CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214998Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 214998: Camzyos (mavacamten) Capsules
Integrated Quality Review #1

Recommendation: Approval

Drug Name/Dosage Form	Camzyos (mavacamten) capsules
Strength	2.5 mg, 5 mg, 10 mg, and 15 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	MyoKardia, Inc.
Submission(s) Reviewed	NDA 214998, DMFs as listed below, and all the submitted CMC amendments.

Quality Review Team

Discipline	Reviewer/Secondary	Branch/division
Drug Substance	Daniel Jansen/ Suong Tran	Branch III/Division of New Drug Active Pharmaceutical Ingredients
Drug Product	Rao Kambhampati/ Mohan Sapru	Branch 5/New Drug Products III of Office of New Drug Products
Process/ Facility	Lixia Cai/ Daniel Obrzut	Branch 7/DPMA III of Office of Pharmaceutical Manufacturing
Biopharmaceutics	Zhuojun Zhao/ Poonam Delvadia	Office of Pharmaceutical Manufacturing Assessment
Regulatory Business Process Manager	GraftonAdams/ Hamet Toure	Branch I/Regulatory Business Process Management I
Application Technical Lead	Theodore Carver	Branch 5/New Drug Products III of Office of New Drug Products
Environmental Analysis (EA)	Rao Kambhampati/ Mohan Sapru	Branch V/New Drug Products III of Office of New Drug Products

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III	(b) (4)		adequate	Information in NDA adequate for review	LOA dated 2/5/2020
	III			adequate	Information in NDA adequate for review	LOA dated 2/4/2020
	III			adequate	Information in NDA adequate for review	LOA dated 1/25/2020
	III			adequate	Information in NDA adequate for review	LOA dated 2/5/2020
	III			adequate	Information in NDA adequate for review	LOA dated 6/17/2021

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	121904	mavacamten

2. CONSULTS: None

Executive Summary

1. **Recommendations and Conclusions on Approvability**

The Office of Pharmaceutical Quality Review team has assessed NDA 214998 with respect to Chemistry, Manufacturing, and Controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports to have. As such, OPQ recommends approval of this NDA from a quality perspective.

2. **Background Summary**

The Applicant, MyoKardia Pharmaceuticals, Inc, is seeking marketing approval for mavacamten capsules, 2.5 mg, 5 mg, 10 mg, and 15 mg , in accordance with Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act. Mavacamten is a small molecule NME that is indicated for the treatment of symptomatic obstructive hypertrophic cardiomyopathy in adults. To support approval of mavacamten for this indication, the application includes clinical data to support safety and efficacy, including results of a pivotal Phase 3 study and other supportive clinical studies. The proposed product is an oral immediate release capsule supplied in four dosage strengths.

3. **Summary of Quality Assessments**

Mavacamten capsules are an immediate-release oral formulation supplied in four strengths: 2.5 mg, 5 mg, 10 mg, and 15 mg in Size 2 hard gelatin capsules with distinguishing color and printing. The drug product contains excipients to maintain the quality of the (b) (4) product, including silicon dioxide, mannitol, hypromellose, croscarmellose sodium, and magnesium stearate. The product is packaged in HDPE bottles with a (b) (4) closure and induction seal liner. The OPQ integrated quality assessment of this NDA includes reviews of drug substance, drug product, manufacturing, biopharmaceutics, and facilities information.

3.1 Drug Substance (mavacamten**)**

The mavacamten drug substance information was reviewed by Dr. Daniel Jansen and found to be adequate. The drug substance is a white to off-white solid consisting of a synthetic small molecule with a molecular weight of 273.33 g/mol. Mavacamten contains a single (b) (4) stereocenter. Sufficient information was provided regarding the physicochemical characterization, molecular structure, and impurity profile of mavacamten. The drug substance exhibits polymorphism but only one stable form, (b) (4) was observed during stability studies. The manufacturing process has been sufficiently described, including conditions, materials, reagents, controls, etc., and appears reasonable. Starting materials are adequately justified, impurity profiles are well-defined, and impurity purging throughout the manufacturing process is well

understood. The information provided for the chemical synthesis, manufacturing, control strategy, drug substance specification, and batch analyses are adequate to demonstrate consistent manufacturing and control of the mavacamten drug substance. The drug substance is [redacted] (b) (4) Reference standards were well-characterized. The primary drug substance container is [redacted] (b) (4) The long-term storage condition for the drug substance evaluated in stability studies is [redacted] (b) (4) A re-test period of [redacted] (b) (4) months has been assigned based on accelerated and long-term stability data.

