

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

219776Orig1s000

PRODUCT QUALITY REVIEW(S)



Title:	New Drug Application (NDA) Integrated Quality Assessment Template	
Document ID:	OPQ-ALL-TEM-0004	
Effective Date:	04 Nov 2022	Revision: 08
Total Pages:	4	



Template Revision: 03



Office of Pharmaceutical Quality

New Drug Application (NDA) 219776 Integrated Quality Assessment



Title:	New Drug Application (NDA) Integrated Quality Assessment Template
Document ID:	OPQ-ALL-TEM-0004
Effective Date:	04 Nov 2022 Revision: 08
Page 2 of 4	



Template Revision: 03

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 219776 Assessment 1

Drug Product Name	Berotralstat Oral Pellets
Dosage Form	Oral pellets
Strength	(b) (4), 96, 108, 132 mg
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	BioCryst Pharmaceuticals, Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original (SD-1)	12-Mar-2025	All
Amendment (SD-2)	09-Apr-2025	Drug substance
Amendment (SD-3)	21-Apr-2025	Environmental Assessment & Manufacturing/Facilities
Amendment (SD-4)	01-May-2025	Drug product
Amendment (SD-6)	02-Jun-2025	Drug product
Amendment (SD-11)	26-Jun-2025	Drug product
Amendment (SD-12)	08-Jul-2025	Biopharmaceutics
Amendment (SD-13)	18-Jul-2025	Manufacturing/Facilities
Amendment (SD-14)	25-Jul-2025	Drug product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Friedrich Burnett	Lawrence Perez
Drug Product	Craig M. Bertha	Julia Pinto
Manufacturing	Sydney Choi	Erin Kim
Microbiology	Sydney Choi	Erin Kim
Biopharmaceutics	Kalpana Paudel	Tapash Ghosh



Title:	New Drug Application (NDA) Integrated Quality Assessment Template
Document ID:	OPQ-ALL-TEM-0004
Effective Date:	04 Nov 2022 Revision: 08
Page 3 of 4	



Template Revision: 03

Labeling	Craig M. Bertha	Julia Pinto
Regulatory Business Process Manager	Teshara Bouie/Stephanie Ngan	
Application Technical Lead	Craig M. Bertha	
Laboratory (OTR)	N/A	
Environmental	Craig M. Bertha	Julia Pinto



Title:	New Drug Application (NDA) Integrated Quality Assessment Template		
Document ID:	OPQ-ALL-TEM-0004		
Effective Date:	04 Nov 2022	Revision:	08
Page 4 of 4			



Template Revision: 03

Table of Contents – Hyperlinks

Quality Assessment Data Sheet

Executive Summary

Drug Substance

Drug Product

Labeling

Manufacturing/Facilities

Biopharmaceutics



Title:	New Drug Application (NDA) Integrated Quality Assessment Template
Document ID:	OPQ-ALL-TEM-0004
Effective Date:	04 Nov 2022 Revision: 08
Total Pages:	1



Template Revision: 03

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	IV		(b) (4)	N/A		Sufficient information in NDA
	III		Adequate	31-Mar-2025	Reviewed as per MaPP 5015.5	

B. OTHER DOCUMENTS: IND, RLD, RS, Approved NDA

Document	Application Number	Description
NDA	214094	Approved application for berotralstat capsules

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other				



Title:	NDA IQA Template Title Page- EXEC SUMMARY		
Document ID:	OPQ-ALL-TEM-0040		
Effective Date:	26 Sep 2023	Revision:	00
Total Pages:	9		



Template Revision: 03

Office of Pharmaceutical Quality

New Drug Application (NDA) 219776 Integrated Quality Assessment

NDA Executive Summary

1. Application/Product Information

NDA Number	219776		
Applicant Name	BioCryst Pharmaceuticals, Inc.		
Drug Product Name	Berotralstat oral pellets		
Dosage Form	Pellets		
Proposed Strength(s)	(b) (4), 96, 108, and 132 mg (as free base)		
NDA Classification	Type 5 – New Formulation or New Manufacturer		
Route of Administration	Oral		
Maximum Daily Dose	132 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Prophylaxis to prevent attacks of hereditary angioedema (HAE) in adults and pediatric patients 2 years of age and older		
Drug Product Description	Seal of packaged unit must be intact. White to off white, plain-faced, round in diameter, with dose-appropriate number of granules (b) (4), as listed below: (b) (4) mg dose: (b) (4) pellets 96 mg dose: 16 pellets 108 mg dose: 18 pellets 132 mg dose: 22 pellets		
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 permitted between 15°C and 30°C (59°F to 86°F) [see USP Controlled Room Temperature].		
Review Team	Discipline	Primary	Secondary

