CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219713Orig1s000

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	219713		
Applicant Name	NUVATION BIO INC		
Drug Product Name	IBTROZI™ (taletrectinib)		
Dosage Form	Capsule		
Proposed Strength(s)	200 mg		
NDA Classification	Type 1 - NME		
Route of Administration	Oral		
Maximum Daily Dose	600 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	IBTROZI™ (taletrectinib) is indicated for the treatment of adult patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC)		
Drug Product Description	Capsules: 200 mg, immediate release, white, opaque, Size 0, hard capsules filled with white to light yellow powder, imprinted with “TAL” and “200” in blue ink on the body of the capsule. Each capsule contains 272 mg of taletrectinib adipate equivalent to 200 mg of taletrectinib.		
Co-packaged product information	N/A		
Device information	N/A		
Storage Temperature/ Conditions	Store IBTROZI at 20°C to 25°C (68°F to 77°F); excursions are permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Kabir Shahjahan	Haripada Sarker

	Drug Product/ Labeling	Amy Funk	Olen Stephens David Claffey (labeling)
	Manufacturing	Jiao Yang	Nathan Davis
	Biopharmaceutics	Haodan Yuan	Hardikkumar Patel
	Microbiology	Jiao Yang	Nathan Davis
	Other (specify)	None	
	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 None

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The applicant has provided sufficient information to assure the identity, strength, purity, and quality of the proposed drug product. All associated manufacturing, testing, packaging facilities were deemed acceptable based on prior history, PAI and district recommendation. Two comparability protocols are also found acceptable after revision. Based on the OPQ review team's evaluation of the information provided in the submission, OPQ recommends APPROVAL of NDA 219713 for IBTROZI™ (taletrectinib) capsules, 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 - Adequate

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

5. **Life-Cycle Considerations**

Established Conditions per ICH Q12: No
Comments: None

Comparability Protocols (PACMP): Yes
Comments:
The applicant submitted two comparability protocols:
(1) Based on DP review, the comparability protocol to add a 90-count container configuration submitted as a CBE-0 is acceptable.
(2) For drug product site addition (b) (4) (b) (4) the applicant revised the comparability protocol to update the reporting category to CBE-30. This is acceptable per OPMA review.

Additional Lifecycle Comments:
This NDA application was reviewed under the scope of ICH S9 for taletrectinib capsules which was confirmed by the non-clinical reviewer via email on 2/18/2025. However, if the indications change for this drug product that do not qualify for the ICH S9 risk approach, a re-review of the (b) (4) risks for the drug product should be considered.

Application Technical Lead Name and Date:

Xing Wang *04/28/2025*

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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 (OPQ-ALL-WI-0006)

NDA Number	219713
Assessment Cycle Number	1
Drug Product Name	Taletrectinib capsules (IBTROZI™), 200 mg

Assessment Recommendation: Adequate, *pending revisions conveyed to OND.*

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

Brief Description of Outstanding Issues:

Revisions related to the salt equivalency statement, listing the inactive ingredients according to USP/NF name and in alphabetical order, and edits to the drug product storage statement detailed below should be implemented to comply with current best labeling practices. After the recommended changes, the labeling will be adequate from the product quality perspective.

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
SDN 2, New/NDA, Rolling submission part #2, includes labeling information	10/23/2024	Draft Prescribing Information (PI) and patient labeling documents
SDN 5, Labeling/Container-Carton Draft	12/12/2024	Updated carton and container labels
SDN 31, Labeling/Container-Carton Draft	03/07/2025	Updated container label in response to drug product IR from 3/4/2025

1.0 PRESCRIBING INFORMATION[1]

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights[2] [21 CFR 201.57(a)(2)]		
Established name(s)[3]	Adequate	IBTROZI Removed (b) (4) (b) (4) in the highlights section.
Route(s) of administration	Adequate	For oral use
Controlled drug substance symbol (if applicable)	N/A	
Initial U.S. Approval [§201.57(a)(3)]	Adequate	Placeholder 20XX

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

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

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

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		
Dosage form(s)[4] and strength(s) in metric system[5]	Adequate	Capsule, 200 mg
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).[6]	Inadequate	This section is missing the statement clarifying whether the capsule strength (200 mg) is based on the active moiety or active ingredient/salt. IBTROZI (taletrectinib) capsules contain 272 mg of taletrectinib adipate equivalent to 200 mg of taletrectinib free base. As a result, we recommend adding "of taletrectinib" to the DOSAGE FORMS AND STRENGTHS section of the Highlights in the PI.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."[7]	N/A	Not scored.
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.[8]	N/A	N/A

Assessment: *Inadequate, will be adequate pending revisions conveyed to OND.*

[4] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018); USP <1151>; USP Nomenclature Guideline
[5] Labeling Review Tool (March 2022, page 13), include limited packaging information; USP <7>
[6] Guidance: *Naming of Drug Products Containing Salt Drug Substances* (June 2015); MAPP 5021.1
[7] Guidance: *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013)
[8] Guidance: *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018); USP <659>

The applicant did not state if the drug product strength listed in the "Dosage Forms and Strengths" section is based on the free base or the salt form. As a result, the wording under this section should state the following:

(b) (4)

The below comment was also added to the edit:

To the Applicant: Added "taletrectinib" to clarify that the 200 mg strength is based on the active moiety and not the active ingredient (salt).