3.2 Drug product (Mavacamten Capsules)

A) Product Design and Specification: The drug product information was reviewed by Dr. Rao Kambhampati and determined to be adequate. The mavacamten drug product is an oral immediate-release formulation consisting of four strengths filled in Size 2 hard gelatin capsules that may be distinguished by cap color and imprint. The four strengths are manufactured using [redacted] (b) (4) The drug product is packaged in HDPE bottles with [redacted] (b) (4) closure and induction seal liner. All excipients in the capsule fill have appropriate functions with respect to maintaining the quality of the immediate release formulation and are indicated to have manufacturing and controls in compliance with their respective USP/NF monographs. The capsule shells are manufactured from compendial excipients and controlled with an adequate specification. The drug product specifications for all strengths include appropriate tests and acceptance criteria with respect to the identity, purity, assay, quality, and stability of the drug product. Based on the 18 months long-term and 6 months accelerated stability data for the commercial formulation tablets and other supportive stability data, the requested expiration dating period of 30 months was found to be acceptable for the drug product stored at 25°C.

B) Drug Product Manufacturing: Dr. Lixia Cai reviewed the drug product manufacturing and found the information to be adequate. Mavacamten capsules are manufactured using [redacted] (b) (4) . The drug substance has poor water solubility and is reported to be physically/chemically stable under the manufacturing process conditions. Commercial scale-up factors of [redacted] (b) (4) fold, depending on the unit operation, are proposed for commercial manufacturing. No overages are proposed. The manufacturing process description was found to be adequate after resolution of issues related to the batch formulas.

C) Biopharmaceutics Aspects: Dr. Zhuojun Zhao performed the biopharmaceutics review of the drug product and found the information in the NDA to be adequate. The proposed quality control dissolution method and acceptance criterion, physiologically based pharmacokinetic (PBPK) modeling and simulation, and the formulation bridging were found to be acceptable. The proposed dissolution method and acceptance criteria were found to be adequately discriminating and acceptable for quality control of the drug product, after revisions were made to the method originally proposed.

D) Container Closure System: The container closure information was reviewed by Dr. Rao Kambhampati and found to be adequate. The container closure system consists of 40 cc HDPE bottles with (b) (4) caps and an aluminum foil induction seal liner. Adequate specifications and drawings were provided for the 40-cc HDPE bottle and (b) (4) cap. Materials of construction were cross-referenced to the appropriate DMFs and LOAs were provided in the NDA. Testing parameters and specifications used for primary packaging components were provided and comply with USP. The noncompendial analytical procedures were adequately described in the NDA.

4. **Assessment of Manufacturing Facilities**

Facility compliance information for the drug substance and drug product were reviewed by Dr. Lixia Cai. The drug substance and drug product manufacturing and testing facilities were each approved based on previous history, indicating acceptable facility status with respect to the responsibilities of each facility. All facilities have been found acceptable after OPMA review (see table below), and the overall manufacturing recommendation for NDA 214998 is approval.

Table of Manufacturing Facilities for NDA 214998:

Facility name and address	FEI	Responsibilities and profile code(s)	Status
(b) (4)			Approve - Based on Previous History
			Approve - Based on Previous History
			Approve - Based on Previous History
			Approve - Based on Previous History
			Approve - Based on Previous History
			Approve - Based on Previous History

5. **Environmental Assessment**: The Applicant requests a categorical exclusion based on 21 CFR 25.31(b), because the estimated introduction concentration at the point of entry into the aquatic environment will be less than 1 ppb, and there are no extraordinary circumstances to the Applicant's knowledge. The information to support this categorical exclusion was reviewed by Dr. Rao Kambhampati and found to be adequate to grant this request.

6. **Expiration Dating and Storage Conditions**: The Applicant provided 18 months of long-term and 6 months of accelerated stability data for three primary batches of the commercial formulation capsules packaged in HDPE bottles, 24 months of supportive long-term data for the commercial formulation capsules and up to 30 months of supportive long-term data for capsules containing an earlier clinical formulation. The requested expiration dating period of 30 months is granted when mavacamten capsules bottles are stored at 25°C.

7. **Quality Labeling**: The container and carton label were reviewed as part of the drug product review. The dosage form description, strength, established name, NDC #, Lot #/Expiry, and storage conditions are adequately described in the carton and container label, which meets relevant regulatory requirements for labeling. Comments regarding the draft USPI were conveyed to the Applicant, and it will be finalized as part of the review. Refer to the labeling review for additional information.