	<i>Drug Substance</i>	Friedrich Burnett	Lawrence Perez
	<i>Drug Product/ Labeling</i>	Craig M. Bertha	Julia Pinto
	<i>Manufacturing</i>	Sydney Choi	Erin Kim
	<i>Biopharmaceutics</i>	Kalpana Paudel	Tapash Ghosh
	<i>Microbiology</i>	Sydney Choi	Erin Kim
	<i>Other (specify)</i>	N/A	
	<i>RBPM</i>	Teshara Bouie/Stephanie Ngan	
	<i>ATL</i>	Craig M. Bertha	
	<i>EA</i>	N/A	
Consults	N/A		

2. Final Overall Recommendation - Approval

a. Expiration Dating: 24 months

b. Additional Comments for Action: N/A

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The applicant has provided additional information in response to Agency information requests and there are no unresolved CMC-related issues remaining. Therefore, approval of the application is recommended from the CMC perspective.

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

Recommendation by Subdiscipline:

Drug Substance - Adequate
Drug Product - Adequate
Quality Labeling - Pending¹
Manufacturing - Adequate
Biopharmaceutics - Adequate

¹The labeling review decision is pending for this IQA due to ongoing negotiations with the applicant. There are only minor labeling deficiencies from the CMC perspective and we expect the applicant will accept our recommendations. Refer to the CMC sections of the final approved labeling.

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: N/A



Title:	NDA IQA Template Title Page- EXEC SUMMARY
Document ID:	OPQ-ALL-TEM-0040
Effective Date:	26 Sep 2023 Revision: 00
Total Pages:	9



Template Revision: 03

Final Quality Risk Assessment

DP attribute/ CQA	Factors that may impact the CQA	O ²	S ^{4,3}	D ⁴	Initial RA FMECA RPN #	Comment & considerations for risk assessment	Final RA	Lifecycle considerations
Appearance	- Variation of color of film coating formulation - Variation of film coating	2	3	2	12	(b) (4)		
Identification	incorrect API and/or excipients formulated	1	3	1	3			
Assay	- assay/purity of input drug substance and excipients (b) (4) - variation of packet fill weights	3	3	2	18			
Degradation Products	- poor packet seal integrity - high degradant levels in the berotralstat - compatibility of APIs with excipients	2	3	3	18			

² O = Probability of Occurrence; S = Severity of Effect; D = Detectability

³ Severity of effect can only be estimated; input from clinical, clinical pharmacology, and pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs (thus a median value of "3" will be used throughout)

NDA 219776 OPQA II/DPQA VIII Filing Review

						(b) (4)		
API Physical form	- polymorph conversion - PSD change during processing to prepare drug - change of drug substance (b) (4) form with food contact	1	3	4	12			
Elemental impurities	- elemental impurities in input materials (API and excipients) - elemental impurities introduced by manufacturing equipment	1	3	5	15			

(b) (4)

NDA 219776 OPQA II/DPQA VIII Filing Review

Nitrosamines	• Nitrosamine risk (b) (4) (b) (4)	3	3	4	36	(b) (4)	2x3x3 = 18	(b) (4)



Title:	NDA IQA Template Title Page- EXEC SUMMARY		
Document ID:	OPQ-ALL-TEM-0040		
Effective Date:	26 Sep 2023	Revision:	00
Total Pages:	9		



Template Revision: 03

Application Technical Lead Name and Date:

Craig M. Bertha, 23-Oct-2025

66 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page



Title:	NDA IQA Template CHAPTER IV-LABELING		
Document ID:	OPQ-ALL-TEM-0045		
Effective Date:	18 Sep 2023	Revision:	00
Total Pages:	26		



Template Revision: 03

Important: Do Not Change the Header or Footer

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	219776
Assessment Cycle Number	1
Drug Product Name	ORLEDAYO (berotralstat) oral pellets (applicant proposes (oral granules))

Assessment Recommendation: Inadequate

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

Brief Description of Outstanding Issues: Minor editing of the package insert, the patient information, and container labels is needed. See below.

