CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217564Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	217564		
Applicant Name	Takeda Pharmaceuticals USA, Inc.		
Drug Product Name	FRUZAQLA (fruquintinib) capsules		
Dosage Form.	Capsule		
Proposed Strength(s)	1 mg and 5 mg		
Route of Administration	Oral		
Maximum Daily Dose	5 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	FRUZAQLA is indicated for the treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild-type, an anti-EGFR therapy.		
Drug Product Description	1 mg: Size 3 hard gelatin capsule with yellow opaque cap and white opaque body, imprinted with “HM013” over “1mg” on the body in black ink 5 mg: Size 1 hard gelatin capsule with a red opaque cap and white opaque body, imprinted with “HM013” over “5mg” on the body in black ink		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	Store at 20°C to 25°C (68°F to 77°F). Brief exposure to 15 °C and 30 °C (59 °F to 86°F) permitted (see USP Controlled Room Temperature).		
Review Team	**Discipline**	**Primary**	**Secondary**

	Drug Substance	Rajan Pragani, Ph.D.	Haripada Sarker, Ph.D.
	Drug Product/ Labeling	Yang Nan, Ph.D.	Thomas Oliver, Ph.D.
	Manufacturing	Md Abdullah Mahmud, Ph.D.	Zhaoyang Meng, Ph.D.
	Biopharmaceutics	Rajesh Savkur, Ph.D.	Anitha Govada, Ph.D.
	Microbiology		
	Other (specify):	None	None
	RBPM	Janell Artis, PharmD	
	ATL	Yang Nan	
Consults	The Division of Microbiology Assessment-I was consulted regarding the microbial control of the drug product. Dr. Bernard Marasa (primary) and Dr. Julie Nemecek (secondary) provided a response to the consult.		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

Based on the stability data submitted to date, the expiry dating period for FRUZAQLA (fruquintinib) capsules shall be **24 months** from the date of manufacture when stored at 20°C to 25°C (68°F to 77°F). Brief exposure to 15°C to 30°C (59°F to 86°F) permitted [see USP Controlled Room Temperature].

b. Additional Comments for Action

None

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

OPQ recommends APPROVAL of NDA 217564 for the commercialization of FRUZAQLA (fruquintinib) capsules (1 mg and 5 mg). Based on our evaluation of the available information, the Applicant provided sufficient

information to support an approval recommendation from the drug product quality perspective. The Applicant provided adequate information on the proposed drug product to ensure the identity, strength, purity, and quality of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. The proposed labeling and labels include adequate information to meet the regulatory requirements.

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

Recommendation by Subdiscipline:

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

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

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments: None

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CHAPTER III: ENVIRONMENTAL

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

R REGIONAL INFORMATION

Environmental

See the above environmental assessment under Regional Information.

Assessment: *Adequate*

As the API production is only (b) (4) kg/year, CDER EA Team confirmed by email that CDER EA Team assessment for this NDA is not needed.

Primary Drug Product Assessor Name and Date:
Yang Nan, Ph.D.

Secondary Assessor Name and Date (and Secondary Summary, as needed)
Thomas Oliver, Ph.D., Director

Yang Nan

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Date: 8/23/2023 10:25:41AM
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Thomas Oliver

Digitally signed by Thomas Oliver
Date: 8/23/2023 10:34:11AM
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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER IV: LABELING

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

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

The draft USPI is provided via the following link: USPI.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Adequate	FRUZAQLA (fruquintinib) capsules, for oral use
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	Dosage form: capsule Strengths: 1 mg and 5 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	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	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	N/A	

applicable to another 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	
Strength(s) in metric system	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	The description of the capsule content may not be necessary. Recommend revision as follows: 1 mg: Size 3 hard gelatin capsule with yellow opaque cap and white opaque body, imprinted with "HM013" over "1mg" on the body in black ink 5 mg: Size 1 hard gelatin capsule with a red opaque cap and white opaque body, imprinted with "HM013" over "5mg" on the body in black ink
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)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	
Dosage form(s) and route(s) of administration	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	N/A	
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	The inactive ingredients in the capsule shell and printing ink are not organized alphabetically. In addition, not all the components in the printing ink are listed. Recommend revision as follows: FRUZAQLA (fruquintinib) capsules for oral administration contain 1 mg or 5 mg of fruquintinib. The inactive ingredients are corn starch, microcrystalline cellulose, and talc. The 1 mg capsule shell contains FD&C Yellow No. 5 (tartrazine), FD&C Yellow No. 6 (sunset yellow FCF), gelatin, and titanium dioxide. The 5 mg capsule shell contains FD&C Blue No. 1 (brilliant blue FCF), FD&C Red No. 40 (allura red AC), gelatin, and titanium dioxide. The printing ink for 1 mg and 5 mg capsules contains dehydrated alcohol, isopropyl alcohol, butanol, ferrosoferric oxide, potassium hydroxide, propylene glycol, purified water, strong ammonia solution, and shellac.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	

If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	N/A	
Pharmacological/Therapeutic class	Adequate	
Chemical name, structural formula, molecular weight	Adequate	
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Adequate	

Section 11 (DESCRIPTION) Continued

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

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

<table>
<tr><th>Item</th><th>Items in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)</th><th>Assessor’s Comments (If an item is Inadequate, provide more details on the issues, as appropriate)</th></tr>
<tr><td colspan="3">HOW SUPPLIED/STORAGE AND HANDLING section</td></tr>
<tr><td>Available dosage form(s)</td><td>Adequate</td><td></td></tr>
<tr><td>Strength(s) in metric system</td><td>Adequate</td><td></td></tr>
<tr><td>Available units (e.g., bottles of 100 tablets)</td><td>Adequate</td><td></td></tr>
<tr><td>Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)</td><td>Adequate</td><td>Description of the capsules is not provided. Recommend revision for “How Supplied” as follows:
<table>
<tr><th>Capsule Strength</th><th>Description</th><th>Package Configuration</th><th>NDC Number</th></tr>
<tr><td>1 mg</td><td>Size 3 hard gelatin capsule with yellow opaque cap and white opaque body, imprinted with “HM013” over “1mg” on the body in black ink</td><td rowspan="2">White high-density polyethylene (HDPE) bottle with child-resistant closure packaged in a carton