8. **List of CMC Deficiencies:** None

OVERALL ASSESSMENT AND SIGNATURES:

At present, there are no outstanding deficiencies related to the drug substance, drug product, process, microbiology, and environmental analysis sections of this NDA. The OPQ overall recommendation for NDA 214998 is *approval.*

Theodore Carver, Ph.D. 10/20/21
Senior Pharmaceutical Quality Assessor
Application Team Lead

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CHAPTER IV: LABELING
NDA 214998

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: The revised Prescribing Information (PI), container labels, and medication guide are adequate from the quality (CMC) standpoint except that the inactive ingredients in the Description section of the PI and in the medication guide need to be arranged in alphabetical order.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Assessor's Comments (choose "Adequate", "Inadequate", or "N/A")	Items in Proposed Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Adequate	[TRADENAME] mavacamten capsules
Route(s) of administration	Adequate	oral
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	Capsules: 2.5 mg, 5 mg, 10 mg, and 15 mg
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 active moiety (e.g., Tablets:	N/A	

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

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	Assessor's Comments (choose "Adequate", "Inadequate", or "N/A")	Items in Proposed Labeling (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)	N/A	
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	N/A	

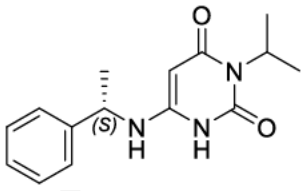
section of the PI (e.g., Section 11).		
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]"* 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	Capsules
Strength(s) in metric system	Adequate	2.5 mg, 5 mg, 10 mg, and 15 mg
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	2.5 mg (b) (4), light purple (b) (4) cap 5 mg (b) (4) (b) (4) yellow (b) (4) cap 10 mg (b) (4) pink (b) (4) cap 15 mg (b) (4) gray (b) (4)
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	Assessor's Comments (choose "Adequate", "Inadequate", or "N/A")	Items in Proposed Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	[TRADENAME] mevacamten
Dosage form(s) and route(s) of administration	Adequate	Capsules for oral use
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.	Inadequate Need to be arranged in alphabetical order.	Silicon dioxide, mannitol, hypromellose, croscarmellose sodium, and magnesium stearate (non-bovine). The capsule shell contains gelatin, titanium dioxide, black iron oxide, red iron oxide, yellow iron oxide, and black edible ink.
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	A selective allosteric cardiac myosin inhibitor.
Chemical name, structural formula, molecular weight	Adequate	3-(1-methylethyl)-6-[[(1S)-1-phenylethyl]amino]-2,4(1*H*,3*H*)-pyrimidinedione.  273.3 (b)(4) g/mol

If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	N/A	

Section 11 (DESCRIPTION) Continued

Item	Assessor's Comments (choose "Adequate", "Inadequate", or "N/A")	Items in Proposed Labeling (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	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

APPEARS THIS WAY ON ORIGINAL

Item	Assessor's Comments (choose "Adequate", "Inadequate", or "N/A")	Items in Proposed Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	Capsules
Strength(s) in metric system	Adequate	2.5 mg, 5 mg, 10 mg, and 15 mg
Available units (e.g., bottles of 100 tablets)	Adequate	Unit-of-use bottles of 30 capsules
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	2.5 mg capsule: Size 2 hard gelatin capsule, light purple opaque cap imprinted with "2.5 mg" in black, and white opaque body imprinted with "Mava" in black, both in radial direction. The capsule contains white to off-white powder. 5 mg capsule: Size 2 hard gelatin capsule, yellow opaque cap imprinted with "5 mg" in black, and white opaque body imprinted with "Mava" in black, both in radial direction. The capsule contains white to off-white powder. 10 mg Capsule: Size 2 hard gelatin capsule, pink opaque cap imprinted with "10 mg" in black, and white opaque body imprinted with "Mava" in black, both in radial direction. The capsule contains white to off-white powder. 15 mg Capsule: Size 2 hard gelatin capsule, gray opaque cap imprinted with "15 mg" in black, and white opaque body imprinted with "Mava" in black, both in radial direction. The capsule contains white to off-white powder.
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.[x]" with x numerical citation to "OSHA Hazardous Drugs."	N/A	

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

Item	Assessor's Comments (choose "Adequate", "Inadequate", or "N/A")	Items in Proposed Labeling (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	Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C to 30°C (between 59°F to 86°F) [see USP Controlled Room Temperature].
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: Not applicable

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Assessor's Comments (choose "Adequate", "Inadequate", or "N/A")	Items in Proposed Labeling (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	Distributed by: **Myokardia Inc., a wholly-owned subsidiary of Bristol-Myers Squibb** Brisbane, CA 94005

2.0 PATIENT LABELING:

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides): Medication Guide is assessed below

Item	Assessor's Comments about Container Labeling (choose "Adequate", "Inadequate", or "N/A")	Items in Proposed Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2]	Adequate	mavacamten
Special preparation instructions (if applicable)	N/A	
Storage and handling information (if applicable)	Adequate	Store [TRADENAME] at room temperature between 68°F to 77°F (20°C to 25°C).
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	mavacamten
Alphabetical listing of inactive ingredients (if applicable)	Inadequate Need to be arranged in alphabetical order.	Silicon dioxide, mannitol, hypromellose, croscarmellose sodium, and magnesium stearate (non-bovine). The capsule shell contains gelatin, titanium dioxide, black iron oxide, red iron oxide, yellow iron oxide, and black edible ink.
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	Distributed by: **Myokardia Inc., a wholly-owned subsidiary of Bristol-Myers Squibb** Brisbane, CA 94005