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
SD-1	12-Mar-2025	Proposed package insert (PI), patient information, carton and container labels

1.0 PRESCRIBING INFORMATION¹

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 Highlights² [21 CFR 201.57(a)(2)]		

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 \(January 2018\)](#)

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)
Established name(s) ³	Inadequate	The labeling experts in OPQ have voiced concern for the use of "oral granules" as the dosage form descriptor for other applications where the drug product is comprised of multiple small "mini tablets" for oral administration and conclude that "oral pellets" would be more appropriate and in line with USP <1151>. See the approved similar dosage forms of NDAs 212477, 212480 and 219104. We sent a request to the PQL Mailbox and the response from Susan Rimmel of 01-Jul-2025 stated that the dosage form descriptor should be "oral pellets."
Route(s) of administration	Adequate	
Controlled drug substance symbol (if applicable)	N/A	
Initial U.S. Approval [§201.57(a)(3)]	Adequate	ORLADEYO (berotralstat) capsules were approved in 2020
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		
Dosage form(s) ⁴ and strength(s) in metric system ⁵	Adequate	
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	Adequate	

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

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

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

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

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored." ⁷	N/A	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package. ⁸	N/A	

Assessment: *Inadequate*

Deficiency: Revise the dosage form descriptor from "oral granules" to "oral pellets" for all labels and labeling to align with the recommendations of USP <1151>.

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

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

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)⁹



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

(b) (4)



Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents)	Adequate	The directions for administration are supported by the food compatibility study undertaken by the applicant (see drug product chapter). However, for clarity section 2.6 should be revised to state that pellets if pellets

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)
and/or soft food ¹⁰ , storage conditions needed to maintain the stability of the reconstituted or diluted product).		mixed with food are not taken within 10 minutes after preparation, the mixture should be discarded.
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food).	Adequate	See comment above
For parenteral products: include statement: <i>"Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."</i> ¹¹	N/A	
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	
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 <i>"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.x"</i> with x numerical citation to "OSHA Hazardous Drugs."	N/A	

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](#)

¹¹ §201.57(c)(3)(iv)

¹² USP General Notices 2.30 Legal Recognition

Assessment: **Inadequate**

See deficiency above regarding the dosage form descriptor.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)¹³



(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Inadequate	See deficiency above regarding the dosage form descriptor
Strength(s) in metric system	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance . Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). No equivalency statement.	Adequate	
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	
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 parenteral administration, use	N/A	

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)
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>).		

Assessment: *Inadequate*

See deficiency above regarding the dosage form descriptor.

1.2.3 Section 11 (DESCRIPTION)¹⁴



(b) (4)

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

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s) ¹⁵ [§ 201.57(c)(12)(i)(A)].	Inadequate	See deficiency comment regarding dosage form descriptor
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Inadequate	See deficiency comment regarding dosage form descriptor
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	
List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order. ¹⁶ Avoid	Inadequate	The oral pellet film coating excipients should be listed in alphabetical order.

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

¹⁶ Per § 201.100(b)(5)(i) and (ii), flavoring and colorants may be designated as such without naming their components except for FD&C Yellow No 5 and FD&C Yellow No 6, which must be listed per § 201.20. Per § 201.100(b)(5)(iii), trace amounts of harmless substances added solely for individual product identification

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)
brand names. [§ 201.57(c)(12)(i)(C)].		
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	
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	
Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].	N/A	
Pharmacological/Therapeutic class ¹⁷ [§ 201.57(c)(12)(i)(E)].	Adequate	Defer to pharmacology/toxicology team regarding the class that is listed
Chemical name ¹⁸ , structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Adequate	
If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)].	N/A	
Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)].	Adequate	
For oral prescription drug products, include gluten statement ¹⁹ (if applicable).	Adequate	The drug product contains pregelatinized starch but the applicant does not choose to include the gluten statement, which is consistent with the guidance recommendations.

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.

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)
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity").	Adequate	
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	

Assessment: *Inadequate*

Deficiency: Revise the list of oral pellet film coating excipients such that they are in alphabetical order where they appear in the labeling.

See deficiency above regarding the dosage form descriptor.

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



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

(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)].	Inadequate	Tablets approved under NDA 214094; see deficiency comment regarding the oral pellet dosage form descriptor
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	
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Adequate	
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)].	Inadequate	The description of the dosage form, i.e., oral pellets, is not provided
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 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	

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)
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures. ^x " with x numerical citation to "OSHA Hazardous Drugs." [§ 201.57(c)(17)(iv)]	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).	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." ²¹	N/A	No latex statement has been included, consistent with the guidance recommendations.
Include information about child-resistant packaging ²² (if chosen by manufacturer).	Adequate	

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

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

Assessment: *Inadequate*

Deficiency: Revise the HOW SUPPLIED/STORAGE AND HANDLING section of the package insert to include a description of the dosage form (e.g., white to off-white, film-coated pellets).