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)[9]

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents and/or soft food[10], storage conditions needed to maintain the stability of the reconstituted or diluted product).	N/A	N/A; Capsule
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food).	Adequate	States: "Take IBTROZI at approximately the same time each day (b) (4) (b) (4) (b) (4) Swallow IBTROZI capsules whole. Do not open, chew, crush, or dissolve the capsule prior to swallowing."
For parenteral products: include statement: *"Parenteral drug products should be inspected visually for particulate matter and discoloration prior to*	N/A	N/A

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

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

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
administration, whenever solution and container permit."[11]		
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.[12] Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	N/A
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	N/A
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.*[x]*"* with x numerical citation to "OSHA Hazardous Drugs."	N/A	N/A

Assessment: *Adequate*

There are no edits from the drug product perspective for Section 2 of the PI. The applicant provided information about taking the drug product without food and this section states that the capsules should be swallowed whole and to not open, chew, crush, or dissolve the capsule prior to swallowing. We defer to Clin Pharm for final review and assessment of Section 2 of the PI.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)[13]

3 DOSAGE FORMS AND STRENGTHS

Capsules: 200 mg, immediate release, white, opaque, Size 0, hard capsules filled with white to light yellow powder, imprinted with "TAL" and "200" in blue ink on the body of the capsule.

[11] §201.57(c)(3)(iv)
[12] USP General Notices 2.30 Legal Recognition
[13] See § 201.57(c)(4); Labeling Review Tool (March 2022, page 29)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	Capsules
Strength(s) in metric system	Adequate	200 mg
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). No equivalency statement.	Inadequate	Missing statement clarifying whether the strength is based on the active moiety or active ingredient (salt). Add in below statement: "Each capsule contains the equivalent of 200 mg of taletrectinib."
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	Aligns with description of the drug product in Section 3.2.P.1.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	N/A
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package (see USP <659>).	N/A	N/A

Assessment: *Inadequate, will be adequate pending revisions conveyed to OND.*

Section 3 of the PI is missing a statement clarifying whether the drug product strengths are based on the active moiety or active ingredient. See suggestion below:

> **3 DOSAGE FORMS AND STRENGTHS**
>
> Capsules: 200 mg, immediate release, white, opaque, Size 0, hard capsules filled with white to light yellow powder, imprinted with "TAL" and "200" in blue ink on the body of the capsule. Each capsule contains the equivalent of 200 mg of taletrectinib.

The below comment was also added to the edit:

To the Applicant: Since the drug product contains a salt as the active ingredient, a statement is needed to clarify whether the strength is based on the active moiety or active ingredient. Refer to MAPP 5021.1 "Naming of Drug Products Containing Salt Drug", USP General Chapter <7> Labeling, and the USP Salt Policy per FDA Guidance.

1.2.3 Section 11 (DESCRIPTION)[14]

(b) (4)

[redacted]

[14] See § 201.57(c)(12); Labeling Review Tool (March 2022, page 56)
[15] Use of "USP" descriptor is not required to be included next to the established name throughout Prescribing Information (PI) labeling. If an applicant wants to use the "USP" descriptor next to the established name in

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Adequate	Capsules, for oral use
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)" [§ 201.57(c)(12)(i)(C)].	Adequate	"IBTROZI (taletrectinib) capsules for oral use are supplied as immediate release hard capsules containing 272 mg of taletrectinib adipate (equivalent to 200 mg of taletrectinib free base)."
List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order.[16] Avoid brand names. [§ 201.57(c)(12)(i)(C)].	Inadequate	Inactive ingredients need to be listed by the USP/NF names and 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. [§ 201.100(b)(5)(iii)].	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	N/A
Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].	N/A	N/A

the PI, recommend limiting its use to the product quality sections of the Full Prescribing Information (FPI) (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) (see page 3 of LRT).