3.0 CONTAINER AND CARTON LABELING

3.1 Container (HDPE 40-cc Bottle) Labels

Drug product capsules are supplied in four different strengths (2.5 mg, 5 mg, 10 mg, and 15 mg). A representative example of the proposed HDPE bottle label for the 15 mg strength capsules is provided below:

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

Item	Assessor's Comments about Container Labeling (choose "Adequate", "Inadequate", or "N/A")	Items in Proposed Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[3], (font size and prominence)	Adequate	mavacamten
Strength(s) in metric system	Adequate	2.5 mg, 5 mg, 7.5 mg, and 15 mg
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	30 Capsules
"Rx only" displayed on the principal display	Adequate	Rx only
NDC	Adequate	2.5 mg: 73625-111-11 5 mg: 73625-112-11 10 mg: 73625-113-11 15 mg: 73625-114-11
Lot number and expiration date	Adequate	Yes, they were printed on all the sample labels.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C to 30°C (between 59°F to 86°F) [see USP Controlled Room Temperature].
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	
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	Included

Item	Assessor's Comments about Container Labeling (choose "Adequate", "Inadequate", or "N/A")	Items in Proposed Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	Distributed by: Myokardia Inc., Brisbane, CA 94005 A wholly-owned subsidiary of Bristol-Myers Squibb.
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	

3.2 Carton Labeling: Not applicable

Assessment of Carton and Container Labeling: *Adequate.* No cartons were proposed.

Overall Assessment and Recommendation: Adequate with the following proposed change:

1) **In the Description section of the Prescribing Information and in Medication Guide, inactive ingredients should be arranged in the alphabetical order.**

Primary Labeling Assessor Name and Date: Rao V Kambhampati, Ph.D. 9/21/2021

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

Rao Kambhampati

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Mohan Sapru

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CHAPTER VI: BIOPHARMACEUTICS

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	214998
Assessment Cycle Number	# 1
Drug Product Name/ Strength	CAMZYOS (mavacamten) IR capsules, 2.5 mg, 5 mg, 10 mg, 15 mg
Route of Administration	Oral
Applicant Name	Myokardia Inc.
Therapeutic Classification/OND Division	Division of Cardiology and Nephrology (DCN)
RLD/IND Number	IND 121904
Proposed Indication	Treatment of symptomatic obstructive hypertrophic cardiomyopathy (oHCM) in adults to improve functional capacity, (b) (4) and symptoms.
Primary Assessors	Zhuojun Joan Zhao, *Ph.D.*
Secondary Assessors	Poonam Delvadia, *Ph.D.*
Assessment	**Adequate**
Recommendation	Based on the review of the overall information, from a Biopharmaceutics perspective, NDA 214998 for CAMZYOS (mavacamten) IR capsules, 2.5 mg, 5 mg, 10 mg, 15 mg is recommended for **APPROVAL**.

Assessment Summary:

Myokardia Inc. submitted a 505(b) (1) application for the proposed CAMZYOS (mavacamten) immediate release (IR) capsules, 2.5 mg, 5 mg, 10 mg, 15 mg for the treatment of adults with symptomatic obstructive hypertrophic cardiomyopathy (oHCM) (b) (4)

The proposed drug product is an immediate release hard gelatin capsule. The proposed starting dose is 5 mg orally once daily without regard to food and the proposed maximum dose is 15 mg once daily.

The Biopharmaceutics review is focused on the evaluation and acceptability of the proposed quality control dissolution method and acceptance criterion, physiologically based pharmacokinetic (PBPK) modeling and simulation as well as the evaluation of the formulation bridging.

Dissolution method and Acceptance Criterion:

Based on the provided dissolution data, the revised dissolution method and dissolution acceptance criteria are found acceptable:

Medium	**Tier 1:** 0.05 %(w/v) SDS in 50 mM Sodium Phosphate, pH 6.8 **Tier 2:** (Step 1) 50 mM Sodium Phosphate, pH 6.8, containing NMT 2000 unit/L of pancreatin (850 ml). (Step 2) After 10 minutes, add 50 mL of 50 mM sodium phosphate pH 6.8 containing 0.9%(w/v) SDS
Apparatus	USP II (Paddle)
Volume	900 mL
Rotation Speed	50 RPM
Temperature	37°C
Acceptance Criteria	Q (b) (4)% in 30 minutes (2.5 and 5 mg) Q= %% in 45 minutes (10 and 15 mg)

Physiologically Based Pharmacokinetic (PBPK) Modeling and Simulation:
The Applicant developed a PBPK model of Mavacamten by integrating in vitro/in vivo measured and in silico predicted physicochemical and biopharmaceutical properties, formulation properties, and plasma pharmacokinetics (PK) in healthy subjects. The Applicant's PBPK model was found inadequate due to the deficiencies identified in the model development and verification steps and thus could not be applied to support the justification for dissolution acceptance criterion in the initial submission dated March 13, 2021.