Each bottle contains 21 capsules.
(b) (4)</td><td>(b) (4)</td></tr>
<tr><td>5 mg</td><td>Size 1 hard gelatin capsule with a red opaque cap and white opaque body, imprinted with “HM013” over “5mg” on the body in black ink</td><td>(b) (4)</td></tr>
</table></td></tr>
<tr><td>Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”</td><td>N/A</td><td></td></tr>
<tr><td>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.</td><td>N/A</td><td></td></tr>
</table>

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	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	The proposed (b) (4) is not acceptable. Recommend revision as follows: Store at 20°C to 25°C (68°F to 77°F). Brief exposure to 15 °C and 30 °C (59 °F to 86°F) permitted (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	No information about child-resistant packaging is provided. See the above recommendation to include child-resistant packaging information.

1.2.5 Other Sections of Labeling

Assessment: The 1 mg capsule shell contains FD&C Yellow Number 5 (tartrazine). Per 21 CFR 201.20, the labeling should bear the following warning statement: "This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity." The Applicant includes such warning statement under the section 5.10 in the USPI, which is acceptable.

In addition, the Applicant includes a warning statement for FD&C Yellow No. 6 under the section 5.10.

1.2.6 Manufacturing Information After Section 17 (for drug products)

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

2.0 PATIENT LABELING

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

The Patient Information contains the ingredient information and storage conditions. The Applicant will be recommended to revise the corresponding sections accordingly per the recommendations in sections 3, 11 and 16.

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2]	Adequate	
Special preparation instructions (if applicable)	N/A	
Storage and handling information (if applicable)	Adequate	The proposed storage conditions (b) (4) is not acceptable. Refer to section 16 for recommendations.
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.	Adequate	
Active ingredient(s) (if applicable)	Adequate	
Alphabetical listing of inactive ingredients (if applicable)	Adequate	Please see section 11 for recommendations. In addition, the Applicant is required to declare the presence of FD&C Yellow No. 5 and FD&C Yellow No. 6
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	

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

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels

1 mg (as an example):

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

3.2 Carton Labeling

1 mg (as an example):

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[3], (font size and prominence)	Adequate	
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	
Net contents (e.g., tablet count, volume of liquid)	Adequate	
"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	
Lot number and expiration date	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	Recommend revision of storage conditions as follows: Store at 20°C to 25°C (68°F to 77°F).
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	

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

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	Adequate	
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.	Adequate	

Assessment of Carton and Container Labeling: ***Adequate provided that the Applicant adequately addressed all the FDA's revision recommendations.***

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

Approval provided the Applicant provides adequate updates on the USPI, container and carton labels per FDA recommendations. See evaluation above.

Primary Labeling Assessor Name and Date:

Yang Nan, Ph.D.

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

David Claffey, Ph.D., Branch Chief

Yang Nan

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David Claffey

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CHAPTER VI: BIOPHARMACEUTICS

NDA Number	NDA 217564-ORIG-1-505(b)(1)
Submission History	12/16/2022 (Seq 0001): Original submission/Rolling submission 3/30/2023 (Seq 0003): Original submission/Rolling submission 5/30/2023 (Seq 0011): Response to the Biopharmaceutics IR #1 7/14/2023 (Seq 0018): Response to the Biopharmaceutics IR #2 7/24/2023 (Seq 0023): Response to the Biopharmaceutics IR #3
Drug Product Name/ Strength	Fruquintinib (HMPL-013) Capsules, 1 mg and 5 mg
Route of Administration	Oral
Applicant Name	Takeda Pharmaceutical Company Ltd.
Therapeutic Classification/ OND Division	DO3
Proposed Indication	Fruquintinib is indicated for the treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; an anti-VEGF therapy; and, if RAS wild-type, an anti-epidermal growth factor receptor (EGFR) therapy.
IND Number	IND 131038
Primary Reviewer	Rajesh Savkur, Ph.D.
Secondary Reviewer	Anitha Govada, Ph.D.
Assessment Recommendation	**Adequate**

EXECUTIVE SUMMARY

In this submission, the Applicant seeks approval of Fruquintinib (HMPL-013) capsules of 1 mg and 5 mg strengths. The proposed drug product is a Vascular Endothelial Growth Factor (VEGF)-receptor kinase inhibitor that is indicated for the treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; an anti-VEGF therapy; and, if RAS wild-type, an anti-epidermal growth factor receptor (EGFR) therapy. NDA-217564-ORIG-1 was initially submitted to the Division of Oncology Products 3 on 12/16/2022 under section 505(b)(1). The proposed drug product is an immediate release product available as 1 mg and 5 mg capsules. The recommended dose is 5 mg administered orally once daily without regard to food for the first 21 days (3 weeks) followed by 1 week off (3 weeks on/1 week off [3/1]) therapy on a 28-day treatment cycle.

***Assessment Summary*:**

The Biopharmaceutics assessment focuses on evaluating (i) the *in vitro* dissolution method development, the dissolution data and the dissolution acceptance criterion, and (ii) the bridging data between the commercial/to-be-marketed drug product manufacturing facility and clinical batches manufacturing facility.

