CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218160Orig1s000

PRODUCT QUALITY REVIEW(S)

Title:	NDA IQA Template Title Page-EXEC SUMMARY
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Office of Pharmaceutical Quality

New Drug Application (NDA)
Integrated Quality Assessment Template

NDA Executive Summary

1. Application/Product Information

NDA Number	218160
Applicant Name	LOXO ONCOLOGY INC., A WHOLLY OWNED SUB OF ELI LILLY AND CO
Drug Product Name	Retevmo (selpercatinib)
Dosage Form	Tablet
Proposed Strength(s)	40 mg, 80 mg, 120 mg, 160 mg
NDA Classification	Type 3 - New Dosage Form
Route of Administration	Oral
Maximum Daily Dose	320 mg
Rx/OTC Dispensed	Rx
Proposed Indication	RETEVMO® is a kinase inhibitor indicated for the treatment of: • Adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a rearranged during transfection (RET) gene fusion, as detected by an FDA-approved test (1.1) • Adult and pediatric patients 12 years of age and older with advanced or metastatic medullary thyroid cancer (MTC) with a RET mutation, as detected by an FDA-approved test, who require systemic therapy1 (1.2) • Adult and pediatric patients 12 years of age and older with advanced or metastatic thyroid cancer with a RET gene fusion, as detected by an FDA-approved test, who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)1 (1.3) • Adult patients with locally advanced or metastatic solid tumors with a RET gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options1 (1.4)

Drug Product Description	The drug product is available as round 40 mg, 80 mg, 120 mg, and 160 mg, debossed, (b) (4) film-coated, immediate-release tablets. The 40 mg tablet is a light gray, round tablet debossed with "Ret" (b) (4) "40" on one side and "5340" on the other. The 80 mg tablet is a dark red-purple, round tablet debossed with "Ret" (b) (4) "80" on one side and "6082" on the other. The 120 mg tablet is a light purple, round tablet debossed with "Ret" (b) (4) "120" on one side and "6120" on the other. The 160 mg tablet is a light pink, round tablet debossed with "Ret" (b) (4) "160" on one side and "5562" on the other.		
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); excursions between 15°C and 30°C (59°F to 86°F) are permitted [see USP Controlled Room Temperature].		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Daniel Chen	Katherine Windsor
	Drug Product/ Labeling	Damien Duveau	Xing Wang
	Manufacturing	Yifan Wang	Zhaoyang Meng
	Biopharmaceutics	Payal Agarwal	Anitha Govada
	Microbiology	Yifan Wang	Zhaoyang Meng
	Other (specify)	N/A	
	RBPM	Janell Artis	
	ATL	Xing Wang	
Consults	None		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

An expiration dating period of 36 months may be granted when stored at the proposed storage conditions.

b. Additional Comments for Action
N/A

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The initial NDA (213246) for capsule dosage form for Retevmo® (selpercatinib) was approved on 08 May 2020. For this NDA (218160), an immediate-release tablet dosage form has been developed as a product redesign in strengths of 40 mg, 80 mg, 120 mg, and 160 mg to replace the current commercial capsule formulation to offer an improved patient experience in terms of the number and size of dosage units. (b) (4) *. A pre-approval inspection was conducted at Lilly Del Caribe, Inc (FEI 2619243) with the recommendation for approval. Overall, the applicant has provided sufficient information in this submission to assure the identity, strength, purity, and quality of the proposed drug product.*

Refer to the review of Office of Clinical Pharmacology (OCP) for recommendation on the bioequivalence between the approved capsule dosage from and the proposed tablet dosage form selpercatinib 160 mg. The biowaiver request for the proposed lower strengths (40 mg, 80 mg, and 120 mg) of selpercatinib tablets is granted under 21CFR§ 320.22 (d)(2), provided the BE study is acceptable by OCP. (Note: The Clinical Pharmacology Reviewer confirmed that there are no BE concerns.)

Based on the OPQ review team's evaluation of the information provided in the submission, OPQ recommends ***APPROVAL of NDA 218160, RETEVMO® (selpercatinib) tablets, for oral use.***

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
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments: None

Application Technical Lead Name and Date:
Xing Wang, Ph.D. *2/29/2024*

Xing Wang

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CHAPTER IV: LABELING

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

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Adequate	The established name is RETEVMO® (selpercatinib) tablets, for oral use.
Route(s) of administration	Adequate	The drug product is administered orally.
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	The four 40-mg, 80-mg, 120-mg, and 160-mg dosage strengths are adequately listed.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	The tablet is not scored.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active	N/A	The active pharmaceutical ingredient is the free base.