See deficiency above regarding the dosage form descriptor.

1.2.5 Other Sections of Labeling

N/A

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.	<i>Inadequate</i>	The street address is not included for the distributor (BioCryst).

Assessment: *Inadequate*

Deficiency: Revise the labels and labeling where the address of the distributor is provided, to list the street address of the distributor as per 21 CFR 201.1(i).

2.0 PATIENT LABELING

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

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

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)



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	Inadequate	See deficiency comment regarding dosage form descriptor
Special preparation instructions (if applicable).	Adequate	Instructions for taking the oral pellets are provided in accordance with the information in the package insert's DOSAGE and ADMINISTRATION section.
Storage and handling information (if applicable).	Adequate	
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differ from the dosage form.	N/A	
Active ingredient(s) (if applicable).	Inadequate	The applicant has chosen to include lists of the active ingredients, but that for the film-coating are not in alphabetical order (as for the DESCRIPTION section of the package insert).

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

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Alphabetical listing of inactive ingredients (if applicable).	Inadequate	See comment above.
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer.	Inadequate	The street address is not included for the distributor (BioCryst). See the deficiency comment above.

Assessment: *Inadequate*

See deficiency comments above.

3.0 CONTAINER AND CARTON LABELING²⁵

²⁵ [Carton and Container Labeling Resources](#)

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

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)].	Inadequate	Yes	See deficiency comment regarding dosage form descriptor
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)]. ²⁸	Adequate	Yes	
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Adequate	No	The cartons and wallets also state: (b) (4)
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 only on the cartons and wallets and not on the unit-dose packets (adequate as per 21 CFR 201.10(i)(2)).

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

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

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)
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)]. ²⁹	Inadequate	Yes	The net content for both the packets, wallets, and cartons are given in terms of the drug mass for each strength, but "per packet" needs to be added in both cases.
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Adequate	Yes	
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	No	The NDC is on the cartons but not the packets.
Lot number and expiration date [§ 201.18 & 201.17].	Adequate	No	The lot number and expiration date are on the packet but not the carton.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	Adequate	Yes	The drug product is provided in unit dose packaging, i.e., there is no in-use period.
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.	
Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5)]	Adequate	Yes	

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)
or limited space per § 201.10(i)(2)].			
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.	
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.	
Linear Bar code [§ 201.25(c)(2)]. ³⁰	Inadequate	No	The wallets and cartons have bar codes, but the packets do not.
Adequate directions for use: "Recommended Dosage: See Prescribing Information" [§ 201.5 & 201.55].	Adequate	No	The cartons and wallets include the statement, but the packets do not.
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	Yes	
"Keep out of reach of children" statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)].	N/A	No	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	Choose an item.	
No text on Ferrule and Cap overseal of a vial of injectable	N/A	Choose an item.	

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)
products unless a cautionary statement is required. (USP <7>).			
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.	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label. ³¹	N/A	Choose an item.	
And others if space is available.	N/A	Choose an item.	

Assessment of Carton Labels and Container Labeling: *Inadequate*

Deficiency: Revise the carton, wallet, and packet labels to indicate the net content per packet, e.g., "108 mg per packet."

Deficiency: Revise the packet labels to include the linear bar code, as per 21 CFR 201.25(c)(2).

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

1. Revise the dosage form descriptor from "oral granules" to "oral pellets" for all labels and labeling to align with the recommendations of USP <1151>.

³¹ USP General Notices 3.20 Indicating Conformance

2. Revise the list of oral pellet film coating excipients such that they are in alphabetical order where they appear in the labeling.
3. Revise the HOW SUPPLIED/STORAGE AND HANDLING section of the package insert to include a description of the dosage form (e.g., white to off-white, film-coated pellets).
4. For clarity, revise section 2.6 of the package insert to state that if pellets mixed with food are not taken within 10 minutes after preparation, the mixture should be discarded.
5. Revise the labels and labeling where the address of the distributor is provided, to list the street address of the distributor as per 21 CFR 201.1(i).
6. Revise the carton, wallet, and packet labels to indicate the net content per packet, e.g., "108 mg per packet."
7. Revise the packet labels to include the linear bar code, as per 21 CFR 201.25(c)(2).

