

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

219083Orig1s000

PRODUCT QUALITY REVIEW(S)



Template Revision: 03

Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	5		



NDA Executive Summary

1. Application/Product Information

NDA Number.	219083		
Applicant Name	Cytokinetics		
Drug Product Name	Myqorzo (aficamten)		
Dosage Form.	Tablet		
Proposed Strength(s)	5 mg, 10 mg, 14 mg, and 20 mg		
Route of Administration	Oral		
Maximum Daily Dose	20 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	For the treatment of adults with symptomatic obstructive hypertrophic cardiomyopathy		
Drug Product Description	The film-coated tablets are purple, embossed with "CK" on one side and the tablet strength in mg on the other. Each tablet strength is a different shape and size: the 5 mg tablets are circles, the 10 mg tablets are triangles, the 15 mg tablets are pentagons, and the 20 mg tablets are ovals.		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	20°C to 25°C		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Mitchell McCloskey	Zhengfu Wang
	<i>Drug Product/ Labeling</i>	Jennifer McCord	Theodore Carver



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	5		



Template Revision: 03

Template Revision: 03

	<i>Manufacturing</i>	Feiyan Jin	Alexander Gontcharov
	<i>Biopharmaceutics</i>	Nadia Ahmed	Bhagwant Rege/Haritha Mandula
	<i>Microbiology</i>	N/A	
	<i>Other (specify):</i>	N/A	
	<i>RBPM</i>	Esther Jones	
	<i>ATL</i>	Theodore Carver	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

A shelf life of 30 months is granted for the drug product when stored at 20°C to 25°C

b. Additional Comments for Action None.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

1) Background

Cytokinetics, Inc. submitted a new 505(b)(1) drug application (NDA) for aficamten 5, 10, 15, and 20 mg immediate release film-coated tablets proposed for the treatment of adults with symptomatic obstructive hypertrophic cardiomyopathy (oHCM). Approval of aficamten tablets, which received Breakthrough Therapy Designation, relies on the results of a Phase 3 clinical study for approval. The OPQ review team comprised drug substance, drug product, manufacturing, and biopharmaceutics reviewers.



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	5		



Template Revision: 03

2) Drug Substance

The drug substance is a novel small molecule synthesized as a single enantiomer. All supporting CMC information is included in Module 3.2.S. During the review, the Applicant addressed concerns regarding impurities with structural alerts for mutagenicity and the need for numeric limits in the three-tiered specification for particle size. The manufacturing process information, controls, and specification were found to be adequate to support the quality of the drug substance. Stability data support the proposed retest period of (b) (4) months for the drug substance, when stored

(b) (4)

3) Drug Product

The drug product is film-coated immediate release tablets manufactured using (b) (4) process. The tablets are manufactured (b) (4) with each strength tablet differing in size and shape. The excipients were determined to be acceptable and at safe levels based on the levels in other applications reported in the Inactive Ingredient Database. (b) (4) in the drug substance was determined to be a critical quality attribute early in the review and addressed in the cross-disciplinary review (see also drug substance and biopharmaceutics reviews) due to solubility concerns and potential impact on the manufacturing process. The risk assessment for nitrosamine impurities in the drug substance and drug product supported a low risk of formation of nitrosamines and no significant risk of nitrosamine drug-substance related impurities. Therefore, no additional controls or tests are included for nitrosamine impurities. Although there are several possible polymorphic forms, only Form (b) (4) was observed (b) (4)

The results for samples tested near end-of-shelf-life using the (b) (4) dissolution method implemented in the commercial specification were acceptable (see biopharmaceutics review). The commercial specification was deemed adequate to support the quality of the drug product. Based on 18 to 24 months of long-term (25 °C/60% RH) stability data and 6 months of accelerated stability data (40 °C/75% RH) from a total of three registration batches in each strength, as well as supporting stability data through 36 months for developmental and clinical batches, a shelf life of 30 months is granted for the drug product.



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	5		



Template Revision: 03

4) Manufacturing

Process – The manufacturing process includes (b) (4)

(b) (4)

Facilities - The facilities were all determined to be approvable based on previous inspection history.

5) Biopharmaceutics

The biopharmaceutics review included review of data to bridge clinical formulations, review of a biowaiver for the lower tablet strengths, and review of the proposed dissolution method for commercial release and stability testing. After the Applicant made significant revisions to the proposed dissolution method including (b) (4) the proposed dissolution method was deemed adequate. In conjunction with the control (b) (4), the controls with respect to drug release were determined to be adequate, and overall the data to support the formulation bridging and biowaiver were adequate.

6) Quality Aspects of Product Labeling

The quality aspects of the product labeling were found to be adequate after requested revisions were implemented.

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

Recommendation by Subdiscipline:

Drug Substance	-	Adequate
Drug Product	-	Adequate
Quality Labeling	-	Adequate
Manufacturing	-	Adequate
Biopharmaceutics	-	Adequate
Microbiology	-	N/A

Environmental Assessment: Categorical Exclusion - Adequate

QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	5		



Template Revision: 03

Comments: None.

Comparability Protocols (PACMP): No

Comments: None.

Additional Lifecycle Comments:

None.



Theodore
Carver

Digitally signed by Theodore Carver

Date: 10/16/2025 06:06:15PM

GUID: 5d963967007fd4bc3c9fab2a6c3eade

60 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page



Title:	NDA IQA Template CHAPTER IV-LABELING		
Document ID:	OPQ-ALL-TEM-0045		
Effective Date:	18 Sep 2023	Revision:	00
Total Pages:	19		



Template Revision: 03

CHAPTER IV: LABELING

For more details about the items in this template, please see [Chapter IV \(Labeling\) of the NDA IQA Guide \(OPQ-ALL-WI-0006\)](#)

NDA Number: 219083	
Assessment Cycle Number	1
Drug Product Name	Myqorzo (Aficamten) tablets

Assessment Recommendation: Adequate

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Adequate	0045
Patient Information	Adequate	0002
Instruction for Use (IFU)	N/A	N/A
Container Labels	Adequate	0045
Carton Labeling	N/A	N/A

Brief Description of Outstanding Issues: None

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
0002	08/14/2024	Medication Guide
0045	09/17/2025	Container Labeling
0045	09/17/2025	Prescribing Information

1.0 PRESCRIBING INFORMATION¹

Assessment of Product Quality Related Aspects of the Prescribing Information:

¹ [Labeling Review Tool \(LRT\) \(March 2022\)](#), including use of consistent terminology for dosage form and unit of measure for strength in the product title and DOSAGE FORMS AND STRENGTHS heading in Highlights, in the DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING sections (see page 2 of LRT)

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION



Item	Item 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 Highlights² [21 CFR 201.57(a)(2)]		
Established name(s) ³	Adequate	Aficamten tablets
Route(s) of administration	Adequate	Oral
Controlled drug substance symbol (if applicable)	N/A	N/A
Initial U.S. Approval [§201.57(a)(3)]	Adequate	YYYY
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		
Dosage form(s) ⁴ and strength(s) in metric system ⁵	Adequate	Film-coated tablets: 5 mg, 10 mg, 15 mg, 20 mg

² Draft guidance: [Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format](#) (January 2018)

³ Established name = [Drug] [Route of Administration] [Dosage Form]. Do use not "USP" descriptor in the product title or within the Highlights (see page 3 of LRT).

⁴ Draft guidance: [Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format](#) (January 2018); USP <1151>; USP Nomenclature Guideline

⁵ Labeling Review Tool (March 2022, page 13), include limited packaging information; USP <7>

Item	Item 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)
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). ⁶	N/A	N/A
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored." ⁷	N/A	N/A
For injectable drug products for parenteral 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. ⁸	N/A	N/A

Assessment: *Adequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) **Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"**

⁶ Guidance: *Naming of Drug Products Containing Salt Drug Substances* (June 2015); MAPP 5021.1

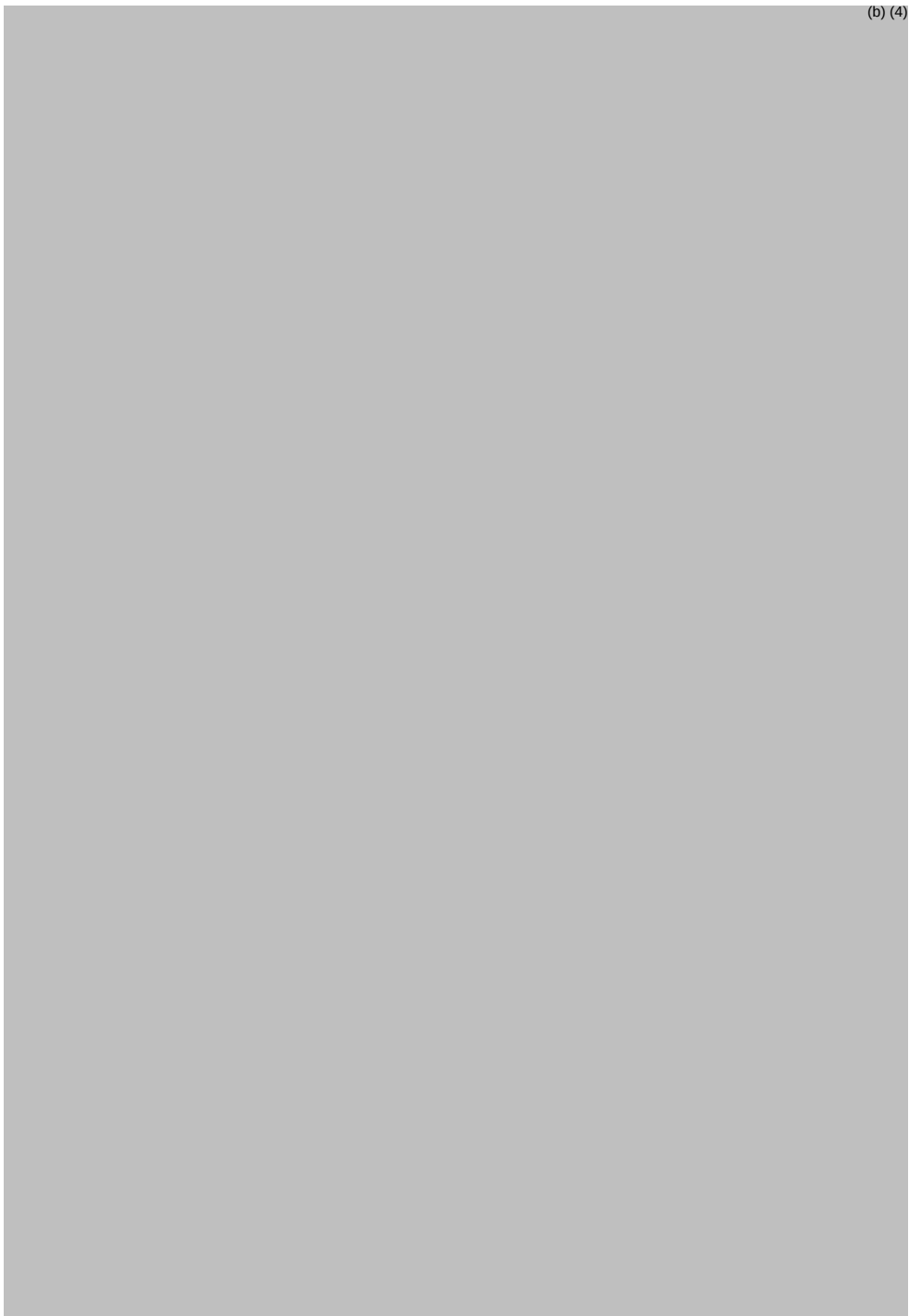
⁷ Guidance: *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013)