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

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)	Adequate	The statement "Swallow the tablets whole. Do no crush or chew the tablets" is provided in Section 2.3 Recommended Dosage
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another	N/A	

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

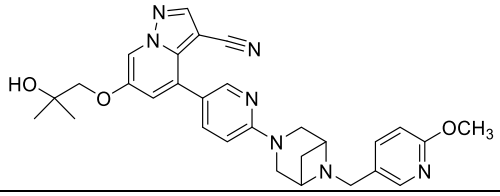
1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	The four dosage forms are adequately listed: 40 mg, 80 mg, 120 mg, 160 mg.
Strength(s) in metric system	Adequate	The strengths are listed in milligrams.
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	The active ingredient is the free base.
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 drug product is adequately provided for each strength in Section 3 Dosage forms and strengths.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	The tablet is not scored.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

Section 11 (DESCRIPTION)

APPEARS THIS WAY ON ORIGINAL

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	The proprietary name is RETEVMO and the established name is selpercatinib.
Dosage form(s) and route(s) of administration	Adequate	The dosage forms and routes of administration are adequately listed.
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	The active ingredient is the free base.
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	The inactive ingredients are listed, using USP/NF names. List the inactive ingredients in alphabetical order.
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	Selpercatinib is adequately categorized as a kinase inhibitor.

Chemical name, structural formula, molecular weight	Adequate	The molecular formula for selpercatinib is $C_{29}H_{31}N_7O_3$ and the molecular weight is 525.61 g/mol. The chemical name is 6-(2-hydroxy-2-methylpropoxy)-4-(6-(6-((6-methoxypyridin-3-yl)methyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile. Selpercatinib has the following chemical structure: 
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	N/A	

Section 11 (DESCRIPTION) Continued

Item	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)

APPEARS THIS WAY ON ORIGINAL

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	The four dosage forms are adequately listed: 40 mg, 80 mg, 120 mg, 160 mg.
Strength(s) in metric system	Adequate	The dosage strengths are adequately provided in milligrams.
Available units (e.g., bottles of 100 tablets)	Adequate	60-count bottle for each dosage strength.
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	The identification of dosage forms, including NDC(s) is adequate. The information is organized in a tabulated format.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

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

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

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	N/A	Not relevant for oral dosage forms.
Include information about child-resistant packaging	Adequate	Although the information is not provided under section 16 of the PI, the container closure is (b) (4), as specified in Section 3.2.P.7 Container Closure System.

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume

parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug review division if the product contains any of these inactive ingredients.

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

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	The statement "Marketed by: Lilly USA, LLC, Indianapolis, IN 46285, USA" is provided in Section 17.

2.0 PATIENT LABELING

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

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2]	Adequate	
Special preparation instructions (if applicable)	N/A	
Storage and handling information (if applicable)	Adequate	The statement [redacted] (b) (4) is provided.
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	Provide a description of the canister containing the desiccant and specify how it differs from the drug product. The mention "Do not eat" should be provided in the patient labeling.
Active ingredient(s) (if applicable)	Adequate	
Alphabetical listing of inactive ingredients (if applicable)	Adequate	List the inactive ingredients in alphabetical order.
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	The statement "Marketed by: Lilly USA, LLC, Indianapolis, IN 46285, USA" is provided.

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

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels

(Copy/paste or refer to a representative example of a proposed container)

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

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[3], (font size and prominence)	Adequate	
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	Route of administration not provided. Not critical for oral drugs.
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	
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.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	

Assessment of Carton and Container Labeling: ***Adequate***

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

ITEMS FOR ADDITIONAL ASSESSMENT

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

Overall Assessment and Recommendation:

The container label and prescribing information comply with all regulatory requirements and are recommended for approval from a CMC perspective

pending revision of what are noted in the Assessor's Comments column above.

Primary Labeling Assessor: Damien Y. Duveau, Ph.D., 02/21/2024.

Secondary Assessor Xing Wang, PhD.