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

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Pharmacological/Therapeutic class[17] [§ 201.57(c)(12)(i)(E)].	Adequate	Kinase inhibitor
Chemical name[18], structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Inadequate	Add in "adipate" as all details described in the PI (molecular formula, molecular weight, and chemical name, and structure) are for taletrectinib adipate and not the free base form (taletrectinib).
If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)].	N/A	N/A
Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)].	Adequate	Stated "Taletrectinib adipate is a white to yellowish powder." Additional drug substance physical and chemical properties are not needed as the capsule will be not opened for use. The instructions for administration include swallowing the capsule whole. CFR 201.57(c)(12)(ii) states that "If appropriate, other important chemical or physical information, such as physical constants or pH, must be stated."
For oral prescription drug products, include gluten statement[19] (if applicable).	N/A	N/A
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity").	N/A	N/A
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure	N/A	N/A

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

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

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

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).		

Assessment: *Inadequate, will be adequate pending revisions conveyed to OND.*

For Section 11 of the PI, the main issues were not listing the inactive ingredients in alphabetical order and according to USP/NF names. Also, "adipate" needs to be added to Section 11 for the API as all details described in this section (molecular formula, molecular weight, chemical name, and structure) are for taletrectinib adipate and not the free base form (taletrectinib). See our recommendations below:

(b) (4)

The below comments were also added to the edits:

To the Applicant: Added "adipate" to clarify that the molecular formula, molecular weight, chemical name, and structure are for taletrectinib adipate.

To the Applicant: We revised the list of inactive ingredients by the USP/NF names if applicable and listed them in alphabetical order. Refer to 21 CFR § 201.57(c)(12)(i)(C) and USP General Chapters <1091> *Labeling of Inactive Ingredients* for additional information.

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)[20]

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) [§ 201.57(c)(17)].	Adequate	Capsules
Strength(s) in metric system. [§ 201.57(c)(17)(i)] If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety. No equivalency statement.	Adequate	N/A; The salt equivalency statement is provided in Section 3 and Section 11. As a result, Dr. Claffey stated that it is not necessary in this section and based on the FDA Guidance, this specific language should be in the Highlights section of the PI for the product title and in the Dosage Forms and Strengths section. Also, the salt equivalency statement should be in the Description section 11.
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Adequate	Bottles of 30 capsules
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s) [§ 201.57(c)(17)(iii)].	Adequate	Size 0 white opaque hard capsules imprinted with "TAL" and "200" in blue ink.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	N/A

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

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package (see USP <659>).	N/A	N/A
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs." [§ 201.57(c)(17)(iv)]	Adequate	The drug product is packaged in a HDPE bottle with a (b) (4) (b) (4) (b) (4) cap (b) (4) (b) (4)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).	Inadequate	Missing "[*see USP Controlled Room Temperature*]" after storage statement.
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."*[21]	N/A	N/A

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

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Include information about child-resistant packaging[22] (if chosen by manufacturer).	N/A	Not provided.

Assessment: *Inadequate, will be adequate pending revisions conveyed to OND.*

For Section 16 of the PI, the applicant is missing "[*see USP Controlled Room Temperature*]" after storage statement. Also, the applicant was asked to clarify if the container closure system includes a carton that contains three bottles of 30 capsules in each bottle totaling 90 capsules per carton. The carton label was provided in SDN 5 on 12/12/2024. If the carton is used, Section 16 will need to be updated accordingly. See our recommendations below:

(b) (4)

The below comments were also added to the edits:

To the Applicant: Clarify if the container closure system includes a carton that contains three bottles of 30 capsules in each bottle totaling 90 capsules per carton. The carton label was provided in SDN 5 on 12/12/2024. Update this section accordingly.

To the Applicant: Updated the storage information to include "[*see USP Controlled Room Temperature*]."

1.2.5 Other Sections of Labeling

N/A

Distributed by: Nuvation Bio Inc., Burlington, MA 01803
IBTROZI™ is a trademark of Nuvation Bio Inc.

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

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

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

Assessment: *Adequate*

There are no edits from the drug product perspective for Section 17 of the PI. The applicant provided the name and location of the distributor company including the city, state, and zip code.

2.0 PATIENT LABELING

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

(b) (4)

[redacted]

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

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[24]	Adequate	IBTROZI
Special preparation instructions (if applicable).	N/A	N/A
Storage and handling information (if applicable).	Adequate	(b) (4)
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differ from the dosage form.	Adequate	The drug product is packaged in a HDPE bottle with a (b) (4) (b) (4) (b) (4) cap (b) (4) (b) (4)
Active ingredient(s) (if applicable).	Inadequate	Need to change to "taletrectinib adipate".
Alphabetical listing of inactive ingredients (if applicable).	Inadequate	Not listed in alphabetical order and according to USP/NF name.
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer.	Adequate	Provided distributor with city, state, and zip code.