⁸ Guidance: *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018); USP <659>

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)⁹

(b) (4)



⁹ See § 201.57(c)(3); draft guidance: [Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format](#) (January 2023); Labeling Review Tool (March 2022, page 25)

(b) (4)

Item	Item 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 and/or soft food ¹⁰ , storage conditions needed to maintain the stability of the reconstituted or diluted product).	N/A	N/A
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release	Adequate	Adequate

¹⁰ Draft Guidance: [Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments](#)

Item	Item 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)
tablets, instructions for mixing with food).		
For parenteral products: include statement: <i>"Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."</i> ¹¹	N/A	N/A
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. ¹² Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	N/A
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	N/A
For hazardous products, include the statement <i>"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures."</i> ^x with x numerical citation to "OSHA Hazardous Drugs."	N/A	N/A

Assessment: Adequate

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) **Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"**

(b) (4)

¹¹ §201.57(c)(3)(iv)

¹² USP General Notices 2.30 Legal Recognition

¹³ See § 201.57(c)(4); [Labeling Review Tool \(March 2022, page 29\)](#)

(b) (4)

Item	Item 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	Tablets
Strength(s) in metric system	Adequate	5 mg, 10 mg, 15 mg, 20 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 (e.g., Tablets: 10 mg of drug-x hydrochloride). No equivalency statement.	N/A	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	Purple tablet in different shapes, debossed with "CK" on one side and the strength in mg on the other
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	N/A
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and	N/A	N/A

Item	Item 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)
imaging bulk package (see USP <659>).		

Assessment: *Adequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) **Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"**

(b) (4)

Item	Item 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		

¹⁴ See § 201.57(c)(12); [Labeling Review Tool \(March 2022, page 56\)](#)

Item	Item 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)
Proprietary and established name(s) ¹⁵ [§ 201.57(c)(12)(i)(A)].	Adequate	MYQORZO tablets for oral use contain aficamten
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Adequate	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)" [§ 201.57(c)(12)(i)(C)].	N/A	N/A
List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order. ¹⁶ Avoid brand names. [§ 201.57(c)(12)(i)(C)].	Adequate	Adequate following edits
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. [§ 201.100(b)(5)(iii)].	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of	N/A	N/A

¹⁵ Use of "USP" descriptor is not required to be included next to the established name throughout Prescribing Information (PI) labeling. If an applicant wants to use the "USP" descriptor next to the established name in the PI, recommend limiting its use to the product quality sections of the Full Prescribing Information (FPI) (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) (see page 3 of LRT).

¹⁶ Per § 201.100(b)(5)(i) and (ii), flavoring and colorants may be designated as such without naming their components except for FD&C Yellow No 5 and FD&C Yellow No 6, which must be listed per § 201.20. Per § 201.100(b)(5)(iii), trace amounts of harmless substances added solely for individual product identification need not be named. If an applicant wants to use the National Formulary (NF) descriptor next to excipients, recommend limiting its use to the product quality sections of the FPI (see page 3 of LRT). Do not list brand names, e.g., Opadry, Eudragit, Polistirex, etc.

Item	Item 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)
absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].		
Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].	N/A	N/A
Pharmacological/Therapeutic class ¹⁷ [§ 201.57(c)(12)(i)(E)].	Adequate	cardiac myosin inhibitor
Chemical name ¹⁸ , structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Adequate	(R)-N-(5-(5-ethyl-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-inden-1-yl)-1-methyl-1H-pyrazole-4-carboxamide. The molecular formula is C ₁₈ H ₁₉ N ₅ O ₂ and the molecular weight is 337.38 g/mol. Structure is present.
If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)].	N/A	N/A
Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)].	Adequate	Present
For oral prescription drug products, include gluten statement ¹⁹ (if applicable).	N/A	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	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	N/A

¹⁷ Listed before "indicated for" in INDICATIONS AND USAGE of Highlights section [§ 201.57(a)(6)]; can also search the term "FDA EPC Text Phrases" in [FDA's Labeling Resources for Human Prescription Drugs](#) for the most recent EPC list.

¹⁸ Chemical names do not need to be capitalized unless it appears at the beginning of a sentence (see *Preferred IUPAC Names Provisional Recommendation*, September 2004; Chapter 1, par. 16 Name writing, p.80-90).

¹⁹ Draft guidance: [Gluten in Drug Products and Associated Labeling Recommendations \(December 2017\)](#)

Assessment: Adequate

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) **Any issues should be listed at the end in “OUTSTANDING ISSUES AND RECOMMENDATIONS”**

(b) (4)

Item	Item 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) [§ 201.57(c)(17)].	Adequate	Film-coated tablets
Strength(s) in metric system. [§ 201.57(c)(17)(i)] 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. No equivalency statement.	Adequate	5 mg, 10 mg, 15 mg, 20 mg
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Adequate	Bottles of 30 tablets
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s) [§ 201.57(c)(17)(iii)].	Adequate	Shape, color, and debossing described

²⁰ See § 201.57(c)(17); [Labeling Review Tool \(March 2022, page 70\)](#). Consider including proprietary name and established name.

Item	Item 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)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	N/A
For injectable drug products for parenteral 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 (see USP <659>).	N/A	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." [§ 201.57(c)(17)(iv)]	N/A	N/A
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).	Adequate	Store at 20°C to 25°C (68°F to 77°F); excursions to 15°C to 30°C (between 59°F to 86°F)
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: " <i>Not made with natural rubber latex.</i> "	N/A	N/A

Item	Item 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)
Avoid statements such as "latex-free." ²¹		
Include information about child-resistant packaging ²² (if chosen by manufacturer).	Adequate	Adequate

Assessment: *Adequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) **Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"**

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.

²¹ Guidance: [Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex](#) (December 2014)

²² Guidance: [Child-Resistant Packaging Statements in Drug Product Labeling](#) (August 2019)

1.2.6 Manufacturing Information After Section 17 (for drug products)²³

Item	Item in Proposed Labeling (choose "Adequate" or "Inadequate")	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	Cytokinetics Incorporated San Francisco, CA 94080

Assessment: *Adequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) **Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"**

2.0 PATIENT LABELING

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

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name ²⁴	Adequate	Aficamten
Special preparation instructions (if applicable).	N/A	N/A
Storage and handling information (if applicable).	Adequate	Store 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 differ from the dosage form.	N/A	N/A
Active ingredient(s) (if applicable).	Adequate	Aficamten
Alphabetical listing of inactive ingredients (if applicable).	Adequate	Not listed in alphabetical order; when edited, will be adequate.

²³ § 201.1(h)(5) and 201.1(i); [Labeling Review Tool \(March 2022, page 74\)](#)

²⁴ Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer.	Adequate	Cytokinetics, Incorporated; San Francisco, CA 94080

Assessment: *Adequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) **Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"**

3.0 CONTAINER AND CARTON LABELING²⁵

3.1 Container Labels²⁶

(b) (4)

3.2 Carton Labeling

This product does not have a carton- an IR was sent to the Applicant to confirm.

²⁵ [Carton and Container Labeling Resources](#)

²⁶ Per § 201.10(h)(2)(i)(1), if the drug container is too small to bear all labeling information required by section 502(e)(1)(A)(ii) and (B) of the FD&C Act, the container label should bear: proprietary name, established name, lot number, the name of the manufacturer, packer, or distributor of the drug.

Item	Item in Proposed Container Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Proprietary name and established name ²⁷ , (font size and prominence) [§ 201.10(g)(2)].	Adequate	N/A	Present
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)]. ²⁸	Adequate	N/A	Present
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	N/A	N/A	Oral use, not required
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP [§ 201.10(d)(1) & 201.100(b)(4), USP <1121>].	N/A	N/A	Not a salt
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)]. ²⁹	Adequate	N/A	30 tablets
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Adequate	N/A	Present
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	N/A	Present
Lot number and expiration date [§ 201.18 & 201.17].	Adequate	N/A	Present
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	Adequate	N/A	Store at 20 °C to 25 °C (68 °F to 77 °F); excursions to 15 °C to 30 °C (59 °F to 86 °F)

²⁷ Established name = [Drug] [Route of Administration] [Dosage Form]

²⁸ Express as "XX mg per tablet" or "XX mg per capsule" for strength of professional samples of solid oral dosage form with small net quantities per container (e.g., 5 or less) or blister pack/carton. See [Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors \(May 2022\)](#)

²⁹ § 201.51(h): A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

Item	Item in Proposed Container Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
For injectable drug products for parenteral 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. (See USP <659>).	N/A	N/A	N/A
Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5) or limited space per § 201.10(i)(2)].	N/A	N/A	Limited space
For parenteral injectable dosage forms, include quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	N/A	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	N/A	N/A
Linear Bar code [§ 201.25(c)(2)]. ³⁰	Adequate	N/A	Present
Adequate directions for use: "Recommended Dosage: See Prescribing Information" [§ 201.5 & 201.55].	Adequate	N/A	Present

³⁰ See § 201.25(b)(1)(i) for a list where bar code is not required, e.g., prescription drug samples, medical gases, radiopharmaceuticals, etc.