Bridging Formulations:
The proposed commercial capsule is different in the (b) (4) of the gelatin capsule from Capsule 2, which was used in pivotal phase 3 study MYK-461-005 and Phase 1 and 2 studies. The Applicant conducted an in vivo BE study (MYK-416-014) to bridge the capsule 1 and 2 formulations, which was found acceptable by the Clinical Pharmacology reviewer. The Applicant also provided dissolution profiles comparing Capsule 2 and commercial formulations using the revised QC method, which indicates equivalent dissolution performance by *f*2 values.

List Submissions being assessed:

Document(s) Assessed	Date Received
Original Submission	March 13, 2021
IR Responses	September 21, 2021 and October 4, 2021

Highlight Key Issues from Last Cycle and Their Resolution: NA

Concise Description of Outstanding Issues): None

B.1 BACKGROUND

The Applicant's initial dissolution method CTMLP-4259 development report PD-ANA-005 (900 mL 0.3% SDS in pH 6.8 buffer using USP II (Paddle) at 50 RPM) [1] was reviewed in IND 121904[2]. The selection of dissolution medium ((b) (4) was found not adequately justified. The Applicant was also informed to provide study to support the Tier 2 condition for the observed cross-linking in Advice/Information Request letter dated June 26, 2020[3].

The Applicant 's dissolution test condition development history is shown in Table 1.

Table 1 Comparison of dissolution method parameters for MYK-461 tablets and capsules

(b) (4)

B.2 DISSOLUTION METHOD SUBMITTED IN NDA SUBMISSION

In the NDA submission, the Applicant provided an updated dissolution method CTMLP-4901 development report PD-ANA-027 using the (b) (4) in the dissolution medium (i.e. 0.05% SDS in pH 6.8 buffer).

Surfactant Amount

Based on the selected testing conditions for previous dissolution method CTMLP-4259 (Table 1), the Applicant examined the dissolution profiles of the proposed highest strength 15 mg of Mavacamten capsules (Capsule 2 formulation, clinical lot # 18C0006 (Patheon lot # CBKDC)), at 50 RPM paddle speed in 50 mM pH 6.8 buffer containing

(b) (4)

[2] DARRTS: IND 121904 REV-QUALBIOPHARM-21 (Primary Review), final date 06/26/2020

[3] DARRTS: IND 121904 Advice-Information Request [IND] (COR-INDAD-02), final date 06/26/2020

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Assessment: Adequate

Based on the provided information, the updated dissolution condition with the [redacted] *i.e. 0.05% SDS in pH 6.8, is adequately justified. Therefore, the proposed dissolution method is acceptable for the QC dissolution testing of the proposed drug product. The proposed dissolution method (CTMLP-4901) could discriminate variation of drug substance particle size distribution, formulation variation* [redacted] *but not the studied variations in process.*

B.3 DISSOLUTION ACCEPTANCE CRITERIA

The Applicant provided the dissolution profiles of Clinical Trial Material (CTM), three registration lots, and a commercial image lot for each strength, shown in **Figure 6** to **Figure 9**.

Figure 6 Dissolution Profiles of Mavacamten Capsules, 2.5 mg in Intended Commercial QC Method CTMLP4901

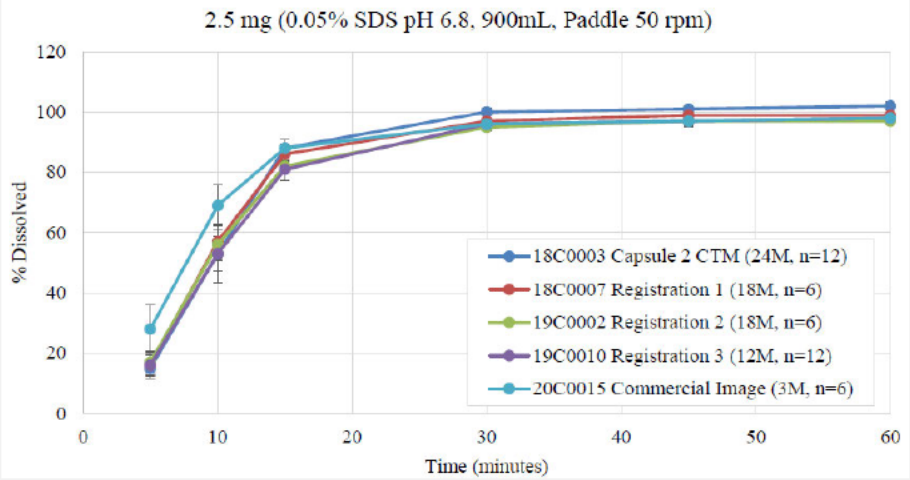


Figure 7 Dissolution Profiles of Mavacamten Capsules, 5 mg in Intended Commercial QC Method CTMLP4901

