wallet and carton labels
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]

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	

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	Present on both wallet and carton labels
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}*

The blister, wallet and carton labels for are not adequate. The established name should be changed to "(oteseconazole capsules), 150 mg" and route of administration should be included. CMC deficiency conveyed to OND:

1. The established name, [redacted] (b) (4) in the blister, wallet and carton labels should be revised to,

"(oteseconazole capsules) 150 mg, for oral use"

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation: Adequate

List of Deficiencies: None

Primary Labeling Assessor Name and Date: 10/19/2021

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

Sheena Hailin Wang

Digitally signed by Sheena Hailin Wang
Date: 10/19/2021 10:32:00PM
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David Claffey

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Date: 10/19/2021 11:21:16PM
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BIOPHARMACEUTICS

NDA: 215888 [505(b)(1)]
Drug Product Name/Strength: VIVJOA® (oteseconazole) Capsule, 150 mg
Route of Administration: Oral
Proposed Indication: (b) (4) recurrent vulvovaginal candidiasis (VVC)
Applicant Name: Mycovia Pharmaceuticals, Inc
Submission Date: 05/27/2021
Primary Reviewer: Kevin Wei, Ph.D.
Secondary Reviewer: Elsbeth G Chikhale, Ph.D.
Recommendation: Approval

EXECUTIVE SUMMARY

Mycovia Pharmaceuticals, Inc. submitted NDA 215888 for Oteseconazole Capsule, 150 mg, as an oral antifungal (b) (4) (b) (4) (b) (4). This Biopharmaceutics review focused on the evaluation of the adequacy of the overall information/data supporting (i) the in vitro dissolution methods and acceptance criterion as quality control (QC) test, and (ii) need for bridging between the clinical and To-Be-Marketed (TBM) drug products.

In vitro dissolution methods and acceptance criterion:
Oteseconazole is a low soluble drug substance as per BCS criteria. The Applicant proposed the following Tier 1 and Tier 2 dissolution methods and acceptance criterion as QC test for Oteseconazole Capsule, 150 mg.

Proposed Tier 1 dissolution method for Oteseconazole Capsule, 150 mg

Dissolution conditions for first 15 minutes	
Dissolution Medium 1	0.01N HCl
Apparatus	USP Apparatus 2 (Paddles) with sinker
Paddle Speed	75 rpm
Dissolution Medium 1 Volume	750 ml
Temperature	(b) (4)
Time Capsules Kept in Medium	15 minutes using Medium 1, then after 15 minutes add Medium 2 while stirring
Dissolution conditions after first 15 minutes	
Dissolution Medium 2	3.0% SLS in 0.01N HCl
Final Dissolution Medium	0.5% SLS in 0.01N HCl
Apparatus	USP Apparatus 2 (Paddles) with sinker
Paddle Speed	75 rpm
Dissolution Medium 2 Volume	150 ml
Total Dissolution Medium Volume	900 ml
Temperature	(b) (4)
Sampling Timepoint	(b) (4) minutes after the initiation of the test.

Proposed Tier 2 dissolution method for cross-linked Oteseconazole Capsule, 150 mg

Dissolution conditions for first 15 minutes	
Dissolution Medium 1	0.01N HCl with Pepsin (750,000 units/L)
Apparatus	USP Apparatus 2 (Paddles) with sinker
Paddle Speed	75 rpm
Dissolution Medium 1 Volume	750 ml
Temperature	(b) (4)
Time Capsules Kept in Medium	15 minutes using Medium 1, then after 15 minutes, add Medium 2 while stirring
Dissolution conditions after first 15 minutes	
Dissolution Medium 2	3.0% SLS in 0.01N HCl
Final Dissolution Medium	0.5% SLS in 0.01N HCl
Apparatus	USP Apparatus 2 (Paddles) with sinker
Paddle Speed	75 rpm
Dissolution Medium 2 Volume	150 ml
Total Dissolution Medium Volume	900 ml
Temperature	(b) (4)
Sampling Timepoint	(b) (4) minutes since the initiation of the test.