Damien Duveau

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Xing Wang

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CHAPTER VI: BIOPHARMACEUTICS

Product Information	RETEVMO® (selpercatinib) Tablets
NDA Number	NDA-218160-ORIG-1 [505(b)(1)]
Assessment Cycle Number	1
Drug Product Name/ Strength	RETEVMO® (selpercatinib), Film Coated Immediate Release Tablets, 40 mg, 80 mg, 120 mg, 160 mg
Route of Administration	Oral
Applicant Name	Loxo Oncology, a wholly owned subsidiary of Eli Lilly and Company
Therapeutic Classification/ OND Division	Oncology OND/OOD/DO2
Listed Drug Product Number	This application Cross-reference to (NDA# 213246 for Retevmo® (selpercatinib) Capsules, 40 mg and 80 mg)
Proposed Indication	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:
Loxo Oncology submitted an original New Drug Application (NDA) for Retevmo® (selpercatinib) immediate-release (IR), film-coated Tablets 40 mg, 80 mg, 120 mg, and 160 mg under 505 (b)(1) regulatory pathway.

Retevmo® (selpercatinib) immediate-release (IR), Capsules (NDA# 213246 from Eli Lilly and Company) in 40 mg and 80 mg strengths was approved by the FDA on May 08, 2020, for the treatment of RET fusion-positive non-small cell lung cancer, TC, and other solid tumors, as well as RET-mutant medullary TC. The indications for the proposed film-coated tablet product are unchanged from the approved commercial capsule product. The tablet was developed to reduce the pill burden (minimize the size of the dosage form and reduce the number of dosage units the patient would be required to take relative to the commercial capsule product).

The recommended dosage of Retevmo based on body weight is:120 mg for patients less than 50 kg, and 160 mg for patients ≥50 kg. Maximum oral daily dose is 240 mg for patients <50 kg and 320 mg for patients ≥50 kg.

This Biopharmaceutics review focuses on the assessment and recommendation on the adequacy of: **1)** the proposed dissolution method and acceptance criterion for the

40 mg, 80 mg, 120 mg, and 160 mg strengths of selpercatinib film coated tablets for quality control purposes, **2)** bridging of proposed tablets and approved capsules dosage forms, **3)** biowaiver request for the proposed lower 40 mg, 80 mg and 120 mg strengths, and **4)** addressing the Clinical Pharmacology's Consult on the impact of dosage form change (*i.e., approved selpercatinib capsules to proposed selpercatinib tablets*) with regard to potential drug-drug interaction (DDI) with acid reducing agents.

1. **In Vitro Dissolution Method and Acceptance Criterion:**
   The following dissolution method and acceptance criterion are deemed adequate and acceptable based on the totality of the information and data provided by the Applicant.

Approved Dissolution Method and Acceptance Criterion for Retevmo® (selpercatinib) immediate-release (IR), film-coated Tablets 40 mg, 80 mg, 120 mg, and 160 mg				
Apparatus	**Speed**	**Volume/ Temp**	**Medium**	**Acceptance Criterion**
		900 mL/ 37 °C		(b) (4)

2. **Bridging of Tablets and Capsules Dosage Forms:**
   To establish the scientific bridge between the approved capsule dosage form [(2 x 80 mg) containing selpercatinib (b) (4) and the highest strength (160 mg) of the proposed Selpercatinib Tablet dosage form [containing selpercatinib (b) (4) data from an *in vivo* bioequivalence study (J2G-MC-JZJZ) were provided. The Office of Clinical Pharmacology (OCP) recommendation on the bioequivalence between the approved capsule dosage from and the proposed tablet dosage form selpercatinib 160 mg, is pending. However, the Clinical Pharmacology Reviewer confirmed that there are no BE concerns.

   There were no CMC changes proposed to the drug product used in the BE study and the final to-be-marketed (TBM) drug product; therefore, bridging between the clinical and TBM products is not needed.

3. **Biowaiver request for the lower strengths:**
   The overall information provided in the submission [*i.e., in vitro dissolution profile similarity data, PK linearity, composition of the formulations (active and inactive ingredients) of the lower strengths are proportionally similar to that of the BE-strength 160 mg*] supports the approval of the biowaiver request. Therefore, the biowaiver request for the proposed lower strengths (40 mg, 80 mg, and 120 mg) of selpercatinib tablets is granted under 21CFR§ 320.22 (d)(2), provided the BE study is acceptable by OCP.

4. **Clinical Pharmacology Consult dated October 31, 2023, regarding the Applicant's request for a waiver of the requirement to submit data from an**

in vivo DDI-study evaluating the interaction of the proposed selpercatinib tablets with acid reducing agents:

Consult: On October 31, 2023, Biopharmaceutics received a consult request (via Email) from the Clinical Pharmacology Reviewer assigned to the current NDA, Dr. Om Anand. In this consult, Biopharmaceutics was requested to review and provide feedback on the applicant's rationale and supporting data for not conducting the required in vivo gastric acid-reducing agent interaction study for the proposed selpercatinib tablets.