- **In Vitro Dissolution Method and Acceptance Criterion:**
  The Applicant developed an in-house dissolution method and submitted a dissolution method development report investigating the selection of each testing parameter. Based on the dissolution data and the information submitted, the following dissolution method and acceptance criterion are recommended and agreed for the Quality Control (QC) test of Fruquintinib Capsules, 1 mg and 5 mg, at batch release and on stability (Table 1).

Table 1: Approved In vitro dissolution method and acceptance criterion for Fruquintinib Capsules, 1 mg and 5 mg

Finalized In vitro dissolution method and acceptance criterion for Fruquintinib Capsules, 1 mg and 5 mg				
Apparatus	**Speed**	**Media Volume/ Temperature**	**Medium**	**Acceptance Criterion**
USP II (Paddle) with sinker	75 rpm	900 mL/ 37 °C	PBS, pH 6.8 with 0.08% SLS	Q = (b) (4)% of Fruquintinib is dissolved in 30 minutes

The initial risk assessment and the strategies to mitigate/reduce the risk to a low level are shown below in Table 2.

Table 2: Risk Assessment

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment	Comments
Particle size distribution of the Fruquintinib API	Medium	A three tier API PSD specification of: $D_{10} \leq$ (b) (4) µm, (b) (4) µm $\leq D_{50} \leq$ (b) (4) µm, $D_{90} \leq$ (b) (4) µm has been proposed. The dissolution method exhibits discriminating ability towards API-PSD	Low	The D_{90} specification has been (b) (4) to $\leq$ (b) (4) µm. The dissolution acceptance criterion and the D_{90} specification would reject batches with a slower dissolution profile (that could be a non-BE to the clinical/validation batches)
Concentration of (b) (4)	Medium	Dissolution Method exhibits limited discriminating capability towards variations in the concentration of (b) (4)	Low	The finalized dissolution method and acceptance criterion exhibit limited discriminating ability towards variations in the concentration of (b) (4). The variability in (b) (4) is not considered as the most relevant critical bioavailability attribute. Therefore, the risk is updated to low.

- **Product Bridging:**
  Bridging of drug product across product development: A single formulation has been used throughout clinical development. There are no changes in the proposed to-be-marketed formulation and the clinical formulation compositions. The only proposed minor change of (b) (4) is not expected to impact the product in vitro performance or in vivo drug release.

  Bridging for manufacturing site change: Three manufacturing sites ((b) (4) and HML Suzhou) were used through the clinical development of the drug product. The proposed manufacturing site for the drug product used in the Phase 3 clinical study and for commercial

manufacture is the HML Suzhou site. An additional, alternate manufacturing site ((b) (4)) has been proposed for commercial manufacturing. Bridging between the drug product batches manufactured from (b) (4) and HML Suzhou manufacturing sites has been established by *in vivo* BE and *in vitro* dissolution studies. Bridging between the HML Suzhou and (b) (4) sites has been demonstrated by *in vitro* dissolution studies.

The list of submissions assessed in the NDA are shown below in Table 3.

Table 3: List of Submissions Being Assessed

IND/NDA	eCTD sequence #	Date of submission	Document
NDA	0001	12/16/2022	Original Submission/Rolling submission
NDA	0003	3/20/2023	Original Submission/Rolling submission
NDA	0011	5/30/2023	Quality/Response to the Biopharmaceutics IR #1
NDA	0018	7/14/2023	Quality/Response to the Biopharmaceutics IR #2
NDA	0023	7/24/2023	Quality/Response to the Biopharmaceutics IR #3

Concise Description of Outstanding Issues *(list bullet points with key information and update as needed)*:
None

OVERALL BIOPHARMACEUTICS RECOMMENDATION:
From a Biopharmaceutics perspective, NDA 217546-ORIG-1 for Fruquintinib Capsules, 1 mg and 5 mg, is **ADEQUATE** and is **RECOMMENDED** for Approval.

BIOPHARMACEUTICS ASSESSMENT

B.1. BCS DESIGNATION:

Assessment: Not Applicable

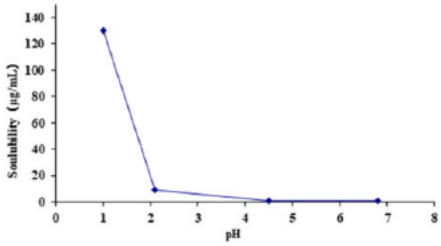
Solubility and Permeability:

The active pharmaceutical ingredient (API), Fruquintinib, is a white to off-white that is soluble in organic solvents (dicholoromethane, methanol, acetone, tetrahydrofuran) and practically insoluble in water. The aqueous solubility profile of the Fruquintinib drug substance across the physiological pH range (as shown below in Table 4 and Figure 1) indicates a pH-independent solubility ranging from 129.9 µg/mL (pH 1.2; in 0.1 M HCl) to 0.9 µg/mL (pH 6.8 Phosphate buffer).

Table 4: Aqueous solubility data of Fruquintinib API (37 °C; 24 hours)

Buffer/pH	Solubility
0.1 M HCl (pH 1.2)	129.9 µg/mL
pH 4.5 Acetate buffer	0.9 µg/mL
pH 6.8 Phosphate buffer	0.9 µg/mL
Purified water	0.7 µg/mL

Figure 1: Aqueous solubility profile of Fruquintinib API (37 °C; 24 hours)



The Caco-2 permeability study indicated that the measured apparent permeability of Fruquintinib in the absorption direction ($P_{app(A\rightarrow B)}$) was ~30×10^{-6} cm/sec at concentrations of 0.5 to 5.0 µM. Co-incubation with Verapamil, an inhibitor of efflux transporters, had no significant effect on the permeability and efflux ratio of Fruquintinib. The mass balance study of Fruquintinib in healthy male volunteers (six volunteers administered a single oral dose of 5 mg/100 µCi [^{14}C]-Fruquintinib) resulted in a ~90% recovery of radioactivity within the period of 336 hours post-dose.