The proposed Tier 1 and Tier 2 (enzymatic) dissolution methods are different than the previously recommended Tier 1 and Tier 2 methods described in the review of the dissolution method development reports under IND 111675 in terms of the time for SLS addition (2-step vs. (b) (4)) for the Tier 1 test and the length of enzyme pre-treatment period (b) (4) minutes vs. 15 minutes) for the Tier 2 test. The submitted data showed no significant difference in dissolution between the use of (b) (4) and proposed 2-step Tier 1 methods, except that slightly lower variability was observed for the registration batches with the use of the proposed 2-step Tier 1 method. In addition, the submitted data indicated that the proposed 2-step Tier 1 method is still discriminating towards the drug substance particle size. For the Tier 2 (enzymatic) dissolution method, the submitted data indicated no significant difference in dissolution between the use of the previous (b) (4) minute and proposed 15-minute enzyme pretreatment period during the Tier 2 test. Therefore, considering the totality of the information, the proposed 2-step Tier 1 and Tier 2 (enzymatic) dissolution methods are deemed acceptable. However, the proposed acceptance criterion of Q (b) (4) % in (b) (4) minutes was found too permissive and the Applicant was recommended to tighten the acceptance criterion to Q (b) (4) % in 45 minutes. As per the Biopharmaceutics IR response dated 10/07/2021 (0033/33), the Applicant accepted the FDA's recommendations and the revised dissolution acceptance criterion of Q (b) (4) % in 45 minutes for both Tier 1 and 2 dissolution test is deemed adequate.

Bridging:

The capsule product used in the pivotal clinical studies only differs from the registration batches and the to-be-marketed (TBM) product in terms of capsule shell color and printing. The phase 3 clinical batch and registration batches were manufactured at the same manufacturing site with a similar manufacturing process, while the batch sizes for registration batches are (b) (4) larger than that for the phase 3 clinical batch. The

submitted comparative dissolution data support the bridging between the clinical product and the TBM drug product with respect to the changes in capsule color, printing, and drug product batch size.

Submitted documents assessed under NDA review

Document number	Date Received
SDN-1 Original submission	05/27/2021
SDN-32 (Response to Biopharmaceutics and Product Information Request)	10/01/2021
SDN-33 (Response to Biopharmaceutics Information Request)	10/07/2021

RECOMMENDATION

From a Biopharmaceutics perspective, NDA 215888 for VIVJOA® (Oteseconazole) Capsule, 150 mg, is recommended for **Approval**. The following dissolution methods and acceptance criterion are deemed acceptable as quality control (QC) test for the proposed drug product.

Acceptable dissolution methods and acceptance criterion:

	Tier 1 (non-enzymatic) method	Tier 2 (enzymatic) method
USP Apparatus	USP Apparatus II (Paddles) with wire helix sinker	
Rotation Speed	75 rpm	
Temperature	37 ± 0.5°C	
Volume	750 mL (Stage 1); 900 mL (Stage 2)	
Dissolution medium	Stage 1: 0.01N HCl; Stage 2: After 15 minutes, while stirring, add about 150 mL of 3.0% SLS in 0.01N HCl to a final concentration of 0.5 % SLS	Stage 1: Pepsin (750,000 units/L) in 0.01N HCl; Stage 2: After 15 minutes, while stirring, add about 150 mL of 3.0% SLS in 0.01N HCl to a final concentration of 0.5 % SLS
Acceptance criterion	Q (b)(4)% in 45 minutes (for both Tier 1 and Tier 2 methods)	

BIOPHARMACEUTICS REVIEW

1. Drug Substance (DS) solubility and permeability

The Applicant submitted the following solubility information for oteseconazole DS (b) (4)

Table 1. Oteseconazole solubility from pH 1.0 to pH 8.0 at room temperature
(*Module 3.2.P. Dissolution Development Report*, Table 7, Page 22)

pH	Solubility µg/mL
1.0	< 0.0657 µg/mL
2.0	< 0.0657 µg/mL
3.0	< 0.0657 µg/mL
4.5	< 0.0657 µg/mL
6.0	< 0.0657 µg/mL
7.0	< 0.0657 µg/mL
8.0	< 0.0657 µg/mL
water	< 0.0657 µg/mL

The submitted data showed that oteseconazole is a poorly soluble DS with an aqueous solubility < 0.0657 µg/mL across the tested pH range.

The Applicant claimed that oteseconazole is a highly permeable DS based on the pharmacokinetic (PK) mass balance study showing >90% absorption of radiolabeled oteseconazole (VMT-VT-1161-CL-016) and measured cLogP of 4.41 (octanol:water).