Item	Item in Proposed Container Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	N/A	Distributed by Cytokinetics, Inc.
"Keep out of reach of children" statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)].	Adequate	N/A	Present
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Adequate	N/A	Dispense with Medication Guide
No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>).	N/A	N/A	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	N/A	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. ³¹	N/A	N/A	N/A
And others if space is available.	N/A	N/A	N/A

³¹ USP General Notices 3.20 Indicating Conformance

Assessment of Carton Labels and Container Labeling: *Adequate*

Any issues should be listed at the end in “OUTSTANDING ISSUES AND RECOMMENDATIONS”

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

Assess consistency of product-quality information in prescription drug labeling (PI, c/c labeling, and FDA-approved patient labeling). See [Carton/Container Labeling Specific Resources](#) for a presentation about inappropriate inconsistencies of product quality information between labeling. If there are inappropriate inconsistencies between the labeling (e.g., established name, strength(s), package type term, discard statement, identifying characteristics, storage, reconstitution/dilution instructions), please list these issues in this section.

Primary Labeling Assessor Name and Date: Jennifer McCord, 09/25/2025

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



Jennifer
McCord

Digitally signed by Jennifer McCord

Date: 10/15/2025 09:23:29AM

GUID: 63221b9c007a3580cbffb5160db88fe7



Theodore
Carver

Digitally signed by Theodore Carver

Date: 10/15/2025 09:29:50AM

GUID: 5d963967007fd4bc3c9fab2a6c3eaded

66 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following
this page

CHAPTER VI: BIOPHARMACEUTICS

[IQA NDA Assessment Guide Reference](#)

Product Information	Aficamten (CK-3773274)
NDA Number	219083
Assessment Cycle Number	NDA-219083-ORIG-1
Drug Product Name/ Strength	Aficamten Tablets/5,10,15,20 mg
Route of Administration	Oral
Applicant Name	Cytokinetics Inc.
Therapeutic Classification/ OND Division	Division of Cardiology and Nephrology (DCN)
RLD/RS Number	New Molecular Entity (NME)
Proposed Indication	For the treatment of adults with symptomatic obstructive hypertrophic cardiomyopathy (oHCM).

Assessment Recommendation: Adequate

Assessment Summary: The applicant, Cytokinetics Inc., submitted a 505(b)(1) application for the proposed Aficamten (5, 10, 15 and 20 mg) immediate-release film-coated tablets proposed for the treatment of adults with symptomatic obstructive hypertrophic cardiomyopathy (oHCM). Through IND meetings, the Applicant sought the Agency's guidance on if the Phase 2 to Phase 3 formulations could be bridged via in vitro bridging since the formulation change is considered a SUPAC Level 1 change as per the SUPAC guidance. The Agency confirmed that in vitro bridging was appropriate to bridge the Phase 2 and Phase 3 formulations and noted that the adequacy of this bridge would be a review issue. Additionally, in the IND meeting minutes, the Applicant inquired whether the planned commercial strengths of 5 mg, 10 mg, 15 mg, and 20 mg could be bridged to the phase 3 clinical trials, in which 5 mg tablets were used for a cumulative dose of 5 mg, 10 mg, 15 mg, 20 mg. The Agency (Biopharmaceutics, Clinical Pharmacology, and the Clinical Divisions) agreed that in vitro multimedia dissolution could be used to support commercial tablet strengths of 5 mg, 10 mg, 15 mg, and 20 mg with comparative multimedia dissolution, and that the adequacy of the bridge would be a review issue. Additionally, the Applicant requested feedback on the proposed dissolution method at the time of the Type B WRO meeting, dated June 09, 2023. The Agency gave the Applicant advice on the proposed dissolution method, along with guidelines on how to develop a discriminating dissolution method, specifically encouraging them to develop a dissolution method that was discriminating towards API PSD as the drug substance demonstrates low solubility.

The proposed drug substance, Aficamten, demonstrates low solubility and is classified as a BCS Class II drug. The Applicant used several dissolution methods during drug product development, as shown in Figure 5. In response to the Agency's request that

the Applicant remove (b) (4) from their previously proposed QC dissolution method, the Applicant proposed a new dissolution method as shown in Figure 1.

(b) (4)

Based on the cumulative data submitted, the risk has been mitigated, and the dissolution method is Adequate from a Biopharmaceutics perspective. However, the acceptance criterion was permissive. Additionally, the Applicant had originally implemented (b) (4). However, the (b) (4) is not recommended to be implemented in their QC dissolution method. Therefore, the Applicant was recommended via IR to adopt “Q= (b) (4)% in 30 minutes” as the acceptance criterion across all strengths and eliminate the infinity time point in their QC dissolution method via IR. In response to this IR, the Applicant has implemented “Q= (b) (4)% in 30 minutes” as the dissolution acceptance criterion and eliminated (b) (4) in their QC dissolution method. Additionally, the Applicant provided stability testing using the current aged stability batches with the newly proposed dissolution method. The provided dissolution data does not demonstrate significant differences from the data generated using the previously proposed dissolution method, as all stability data provided meets the acceptance criterion at Stage 2.

The Applicant has conducted a relative in-vivo bioavailability study between Phase 1 and Phase 2 formulations. The 2-way crossover study has been determined to be adequate per the Clinical Pharmacology Review. The Phase 2 and Phase 3 formulations as well as the Phase 3 to commercial formulations have been adequately bridged via in vitro multimedia (0.1 N HCl, pH 4.5 acetate buffer, pH 6.8 phosphate buffer) comparative dissolution studies.

The 5 mg strength has been adequately bridged from the Phase 3 to the commercial formulations (minor changes) through multimedia (0.1 N HCl, pH 4.5 acetate buffer, pH 6.8 phosphate buffer) comparative dissolution studies. In response to the Agency’s IR, the Applicant has requested a biowaiver of the 10 mg, 15 mg, and 20 mg strength. The proposed biowaiver of the 10 mg, 15 mg, and 20 mg strengths is acceptable based on the BA/BE data provided for the highest dose of the drug product, the adequacy of the in vivo studies of the 5 mg strength as well as PK linearity beyond the therapeutic

dose range (up to 30 mg dose, as determined by the Clinical Pharmacology Reviewer), the compositional dose proportionality (b) (4), and the comparative dissolution conducted in three media (pH 1.2, 4.5, and 6.8) which demonstrates similarity, as indicated by $f_2 > 50$.

Figure 1: Approved Dissolution Method and Acceptance Criterion

Apparatus	Speed	Medium/Volume	Temp	Acceptance Criterion
USP II (Paddle)	50 rpm	pH 4.5; 50 mM Sodium Acetate buffer/ 900 mL	37°C ± 0.5 °C	Q= (b) (4)% in 30 minutes

Figure 2: CQA Table

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
API PSD	High	The proposed drug substance is a low solubility drug substance (BCS Class II), and the dissolution method is not discriminating towards API PSD.	Medium (After cycle 1)	The risk has been mitigated through setting a three-tier acceptance criteria for the API PSD.

Figure 3: Table of Submissions Assessed:

Document(s) Assessed	Date Received
NDA-219083-ORIG-1 SD 1	07/30/2024
NDA-219082-ORIG-1 SD 4	09/26/2024
NDA-219082-ORIG-1 SD 10	12/31/2024
NDA-219082-ORIG-1 SD 19	03/07/2025
NDA-219082-ORIG-1 SD 29	04/15/2025
NDA-219083-ORIG-1 SD 31	04/30/2025
NDA-219083-ORIG-1 SD 32	05/30/2025
NDA-219083-ORIG-1 SD 40	07/21/2025
NDA-219083-ORIG-1 SD 44	09/12/2025
NDA-219083-ORIG-1 SD 47	10/07/2025

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

Concise Description of Outstanding Issues: N/A

Background:

On 07/30/2024, the applicant, Cytokinetics Inc., submitted a 505(b)(1) application for the proposed Aficamten (5, 10, 15 and 20 mg) immediate-release film-coated tablets proposed for the treatment of adults with symptomatic obstructive hypertrophic cardiomyopathy (oHCM). (b) (4)

The proposed commercial formulation is identical to the Phase 3 formulation except for a change in the (b) (4)

Differences in dosage strength are made by (b) (4)

Throughout the drug development process, the Applicant had several meetings with the Agency, as summarized below:

IND Meeting #1: IND 138814 Meeting Minutes dated June 8, 2021

The Applicant requested that the Agency confirm that the changes from the Phase 2 to the Phase 3 formulations were considered SUPAC Level 1 changes and that no bioequivalence (BE) studies were needed to bridge these formulations.

The Agency replied that based on the current information, the bridge could be conducted with in vitro studies through comparative dissolution in line with the SUPAC Level 1 component and composition changes found in the SUPAC IR guidance, as shown in Figure B1 in Appendix B.

IND Meeting #2: IND 138814 Meeting Minutes dated August 12, 2022:

The Applicant inquired if the planned commercial strengths of 5 mg, 10 mg, 15 mg, and 20 mg could be bridged to the phase 3 clinical trials, in which 5 mg tablets were used for a cumulative dose of 5 mg, 10 mg, 15 mg, 20 mg, and 40 mg.

The Agency (Biopharmaceutics, Clinical Pharmacology, and the Clinical Divisions) agreed that in vitro multimedia dissolution could be used to support commercial tablet strengths of 5 mg, 10 mg, 15 mg, and 20 mg with comparative multimedia dissolution, as shown in Figure B2 in Appendix B.

IND Meeting #3: IND 138814 Type B Meeting WRO dated June 09, 2023:

The Applicant asked for feedback on their dissolution method and specifications at the current stage in dissolution development.