***Reviewer's assessment*:**

Based on the BCS classification system, the Applicant has classified the Fruquintinib API as a BCS Class 2 compound. However, the Applicant has not requested a formal claim for the BCS designation. Hence, the BCS class of the Fruquintinib API has not been assessed.

(b) (4)

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Discriminating ability of the proposed dissolution method: To evaluate the discriminating power of the proposed dissolution method, the release profiles of batches with intentional variations in the critical bioavailability attributes (CBAs) that impact the dissolution of the API and the bioavailability of the drug product were evaluated. The results are summarized below:

(i) Variations in the API-PSD: With the Fruquintinib API being a low-solubility drug substance, the particle size distribution (PSD) of the API was considered as a critical material attribute (CMA) that impacts the dissolution and bioavailability of the drug product. The dissolution data of batches with API-PSD D_{90}: (b) (4) µm (B# 20210826-01) and D_{90}: (b) (4) µm (B# 9032109181) is shown below in Table 7.

Table 7: API-PSD and dissolution data of batches varying in the PSD

Batch information	API-PSD (D_{90})	Mean % dissolved (min)						*f2*
		5	10	15	20	30	45	
B# 20210826-01	(b) (4) µm	34.5	75.2	90.7	94.5	96.0	96.9	35.6
B# 9032109181	µm	23.3	56.1	67.5	71.4	76.1	79.5	

The magnitude of increase in the API-PSD ((b) (4) µm to (b) (4) µm) is considered a meaningful change when demonstrating discriminating ability of the dissolution method. Based on the submitted information, the variant batch with the larger API-PSD exhibits a slower dissolution profile that differs from the batch with the smaller API-PSD (*f*2 <50). Thus, the proposed dissolution method possesses discriminating ability to variations in the CMA (PSD of the Fruquintinib API).

(ii) Variations in the concentration of (b) (4): The excipients used in drug product are MCC, corn starch, and talc (Table 8A). (b) (4) The Applicant stated that variations in the concentration of (b) (4) had no effect on the dissolution due to its low proportion. (b) (4) also had no impact on the dissolution. Thus, the dissolution method was evaluated for its ability to discriminate against variations in the concentration of (b) (4)

Table 8A: Formulation composition of the 5 mg Fruquintinib capsules

Strength	5-mg Capsule		
Components	**Amount (mg)**	**w/w (%)**	**Function**
Fruquintinib	5.00	(b) (4)	Drug substance
Corn starch	(b) (4)		(b) (4)
Microcrystalline cellulose (b) (4)			
Talc			
Total		100.00	--
Empty gelatin capsules	Size 1	--	Capsule shell

The dissolution data of the batch with the optimal composition (B# 20210826-01) and altered composition (within a ± (b) (4)%; Batches #9032111112, #22522062802 and #9032111111) is shown below in Table 8B.

Table 8B: (b) (4) composition and dissolution data of batches varying in its composition

Batch information	(b) (4) composition	Mean % dissolved (min)						*f2*
		5	10	15	20	30	45	
B# 20210826-01	Optimal	34.5	75.2	90.7	94.5	96.0	96.9	—
B# 9032111112	(b) (4)	20.8	52.1	76.6	86.7	90.7	91.6	40.2
B# 22522062802		26.5	68.1	86.4	92.2	94.2	94.9	>85% dissolved in 15 min
B# 9032111111		48.9	80.8	90.0	92.3	93.5	93.9	>85% dissolved in 15 min

Based on the submitted information, the variant batch with (b) (4) (B# 9032111112) exhibits a dissolution profile that differs from (is slower than) the optimal batch (*f*2 <50). However, variant batches with (b) (4) exhibited dissolution profiles that were similar to the optimal batch (>85% dissolution at the 15-minute time-point). Since the dissolution data indicated a high variability at the initial two time-time-points (%RSD >25% at the first [5-minute] time-point and >15% at the second [10-minute] time-point), in the IR#1 (Appendix 2), the Applicant was requested to submit the complete dissolution data for all the clinical/validation batches of the 5 mg strength (i.e., Batches #20210826-01, #9032111112, #22522062802 and #9032111111, #1604FP1221-01, #1908012A, #200504A, #2012042A, #2101012A, #2107052A, #210603A, #210604A, #210605A, #210907AB, #210908AB and #210909AB). A comparison of the dissolution profiles of the variant batch with (b) (4) (B# 9032111112) to the optimal batch (B #20210826-01) and the clinical/validation batches using bootstrapping *f*2 and Multivariate analysis (MVA) is shown below in Table 8C.

Table 8C: Dissolution profile comparison of variant batch (B# 9032111112) to the optimal/clinical/validation batches using bootstrapping *f*2 and Multivariate analysis/Multivariate Statistical Distance (MVA/MSD)

Optimal/Clinical/Validation Batch information	Conventional *f*2 against Variant Batch	Bootstrapping *f*2 against Variant Batch (Lower bound 90% CI) ; Reviewer's assessment	MVA/MSD analysis against Variant Batch Reviewer's assessment
Optimal B# 20210826-01	40.22	41.1 (<50); Not similar	Not similar
B# 1604FP1221-01	36.95	37.3 (<50); Not similar	Not similar
B# 1908012A	37.22	37.3 (<50); Not similar	Not similar
B# 200504A	43.73	44.2 (<50); Not similar	Not similar
B# 2012042A	45.47	46.1 (<50); Not similar	Not similar
B# 2101012A	47.86	49.2 (<50); Not similar	Similar
B# 2107052A	41.66	41.8 (<50); Not similar	Not similar
B# 210603A	41.63	42.6 (<50); Not similar	Not similar
B# 210604A	33.38	33.6 (<50); Not similar	Similar
B# 210605A	42.61	42.8 (<50); Not similar	Similar
B# 210907AB	52.16	52.6 (<50); Not similar	Not similar
B# 210908AB	34.99	35.6 (<50); Not similar	Not similar
B# 210909AB	56.55	56.8 (<50); Not similar	Not similar