Assessment: The Applicant provided drug substance solubility data and in vitro dissolution data to support their request for a waiver of the requirement for the submission of data from a drug-drug interaction (DDI) study evaluating the possible interaction of selpercatinib with acid reducing agents. This Reviewer notes that the differences between the proposed product, (Selpercatinib Tablets) and the approved product (Selpercatinib Capsules), are the change in the formulation components and manufacturing processes. Based on the overall data showing very rapid and similar dissolution/drug release for the selpercatinib tablets and capsules dosage forms, this Reviewer considers that the risk for a potential DDI with the concomitant administration of the selpercatinib tablets dosage form with ARAs, remains the same as that of the selpercatinib capsule dosage form. Therefore, the Applicant's rationale and supporting data for not conducting an in vivo gastric acid-reducing agents interaction study is acceptable.

From the Biopharmaceutics perspective, the submission of a DDI study evaluating the interaction of selpercatinib tablets with acid reducing agents for the selpercatinib tablet dosage form is not needed, and the Applicant's request for a DDI-waiver is appropriate and acceptable. Biopharmaceutics recommends the Clinical Pharmacology Reviewer, to grant the DDI-waiver.

BIOPHARMACEUTICS OVERALL RECOMMENDATION:

From the Biopharmaceutics perspective, NDA-218160-ORIG-1 for the proposed RETEVMO® (selpercatinib), Film Coated Immediate Release Tablets, 40 mg, 80 mg, 120 mg, and 160 mg is recommended for **Approval**.

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
Dissolution	Medium	(b) (4)	Low	(b) (4)
Dissolution	Medium		Low	

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
Original Submission, SDN# 001	06/13/2023
IR Response # 1, SDN # 10	12/07/2023
IR Response # 2, SDN# 16	02/13/2024

Highlight Key Issues from Last Cycle and Their Resolution: n/a

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

B.1 BCS DESIGNATION

Assessment: n/a

Solubility: Two polymorphs of selpercatinib ((b) (4)) were identified. (b) (4) is the major component of all drug substance lots for the approved Capsule formulation (NDA 213246). The synthesis of the DS in NDA 213246 differs from the current NDA 218160 (b) (4) The drug substance batch release controls include specification of D90=NMT (b) (4) µm and was found adequate by the DS Reviewer.

In addition, the Applicant conducted a bioequivalence study between the currently marketed Capsule with (b) (4) DS (DS particle size: D_{90} = (b) (4) µm) and the proposed (b) (4) tablet (DS particle size: D_{90} = (b) (4) µm) and demonstrated that the two drug products are bioequivalent, despite the difference in formulation, (b) (4) and particle size.

As shown in **Table 1**, selpercatinib (b) (4) have similar solubility profile across the pH range. It is highly soluble at acidic conditions (up to pH 4.0 only) and decreases with increase in pH from pH 4.5 onwards. The solubility of API as per BCS is 0.640 µg/mL [highest dose strength (160 mg) in 250 mL]. Therefore, selpercatinib is considered as low soluble drug substance (BCS II or IV).

Permeability: No information available. As per the approved RETEVMO Capsule label, the mean absolute bioavailability of RETEVMO capsules is 73%.

Dissolution: The proposed to-be-marketed Selpercatinib Tablet shows very rapid dissolution (>85% release in 15 minutes) using the proposed dissolution testing parameters of 0.1 N HCl using USP Apparatus II at 75 rpm paddle speed without any surfactant. However, dissolution is slow or incomplete at or above pH 4.5. Therefore, not considered to be BCS Class 1 or BCS III drug product.

Table 1. Solubility of selpercatinib ((b) (4) and (b) (4) across physiological pH

Solvent[a]	Solubility of (b) (4) (mg/mL)	Equilibrium pH	Solubility of (b) (4) (mg/mL)	Equilibrium pH
Water	0.0016	6.975	0.0036	7.146
0.1N HCl[b]	≥10	1.285	≥10	1.297
0.01N HCl	5.055[c]	3.717	4.7700	3.634
pH 4.0 Citrate/Phosphate	1.075[c]	4.006	0.7116	4.134
pH 4.5 Acetate (USP)	0.2822[c,d]	4.491	0.1694[d]	4.496
pH 6.0 Phosphate (USP)	0.0108	6.014	0.0086	6.027
pH 7.5 Phosphate (USP)	0.0017	7.519	0.0022	7.526
0.01N NaOH	0.0016	10.654	0.0011	9.985
SGF[e]	1.389[f]	2.642	1.440[f]	2.644
FaSSIF[g]	0.0073	6.499	0.0096	6.445
FeSSIF[h]	0.3176	4.933	0.2277[d]	4.928