Assessment: *Inadequate, will be adequate pending revisions conveyed to OND.*

For the patient labeling, the edits include updating the active ingredient to the salt form and listing the inactive ingredients alphabetically and according to the USP/NF name. See our recommendations below:

PATIENT INFORMATION
IBTROZI™ [ib-TRO-zee]
(taletrectinib) capsules,
for oral use

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

How should I store IBTROZI?

- Store IBTROZI at room temperature between 68°F to 77°F (20°C to 25°C).

Keep IBTROZI and all medicines out of the reach of children.

General information about the safe and effective use of IBTROZI.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use IBTROZI for a condition for which it was not prescribed. Do not give IBTROZI to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about IBTROZI that is written for health professionals.

(b) (4)

The below comments were also added to the edits:

To the Applicant: State the correct active ingredient "taletrectinib adipate" (b) (4) (b) (4) for the drug product.

To the Applicant: We revised the list of inactive ingredients by the USP/NF names if applicable and list in alphabetical order. Refer to 21 CFR § 201.57(c)(12)(i)(C) and USP General Chapters <1091> Labeling of Inactive Ingredients for additional information.

3.0 CONTAINER AND CARTON LABELING[25]

3.1 Container Labels[26]

Container (bottle) label, submitted in SDN 31, 03/07/2025

[25] Carton and Container Labeling Resources

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

3.2 Carton Labeling

Carton label, submitted in SDN 3, 12/12/2024

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Proprietary name and established name[27], (font size and prominence) [§ 201.10(g)(2)].	Adequate	Yes	IBTROZI™
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)].[28]	Adequate	Yes	200 mg

[27] Established name = [Drug] [Route of Administration] [Dosage Form]
[28] Express as " XX mg per tablet" or "XX mg per capsule" for strength of professional samples of solid oral dosage form with small net quantities per container (e.g., 5 or less) or blister pack/carton. See Guidance:

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	N/A	Choose an item.	For oral use; not needed as it adds clutter to the labels
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP [§ 201.10(d)(1) & 201.100(b)(4), USP <1121>].	Adequate	No	The salt equivalency statement is adequate on the carton; however, the statement is not correct on the bottle (container) label. The applicant provided an updated bottle label in SDN 31 on 03/07/2025 in response to the CMC IR that was issued on 03/04/2025.
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)].[29]	Adequate	No	30 capsules on the bottle label and 90 capsules on the carton label. The carton label also states (b) (4) (b) (4)
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Adequate	Yes	N/A
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	Yes	N/A
Lot number and expiration date [§ 201.18 & 201.17].	Adequate	Yes	Location for the Lot and Expiration date is provided. Refer to the review by DMEPA for additional information.
Storage conditions. If applicable, include a space on	Adequate	Yes	

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)

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

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
the carton labeling for the user to write the beyond-use-date (BUD).			
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement. (See USP <659>).	N/A	Choose an item.	N/A
Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5) or limited space per § 201.10(i)(2)].	N/A	Choose an item.	Oral drug.
For parenteral injectable dosage forms, include quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	N/A	Choose an item.	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	Choose an item.	N/A
Linear Bar code [§ 201.25(c)(2)].[30]	Adequate	Yes	Refer to the review by DMEPA for additional information.

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

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Adequate directions for use: "Recommended Dosage: See Prescribing Information" [§ 201.5 & 201.55].	Adequate	Yes	N/A
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	Yes	Provided the distributor information on the bottle and carton label. Also, the applicant stated "Origin: China".
"Keep out of reach of children" statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)].	Adequate	Yes	N/A
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	Choose an item.	N/A
No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>).	N/A	Choose an item.	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	Choose an item.	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	N/A	Choose an item.	N/A

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
shall be plainly stated on its label.[31]			
And others if space is available.	N/A	Choose an item.	The applicant stated "Swallow capsules whole" on the bottle and carton label. We defer to DMEPA if this is needed or should be removed to avoid clutter on both labels.

Assessment of Carton Labels and Container Labeling: *Adequate,* the CMC deficiencies were conveyed to the applicant and are determined to be adequate after the applicant made the suggested revisions summarized below.

There was one issue that needed to be addressed regarding the container label. As a result, drug product issued the below IR to the applicant after consult with the DMEPA reviewer, Dr. Janine Stewart. We consulted Dr. Stewart on 02/21/2025 via email asking for any other potential issues with the carton and container labels and asked for any edits of the below IR before sending them to the OND RPM. Dr. Stewart responded on 03/04/2025 via email stating that she did not have any edits for the CMC IR. Also, DMEPA identified an additional issue that is listed below and will be issuing an IR from DMEPA separately.