Based on the bootstrapping *f*2 analysis, this Reviewer concludes that the variant batch with (b) (4) (B# 9032111112) exhibits a dissolution profile that differs from the optimal/clinical/validation batches. Although two of the clinical/validation batches – B#s 210907AB and 210909AB yielded *f*2 values >50, based on the lower bound 90% CI being <50, this Reviewer concludes that the dissolution profiles of these batches differ from the variant batch. This Reviewer notes that MVA analysis could not confirm the differences in the dissolution profiles for B#s 2101012A, 210604A and 210605A. Based on the totality of the information/analysis, this Reviewer concludes that the proposed dissolution method possesses limited discriminating ability to variations in the CFV (concentration of (b) (4) (b) (4).

(iii) Variations in the process parameters: The drug product manufacturing process involves (b) (4) , the Applicant stated that neither the (b) (4) nor the (b) (4) step is expected to affect the dissolution rate of the Fruquintinib capsules. Thus, there are no CPPs that impact the dissolution of the drug product. This Reviewer finds this acceptable.

Based on the totality of the submitted information, the proposed dissolution method possesses discriminating ability with respect to variations in the CMA (PSD of the Fruquintinib API) and limited discriminating ability towards variations in the CFV (concentration of (b) (4)). Although the dissolution method exhibits a high variability at the initial two (5- and 10-minute) sampling time-points, based on the information submitted in the response to IR#2 (sequence 0018; Appendix 2), this variability is not expected to impact the *in vivo* performance and quality of the drug product. Based on the ability of the dissolution method to exhibit a complete (≥85%) drug release and demonstrate discriminating ability, the proposed dissolution method is found acceptable.

The dissolution method as agreed upon by the Applicant and the FDA for the proposed drug product is shown below Table 9A:

B.2.2. Dissolution Data and Acceptance Criterion:

The acceptance criterion of the drug product as proposed by the Applicant and recommended by the FDA are shown below in Table 9A.

Table 9A: Dissolution method and acceptance criterion proposed by the Applicant/recommended by the FDA

Dissolution method Proposed and finalized				Dissolution acceptance criterion Proposed and finalized		
Source	Apparatus	Media/ Volume	Agitation speed/ Temperature	Proposed (seq 0003)	Recommended (IR#2)	Finalized and Agreed
In-house	USP apparatus 2 with sinker	Medium: PBS, pH 6.8 + 0.08% SLS 900 mL	75 rpm 37±0.5 C	30 min: NLT (b)(4)% (Q)	(b)(4) min: NLT (b)(4)% (Q)	30 min: NLT (b)(4)% (Q)

***Reviewer's assessment*:**

The Applicant proposed an acceptance criterion of NLT (b)(4)% (Q) in 30 minutes. Based on the submitted dissolution data (Appendix 1), (b)(4)% of the drug dissolution in (b)(4) minutes was observed for the clinical/validation batches of the proposed drug product (1 mg and 5 mg strengths). Based on the submitted data, clinical/validation batches for the 1 mg and 5 mg strengths comply with a (b)(4) at stage 2 or stage 3 testing. Therefore, the FDA recommended (b)(4) acceptance criterion of Q = (b)(4)% in (b)(4) minutes via information request# 2 (Refer to Appendix 1). In response to IR# 2, the Applicant requested to retain the original proposed acceptance criterion and submitted information to further support their proposed acceptance criterion of Q = (b)(4)% in 30 minutes (sequence 0018), The acceptance criterion would possess the ability to reject variant batches with larger API-PSD that would exhibit a slower dissolution profile (e.g., B# 9032109181; Table 9B). Based on the totality of the submitted information, the acceptance criterion of "NLT (b)(4)% (Q) in 30 minutes" is found acceptable.

Table 9B: Justification for selected acceptance criterion to reject variant batches

Batch information	Mean % dissolved (30 min)	*f2*
Final acceptance criterion	**NLT (b)(4)% (Q)**	—
All clinical/validation batches (5 mg) API-PSD D_{90}: NMT (b)(4) µm Composition: (b)(4)	(b)(4)%	—
Variant B# 9032109181 API-PSD D_{90}: (b)(4) µm	76.1	<50
Variant B# 9032111112 Composition: (b)(4)	90.7	<50

This Reviewer acknowledges that the set acceptance criterion is not sensitive to changes in the concentration of (b)(4) This Reviewer concludes that this parameter (or the range that has been altered for this parameter) is not a significant CQA to impact the dissolution of the drug product. Based on the totality of the data/information, the final acceptance criterion of NLT (b)(4)% (Q) for the proposed drug product has been agreed upon by the Applicant and the FDA.

B.2.3. Dissolution data during Stability:
Stability studies were initially conducted on the three registration batches of the 1 mg (210910AB, 210911AB and 211001AB) and 5 mg (210907AB, 210908AB and 210909AB) strengths using the proposed dissolution method/acceptance criterion. Primary stability data was generated under long term (25 °C/60% RH), accelerated (40 °C /75% RH) and intermediate storage conditions (30 °C/65% RH). In the response to the IR# 3 (sequence 0023; Appendix 2), the Applicant stated that no dissolution failures would be expected with the final dissolution method/acceptance criterion that has been agreed upon by the Applicant and the FDA.