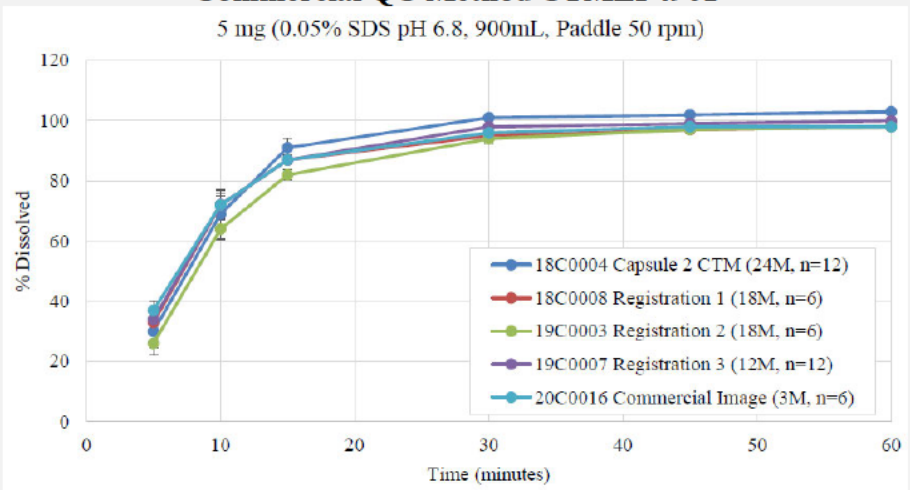


Figure 8 Dissolution Profiles of Mavacamten Capsules, 10 mg in Intended Commercial QC Method CTMLP4901

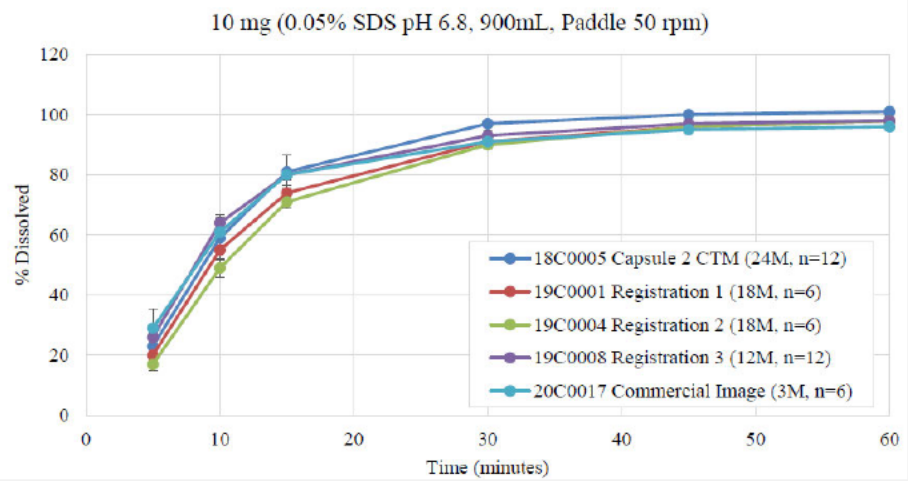
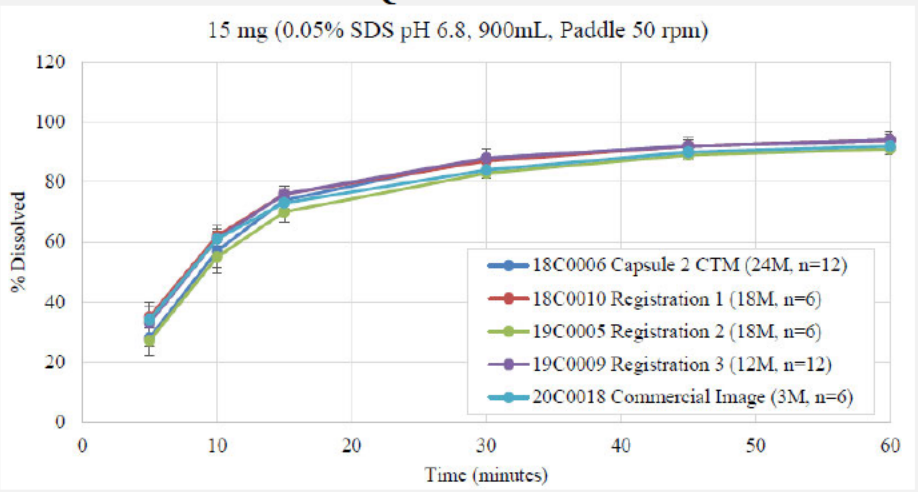