[a] Descriptions are consistent with the USP, Ph.Eur., and Japanese Pharmacopoeias.
[b] Solubility for 0.1N HCl was measured at 21.5°C (ambient).
[c] (b) (4)

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: ADEQUATE

The Applicant's proposed dissolution method and acceptance criterion are shown in **Table 2**. The selection of the proposed dissolution medium and the apparatus was made by the Applicant by screening for dissolution profiles that supported very rapidly dissolving drug product (>85% released in 15 minutes). The Applicant provided the dissolution method development report for their selpercatinib tablets and the provided information is discussed in detail in the Justification section below.

Table 2. Proposed Dissolution Testing Conditions and Acceptance Criterion for Selpercatinib Tablets, 40 mg, 80 mg, 120 mg and 160 mg.

Apparatus	II (Paddle)
Media	0.1 N HCl
Volume (mL)	900
Temperature (°C)	37 (b) (4) °C
Paddle Speed (rpm)	75
Acceptance criterion	Q = (b) (4) % at 15 minutes

Selpercatinib exhibits high solubility at gastric pH in both (b) (4) and (b) (4) The two forms (approved capsule formulation with (b) (4) and proposed tablet formulation with (b) (4) demonstrates similar *in vivo* performance. Therefore, the Applicant has proposed a dissolution method to ensure complete and rapid dissolution of drug product. Selection of the individual parameters are discussed below:

(b) (4)

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Discriminating Ability: The Applicant evaluated the discriminating ability of the proposed dissolution testing conditions toward intentional variations in unit formula and demonstrated no impact on dissolution across variations in film coating (b) (4) (b) (4), drug substance particle size[3], tableting process and stability conditions. As shown in **Figure 7**, tablets manufactured with varying API PSD (D_{90} (b) (4) µm, D_{90} (b) (4) µm, D_{90} (b) (4) µm) demonstrated complete drug release (>90%) within 15 minutes. Granules of these two batches represent some of the largest (EL19606-073-11) and some of the smallest (EL19606-073-12) granule particle sizes explored, with EL19606-073-11 also presenting one of the broadest granule particle size distributions. This is consistent with *in vivo* evaluation of particle size effects where the BE study (J2G-MC-JZJZ) demonstrated similar *in vivo* performance for two formulations with greatly different drug substance particle size (D_{90} (b) (4) µm- (b) (4) µm) and (b) (4)

In addition, no impact of film coating was observed on the dissolution profile of the proposed product (**Figure 8)** that compares the dissolution profile of batch EL19606-088C at (b) (4) wt. gain coating (b) (4) with that of bio-batch D422519 (used in Study-J2G-MC-JZJZ). Both tested drug

[2] Sensitivity of release profile towards changes in formulation, process parameters, material attributes, and stress conditions are described in detail in Section 3.2.P.2.3.8.5
[3] Dissolution testing across the range of drug substance particle size x90 at the representative commercial equipment scale are summarized in Section 3.2.P.2.3.8 (Dissolution Method Development Report)

product batches display full release by 15 minutes, indicating low risk and film weight gains up to and including (b) (4).

Although the Applicant provided evidence (b) (4) rpm paddle speed at 15 minutes timepoint, as evidenced by the reported drug release of (b) (4) in (b) (4) minutes, (b) (4) did not appear to be a problem. Therefore, the Applicant's justification for the use of (b) (4) 75 rpm paddle rotation speed was not fully supported. Therefore, through IR# 2 dated 02/05/2024, the Applicant was asked (b) (4)

(b) (4)

(b) (4)

[4] \\CDSESUB1\EVSPROD\nda218160\0016\m1\us\spr-quality-responses-to-questions-feb-2024.pdf

1. The dissolution method has demonstrated to be robust.
2. (b) (4)
3.

In addition, the Applicant stated that data from one batch of tablets with 6 units were only available using the above mentioned FDA recommended methods, and therefore these data were insufficient to propose a statistically determined acceptance criterion using either of these methods.