Reviewer's Assessment:
A minimum solubility of 2.4 mg/mL (based on the highest single therapeutic dose of 600 mg (4x150 mg capsules)) across the physiological pH range is required to be considered a highly soluble DS as per BCS criteria. The submitted solubility data measured at room temperature indicated that oteseconazole is a low soluble DS. It's noted that (b) (4) (b) (4) *is used in manufacturing for Phase 2b studies (onward) and proposed for the TBM product. The median Tmax for Oteseconazole Capsules is 4-10 hrs. (5.0 hrs., 4.9 hrs. and 6.7 hrs under fasted, low-fat and high-fat fed conditions., respectively) (BA study VMT-VT-1161-CL-013) and the absolute BA is estimated to be about 75-94%.*

2. Evaluation of dissolution conditions

The proposed drug product, Oteseconazole (originally named VT-1161) Capsule, 150 mg, has been developed under IND 111675. The preliminary dissolution method development information and data were submitted in SDN-77 and SDN-88 under IND 111675. The previous Biopharmaceutics reviews for the dissolution method development reports submitted under SDN-77 and SDN-88 can be found in DARRTs.

Submitted dissolution method development reports assessed under IND 111675:

Document number	Date Received	Biopharmaceutics Review	Date Responded
SDN-77 Dissolution Method Development Report	05/07/20	REV-QUALBIOPHARM-21 (Primary Review)[1]	08/07/20
SDN-88 Dissolution Method Development Report	11/25/20	REV-QUALBIOPHARM-21 (Primary Review)[2]	03/09/21

(b) (4)

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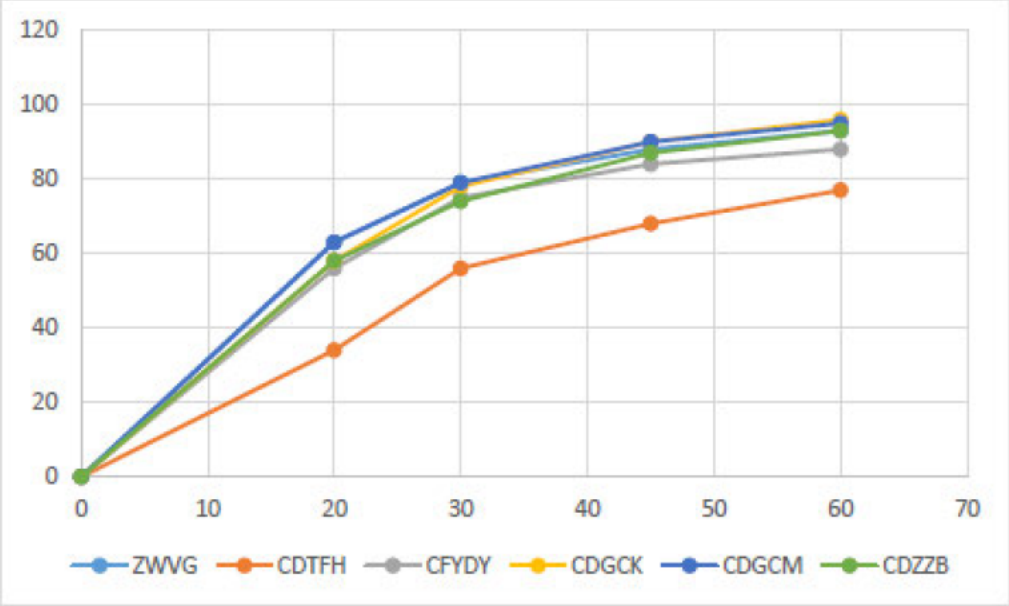
3. Evaluation of discriminating ability

In the NDA submission, the Applicant evaluated the discriminating ability of the proposed 2-step Tier 1 method towards the DS particle size distribution using product batches manufactured with both [redacted] (b) (4) DS (CFYDY, ZWVG, CDZZB, CDGCK and CDGCM) and [redacted] (b) (4) DS (CDTFH).