***Reviewer's Assessment*:**
In the response to the IR# 3 (sequence 0023; Appendix 2), the Applicant acknowledged the FDA's acceptance of the proposed dissolution acceptance criterion [Q = (b) (4)% in 30 minutes]. The Applicant also indicated that no dissolution failures would be expected with the final dissolution method/acceptance criterion. Assessment of the stability data is under the purview of the CMC/DP Reviewer.

B.3. CLINICAL RELEVANCE OF DISSOLUTION METHOD/ACCEPTANCE CRITERION (*e.g., IVIVR, IVIVC, In Silico Modeling, Small scale in vivo*):
Assessment: Adequate

***Reviewer's assessment*:**
The clinical pharmacology of the drug product was characterized based on thirteen clinical studies in healthy subjects and cancer patients along with four model-based pharmacometric analyses. Based on the results of the clinical studies, after oral administration, the T_{max} of the drug was ~2 hours. The short T_{max} is supported by the dissolution data wherein >85% of the drug dissolution was observed in 30 minutes. The rapid dissolution is supported by the acceptance criterion of Q = (b) (4)% in 30 minutes. In the absence of modeling data, the *in vivo* relevance of the dissolution method cannot be established. The proposed dissolution method and acceptance criterion serve as quality control of the drug product.

B.12. BRIDGING OF PRODUCTS:
Assessment: Adequate

***Bridging of Formulations*:** The proposed drug product formulation composition includes the drug substance with three excipients (MCC, corn starch, and talc) filled into hard gelatin capsules. The formulation development work resulted in the 1 mg and 5 mg strengths of the drug product for clinical use. The same formulation was used throughout clinical development and is proposed as the to-be-marketed formulation. The differences between the proposed commercial product versus the drug product used in the clinical studies are minor changes (b) (4) as shown in Table 10.

(b) (4)

Reviewer's Assessment:
A single formulation has been used throughout clinical development and is proposed as the to-be-marketed formulation. The changes (b) (4) are not mentioned in the SUPAC-IR *Guidance*. Based on the ability of the drug product to comply with the acceptance criterion (Q = (b) (4)% in 30 minutes) and clinical data indicating a lack of impact of variability in dissolution at the early time-points on the *in vivo* performance and quality of the drug product, this Reviewer concludes that the established dissolution acceptance criterion would ensure product quality due to changes (b) (4)

Bridging of Manufacturing sites: Three sites have been used to manufacture the product used in the clinical studies (Table 11A).

Table 11A: Details of manufacturing site and size of batches

Manufacturer	(b) (4)		HUTCHMED (Suzhou) Limited, Suzhou, CHINA [HML Suzhou]	(b) (4)
Batch size	(b) (4)			
Use	Phase 1	Phase 2, 3	Phase 3 Commercial	Commercial
	Dissolution & BA	**Dissolution & BA**	**Dissolution**	

(i) *Bridging of products manufactured at the* (b) (4) *and* (b) (4) *sites*: This was supported by a relative bioequivalence study using B# 120603 (b) (4) and B# 1401FP1221-01 (b) (4) (b) (4) (Study# 2013-013-00CH2; Table 11C) and adequate *in vitro* dissolution profile

comparison for the 5 mg strength (Table 11B) using B# 130961 (b) (4) and B# 1604FP1221-01 (b) (4). Refer to Appendix 2.

(ii) *Bridging of products manufactured at the (b) (4) and HML Suzhou sites*: This was supported by a relative bioequivalence study using B# 1401FP1221-01 (b) (4) and B# 210603A (HML Suzhou) (Study# 2014-013-00CH5; Table 11E) and an adequate *in vitro* dissolution profile comparison for the 5 mg strength (Table 11D) using B# 1604FP1221-01 (b) (4) and B# 210603A (HML Suzhou). Refer to Appendix 2.

(iii) *Bridging of products manufactured at the HML Suzhou and (b) (4) sites*: In addition to the HML Suzhou site being the manufacturing site for the drug product used in the Phase 3 clinical study and also for commercial manufacture, the Applicant proposes to include (b) (4) (b) (4) as an alternate commercial manufacturing site. Bridging of products manufactured at the HML Suzhou and (b) (4) sites was supported by an *in vitro* dissolution profile comparison (Tables 11F and 11G) using the 5 mg [B# 210907AB (HML Suzhou) and B# TC0146 (b) (4) and the 1 mg [B# 210910AB (HML Suzhou) and B# TC0147 (b) (4) strengths. Refer to Appendix 2.

Reviewer's Assessment:
As shown in Table 8a, three manufacturing sites were used through the clinical development of the drug product. In addition to the HML Suzhou site being the manufacturing site for the drug product used in the Phase 3 clinical study and also for commercial manufacture, the (b) (4) site has been included as an alternate commercial manufacturing site. As per the SUPAC-IR *Guidance*, the change in the manufacturing sites can be considered as a Level 3 change (change in the manufacturing site to a different campus - that is not on the same original contiguous site or adjacent city blocks). The documentation recommended to support a Level 3 change for an IR product with a low-solubility API is a multi-point dissolution profile comparison in the application/compendial medium. An *in vivo* BE documentation is not required.

(i) *Bridging of products manufactured at the (b) (4) and (b) (4) sites*: This change in the manufacturing site was supported using the 5 mg strength by an *in vitro* dissolution profile comparison (Table 11B) using B# 130961 (b) (4) and B# 1604FP1221-01 (b) (4).