Reviewer's Assessment: The Applicant's justification for the use of USP Apparatus II at 75 rpm (b) (4) citing the (b) (4) Guidance is not fully supported. The cited guidance provides (b) (4) recommendations; however, FDA's policy and recommendations change with time because they are frequently updated to follow FDA's current thinking. Therefore, the cited (b) (4) Guidance should only be used as the starting point for general recommendations regarding the development of a product specific optimal discriminating dissolution method. However, complete data supporting the selected testing conditions should be always generated and submitted to FDA.

In conclusion, the proposed dissolution method, USP Apparatus 2 (paddles) at 75 rpm with 900 mL of 0.1N HCl is found **Acceptable** by considering the following supportive information:

1. The proposed product is an immediate release dosage form intended to rapid drug release within gastric transit time and pH range.
2. The Critical Material Attributes (CMAs) of the drug substance are controlled adequately (API particle size distribution, polymorphic forms)
3. The drug substance solubility is high across gastric pH range.
4. No impact of the identified CQA of the proposed product (dissolution or drug release) on bioavailability.
5. (b) (4) dissolution acceptance criterion Q= (b) (4)% in 15 min.
6. No significant impact of API particle size on the clinical efficacy of the proposed test product.

[5] https://online.uspnf.com/uspnf/document/1_GUID-CE0902BA-77AC-422D-8BF0-A221B5DE6012_5_en-US?source=Search%20Results&highlight=1092#C1092S42

7. The proposed Tablet dosage form and the approved Capsule dosage form are bioequivalent (pending OCP's recommendation).
8. Dissolution specifications ensure complete drug release earlier than the reported T_{max} of ~1.5 hr.

Dissolution Acceptance Criterion: The proposed strengths of selpercatinib tablets dissolve very rapidly and complete (40 mg, 80 mg, 120 mg, and 160 mg) using the above FDA's accepted dissolution method. Based on a risk-based approach indicating low risk and the provided overall dissolution and clinical-BE information, this Reviewer considers that the proposed dissolution acceptance criterion will adequately control the product's quality and ensures its clinical performance. Therefore, the proposed acceptance criterion of Q = (b) (4)% in 15 min is found adequate and **Acceptable** for all the proposed strengths of Selpercatinib Tablets at release and on stability.

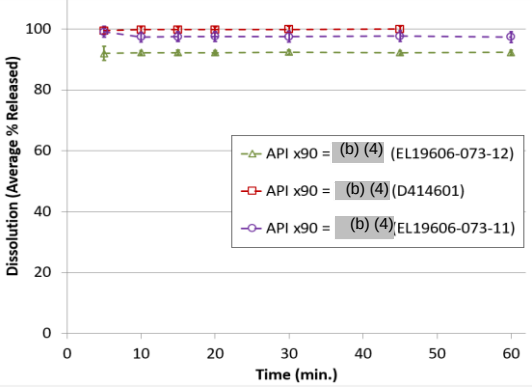

Fig. 7. Dissolution profiles for 40 mg Tablets containing drug substance lots with Various PSD

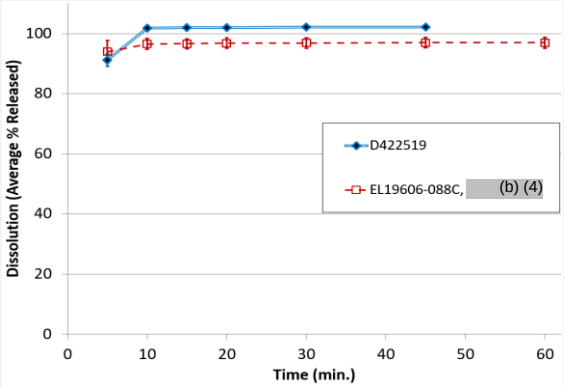

Fig. 8. Dissolution Profiles for 160 mg Selpercatinib Tablets made at target (D422519) and compared with multiple negative-effect formulation/process deviations.

B.12 BRIDGING OF FORMULATIONS

Assessment: ADEQUATE

Bridging Throughout Product's Development: n/a
The proposed to-be-marketed (TBM) commercial product of selpercatinib tablets, 160 mg is the same as the clinical selpercatinib tablets, 160 mg product used in the BE-study. Also, the same manufacturing site was used for the clinical and proposed TBM-commercial drug products. Therefore, the bridging between the clinical and commercial selpercatinib tablets products is not needed.