Table 2. Selected batches used in evaluating discriminating ability on DS particle size (*Module 3.2.P. Dissolution Communications*, Table 5, Page 12)

Capsule Batch Number	API Batch Number	Capsule Batch Purpose	API Particle Size (µm)		
			D10	D50	D90
CDTFH	884W1S0001 [redacted] (b) (4)	Development	[redacted] (b) (4)		
CFYDY	884W1S0008M	Development			
ZWVG	2060492-6754	Phase 3			
CDZZB	884W1S0004M	Registration			
CDGCK	884W1S0003M	Registration			
CDGCM	884W1S0002M	Registration			

Figure 3. Dissolution profile of the selected batches used to evaluate the discriminating ability towards DS particle size
(*Module 3.2.P. Dissolution Communications*, Figure 2, Page 13)



During the IND review (SDN 77), the Applicant has evaluated the discriminating ability of the originally proposed [redacted] (b) (4) method [redacted] (b) (4) [redacted] (b) (4) towards the selected Critical Process Parameters (CPPs) (e.g., [redacted] (b) (4)) using small scale DOE

batches manufactured with a multivariate study design. The study result indicated that the proposed dissolution conditions are discriminating towards CPPs. The Applicant stated that the discriminating ability (b) (4) (b) (4) (b) (4) used in the proposed drug product is unlikely to impact the dissolution.

Reviewer's Assessment:

The submitted data indicated that the proposed 2-step Tier 1 method is discriminating towards the DS particle size and can reject the drug product manufactured with (b) (4) (b) (4) DS (D_{90}: (b) (4) µM) when an acceptance criterion of Q=(b) (4) in 45 minutes is implemented. It's noted that the Applicant has proposed PSD control of D_{90} NMT (b) (4) µM in DS specifications.

4. Evaluation of dissolution acceptance criterion

In the NDA submission, the Applicant proposed an acceptance criterion of Q (b) (4)% in (b) (4) minutes for both Tier 1 and Tier 2 methods.

Reviewer's Assessment:

The Applicant has submitted complete dissolution profile data using the proposed 2-step Tier 1 dissolution method for the Phase 3 batch ZZGZ at 26M (test in 07/2020) and 32M (test in 01/2021), and registration batches CDGCK01, CDGCM01 and CDZZB01 at 6, 9,12M (see section 5 below). As requested in the Biopharmaceutics Information Request (IR) dated 09/272021, complete dissolution data for registration batches at 18M were also submitted in the Biopharmaceutics IR response dated 10/01/2021.

Dissolution data for clinical batch ZZGZ using 2-step Tier 1 method at 26M and 32M (26M data from 3.2.P. Dissolution Development Report, Fig.28 (Tab. 65), Pg.72 (125); 32M data from 3.2.P. Dissolution Communications, Tab. 4, Pg. 8-9)

Time (Minutes)	% Dissolved					
	26M (n=12)			32M (n=6)		
	Average	Range	%RSD	Average	Range	%RSD
20	63	(b) (4)	15.0	74	(b) (4)	8.0
30	79		11.7	87		5.9
45	88		7.8	96		4.2
60	93		5.4	95		3.1

The submitted dissolution data for the clinical and registration batches (see section 5 below) indicated that the proposed dissolution criterion of Q=(b) (4)% in (b) (4) minutes is too permissive. Thus, the Applicant was recommended to tighten the dissolution criterion to Q=(b) (4)% in 45 minutes (Biopharmaceutics IR dated 10/04/2021). As per the IR response dated 10/06/2021, the Applicant accepted the FDA's recommendations and the revised dissolution acceptance criterion of Q=(b) (4)% in 45 minutes for Tier 1 and 2 dissolution test is deemed adequate.

5. Evaluation of dissolution data from stability studies

The registration batches (CDGCK, CDGCM and CDZZB) were manufactured in 12/2019, packaged [redacted] (b) (4) in 02/2020 (stability initiated). The Applicant submitted dissolution profile data for the registration batches using both proposed 2-step Tier 1 method and originally proposed [redacted] (b) (4) method [redacted] (b) (4) [redacted] (b) (4) at 6 months to bridge the dissolution method change during the stability studies.

In the original NDA submission, the Applicant submitted the complete dissolution data for the registration batches stored at long term condition (25°C/60% RH) at 6M, 9M and 12M using the proposed 2-step Tier 1 method.

Table 3. Dissolution data for the registration batches (CDGCK, CDGCM and CDZZB) stored at long term condition (25°C/60% RH) 6M, 9M and 12M
(*Module 3.2.P.8.1 Stability Summary and Conclusion*, Table 7, Page 8)