Table 11B: Dissolution profile comparison of Fruquintinib capsules, 5 mg – comparing (b) (4) (Ref) and (b) (4) (Test) batches using bootstrapping *f*2 and Multivariate analysis (MVA)

Batch information	Bootstrapping *f*2 against Reference Batch (Lower bound 90% CI) ; Reviewer's assessment	MVA analysis against Reference Batch Max MSD (Upper 90% CI) ; Reviewer's assessment
B# 130961 ((b) (4); Reference)	—	—
B# 1604FP1221-01 ((b) (4); Test)	77.92 (>50); Similar	3.69 (<3.69); Similar

The comparative dissolution data indicates a similarity in the dissolution profiles (based on bootstrapping *f*2 and MVA analysis). Furthermore, both the products satisfy the acceptance criterion (Q = (b) (4)% in 30 minutes). From a Biopharmaceutics perspective, this Reviewer finds the *in vitro* dissolution bridging of the products manufactured at the two sites to be acceptable.

In addition to the *in vitro* dissolution bridging, a relative bioequivalence study was conducted to bridge the products manufactured at the two sites – B# 120603 (b) (4) and B# 1401FP1221-01 (b) (4) (Study# 2013-013-00CH2; Table 11C).

Table 11C: PK parameters of Fruquintinib capsules, 5 mg – comparing (b) (4) (Reference) and (b) (4) (Test) batches

PK Parameter	N	Geometric Least Squares Mean		Bioequivalence (Test/Reference)		Intrasubject Variation CV, %
		Test B# 1401FP1221-01	Reference B# 120603	GMR, %	90% CI of GMR, %	
C_{max}, ng/mL	22	166.73	156.50	106.54	(100.15, 113.33)	11.94
AUC_{0-t}, ng•h/mL	22	5656.09	5592.59	101.14	(97.91, 104.47)	6.25
AUC_{inf} ng•h/mL	22	5868.16	5819.05	100.84	(97.58, 104.22)	6.34

Based on the submitted information, the batches manufactured at the two sites are BE to each other (90% CI values for C_{max}, AUC_{0-t} and AUC_{inf} are between the range of 80%–125%). The *in vivo* bioavailability study will be further evaluated by the Clinical Pharmacology Reviewer.

(ii) *Bridging of products manufactured at the (b) (4) and HML Suzhou sites*: This change in the manufacturing site was supported using the 5 mg strength by an *in vitro* dissolution profile comparison (Table 11D) using B# 1604FP1221-01 (b) (4) and B# 210603A (HML Suzhou).

Table 11D: Dissolution profile comparison of Fruquintinib capsules, 5 mg – comparing (b) (4) (Ref) and HML Suzhou (Test) batches using bootstrapping *f*2 and Multivariate analysis (MVA)

Batch information	Bootstrapping *f*2 against Reference Batch (Lower bound 90% CI) ; Reviewer's assessment	MVA analysis against Reference Batch Max MSD (Upper 90% CI) ; Reviewer's assessment
B# 1604FP1221-01 ((b) (4); Reference)	—	—
B# 210603A (HML Suzhou; Test)	70.61 (>50); Similar	3.44 (<3.44); Similar

The comparative dissolution data indicates a similarity in the dissolution profiles (based on bootstrapping *f*2 and MVA analysis). Furthermore, both the products satisfy the acceptance criterion (Q = (b) (4)% in 30 minutes). From a Biopharmaceutics perspective, this Reviewer finds the *in vitro* dissolution bridging of the products manufactured at the two sites to be acceptable.

In addition to the *in vitro* dissolution bridging, a relative bioequivalence study was conducted to bridge the products manufactured at the two sites – using B# 1401FP1221-01 (b) (4) and B# 1315040121 (HML Suzhou) (Study# 2014-013-00CH5; Table 11E).

Table 11E: PK parameters of Fruquintinib capsules, 5 mg – comparing (b) (4) (Ref) and HML Suzhou (Test) batches

PK Parameter	N	Geometric Least Squares Mean		Bioequivalence (Test/Reference)		Intrasubject Variation CV, %
		Test B# 1315040121	Reference B# 1461FP1221-01	GMR, %	90% CI of GMR, %	
C_{max}, ng/mL	24	155	166	93.06	(86.23, 100.43)	15.46
AUC_{0-t}, ng•h/mL	24	5370	5560	96.68	(93.12, 100.37)	7.57
AUC_{inf} ng•h/mL	24	5620	5810	96.81	(93.24, 100.52)	7.59

Based on the submitted information, the batches manufactured at the two sites are BE to each other (90% CI values for C_{max}, AUC_{0-t} and AUC_{inf} are between the range of 80%–125%). The *in vivo* bioavailability study will be further evaluated by the Clinical Pharmacology Reviewer.

(iii) *Bridging of products manufactured at the HML Suzhou and (b) (4) sites*: This change in the manufacturing site was supported by an *in vitro* dissolution profile comparison using the 1 mg [B# 210910AB (HML Suzhou) and B# TC0147 (b) (4)] and 5 mg strengths [B# 210907AB (HML Suzhou) and B# TC0146A (b) (4)]

For the 5 mg strength (Table 11F), the comparative dissolution data indicates differences in the dissolution profiles (based on bootstrapping *f*2 and MVA/MSD analysis) for dissolution testing conducted at (b) (4) and HML Shanghai (based on bootstrapping *f*2). However, a similarity in the dissolution profiles was observed for dissolution testing conducted at HML Shanghai using MSD analysis. Based on the ability of the drug product to comply with the acceptance criterion (Q = (b) (4)% in 30 minutes) and clinical data indicating a lack of impact of variability in dissolution at the early time-points on the *in vivo* performance and quality of the drug product, this Reviewer concludes that minor variations in the dissolution profiles at the early time-points would not have any adverse impact on the quality of the drug product.