- As proposed, the net quantity statement on the principal display panel "90 capsules" is not the most accurate description of the packaging configuration. Revise the net quantity statement to read "3 bottles x 30 capsules each" to more accurately describe how IBTROZI is supplied.
  - Consider removing the statement (b) (4) (b) (4)

As a result, the below CMC IR for the container label was issued to the applicant on 3/4/2025 by the OND RPM, Raniya Al-Matari, with a response deadline of COB on 03/19/2025.

NDA 219713, Carton and Container Labels, CMC IR

[31] USP General Notices 3.20 Indicating Conformance

1. We acknowledge that the bottle label in SDN 5 (submitted 12/12/2024) for the drug product states, “Each capsule contains 200 mg taletrectinib.” However, the salt equivalency statement should include the amount of active ingredient used in the drug product. Update the statement to “Each capsule contains 200 mg taletrectinib (equivalent to 272.1 mg taletrectinib adipate)” to the bottle label to match the statement on the carton label. Refer to the USP Salt Policy per FDA Guidance, "Naming of Drug Products Containing Salt Drug Substances" for additional information.

The applicant provided an updated bottle label in SDN 31 on 03/07/2025 in response to the CMC IR that was issued on 03/04/2025. The updated container label now states “Each capsule contains 200 mg taletrectinib (equivalent to 272.1 mg taletrectinib adipate)” to match the statement on the carton label.

The provided information is adequate from the product quality perspective. Refer to the DMEPA review for additional information and assessment of the container and carton labels if needed.

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

Recommendations and revisions have been conveyed to OND. Labeling will be adequate from the product quality perspective once the changes have been implemented by the applicant.

Primary Labeling Assessor Name and Date:

Amy Funk, Ph.D., 03/12/2025

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

David Claffey, Ph.D., 03/12/2025

Amy Funk

Digitally signed by Amy Funk
Date: 3/12/2025 07:40:58AM
GUID: 627129ed000baa2067f25a0f8a885903

David Claffey

Digitally signed by David Claffey
Date: 3/12/2025 07:47:33AM
GUID: 508da71e00029e20b201195abff380c2

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CHAPTER VI: BIOPHARMACEUTICS

Product Information	Capsules/Immediate Release
NDA Number	NDA-219713-ORIG-1 (505(b)(1))
Assessment Cycle Number	1
Drug Product Name/ Strength	Taletrectinib Capsules, 200 mg
Route of Administration	Oral
Applicant Name	Nuvation Bio Inc.
Therapeutic Classification/ OND Division	CDER/OND/OOD/DO2
LD/Cross referenced NDA	New Molecular Entity (NME)
Proposed Indication	Taletrectinib is a kinase inhibitor indicated for the treatment of adult patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC)
Primary Reviewer	Haodan Yuan, Ph.D.
Secondary Reviewer	Hardikkumar Patel, Ph.D.

Assessment Recommendation: **Adequate**

A. Assessment Summary:

The Applicant submitted this NDA seeking approval for Taletrectinib Capsules, 200 mg under 505(b)(1) regulatory pathway. The drug substance, Taletrectinib adipate is a new molecular entity (NME). Taletrectinib is a kinase inhibitor indicated for the treatment of adult patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC). Taletrectinib was granted Orphan Drug Designation on 16 July 2024.

Review Objective: The focus of the current Biopharmaceutics review is to assess the dissolution method and drug release specifications for the proposed drug product quality control (QC) and the scientific bridging of the clinical formulation to the proposed commercial formulation.

Recommendation: Based on the totality of data/information provided, the following dissolution testing method and acceptance criterion are approved for the QC of the proposed drug product at batch release and throughout stability program/shelf-life.

Final Dissolution Method and Acceptance Criterion

Apparatus	USP II (Paddle with Sinkers)
Rotation Speed	50 rpm
Medium	0.05 mol/L acetic acid - sodium acetate buffer, pH 4.0
Volume / Temperature	900 mL / 37±0.2°C
Acceptance Criterion	NLT (b)(4)% (Q) in 30 minutes

Formulation bridging: The proposed commercial product is qualitatively and quantitatively identical to the drug product used for pivotal clinical studies but are differentiated through use of ink printing on commercial batches; clinical batches did not have ink printed. The Applicant established the scientific bridge between the clinical batch and the proposed commercial batches using comparable dissolution data generated using the proposed in vitro dissolution method.

Biowaiver: Only one dosage strength (200 mg) is being sought for approval; biowaiver is not applicable for this application.

Overall recommendation: From a Biopharmaceutics perspective, NDA 219713 for Taletrectinib Capsules, 200 mg is recommended for APPROVAL.

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking	Comments
Particle size distribution (PSD) of the drug substance	Medium	Drug substance particle size may impact drug product dissolution	Low	The proposed dissolution method shows sensitivity to the changes in taletrectinib PSD in the drug product. In addition, the Applicant has proposed three tier PSD limits for the drug substance.
Amount of (b) (4) in the formulation	Medium	The amount of (b) (4) may impact to the dissolution of the proposed drug product	Low	The proposed dissolution method shows sensitivity to the changes in (b) (4) amount in the drug product formulation. The (b) (4) amount in the formulation is targeted at (b) (4)%.