Batch Number	Time (minutes)	% Dissolved											
		6 months				9 months				12 months			
		Avg	Min	Max	%RSD	Avg	Min	Max	%RSD	Avg	Min	Max	%RSD
CDGCK01	20	73	[redacted] (b) (4)		13.6	71	[redacted] (b) (4)		10.6	70	[redacted] (b) (4)		10.9
	25	*			*	81			8.5	83			9.5
	30	90			9.1	87			6.8	88			8.3
	45	97			6.5	94			5.1	95			5.0
	60	99			5.2	96			4.6	99			3.3
CDGCM01	20	73			13.4	65			15.0	67			13.4
	25	*			*	76			12.3	80			10.3
	30	87			11.4	83			10.3	85			8.7
	45	94			8.2	92			5.9	93			6.3
	60	97			6.3	96			3.7	97			5.2
CDZZB01	20	72			8.2	68			10.0	70			9.1
	25	*			*	78			9.2	82			8.6
	30	87			5.7	84			8.6	87			7.6
	45	95			4.7	92			6.8	95			5.9
	60	98			3.7	95			5.1	98			4.8

Reviewer's Assessment:

As requested by the Biopharmaceutics IR dated 09/272021, complete dissolution data for registration batches at 18M were submitted as shown below. The submitted dissolution data indicated that no significant trend in dissolution for the registration batches was observed during storage at long term conditions, and all registration batches can meet a dissolution acceptance criterion of Q= [redacted] (b) (4) % in 45 minutes (S2 may be needed) throughout the stability program.

Dissolution data for registration batches CDGCK01, CDGCM01, CDZZB01 at 18M (Module 1.11.1 Response to FDA Request for Information (0032), Table 7-9, Page 16-18)

Time (min.)	% Dissolved (n=6)											
	CDZZB01				CDGCK01				CDGCM01			
	Avg	Min	Max	%RSD	Avg	Min	Max	%RSD	Avg	Min	Max	%RSD
20	66	(b) (4)		10.0	69	(b) (4)		9.1	72	(b) (4)		15.3
25	76			8.7	82			5.4	77			18.1
30	81			7.6	88			4.3	87			10.9
45	90			5.8	94			2.3	95			7.0
60	94			4.2	97			1.7	98			5.5

6. Bridging

6.1 Formulation Development

(b) (4)

(b) (4)

[redacted]

6.2 Bridging between the Tablet product and the Capsule product

The Applicant has conducted a relative bioavailability (BA) study to bridge the Tablet product used in the phase 2b study to the Capsule product used in the pivotal clinical studies (Relative BA study CL-013).

Table 5. Pharmacokinetic data for relative BA study VMT-VT-1161-CL-013 (*Module 3.2.P. Drug Product*, Table 11, Page 16)

Treatment	Tmax (h)	Cmax (ng/mL)	AUC0-72 (ng·h/mL)	LSM Ratio Cmax	LSM Ratio AUC0-72
Capsule* (fasted)	5.0	563	17,580	Ref	Ref
Capsule* (low fat)	4.9	637	17,590	1.17	1.02
Capsule* (high fat)	6.7	821	22,970	1.45	1.29
Tablet† (high fat)	5.3	805	21,310	n.d.	n.d.

*batch number 175056; †batch 1512138

Reviewer's Assessment:
The PK data submitted in the relative BA studies has been reviewed by the Clinical Pharmacology reviewer (pending).

6.3 Bridging between the clinical (pivotal) product and the TBM drug product

The (Phase 3) pivotal studies used as the basis of approval (labeling) for this NDA are CL-011, CL-012 and CL-017 in which the clinical batch ZWVG (packaged batch ZZGZ) was used in all pivotal clinical studies. The batch manufacturing details, and composition information for pivotal clinical and registration batches are provided as follows:

Table 6. Batch details for pivotal clinical and registration batches
(*Module 3.2.P. Dissolution Development Report*, Table 4, Page 19)

Bulk Batch Number	17B056A	ZWVG[1]	CDGCK[2] & CDGCM[2]	CDZZB[2]
Date of Manufacture	Feb 2017	Apr 2018	Dec 2019	
Batch Use	Clinical (relative BA)	Clinical/ Stability (Phase 3)	Registration Stability	
Formulation	Phase 3 (Table 5)	Phase 3 (Table 5)	Proposed Commercial (Table 5)	
Drug Substance Site of Manufacture/ (b) (4)	(b) (4)			
Site of Manufacture				

Table 7. Composition of pivotal clinical and registration/TBM products
(*Module 3.2.P. Dissolution Development Report*, Table 4, Page 19)

Component	Quantity per Capsule (mg)	
	Phase 3 Capsule Formulation	Proposed Commercial Formulation
(b) (4)		

To bridge the clinical product to the registration/TBM products, the Applicant submitted dissolution profile comparison between the phase 3 clinical batch ZZGZ and registration batches CDGCK, CDGCM and CDZZB using the proposed 2-step Tier 1 method.