Figure 9 Dissolution Profiles of Mavacamten Capsules, 15 mg in Intended Commercial QC Method CTMLP4901



The data showed the consistency in dissolution performance cross the strengths (i.e. >85% at 30 minutes), except Registration lot 19C0005/CCDMP (15 mg) in **Figure 9**. The Applicant states that the Registration lot 19C0005/CCDMP appeared to have comparable, but slightly slower, release profile than the other lots and claimed that this slightly slower release was attributed to batch-to-batch and analysis variability, as no specific cause could be identified. All registration lots (15 mg), when compared to the CTM lot 18C0006 by f2 similarity factor calculation were shown to be similar with f2 values >50 (Table 3).

Table 3: Dissolution Profile Comparison *f2* similarity factors of Capsule 2 15 mg Capsules CTM versus Registration Lots in 0.05% SDS pH 6.8 buffer

Reference Lot CTM 15 mg capsules	**f2 (Reg 1 Lot # 18C0010 / CBZCC[1])**	**f2 (Reg 2 Lot # 19C0005 / CCDMP[2])**	**f2 (Reg 3 Lot # 19C0009 / CCXWH[3])**	**f2 (Commercial Image Lot # 20C0018A / CFPFK[4])**
Lot # 18C0006/CBKDC[5]	84	58	92	71

The Applicant proposes an acceptance criterion of Q = (b) (4)% dissolved at (b) (4) minutes for the proposed Mavacamten capsules based on physiologically based pharmacokinetic (PBPK) modeling, in which dissolution release meeting the proposed specification using the proposed QC method (CTMLP-4901) would achieve the intended exposure.

Assessment: *{Adequate}*
The Applicant's PBPK model was found not acceptable in Section B.5 below and thus the initially proposed dissolution acceptance criterion of Q= (b) (4)% at (b) (4) minutes was found not supported by the data or PBPK model either. Based on the dissolution data in dissolution method development report PD-ANA-027, dissolution acceptance criteria of (b) (4) *were recommended in IR letter dated September 22, 2021 (Appendix 4).*

In the IR response dated October 1, 2021, the Applicant proposed the following acceptance criteria. Based on the justification provided by the Applicant, the criteria were found acceptable for the QC of the proposed CAMZYOS (mavacamten) IR capsules.

Revised Dissolution Acceptance Criteria
2.5 and 5 mg NLT (b) (4)% (Q) at 30 minutes
10 and 15 mg NLT % (Q) at 45 minutes

B.4 TIER 2 DISSOLUTION METHOD

The Applicant states that gelatin crosslinking likely occurred for all strengths stored under 40°C/75%RH accelerated condition, (b) (4)

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(b) (4)

Assessment: {Adequate}
The implementation of Tier 2 testing with pancreatin for gelatin crosslinking is acceptable. The Applicant demonstrated the need of pretreatment step and justified the pretreatment condition (i.e. USP II (padded) 850 mL 2000 units/L pancreatin in 50 mM Sodium Phosphate Buffer, pH 6.8 at 50 RPM for 10 minutes).

B.5 PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK) MODELING AND SIMULATION

(b) (4)

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(b) (4)

Assessment: {Inadequate}
The Applicant's PBPK study report NC-20-0054[5] was presented and discussed with PBPK Committee on September 2, 2021[6]. The Applicant's PBPK model was found inadequate to support the justification for the dissolution acceptance criterion for the following reasons:

(b) (4)

(b) (4)

(b) (4)

Therefore, the Applicant was informed the deficiencies identified in the Model development and verification steps in IR letter dated (Appendix 3). The proposed PBPK model is not adequate to support the justification for dissolution acceptance criterion.

B.6 BRIDGING OF FORMULATIONS

The Applicant's formulation development studies are shown in **Table 6**.

Table 6: Formulation Development Studies

Dosage Form (No.)	Objective	Description
[redacted] (b) (4)		

Assessment: (N/A)

The proposed commercial capsule is different in the [redacted] (b) (4) *of the gelatin capsule from Capsule 2, which was used in pivotal 3 study MYK-461-005 and Phase 1 and 2 studies. The Applicant provided BE study MYK-416-014 and in vitro comparative dissolution studies in multi-pH conditions* [redacted] (b) (4) *comparing Capsule 1 and 2 formulations and dissolution profiles comparing Capsule 2 and commercial formulations using the proposed QC method (Figure 6 to Figure 9). Based on the reviewer's calculated f2 (similarity factor), the data using the QC dissolution method (CTMLP-4901) indicates equivalence dissolution performance for the capsule 2 CTM and commercial Image for all strengths and the BE study MYK-416-014 comparing capsule 1 and 2 formulations was found acceptable by the Clinical Pharmacology reviewer.*

Dissolution Similarity (f2 values) Comparing Capsule 2 and Commercial Image			
2.5 mg	***5 mg***	***10 mg***	***15 mg***
18C0006 vs 20C0018	*18C0005 vs. 20C0017*	*18C0004 vs. 20C0016*	*18C0003 vs. 20C0015*
71.48	*66.36*	*65.34*	*52.45*

B.7 BIOWAIVER REQUEST

Assessment: N/A

As all proposed strengths were used in Phase 3 study MYK461-005, a biowaiver is not submitted nor required for this NDA.