Scientific Bridging of Tablets and Capsules: A bioequivalence study (J2G-MC-JZJZ) was conducted to bridge the highest strength (2 x 80 mg) of the approved capsules dosage form containing selpercatinib (b) (4) to the highest

strength (160 mg) of the proposed commercial selpercatinib tablets dosage form containing selpercatinib (b) (4) This *in vivo* clinical BE study J2G-MC-JZJZ is being reviewed by the Office of Clinical Pharmacology (OCP). Although as of 2/28/2024, the OCP review is pending, the OCP's assigned reviewer confirmed that the preliminary assessment of the single dose BE study of Selpercatinib Tablets (160-mg) compared to the approved Selpercatinib Capsules (2 × 80 mg) appears adequate. Therefore, if needed, this section will be updated as appropriate.

B. 13 BIOWAIVER REQUEST

Assessment: ADEQUATE

1. Biowaiver Request for the lower 40 mg, 80 mg, and 120 mg strengths of selpercatinib tablets: The Applicant requested a waiver for the requirement to submit data from an *in vivo* bioavailability study evaluating the lower strengths (40 mg, 80 mg, and 120 mg) of selpercatinib tablets under the 21 CFR 320.22(d)(2) regulation.

The Applicant's proposed strategy and the data needed to support the bioavailability waiver (biowaiver) request was previously discussed with and agreed upon by the FDA (Preliminary Meeting minutes May 27 2021, and Oct 31 2022: IND 133193). As per 21 CFR § 320.22(d)(2) regulation, the Applicant was recommended to submit the following information to support biowaiver request:

I. **In vivo BA/BE data:** The in vivo BA/BE results of the highest strength 160 mg of the proposed product will be reviewed by the OCP.

II. **The drug product is in the same dosage form, but in a different strength:**
All strengths (40 mg, 80 mg, 120 mg and 160 mg) are in the same dosage form (film coated tablets for immediate release)[6]

III. **Proportional Similarity in Composition:** The 40 mg, 80 mg and 120 mg tablet strengths are proportionally similar to the strength 160 mg used in the BE study. The manufacturing process for all tablet strengths is identical (b) (4)

IV. **Comparative dissolution data:** Multimedia dissolution studies was performed on all the four strengths (40 mg, 80 mg, 120 mg, and 160 mg) of the representative bulk batch of the drug product across the physiological pH range (pH 1.0 to 6.8). 0.1 N HCl, (b) (4) were used as dissolution medium for this study. Results of the *in vitro* multimedia dissolution test comparing the 40 mg, 80 mg, and 120 mg strength tablets to the 160-mg strength **EL19606-056** tablet is shown in **Figures 1, 2, 3, and 4** respectively. The dissolution profile

[6] \\CDSESUB1\EVSPROD\nda218160\0001\m3\32-body-data\32p-drug-prod\selpercatinib-tablet-01\32p1-desc-comp\descrip-and-comp.pdf

similarity test result (160 mg versus 40 mg, 80 mg, and 120 mg), f2, is shown in **Table 3**, profiles for pH 1.2 show more than (b) (4)% released in 15 minutes and therefore similarity statistic was not calculated and is found **adequate**. Since the bioequivalence between the approved Selpercatinib Capsules and the proposed Selpercatinib Tablets was established in the human bioequivalence study JZJZ, the multimedia dissolution direct comparison between capsules and tablets was not necessary and found **adequate.**

Table 3. Tablet Dissolution Profile Similarity Test

	Similarity Results, Reference (160 mg) vs. test (120, 80, or 40 mg)		
Test Conditions	**160 mg vs. 120 mg**	**160 mg vs. 80 mg**	**160 mg vs. 40 mg**
pH 1.2 HCl with 0.2% NaCl	≥ (b) (4)% in 15 min	≥ (b) (4)% in 15 min	≥ (b) (4)% in 15 min
pH 4.25 Citrate-Phosphate Buffer	f_2 = 93.0 ≥50	f_2 = 72.5 ≥50	f_2 = 70.7 ≥50
pH 6.8 Phosphate Buffer	< (b) (4)% in 360 min	< (b) (4)% in 360 min	< (b) (4)% in 360 min

Note: The time points for the f_2 calculations were 30, 60, 90, and 120 min for 40-mg and 80-mg comparisons, and 30, 60, 90, 120, and 180 min for the 120-mg comparison.

v. **Dose proportionality:** An exploratory assessment of selpercatinib dose proportionality in the therapeutic dose range of 40 to 160 mg was conducted based on the power model (log-transformed linear regression) for Cycle 1 Day 1 and Cycle 1 Day 8, respectively. See Section 2.7.1.4.4.2.2 of 2.7.1.4 for details. Results suggest dose proportionality can be declared for C_{max} and $AUC_{(0\text{-}12)}$ over the dose range from 40 to 160 mg, considering that 90% CI of slope estimates lie entirely within the acceptable region. This supports the selection of the highest strength of 160 mg for in vivo BE testing in the Study JZJZ.