The Agency gave them feedback on what data to provide to support the selection of their dissolution method, as shown in Figure B3 in Appendix B. Specifically, the Agency gave the Applicant feedback on their dissolution method development and discriminating ability and encouraged them to develop a dissolution method that was discriminating towards API PSD as the drug substance demonstrates low solubility.

B.1 BCS DESIGNATION

Assessment: The Applicant has claimed BCS Class II (Low solubility, high permeability). Based on the data provided, the Reviewer agrees that Aficamten falls under BCS Class II.

Solubility: Based on the provided physiological [solubility](#) data, the Applicant has demonstrated that the highest proposed strength (20 mg) is not soluble in less than 250 mL of media, under all physiological pH conditions tested.

Permeability: Propranolol (used as the model high permeability compound) had an apparent permeability in the apical-to-basolateral direction of 18.9×10^{-6} cm/s. Aficamten had an apparent permeability in the apical-to-basolateral direction: 41.4×10^{-6} cm/s, which is greater than the model high permeability compound. The Applicant used Digoxin as the probe substrate to show efflux, and the Applicant has shown that Aficamten demonstrates no significant efflux (efflux ratio: 0.7, which is less than 2). Based on the data provided (Figure 4), the Applicant has demonstrated that Aficamten does not demonstrate significant efflux and is considered highly permeable.

Figure 4: Aficamten Permeability Studies

Plates	12-well
Seed Date	11/16/2016
Passage Number	64
Age at QC (days)	20
Age at Experiment (days)	21
Acceptance Criteria	
Atenolol P_{app} , 10^{-6} cm/s	0.19
Propranolol P_{app} , 10^{-6} cm/s	18.9
Digoxin A-to-B P_{app} , 10^{-6} cm/s	0.37
Digoxin B-to-A P_{app} , 10^{-6} cm/s	11.0
Digoxin Efflux Ratio	19.4

5. EXPERIMENTAL RESULTS

Test Article	Direction	Recovery (%)	P_{app} (10^{-6} cm/s)			Efflux Ratio	Absorption Potential Classification	Significant Efflux
			R1	R2	AVG			
CK3773274 batch 02	A-to-B	119	47.2	35.6	41.4	0.7	High	No
	B-to-A	124	30.9	28.6	29.8			

6. INTERPRETATION AND ADVANCEMENT POTENTIAL

Absorption Potential Classification: P_{app} (A-to-B) $< 1.0 \times 10^{-6}$ cm/s: **Low**
 P_{app} (A-to-B) $\geq 1.0 \times 10^{-6}$ cm/s: **High**

Significant Efflux: $ER \geq 2.0$ and P_{app} (B-to-A) $\geq 1.0 \times 10^{-6}$ cm/s

Dissolution: The Applicant has demonstrated that Aficamten demonstrates slow dissolution [\(b\) \(4\)](#). Please refer to assessment below for additional details.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: *{Adequate}*

The Applicant has used several dissolution methods throughout the Phase 1, 2 and 3 trials as well as throughout drug product development of the commercial formulation as summarized in Figure 5. For further details on dissolution methods that were

formerly used but are no longer proposed for implementation as a QC dissolution method, please see Appendix A: Dissolution Method Development for Previously Proposed Dissolution Methods.

Figure 5: Summary of Dissolution Method Development

Clinical Development Phase	Phase 1	Phase 2	Phase 3	Primary Stability	Primary Stability/Commercial
Applicable Formulation	(b) (4)	Film-coated tablets	Film-coated (b) (4) tablets	Film-coated (purple) tablets	Film-coated (purple) tablets
Formulation Drug Loading (w/w)	(b) (4)				(b) (4)
Intended Formulation Dosage Range (mg)					5 - 20
USP Apparatus Type					2
Medium					50 mM pH 4.5 Acetate Buffer (b) (4)
Medium Volume (mL)					900
Paddle Speed (rpm)					50
Sample Analysis					HPLC

chromatography; (b) (4) HPLC = high performance liquid

In response to the Agency's recommendation to implement the originally proposed dissolution method but (b) (4) in the dissolution medium, the Applicant has proposed a new dissolution method (Figure 1) (b) (4).

In developing a new (b) (4) dissolution method, the Applicant explored multimedia pH dissolution studies (pH 1.2, 4.5, 6.8) and has determined that the drug product demonstrates pH-independent solubility. The Applicant then explored the rotational speed and determined that 50 RPM was a suitable rotational speed, which demonstrated complete release (>85%) in 30 minutes with low variability. The Applicant evaluated the robustness of each dissolution method parameter, which is adequate. Additionally, the dissolution analytical method and validation was found adequate by the drug product reviewer (See Drug Product Review for further details).

The Applicant claimed that the (b) (4) drug release medium inhibits the ionization of (b) (4) in the formulation and reduces the drug substance release with higher data variability, and the (b) (4) also demonstrated higher variability. Therefore, the Applicant has chosen pH 4.5 buffer as the drug release medium. Based on the complete dissolution development studies, the Applicant has proposed the dissolution method shown in Figure 1.

To investigate the discriminating ability of the proposed dissolution method, the Applicant studied the impact of the (b) (4) on dissolution and the impact of disintegrant as shown in Figure 6. The Applicant was not able to demonstrate the discriminating ability of the proposed dissolution method (b) (4) but they were able to demonstrate limited discriminating ability of the aberrant formulations with (b) (4), as supported by dissolution profile dissimilarity ($f_2 < 50$). See

Figure 7. It is noted that the (b) (4), which is beyond the normally recommended range for meaningful changes.

Although the dissolution method has limited discriminating ability and the drug substance is a low solubility drug substance, it is noted that rapid dissolution is observed across multimedia pH, likely due to (b) (4) in the drug product. The risk is medium due to the rapid dissolution observed and the limited discriminating ability of the proposed dissolution method.

To further mitigate the risk of this low solubility drug substance, the Applicant was recommended to implement a three-tier API PSD specification via IR. In response to the IR, the Applicant has implemented a three-tier API PSD (Figure 8), which the drug substance reviewer has found adequate. See the Drug Substance Review for further details.

Based on the cumulative data submitted, the risk has been mitigated, and the dissolution method is adequate from a Biopharmaceutics perspective. However, the originally proposed acceptance criterion was permissive. Additionally, the Applicant had originally implemented (b) (4)

(b) (4)
Therefore, the Applicant was recommended via IR to adopt “Q= (b) (4) % in 30 minutes” as the acceptance criterion across all strengths and eliminate (b) (4) in their QC dissolution method via IR. In response to the Agency’s IR, the Applicant has eliminated (b) (4) and implemented the dissolution acceptance criterion of “Q= (b) (4) % in 30 minutes”.

The Applicant had originally conducted stability testing using only the previously proposed dissolution method. Although the Applicant had committed to conducting all future stability and batch release testing using the newly approved dissolution method, no stability data had been provided using the new method. Therefore, the Applicant was requested via IR to test stability batches using both dissolution methods to ensure there is no significant difference in stability dissolution testing between the two test methods. In response to the Agency’s IR, the Applicant has conducted stability testing using the current aged stability batches with the newly proposed dissolution method. The provided dissolution data does not demonstrate significant differences from the data generated using the previously proposed dissolution method, as all stability data provided meets the acceptance criterion at Stage 2.

Based on the totality of the data submitted, the dissolution method and acceptance criterion as shown in Figure 1 are adequate from a Biopharmaceutics perspective.

Figure 6: Control vs Intentionally Aberrant Formulations used in discriminating ability studies

Sample Type	Lot	Dose	Control vs Aberrant Tablets Description
(b) (4)			

Figure 7: Comparative Dissolution Profiles to demonstrate the discriminating ability of the proposed dissolution method

Lot	Mean %Dissolved (%RSD), n = 12							
	10 minutes	15 minutes	20 minutes	30 minutes	45 minutes	60 minutes	75 minutes	f ₂
KL-0072	71 (3.0)	78 (1.6)	82 (1.7)	85 (1.9)	88 (2.1)	90 (2.2)	95 (0.9)	
KL-0098	45 (6.2)	55 (2.8)	62 (1.6)	69 (1.4)	76 (1.3)	81 (1.1)	88 (0.5)	33
KL-0053	76 (3.1)	82 (1.6)	86 (1.2)	90 (1.5)	93 (1.6)	94 (1.7)	99 (0.9)	
KL-0082	66 (3.4)	72 (2.1)	76 (1.8)	81 (1.8)	84 (1.9)	87 (2.0)	93 (0.6)	50

Figure 8: Proposed Limits for D90, D50, and D10 API PSD

	Mean	Standard Deviation	Proposed Limit
D90:	(b) (4)		NMT (b) (4)
D50:			NMT
D10:			NMT

NMT = not more than

Assessment: {Adequate/Inadequate}
N/A

Assessment: {Adequate/Inadequate}
N/A

Assessment: {Adequate/Inadequate}
N/A

Assessment: {Adequate}

The Applicant's initial bridging strategies from Phase 1 to the proposed commercial formulation were not clear. Therefore, an IR was sent (dated 12/18/24) requesting clarification on the bridging strategies. In response to this IR, the Applicant has provided more detailed information on their bridging strategies. The Applicant has 4 formulations throughout their development (Phase 1, Phase 2, Phase 3, and commercial formulation). The Applicant has provided a summary of the formulations in Figure 9.

Figure 9: Formulation Comparison for Phase 1, Phase 2, Phase 3, and Commercial Formulations

Ingredients	Phase 1 ^a	Phase 2	Phase 3	Proposed Commercial				
				(b) (4)				
				% w/w	mg/tablet			
				(b) (4)	5 mg	10 mg	15 mg	20 mg
Aficamten drug substance			(b) (4)					(b) (4)
Mannitol								
Microcrystalline cellulose								
Croscarmellose sodium								
Hydroxypropyl cellulose								
Sodium lauryl sulfate								
Total (coated tablets)					51.5	103.0	154.5	206.0

N/A: not applicable

(b) (4)

Bridging Between Phase 1 and Phase 2 Formulations:

The Applicant has conducted a relative in-vivo bioavailability study between the Phase 1 (b) (4) formulation and the Phase 2 (tablet with (b) (4) w/w drug load) formulations. The acceptability of the 2-way crossover study with 12 adults has been determined to be adequate per the Clinical Pharmacology Reviewer. See the Clinical Pharmacology Review for further details.