Table 11F: Dissolution profile comparison of Fruquintinib capsules, 5 mg – comparing HML Suzhou (Ref) and (b) (4) (Test) batches using bootstrapping *f*2 and Multivariate analysis/Multivariate Statistical Distance (MVA/MSD)

Batch information	Dissolution test site	Bootstrapping *f*2 against Reference Batch (Lower bound 90% CI) ; Reviewer's assessment	MVA/MSD analysis against Reference Batch Max MSD (Upper 90% CI) ; Reviewer's assessment
B# 210907AB (HML Suzhou; Reference)	(b) (4)	—	—
B# TC0146 (b) (4); Test)		57.03 (<50); Not similar	2.31 (>2.31); Not similar
B# 210907AB (HML Suzhou; Reference)	HML Shanghai	—	—
B# TC0146 (b) (4); Test)		60.59 (<50); Not similar	3.36 (<3.36); Similar

For the 1 mg strength (Table 11G), the comparative dissolution data indicates differences in the dissolution profiles (based on bootstrapping *f*2 and MVA analysis) for dissolution testing conducted at (b) (4). However, a similarity in the dissolution profiles was observed for dissolution testing conducted at HML Shanghai. Based on the ability of the drug product to comply with the acceptance criterion (Q = (b) (4)% in 30 minutes) and clinical data on the 5 mg strength indicating a lack of impact of variability in dissolution at the early time-points

on the *in vivo* performance and quality of the drug product, this Reviewer concludes that minor variations in the dissolution profiles at the early time-points would not have any adverse impact on the quality of the drug product.

Table 11G: Dissolution profile comparison of Fruquintinib capsules, 1 mg – comparing HML Suzhou (Ref) and (b) (4) (Test) batches using bootstrapping *f*2 and Multivariate analysis/Multivariate Statistical Distance (MVA/MSD)

Batch information	Dissolution test site	Bootstrapping *f*2 against Reference Batch (Lower bound 90% CI) ; Reviewer's assessment	MVA/MSD analysis against Reference Batch Max MSD (Upper 90% CI) ; Reviewer's assessment
B# 210910AB (HML Suzhou; Reference)	(b) (4)	—	—
B# TC0147 ((b) (4) ; Test)		56.35 (<50); Not similar	2.27 (>2.27); Not similar
B# 210910AB (HML Suzhou; Reference)	HML Shanghai	—	—
B# TC0147 ((b) (4) ; Test)		70.20 (>50); Similar	2.24 (<2.24); Similar

Based on the totality of the submitted information, this Reviewer finds the overall bridging of the products across the four manufacturing sites to be acceptable.

***Bridging of batch sizes*:**
***Reviewer's Assessment*:**
As shown in Table 11A, the sizes of the clinical/validation and the proposed commercial batch size ranges from (b) (4) kg to (b) (4) kg. Bridging of the batch sizes has been satisfactorily demonstrated as part of the bridging of the manufacturing sites. An additional bridging of the batch sizes is not required.

B.13. BIOWAIVER REQUEST:

Assessment: Not Applicable

There are two strengths of the drug product – 1 mg and 5 mg. Bioavailability studies were performed on the 1 mg and 5 mg strengths. The Applicant has not requested any waiver of *in vivo* bioavailability/bioequivalence studies.

***Reviewer's Assessment*:**
There is no request for a waiver of *in vivo* bioavailability/bioequivalence studies as BA/BE studies were performed on the 1 mg and 5 mg strengths. These studies will be assessed by the Clinical Pharmacology Reviewer.

R. REGIONAL INFORMATION:

Life Cycle Management Considerations and Risk Mitigation Strategies

***Reviewer's Assessment*:**
In sequence 0003, the Applicant proposed a three-tier API-PSD specification of $D_{10} \leq$ (b) (4) µm, (b) (4) µm $\leq D_{50} \leq$ (b) (4) µm, $D_{90} \leq$ (b) (4) µm. With the Fruquintinib API being a low-solubility drug substance, the particle size distribution (PSD) of the API is a critical material attribute (CMA) that impacts the dissolution and bioavailability of the drug product. As part of the discriminating ability of the dissolution method, the drug product with API-PSD D_{90}: (b) (4) µm exhibited a dissolution profile that was slower than the product with API-PSD D_{90}: (b) (4) µm. Based on the API-PSD D_{90} values in

the drug product clinical batches being NMT (b) (4) µm (Table 12), in the response to IR#2 (sequence 0002; Appendix 2) and IR#3 (sequence 0023; Appendix 2), the API-PSD D_{90} has been revised from ≤ (b) (4) µm to ≤ (b) (4) µm.

Table 12: Fruquintinib API PSD in the drug product

Batch No.	D10 (µm)	D50 (µm)	D90 (µm)
HMPL-013-081114-1-11-2	Not tested	Not tested	Not tested
417-78-1	Not tested	Not tested	Not tested
101104	Not tested	Not tested	Not tested
100501[a]	(b) (4)		
100503	Not tested	Not tested	Not tested
PT-C13052210-AF13001	Not tested	Not tested	Not tested
PT-C13052210-AF13001MA	(b) (4)		
PT-C13052210-AF13002M			
PT-C13052210-AF15001M			
PT-C13052210-AF15002M			
PT-C13052210-AF15003M			
C13052210-AF15006M			
C13052210-AF17001M			
CPo85510206-020801			
CPo85510206-030801			
CPo85510206-040801			
C13052210-AF18003M			
JM-C13052210-AF19001M			
JM-C13052210-AF20001M			
JM-C13052210-AF20002M			
CPo127891-01-06-01-17-01			

The dissolution acceptance criterion of "Q = (b) (4) % in 30 minutes" and the three-tier API-PSD specification with "D_{90}: ≤ (b) (4) µm" possess the ability to reject batches with slower dissolution profiles. This mitigates the risk from a Biopharmaceutics perspective to a low level and ensures that the quality of the drug product is maintained through the life-cycle.

BIOPHARMACEUTICS PENDING DEFICIENCIES:
None

10 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

Rajesh Savkur

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Anitha Palamakula Govada

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