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
SN-0001 New NDA	**9/30/2024**
SN-0014 Stability Summary	**1/29/2025**
SN-0027 Response to CMC Pre-NDA feedback; Dissolution Profile Comparison	**2/28/2025**

Highlight Key Issues from Last Cycle and Their Resolution: Not Applicable

Concise Description of Outstanding Issues *(list bullet points with key information and update as needed)*: Not Applicable

B.1 BCS DESIGNATION

Assessment: There is no official BCS designation request for the proposed drug product.

Solubility: The solubility of the drug substance taletrectinib adipate at 37°C in various aqueous media is summarized in Table 3 of 3.2.P.2.2 Drug Product.

Table 1. pH-Solubility of taletrectinib adipate at 37°C

Medium	Solubility (mg/mL)	Sink Condition achieved? [a] (Yes/No)
Water	1.717	(b) (4)
pH 1.0 hydrochloric acid solution	>20.000	
pH 1.2 hydrochloric acid solution	>20.000	
pH 4.0 acetate buffer	6.120	
pH 4.5 acetate buffer	4.980	
pH 5.0 acetate buffer	1.987	
pH 5.5 acetate buffer	2.381	
pH 6.0 phosphate buffer	1.420	
pH 6.8 phosphate buffer	0.440	
Fasted State Simulated Gastric Fluids (FaSSGF)	>20.000	
Fasted State Simulated Intestinal Fluids (FaSSIF)	0.313	
Fed State Simulated Intestinal Fluid (FeSSIF)	0.547	

[a] Based on a volume of 900 mL dissolution medium and a unit dosage strength of 272.1 mg taletrectinib adipate (equivalent to 200 mg taletrectinib). The minimum solubility to achieve sink condition is (b) (4) mg/mL of taletrectinib adipate (equivalent to (b) (4) mg/mL of taletrectinib free base).

The results show that the solubility of the drug substance is pH-dependent, with high solubility in low pH medium (up to pH 6.0) and low solubility at pH 6.8 and above. Based on 900 mL dissolution medium volume and dosage strength of 272.1 mg taletrectinib adipate (equivalent to 200 mg taletrectinib), the minimum solubility to achieve sink condition is (b) (4) mg/mL of taletrectinib adipate (equivalent to (b) (4) mg/mL of taletrectinib free base). Therefore, the sink condition is achieved at pH (b) (4) (b) (4)

Permeability: The Applicant claims high permeability for taletrectinib based on In-Vitro permeability studies using (Caco-2 cell monolayers).

B. 2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

The proposed drug substance taletrectinib is a new molecular entity (NME). The Applicant proposed following quality control dissolution method and acceptance criterion for the proposed drug product (Analytical Procedures, Pg 18/21):

Proposed Dissolution Method and Acceptance Criterion

Apparatus	USP II (Paddle with Sinkers)
Rotation Speed	50 rpm
Medium	0.05 mol/L acetic acid - sodium acetate buffer, pH 4.0
Volume / Temperature	900 mL / 37±0.5°C
Acceptance Criterion	NLT (b) (4)% (Q) in 30 minutes

The Applicant has provided dissolution method parameters justification including discriminating ability of the proposed dissolution method (3.2.P.2.2 Drug Product, Pg 6-58).

(b) (4)

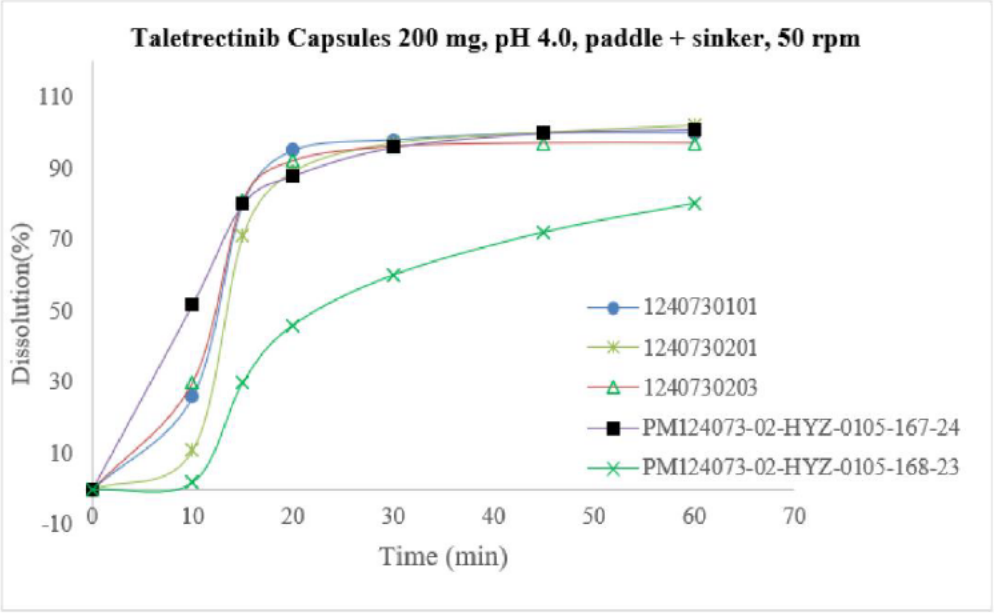
(b) (4)