Bridging Between Phase 2 and Phase 3 Formulations:

Between the Phase 2 and Phase 3 formulations, the Applicant (b) (4) Aficamten from (b) (4) w/w to (b) (4) w/w and (b) (4)

(b) (4) Since the change in excipients (b) (4), this change is considered a SUPAC Level 1 change, as per the drug product reviewer. Per the SUPAC IR guidance, a SUPAC level 1 change in excipients would require meeting the Application/compendial dissolution requirements. However, there was no approved dissolution method at the time of this study, and the Applicant had originally conducted a comparative dissolution study for the 5 mg strength. Both dissolution profiles demonstrate very rapid dissolution (>85% drug release in 15 minutes).

Bridging Between Phase 3 and Commercial Formulations:

Phase 3 in vivo clinical trials used multiples of the 5 mg tablet to achieve dosing of 5 mg, 10 mg, 15 mg, and 20 mg, which are all made from (b) (4) that was used in the Phase 3 clinical trials. Additionally, (b) (4) in the phase 3 clinical trial and commercial drug product. In support of this bridge, the Applicant has conducted multimedia comparative dissolution (in alignment with the Agency's advice in an IND meeting dated 8/25/22).

To bridge the clinical batch formulations of the 5 mg tablet (Phase 2 to Phase 3) and (Phase 3 to commercial formulation), the Applicant had originally provided multimedia comparative dissolution studies with multimedia pH drug release medium (b) (4)

(b) (4) In response to 2 IRs (dated 02/24/25 and 04/07/25), requesting multimedia dissolution (in 0.1 N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer) (b) (4) to support the clinical bridging, the Applicant has provided comparative dissolution profile studies between Phase 2 and Phase 3 formulations as well as between Phase 3 and the commercial formulations using multimedia dissolution (b) (4) as summarized in Figure 10.

To conduct these comparative dissolution studies, the Applicant has provided 3 batches of each strength (5 mg, 10 mg, 15 mg, and 20 mg) for the commercial formulation, 2 batches of the Phase 3 formulation (at the 5 mg strength but with 4 tablets per vessel used to represent a 20 mg dose strength), and one batch of the Phase 2 formulation (at the 5 mg strength but with 3 tablets used per vessel to represent the 15 mg strength). All comparative multimedia dissolution profiles across all strengths and conditions tested are similar, with the 20 mg, 15 mg, and 10 mg strengths demonstrating similar dissolution profiles ($f_2 > 50$) at all conditions tested (0.1 N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer) and the 5 mg strengths demonstrating rapid drug release (>85% in 30

minutes) at all conditions tested (0.1 N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer). See Figures 11-19. All multimedia comparative bridging studies are adequate from a Biopharmaceutics perspective, and the Applicant has adequately bridged the 5 mg Phase 2 to Phase 3 formulation as well as the 5 mg Phase 3 to commercial formulations.

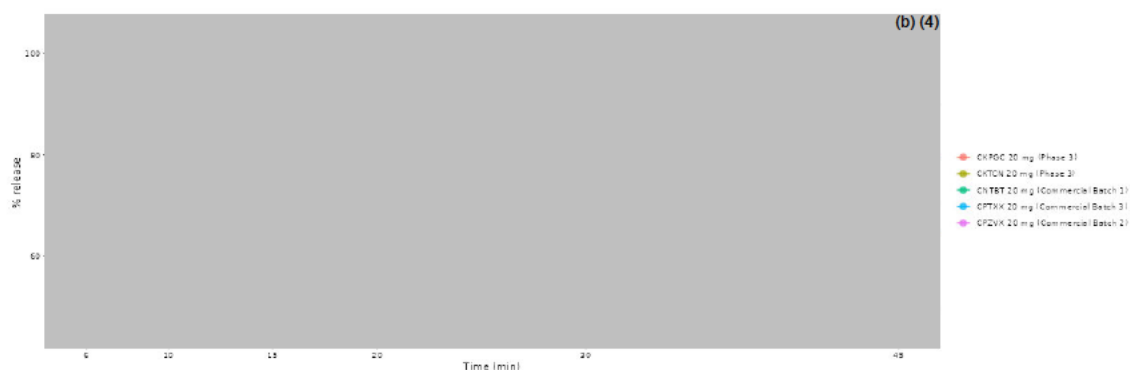
Figure 10: Batches used to support bridging of clinical formulations

	Commercial formation (registration stability batch 1)	Commercial formation (registration stability batch 3)	Commercial formation (Supportive stability batch 2)	Phase 3	Phase 2
5 mg	CNTBM	CPTXH	CPZVZ	CKTCN CKPGC	CMFGX
10 mg	CNTBP	CPTXS	CPZWC	N/A	N/A
15 mg	CNTBS	CPTXV	CPZWD	N/A	N/A
20 mg	CNTBT	CPTXX	CPZVX	N/A	N/A

Figure 11: 0.1 N HCl 20 mg comparative dissolution



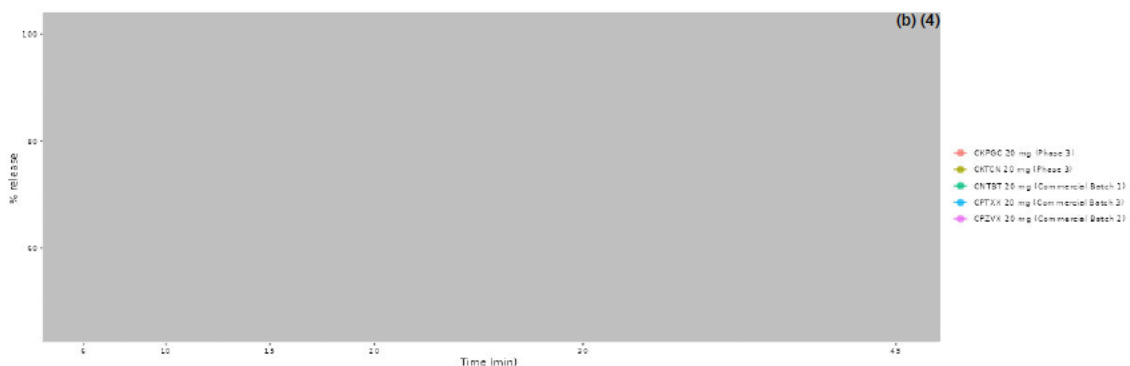
Figure 12: pH 4.5 Acetate Buffer 20 mg Comparative Dissolution



Mean plot: Red horizontal line: Q(%); Blue horizontal line: Q-15%

Name	F2-Value
CKTCN 20 mg (Phase 3) Vs CKPGC 20 mg (Phase 3)	66.94
CKTCN 20 mg (Phase 3) Vs CNTBT 20 mg (Commercial Batch 1)	59.57
CKTCN 20 mg (Phase 3) Vs CPTXX 20 mg (Commercial Batch 3)	63.59
CKTCN 20 mg (Phase 3) Vs CPZVX 20 mg (Commercial Batch 2)	65.05
CKPGC 20 mg (Phase 3) Vs CNTBT 20 mg (Commercial Batch 1)	74.37
CKPGC 20 mg (Phase 3) Vs CPTXX 20 mg (Commercial Batch 3)	76.64
CKPGC 20 mg (Phase 3) Vs CPZVX 20 mg (Commercial Batch 2)	85.51
CNTBT 20 mg (Commercial Batch 1) Vs CPTXX 20 mg (Commercial Batch 3)	89.63
CNTBT 20 mg (Commercial Batch 1) Vs CPZVX 20 mg (Commercial Batch 2)	85.51
CPTXX 20 mg (Commercial Batch 3) Vs CPZVX 20 mg (Commercial Batch 2)	89.63

Figure 13: pH 6.8 Phosphate Buffer 20 mg Comparative Dissolution



Mean plot: Red horizontal line: Q(%); Blue horizontal line: Q-15%

Name	F2-Value
CKTCN 20 mg (Phase 3) Vs CKPGC 20 mg (Phase 3)	89.63
CKTCN 20 mg (Phase 3) Vs CNTBT 20 mg (Commercial Batch 1)	67.92
CKTCN 20 mg (Phase 3) Vs CPTXX 20 mg (Commercial Batch 3)	77.70
CKTCN 20 mg (Phase 3) Vs CPZVX 20 mg (Commercial Batch 2)	69.37
CKPGC 20 mg (Phase 3) Vs CNTBT 20 mg (Commercial Batch 1)	73.77
CKPGC 20 mg (Phase 3) Vs CPTXX 20 mg (Commercial Batch 3)	80.19
CKPGC 20 mg (Phase 3) Vs CPZVX 20 mg (Commercial Batch 2)	75.91
CNTBT 20 mg (Commercial Batch 1) Vs CPTXX 20 mg (Commercial Batch 3)	77.42
CNTBT 20 mg (Commercial Batch 1) Vs CPZVX 20 mg (Commercial Batch 2)	93.62
CPTXX 20 mg (Commercial Batch 3) Vs CPZVX 20 mg (Commercial Batch 2)	75.91