R. REGIONAL INFORMATION

Comparability Protocols: N/A

Post-Approval Commitments: N/A

Lifecycle Management Considerations: N/A

APPENDIX 1: Dissolution Data of lot 18C0006/CBKDC (15mg)

(b) (4)

Table 8: Individual vessel dissolution data in pH 6.8 buffer with 0.05% SDS at 50 RPM paddle speed

Time (min)	v1 %D	v2 %D	v3 %D	v4 %D	v5 %D	v6 %D	v7 %D	v8 %D	v9 %D	v10 %D	v11 %D	v12 %	Mean %D	Min %D	Max %D	SD %D	CV (%)
5	(b) (4)												27.7	(b) (4)		3.6	12.9
10													63.1			4.5	7.2
15													76.5			2.0	2.6
30													88.2			1.5	1.7
45													92.6			1.6	1.8
60													96.5			1.6	1.7

(b) (4)

APPENDIX 2: Dissolution Data Using pH 6.8 buffer with 0.05% SDS at 50 RPM paddle speed

Table 12: Dissolution data of Registration Lot 18C0010/CBZCC (15 mg)

Time (min)	v1 %D	v2 %D	v3 %D	v4 %D	v5 %D	v6 %D	v7 %D	v8 %D	v9 %D	v10 %D	v11 %D	v12 %	Mean %D	Min %D	Max %D	SD %D	CV (%)
5												(b) (4)	24.3		(b) (4)	2.6	10.8
10													64.3			2.8	4.4
15													76.4			1.0	1.3
30													87.1			1.2	1.3
45													92.0			1.7	1.8
60													95.0			1.8	1.9
75													97.1			1.4	1.5

Table 13: Dissolution data of Registration Lot 19C0005/CCDMP (15 mg)

Time (min)	v1 %D	v2 %D	v3 %D	v4 %D	v5 %D	v6 %D	v7 %D	v8 %D	v9 %D	v10 %D	v11 %D	v12 %	Mean %D	Min %D	Max %D	SD %D	CV (%)
5												(b) (4)	20.3		(b) (4)	3.3	16.1
10													56.9			2.8	4.9
15													69.3			1.6	2.3
30													81.0			1.5	1.8
45													87.0			1.4	1.6
60													90.3			1.3	1.4
75													94.2			1.2	1.3

Table 14: Dissolution data of Registration Lot 19C0009/CCXWH (15 mg)

Time (min)	v1 %D	v2 %D	v3 %D	v4 %D	v5 %D	v6 %D	v7 %D	v8 %D	v9 %D	v10 %D	v11 %D	v12 %	Mean %D	Min %D	Max %D	SD %D	CV (%)
5												(b) (4)	26.3		(b) (4)	3.6	13.7
10													64.1			2.4	3.8
15													76.3			2.1	2.8
30													87.1			2.2	2.5
45													92.0			2.1	2.3
60													94.5			2.3	2.5
75													97.0			2.6	2.6

Table 15: Dissolution data of Commercial Image lot 20C0018A/CFPFK (15 mg)

Time (min)	v1 %D	v2 %D	v3 %D	v4 %D	v5 %D	v6 %D	v7 %D	v8 %D	v9 %D	v10 %D	v11 %D	v12 %	Mean %D	Min %D	Max %D	SD %D	CV (%)
5												(b) (4)	20.8		(b) (4)	2.6	12.7
10													62.8			1.2	1.9
15													74.7			2.5	3.3
30													86.3			0.8	0.9
45													91.8			1.0	1.1
60													94.7			1.0	1.0
75													98.0			1.3	1.3

(b) (4)

Table 16: Dissolution data of Capsule 2 process variant 0508 (15 mg) (b) (4) capsules

Time (min)	v1 %D	v2 %D	v3 %D	v4 %D	v5 %D	v6 %D	Mean %D	Min %D	Max %D	SD %D	CV (%)
5	(b) (4)						18.9	(b) (4)		8.2	43.5
10							62.1			3.0	4.9
15							74.7			1.2	1.6
30							84.7			0.8	0.9
45							89.9			0.5	0.5
60							92.5			0.4	0.4
75							96.3			0.3	0.3

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