The applicant selected the proposed dissolution method: [USP apparatus II (paddle) with spiral sinker, paddle speed of 50 rpm, 900 mL 50 mM pH4.0 acetated buffer at 37 °C] based on the data discussed above.

Discriminating Ability: The Applicant investigated the dissolution method's discriminating ability towards the following Critical Bioavailability Attributes (CBAs).

- ***Critical Material Attributes (CMAs): particle size distribution (PSD) of the drug substance***: The PSD of the proposed drug substance taletrectinib is controlled at d10: (b) (4) µm, d50: (b) (4) µm d90: (b) (4) µm (drug substance specification). The proposed drug product taletrectinib capsules with drug substance in different particle sizes were prepared and used for a comparative dissolution test using the proposed dissolution method (PDR, Table 33, Table 34 and Figure 11). The proposed dissolution method has discriminating ability against changes in drug substance particle size (b) (4)
(b) (4)
(b) (4)

Figure 1: Comparative dissolution profiles of the proposed drug product manufactured with different drug substance PSDs



- ***Critical Formulation Attributes (CFAs): Impact of amount*** (b) (4) ***in formulation on dissolution:***

Amount (b) (4)***:*** To evaluate the impact of (b) (4) amount on the dissolution, the Applicant manufactured the drug product batch with high ((b) (4)%) (b) (4) amount compared to the target product ((b) (4)%). The dissolution profile of the batch containing high (b) (4) amount showed slower dissolution compared to the target product (f2 <50, Table 2).

Table 2. f2 value calculated by the reviewer for of the variant batch

Test Batch	Reference Batch 1240730203
PM124073-02-HXY-0180-068-29	36

Amount (b) (4)***:*** To evaluate the impact of different amount of (b) (4) on the dissolution, the Applicant manufactured the drug product batches with lower ((b) (4)%) and higher ((b) (4)%) (b) (4) amount compared to the target product (b) (4) The results showed no significant difference in dissolution among the three drug product batches using the proposed dissolution method (f2 >50, Table 3).

Table 3. f2 values calculated by the reviewer for the variant batches

	PM124073-02-HYZ-0138-005-24
PM124073-02-WCY-0180-024-13	62
PM124073-02-WCY-0180-024-14	56

- ***Critical process parameters (CPPs)*** The Applicant evaluated the proposed dissolution method against changes in drug product manufacturing process (b) (4) The results showed (b) (4) (b) (4) (b) (4) However, the discriminating ability for this parameter variation is not supported by the calculated f2 (table 4) and the proposed dissolution method criterion.