Figure 14: 0.1 N HCl 15 mg Comparative Dissolution

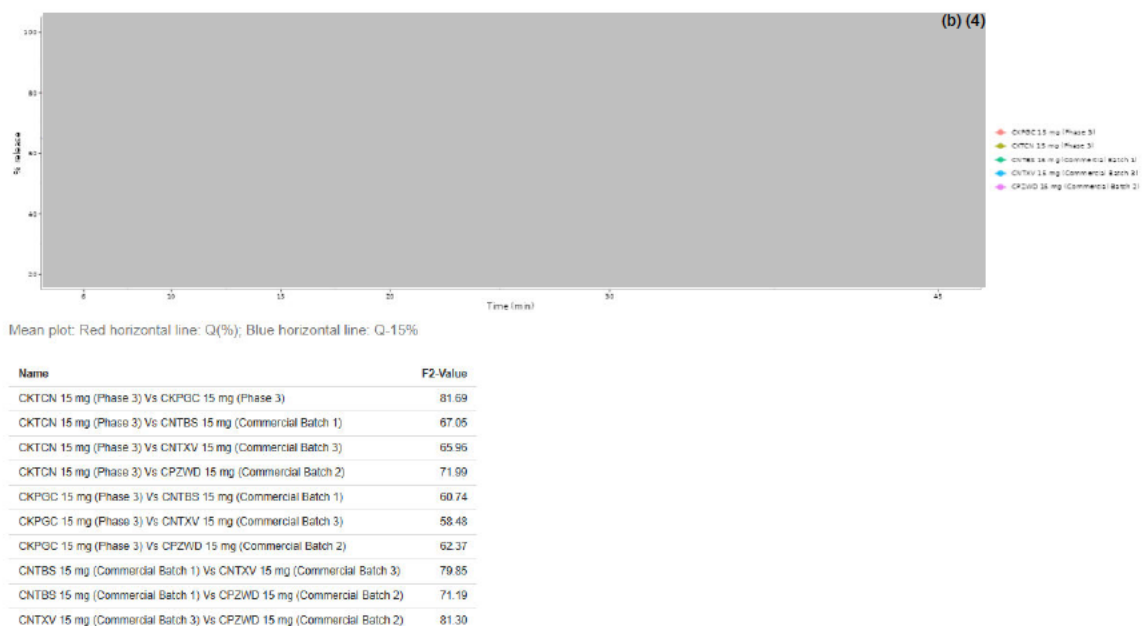


Figure 15: pH 4.5 Acetate Buffer 15 mg Comparative Dissolution

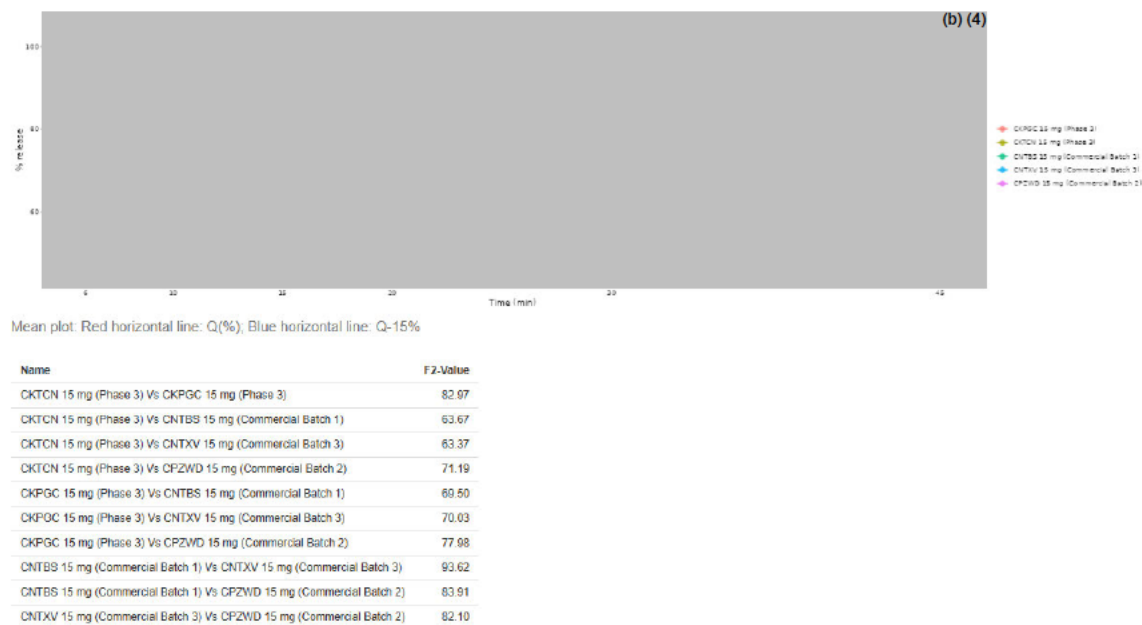


Figure 16: pH 6.8 Phosphate Buffer 15 mg Comparative Dissolution

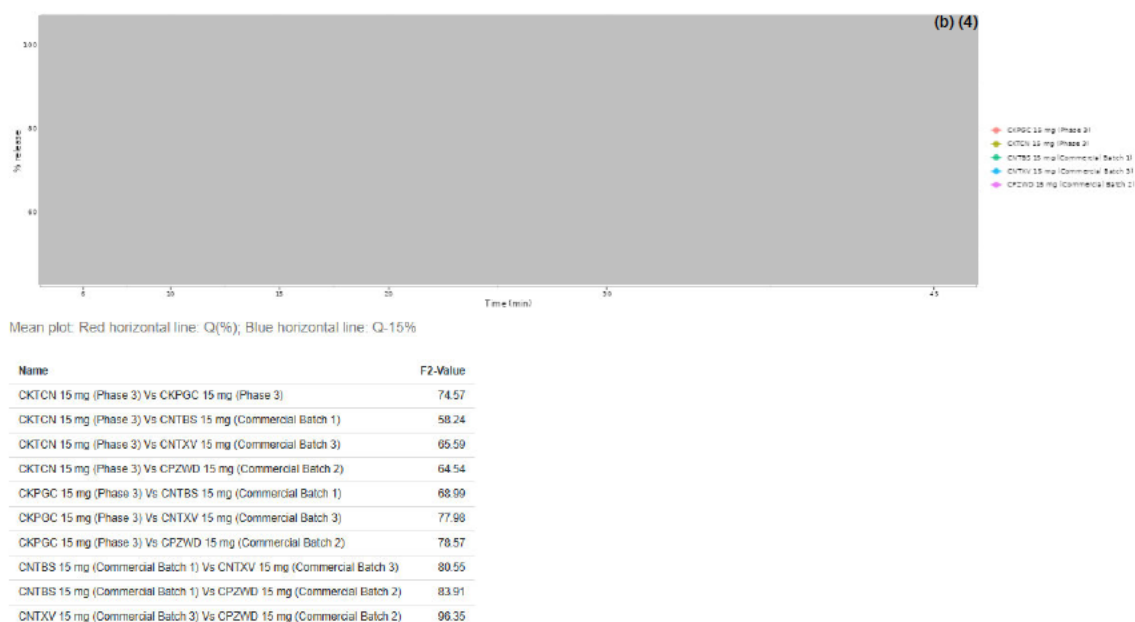


Figure 17: 0.1N HCl 10 mg Comparative Dissolution

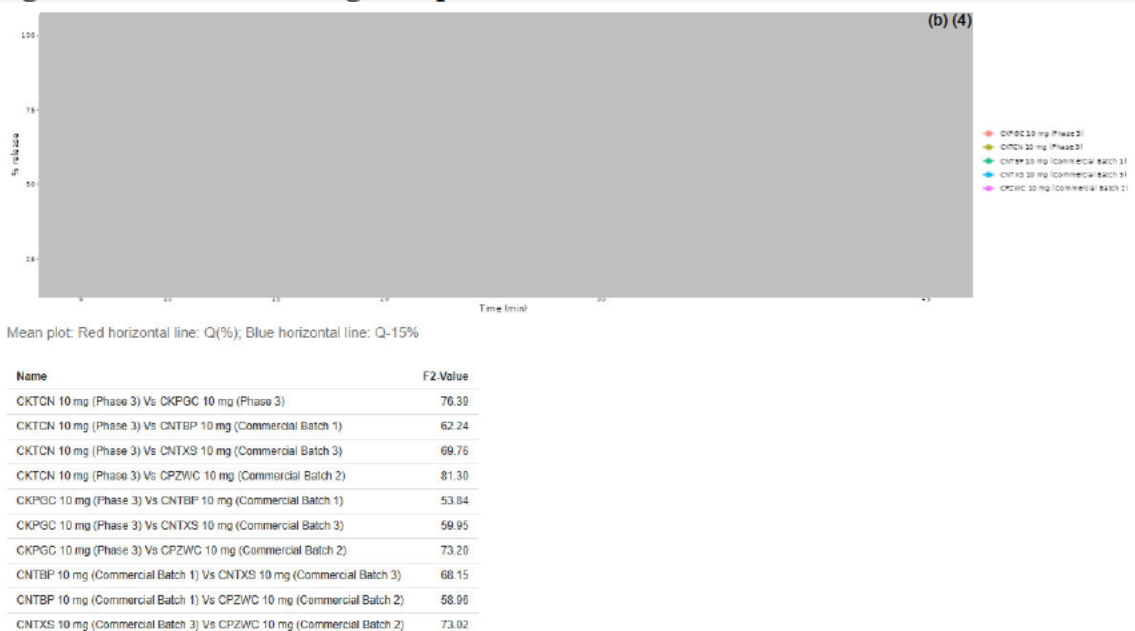


Figure 18: pH 4.5 Acetate Buffer 10 mg Comparative Dissolution

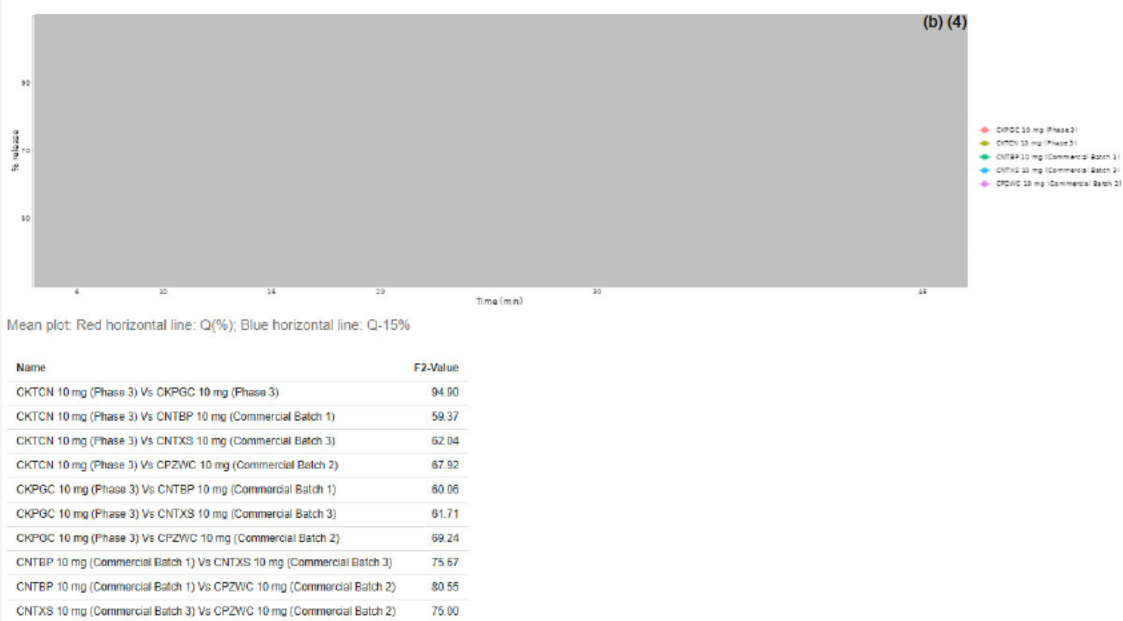
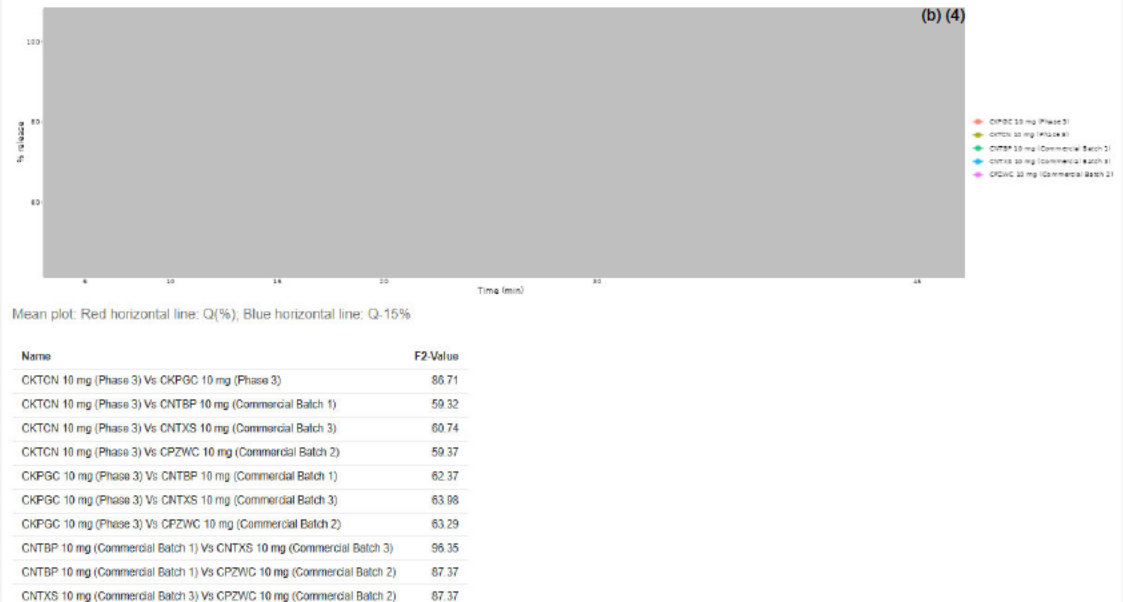


Figure 19: pH 6.8 Phosphate Buffer 10 mg Comparative Dissolution



B. 13 BIOWAIVER REQUEST

Assessment: *{Adequate}*

The Applicant has proposed 4 strengths (5 mg, 10 mg, 15 mg, and 20 mg). Although the Applicant has tested 5 mg, 10 mg, 15 mg, and 20 mg doses in the Phase 3 clinical trials, these doses were tested using increments of the 5 mg strength. Therefore, the Agency sent an IR asking the Applicant to request a biowaiver of the 10 mg, 15 mg, and 20 mg strengths. In response to the Agency's IR, the Applicant has requested a biowaiver of the 10 mg, 15 mg, and 20 mg strength. The proposed biowaiver of the 10 mg, 15 mg, and 20 mg

strengths is acceptable based on the BA/BE data provided for the highest dose of the drug product, the adequacy of the in vivo studies of the 5 mg strength as well as PK linearity beyond the therapeutic dose range (up to 30 mg dose, as determined by the Clinical Pharmacology Reviewer), the compositional dose proportionality (b) (4)

shown in Figure 8, and the comparative dissolution conducted in three media (pH 1.2, 4.5, and 6.8) which demonstrates similarity, as indicated by $f_2 > 50$. In addition to the multimedia dissolution conducted on each strength (documented in the Bridging of Formulations section, the Applicant has shown similarity ($f_2 > 50$) across all strengths (5 mg, 10 mg, 15 mg, and 20 mg) for all Phase 3 and commercial batches across multimedia pH conditions (0.1 N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer), as shown in Figures 20-22. Based on the totality of the data provided, the biowaiver request for the 10 mg, 15 mg, and 20 mg strengths is Acceptable.

Figure 20: 0.1N HCl All Strengths (5 mg, 10 mg, 15 mg, and 20 mg) Comparative Dissolution



Figure 21: pH 4.5 Acetate Buffer All Strengths (5 mg, 10 mg, 15 mg, and 20 mg) Comparative Dissolution

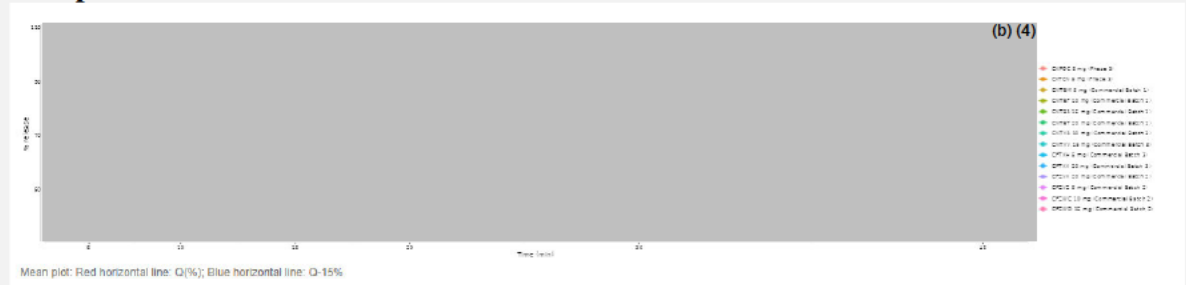
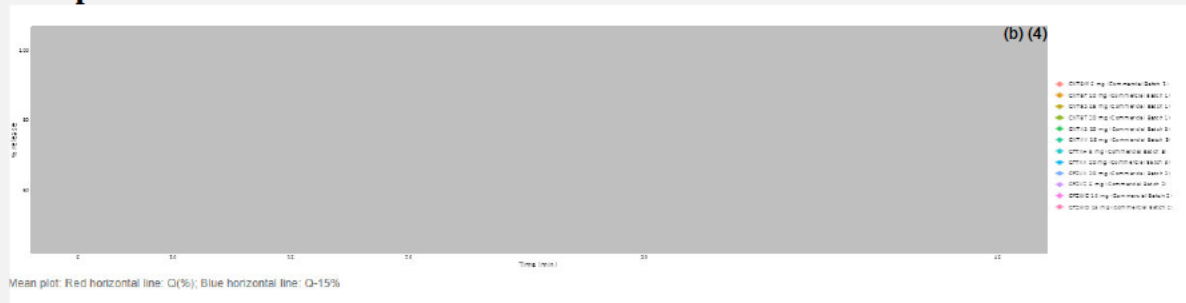


Figure 22: pH 6.8 phosphate buffer all strengths (5 mg, 10 mg, 15 mg, and 20 mg) Comparative Dissolution



R. REGIONAL INFORMATION

Comparability Protocols

Assessment: {*Adequate/Inadequate*}

N/A

Post-Approval Commitments

Assessment: {*Adequate/Inadequate*}

N/A

Lifecycle Management Considerations

N/A

BIOPHARMACEUTICS LIST OF DEFICIENCIES

IR#1: Deficiencies Communicated to the Applicant (Dated 12/18/24):

1. Please provide a summary of bridging strategies between different formulations from the initial formulations to the proposed commercial formulation in your clinical studies. In vitro data needed to support the bridging between formulations can be found in the SUPAC IR Guidance. Specifically, please provide comparative dissolution multi-point profile data for both batches (with varying formulations) [individual (n=12), mean, SD, % CV at each time point and mean profiles). Report the dissolution data as the cumulative percentage of drug dissolved (the percentage is based on the drug product's label claim). Provide formulation details alongside the supportive comparative dissolution profiles.

Applicant's Response (Dated 12/31/24):

The Applicant responded with a summary of the bridging strategy (as shown in the Bridging of Formulations section).