Figure 4. Dissolution profile comparison between the clinical batch ZZGZ and registration batches CDGCK, CDGCM and CDZZB
(*Module 3.2.P. Dissolution Development Report*, Figure 28, Page 72)

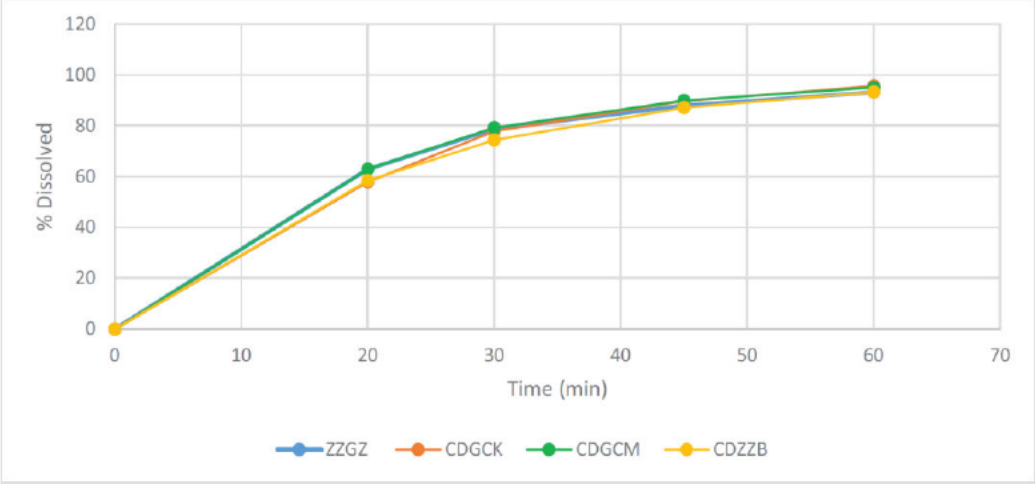


Table 8. Dissolution profile comparisons for registration batches (CDGCK, CDGCM, CDZZB) to the Phase 3 batch (ZZGZ) using the 2-Step dissolution method
(*Module 3.2.P. Dissolution Development Report*, Table 38, Page 73)

Timepoint and f1/f2 comparison	Mean % Dissolved (%RSD)			
	ZZGZ (reference)	CDGCK (test)	CDGCM (test)	CDZZB (test)
20 min	63 (15.0)	58 (17.3)	63 (14.1)	58 (20.4)
30 min	79 (11.7)	78 (10.7)	79 (8.7)	74 (14.6)
45 min	88 (7.8)	90 (7.4)	90 (4.7)	87 (8.4)
f1	-	3.5	0.9	4.8
f1 between 0-15?	-	Yes	Yes	Yes
Batches different?	-	No	No	No
f2	-	74	91	69
f2 between 50-100?	-	Yes	Yes	Yes
Batches similar?	-	Yes	Yes	Yes

Reviewer's Assessment:

The submitted information showed that the capsule drug product used in the pivotal clinical studies only differs from the TBM product in the appearance of capsule shell (color and printing). The pivotal clinical batch and registration batches (TMB product) were manufactured at the same manufacturing site (Patheon, also proposed for the TBM product) using a similar process (adjustment may be made due to the batch size) but the batch sizes for the registration batches and TBM product are (b) (4) *larger than the batch size for the pivotal clinical batch. The submitted comparative dissolution data using the proposed 2-step Tier 1 method indicated that the dissolution profiles of the phase 3 clinical batch and registration batches are similar (f2>50), hence support the bridging between the clinical product and the registration batches/TBM drug products with respect to the changes in capsule color, printing, and drug product batch size.*

Appendix I. Biopharmaceutics Information Requests

Biopharmaceutics Information Request (IR) conveyed to the Applicant on 09/272021

(b) (4)

Biopharmaceutics Information Request (IR) conveyed to the Applicant on 10/04/2021

(b) (4)

Kevin Wei

Digitally signed by Kevin Wei
Date: 10/18/2021 11:54:22PM
GUID: 59e9fc4600508706ab6b474203201f10

Elsbeth Chikhale

Digitally signed by Elsbeth Chikhale
Date: 10/19/2021 11:35:02AM
GUID: 50743ccc000031928b54eba1769a5df9

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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