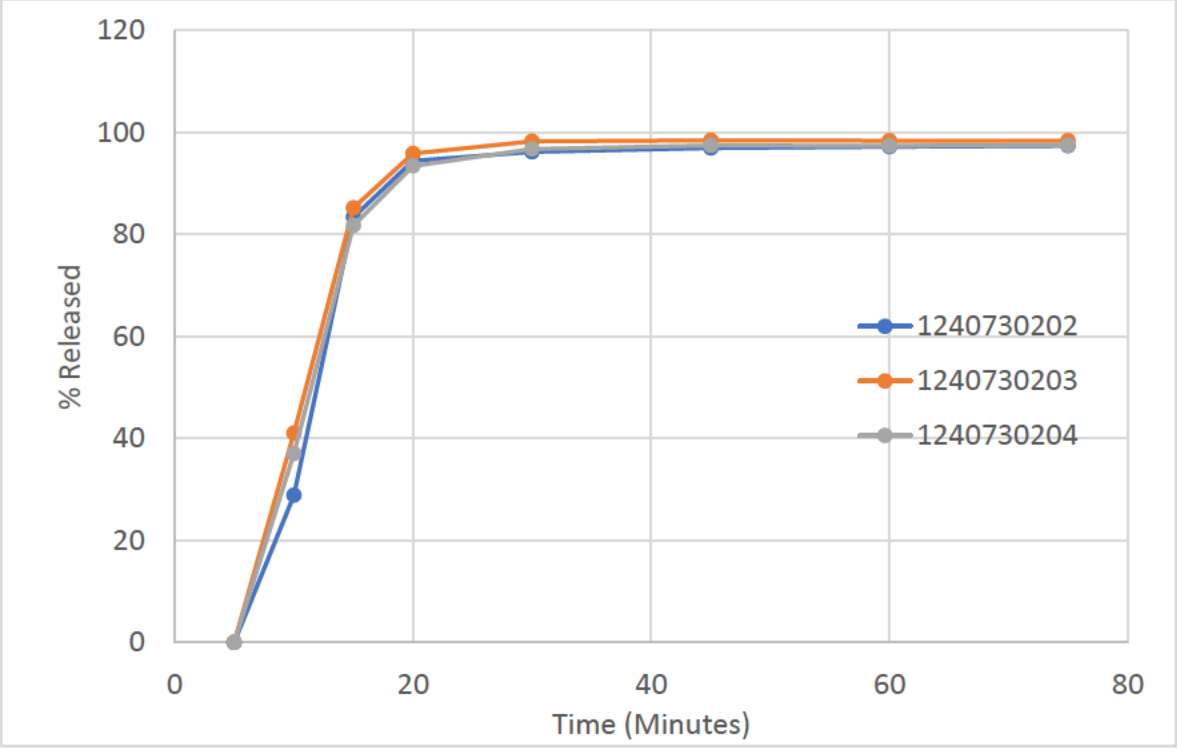
Table 4. f2 values calculated by the reviewer for the variant batches

Test Batch	Reference Batch PM124073-02-HYZ-0138-005-24
PM124073-02-HYZ-0180-012-19	52

Based on the information outlined above, the proposed dissolution method has a discriminating ability against changes in drug substance particle size and (b) (4) amount.

Acceptance Criterion: Based on the dissolution profiles of the clinical and registration batches, the proposed dissolution acceptance criterion of 'NLT (b) (4) %(Q) at 30 minutes" is acceptable.

Figure 2. Dissolution profiles of the registration batches using the proposed dissolution method



Recommendation: Based on the overall dissolution method development data and the clinical data provided, the following dissolution method and acceptance criterion is approved for the QC of the proposed drug product at batch release and throughout stability program/shelf-life:

Table 5: Final Dissolution Method and Acceptance Criterion

Apparatus	USP II (Paddle with Sinkers)
Rotation Speed	50 rpm
Medium	0.05 mol/L acetic acid - sodium acetate buffer, pH 4.0
Volume / Temperature	900 mL / 37±0.5°C
Acceptance Criterion	NLT (b) (4)% (Q) in 30 minutes

B. 12. BRIDGING

Assessment: Adequate

Formulation bridging: The proposed commercial product is qualitatively and quantitatively identical to the drug product used for pivotal clinical studies but are differentiated through use of ink printing on commercial batches; clinical (registration) batches are a plain size "0" capsule that does not have imprinted IDs, while the proposed final

This change is not expected to have an impact on the dissolution of the proposed drug product. However, the Applicant manufactured a small bridging batch (batch number 124073050102) with imprinted ID on the capsules with identical presentation as the proposed commercial product. The comparative dissolution data of the bridging batch to the registration/PPQ using the proposed dissolution method were provided. The registration batches and the bridging batch showed comparable dissolution profiles, hence the scientific bridging of the registration batches to the proposed commercial product is established (Table 44 and Figure 19 of 3.2.P.2.2 Drug Product).

Manufacturing site: The drug product manufacturing site for clinical batches and commercial batches is the same (Section 4.1 of 3.2.P.5.4 Batch Analyses).

B. 13. BIOWAIVER REQUEST

Assessment: Not Applicable

Only one dosage strength (200 mg) is being sought for approval; biowaiver is not applicable to this application.

R. REGIONAL INFORMATION

***Comparability protocol: Addition of drug product manufacturers*:** The Applicant plans to register additional drug product manufacturing site for Taletrectinib capsules after approval of this application using CBE-0. The Applicant proposes to provide comparative dissolution data for 3 batches manufactured at an alternate manufacturing site and 3 batches manufactured at the current manufacturing site. The post approval changes will be evaluated based on the totality of the data submitted.

OVERALL CONCLUSION/RECOMMENDATION:

From a Biopharmaceutics perspective, NDA 219713 for IBTROZI (taletrectinib) Capsules, 200 mg is recommended for APPROVAL.

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None.

Hardikkumar Patel

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Date: 4/10/2025 12:00:09PM
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Haodan Yuan

Digitally signed by Haodan Yuan
Date: 4/10/2025 11:58:18AM
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