IR#2: Deficiencies communicated to the Applicant (Dated 02/24/25):

1. We acknowledge that the proposed drug substance is considered low solubility (BCS Class II). However, the proposed drug product (b) (4) and very rapid dissolution is observed using the currently proposed dissolution method. The use (b) (4) in the proposed dissolution method should be adequately justified. It is noted that similar drug release is demonstrated between 0.1% CTAB and 0.05% CTAB. We recommend submitting dissolution data using the biobatch and exhibit batches across all strengths (b) (4) 0.01%, 0.02%, 0.03%, and 0.04% CTAB.
2. The discriminating ability of your currently proposed dissolution method has not been adequately demonstrated. We recommend providing:

- A. Data supporting the discriminating ability of the selected dissolution method.
In general, ensure that the testing conducted to demonstrate the discriminating ability of the selected dissolution method compares the dissolution profiles of the target commercial drug product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical material attributes, critical formulation variables, and critical process parameters (e.g., ± 10 -20% change to the specified values or ranges for these variables). We recommend that you investigate the discriminating ability of the proposed dissolution method towards particle size distribution (PSD) and the known polymorphs of the proposed API. Submit the dissolution profile data and similarity testing results obtained with appropriate statistical test (e.g., f_2 values) comparing the aberrant and target drug products. In addition, if available, submit data showing that the selected dissolution method is able to reject product that is not bioequivalent to the reference-target drug product.
 - B. A list of the critical material attributes (CMAs) and critical process parameters (CPPs) affecting dissolution.
 - C. Supportive validation data for the dissolution methodology (bench testing) and analytical method used for assaying the dissolution samples (specificity, precision, accuracy, linearity/range, stability, robustness, etc. For general recommendations on method validation, refer to the USP Chapters “The Dissolution Procedure: Development and Validation” <1092> and “Validation of Compendial Methods” USP Chapter <1225>.
 - D. Complete dissolution multi-point profile data for each variable tested during method development, assessment of discriminating ability, and validation [individual (n=12), mean, SD, % CV at each time point and mean profiles). Report the dissolution data as the cumulative percentage of drug dissolved (the percentage is based on the drug product’s label claim).
3. It is noted that the in vitro dissolution data submitted to bridge formulations was conducted with dissolution media (b) (4). To support the bridge between the Phase 2 formulation and the Phase 3 formulation as well as the bridge between the Phase 3 formulation and proposed commercial formulation, provide comparative multimedia dissolution profile data with (b) (4) added to the media.
 4. Provide multi-point dissolution data (n=12, sampling every 2 hours) from the pivotal clinical/PK drug product-batches and primary registration batches using an appropriately discriminating dissolution method for the setting of the dissolution acceptance criterion of the proposed drug product (i.e., sampling time points and limits). Ensure that the in vitro dissolution profile is complete or if incomplete dissolution occurs, where the plateau of drug dissolved is reached (i.e., no increase over 3 consecutive time-points). Base the dissolution acceptance criterion on the average in vitro dissolution data of each batch/lot under study, equivalent to USP Stage 2 testing (n = 12). Select the sampling time point where $Q = \frac{(b)}{(4)}\%$ dissolution occurs.

Applicant's Response (Dated 03/07/25):

1. The Applicant has responded that the drug release is comparable between different levels (b) (4) and that the variation is high with a (b) (4). Therefore, the Applicant is proposing to (b) (4).
2. The drug release observed is rapid due to (b) (4) present in the formulation. Although the changes in the aberrant formulations are not small/meaningful changes, the Applicant was able to show limited discriminating ability even (b) (4). Therefore, the applicant will be recommended to implement the dissolution method (b) (4).
3. The Applicant notes that multimedia dissolution was not conducted at the time of the Phase 2 and Phase 3 trials and referred the Agency to the IND 138814 Meeting Minutes (Dated June 7, 2021) to support that the Agency had confirmed that in vitro data in place of in vivo data could be used to bridge Phase 2 and Phase 3 clinical trials. However, the Agency did not approve the dissolution method at that stage, and the Agency did not agree that a (b) (4) dissolution medium was an acceptable bridge between formulations. To support the bridge between Phase 2 and Phase 3 formulations as well as between Phase 3 and the proposed commercial formulation, the Agency still recommended the Applicant to submit multimedia dissolution profile data with (b) (4).
4. The Applicant provided exhibit batch data using the originally proposed dissolution method, (b) (4). The Agency recommended that they provide exhibit batch data (b) (4).

IR#3: Deficiencies Communicated to the Applicant (Dated 04/07/25):

1. We acknowledge that drug release is similar between drug release media tested (b) (4). Therefore, your proposal (b) (4) is not justified as dissolution profile data submitted (b) (4) demonstrates complete release (>85%) at 30 minutes. We recommend that you implement the following dissolution method (900 mL of 0.01 N HCl; USP Apparatus II at 57 RPM) and provide corresponding dissolution profile data (n=12) for all exhibit batches.
2. Please note that in the meeting minutes referenced (IND 138814, dated June 07, 2021), the Agency agreed that an in-vivo BE study was not needed to bridge Phase 2 to Phase 3 formulations. However, the Agency did not approve your currently proposed dissolution method at that stage, and the Agency did not agree that (b) (4) dissolution medium was an acceptable bridge between formulations. Additional data are needed to bridge the formulations (Phase 2 to Phase 3 & Phase 3 to proposed commercial formulation), and therefore, we again request that you provide the results of multimedia dissolution studies (b) (4).

Applicant's Response to Deficiencies (Dated 04/15/2025):

The Applicant has responded to our IR. In response to our request that they implement a QC dissolution method with the originally proposed dissolution medium (b) (4) the Applicant has changed (b) (4) with a note that they will submit the dissolution data to support these changes by May 30, 2025, and that dissolution data for the stability batches and multimedia dissolution bridging will be submitted by June 6, 2025.

Additional Applicant's Responses to Deficiencies (Dated 04/30/25):

In response to the Biopharmaceutics IR, the Applicant has provided new dissolution procedures and validation for the newly proposed (b) (4) dissolution method.

Additional Applicant's Responses to Deficiencies (Dated 05/30/25):

The Applicant has provided a dissolution method development report, with new data to support the selection of the proposed (b) (4) dissolution method, with a newly proposed drug release medium. Additionally, they have provided discriminating ability studies and new exhibit batch dissolution profile data using the newly proposed (b) (4) dissolution method.

Furthermore, the Applicant has provided multimedia dissolution studies (b) (4) in support of the clinical bridging.

IR#4: Deficiencies Communicated to the Applicant (from Biopharmaceutics and Drug Substance, Dated 07/14/25):

1. We acknowledge that particle size is controlled in the drug substance specification at $D_{90} \leq (b) (4) \mu m$. The acceptance criteria for D50, D10, or mean particle size are defined as "report." Since your drug substance demonstrates low solubility, and the dissolution method has not been shown to be discriminating with respect to particle size, revise the drug substance specification to include numeric acceptance criteria for D10, D50, and D90 based on results of clinical batches, primary and supportive stability batches, and PPQ batches, as listed in section 3.2.S.4.4. These acceptance criteria are needed in the drug substance specification to ensure adequate control of the drug substance particle size as recommend in the ICH Q6A guidance, Specification: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances.

Applicant's Response to the Deficiency (Dated 07/21/24):

The Applicant has implemented a three-tier acceptance criteria for API PSD, which the drug substance reviewer has found adequate. There are no additional concerns from a Biopharmaceutics perspective since the risk of this low solubility API has been mitigated through the setting of a three-tier API PSD.

Table 1: Proposed Limits for D90, D50, and D10

	Mean	Standard Deviation	Proposed Limit
D90:	(b) (4)	(b) (4)	NMT (b) (4)
D50:			NMT
D10:			NMT

NMT = not more than

IR#5: Deficiencies communicated to the Applicant (Dated 09/05/25):

1. Based on the submitted in vitro dissolution profile data, the proposed dissolution acceptance criterion of "Q= (b) (4) % in (b) (4) minutes" is permissive for your proposed Aficamten Tablets and NOT acceptable. The following data-driven dissolution acceptance criterion is recommended: "Q=80% in 30 minutes". Implement the recommended acceptance criterion for all the strengths of your drug product at release and on stability and update the specifications of your drug product with the revised acceptance criterion for the dissolution test, accordingly.

In addition, please be advised, that all proposed exhibit batches are expected to meet the revised dissolution acceptance criterion in your stability program through your proposed expiry period. If dissolution failures are observed on stability these should be described. Discuss any corrective actions to avert such dissolution failures and provide a new batch to demonstrate correction of the issue, if needed.

Additionally, we recommend retaining the same rotational speed (50 RPM) throughout the QC dissolution test, without increasing the rotational speed (b) (4)

Applicant's Response to the Deficiency (dated 09/12/2025): In response to this IR, the Applicant has implemented "Q=80% in 30 minutes" as the dissolution acceptance criterion and eliminated the (b) (4) in their QC dissolution method.

IR#6: Deficiencies Communicated to the Applicant (Dated 09/24/25):

1. Please include a biowaiver request in the NDA submission for the strengths not tested clinically (20 mg, 15 mg, 10 mg). Acceptability of the waiver is based upon BA/BE data has been provided for the highest dose of the drug product; Evidence of PK linearity over the therapeutic dose range has been demonstrated; All strengths are compositionally proportional (b) (4); and Dissolution profile comparisons between the strength for which in vivo BA/BE has been demonstrated, and all other strengths meet f2 similarity requirement in three different pH media (pH 1.2,

4.5, and 6.8) using similar dissolution conditions, in addition to the proposed dissolution method.

2. You have provided data comparing the (b) (4) dissolution method with the originally proposed dissolution method after possible drug product manufacturing aberrations. However, it is unclear if there are changes that affect in vitro release for the drug product near the end of shelf life, which may be detectable using the more discriminating (b) (4) dissolution method. Therefore, provide dissolution testing data for aged stability batches of each strength with both the (b) (4) QC dissolution method and previously proposed QC dissolution method.

Applicant's Response to the Deficiency (dated 10/07/2025):

1. In response to the Agency's IR, the Applicant has submitted a biowaiver request in the NDA submission under Module 1.12.15 while highlighting the data required for the biowaiver, including the PK linearity over the dose range, the compositional proportionality across all tablet strengths (b) (4), and dissolution profile similarity ($f_2 > 50$).

2. Additionally, the Applicant has provided dissolution profiles of the stability batches using the (b) (4) dissolution method. The provided dissolution data does not demonstrate significant differences from the data generated using the previously proposed dissolution method, as all stability data provided meets the acceptance criterion at Stage 2. Furthermore, the drug product reviewer, Dr. Jennifer McCord has confirmed that she has no concerns with the recently submitted stability data generated using the new dissolution method.

Primary Biopharmaceutics Assessor's Name and Date: Dr. Nadia Ahmed, 9/23/2025

Secondary Assessor Name and Date (and Secondary Summary, as needed): Dr. Haritha Mandula and Dr. Bhagwant Rege 10/14/25



Nadia
Ahmed

Digitally signed by Nadia Ahmed

Date: 10/14/2025 02:08:26PM

GUID: 5e0e0b9100939fa4af29f1127f130ee2



Bhagwant
Rege

Digitally signed by Bhagwant Rege

Date: 10/14/2025 02:10:10PM

GUID: 508da7020002876d9787e86a3cc8acf5



Theodore
Carver

Digitally signed by Theodore Carver

Date: 10/16/2025 06:12:44PM

GUID: 5d963967007fd4bc3c9fab2a6c3eade

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/

THEODORE E CARVER
10/16/2025 06:19:31 PM