Recommendation:

The following supporting information/data: **(1)** all the proposed lower strengths of the drug product have the same dosage form and manufacturing process as that of the 160 mg tablets used in the bio-study; **(2)** the proposed lower strengths of the drug product are proportionally similar in the formulation compositions (active and inactive ingredients) across all the strengths, **(3)** comparable in vitro dissolution profiles for all the four strengths, and **(4)** evidence of linear PK over the clinically relevant dose range (20 mg to 240 mg) and BE determination between the proposed selpercatinib 160 mg tablet and the approved selpercatinib 2 x 80 mg capsule product, are **Acceptable** and the biowaiver request for the lower 40 mg, 80 mg, and 120 mg strengths of Selpercatinib Tablets, is **Granted,** provided the BE study is acceptable by OCP.

CLINICAL PHARMACOLOGY CONSULT REQUEST

Waiver Request for an In Vivo Drug-Drug Interaction (DDI) Study with Acid Reducing Agents (ARA's):

Consult: On October 31, 2023, Biopharmaceutics received a consult request (via Email) from the Clinical Pharmacology Reviewer assigned to this NDA, Dr. Om Anand. In this consult, Biopharmaceutics was requested to review and provide feedback on the applicant's rationale and supporting data for not conducting the required in vivo gastric acid-reducing agent interaction study for the proposed selpercatinib tablets. Specifically, the Applicant was requesting a waiver for the requirement to submit data from an in vivo DDI study evaluating the interaction between the proposed selpercatinib tablets and acid reducing agents.

Assessment: As discussed previously, the polymorphic forms ((b) (4) and (b) (4) of selpercatinib are very similar in terms of solubility (Table 1). Similarity of solubilities for (b) (4) and (b) (4) indicate that reduction of gastric pH by co-administration of acid reducing agents, will have similar impact on the *in vivo* performance of drug products formulated with either Form. In addition, a change in the (b) (4) will have a minimal impact on the in vivo absorption of selpercatinib across the physiological range of gastric pH, as demonstrated in the BE study conducted by the Applicant for the proposed 160 mg Selpercatinib Tablets ((b) (4) and the approved (2 × 80-mg) Selpercatinib Capsules ((b) (4)

Additionally, based on the pH-solubility studies conducted for both forms ((b) (4) and (b) (4) and the dissolution profile data at different pH conditions provided solely for the newly proposed selpercatinib tablets dosage form, there is probability that potential DDI with ARA's would occur. However, the expected risk for the occurrence of DDI with ARAs is the same for the proposed selpercatinib tablets and the approved selpercatinib capsules, and no additional risks are identified for the tablets dosage form.

Recommendation: Because a similar DDI behavior with ARAs is expected for both, the selpercatinib tablets and the selpercatinib capsules, Biopharmaceutics considers that the Applicant's following proposals: **(1)** Not to conduct an in vivo gastric acid-reducing agent interaction study (DDI-waiver), and **(2)** To have a similar labeling DDI-statement[7] as the one included in the labeling of the approved selpercatinib capsules product, are **Acceptable**. Therefore, Biopharmaceutics recommends that Clinical Pharmacology grants the Applicant's DDI-waiver request.

REVIEWER's OVERALL CONCLUSIONS AND RECOMMENDATION

Based on overall information and data submitted, the following proposed dissolution method: 900 mL of 0.1 N HCl using USP Apparatus 2 (paddles) at 75 rpm, and dissolution acceptance criterion of NLT (b) (4)% (Q) in 15 minutes are **Acceptable** for batch release and stability testing of all the strengths of Selpercatinib Tablets, and the biowaiver request for the lower 40 mg, 80 mg, and 120 mg strengths of Selpercatinib Tablets is **Granted,** provided the BE study is acceptable by OCP. From the Biopharmaceutics perspective, NDA 218160 for RETEVMO® (selpercatinib) Tablets, 40 mg, 80 mg, 120 mg, and 160 mg is recommended for **APPROVAL**.

[7] https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/213246s008lbl.pdf

R. REGIONAL INFORMATION

Comparability Protocols

Assessment: n/a

Post-Approval Commitments

Assessment: n/a

Lifecycle Management Considerations

None.

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None.

Anitha Palamakula Govada

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Payal Agarwal,

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Date: 2/28/2024 10:31:46PM
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/s/

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