Primary Labeling Assessor Name and Date:

Craig M. Bertha, CMC Reviewer 18-Sep-2025

Secondary Assessor Name:

Julia Pinto, Unit Supervisor



Craig
Bertha

Digitally signed by Craig Bertha
Date: 9/29/2025 05:46:07AM
GUID: 50841a65000098a9383c817879a6a84d



Julia
Pinto

Digitally signed by Julia Pinto
Date: 9/29/2025 09:05:02AM
GUID: 5050dbcb00001294a888a4bdc20a3a58

22 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

BIOPHARMACEUTICS

Product Background:

NDA: NDA-219776-ORIG-1

Drug Product Name / Strength: Berotralstat oral granules (Orladeyo)/ (b) (4) mg, 96 mg, 108 mg, 132 mg

Route of Administration: Oral

Applicant Name: BioCryst Pharmaceuticals, Inc.

Submission:

BioCryst Pharmaceuticals, Inc. has submitted [NDA 219776](#) for the approval of berotralstat oral granules (new proposed dosage form) for the treatment of hereditary angioedema (HAE). Berotralstat acts as a plasma kallikrein inhibitor, preventing proteolytic cleavage to form bradykinin, which is a known potent vasodilator. Berotralstat oral granules (also referred to as mini-tablets) are developed to be a once daily, immediate release solid oral dosage form. The submission is to expand the use of berotralstat for routine prophylaxis to prevent attacks of HAE in pediatric patients 2 to < 12 years of age. Berotralstat was granted Orphan Drug Designation on November 1, 2017. A priority review was requested by the Applicant and has been granted. This application includes a cross reference to the previously approved NDA 214094. NDA 214094 (berotralstat immediate release capsules 110 mg and 150 mg) was approved on 03 December 2020 for prophylaxis to prevent attacks of HAE in patients 12 years of age and older. The approved dissolution method for berotralstat immediate release capsules uses USP Apparatus II (with 4-turn sinkers) at 50 rpm and 500 mL of 0.1N HCl at 37.0°C. The approved acceptance criterion for the capsules is Q = (b) (4) % in 30 minutes.

Four strengths of the drug product are proposed in the application. It is noted that the final strengths of the product are determined by the number of oral pellets (each pellet = (b) (4) mg) filled into packets. The proposed commercial dosing regimens are as follows:

Weight	Dosage (oral granules)
(b) (4)	One 78 mg packet
24 kg to < 32 kg	One 96 mg packet
32 kg to < 40 kg	One 108 mg packet
≥ 40 kg	One 132 mg packet

Review Recommendation: Adequate

Review Summary:

The Biopharmaceutics review is focused on the evaluation of dissolution method and acceptance criterion for berotralstat oral granules and bridging between the pivotal clinical trial and to-be-marketed formulation.

Dissolution Method and Acceptance Criteria: Adequate

The following dissolution method and acceptance criterion are proposed for the release of berotralstat from oral granules:

USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Acceptance criterion
II (Paddle)	75	0.1 N HCl/37°C ± 0.5°C	500	Q = $\frac{(b)}{(4)}$ % in 30 minutes

Based on the submitted data, the Applicant was requested to change dissolution testing from 75 rpm to 50 rpm in 500 mL of 0.1 N HCl at 37°C for quality control purposes. The Applicant was also requested to $\frac{(b)}{(4)}$ dissolution acceptance criterion to Q = $\frac{(b)}{(4)}$ % in 30 minutes. In the IR response dated 07/04/2025, the Applicant accepted the recommended method change and committed to using the new method (50 rpm) for all future batches at release and on stability. As the stability program with exhibit batches is ongoing using the proposed dissolution method and acceptance criterion, the applicant requested that they should be permitted to use the changes in the method (75 rpm to 50 rpm) and acceptance criterion (Q = $\frac{(b)}{(4)}$ % at 30 min to Q = $\frac{(b)}{(4)}$ % at 30 min) in the future manufactured batches. They specifically requested that current process validation batches will continue using the existing 75 rpm method but proposed to update all relevant documentation after new method validation is complete and will implement that as well as the Agency recommended acceptance criterion (Q = $\frac{(b)}{(4)}$ % in 30 minutes) in all future batches. Upon review, the Applicant’s response appears reasonable, and the Agency accepted the applicant’s commitment to implement the new method and acceptance criterion upon proper validation and for all future batches.

Therefore, the currently proposed dissolution method (Apparatus II at 75 rpm in 500 mL of 0.1 N HCl) and acceptance criterion (Q = $\frac{(b)}{(4)}$ % in 30 minutes) for berotralstat oral granules are approved on an interim basis for the ongoing stability program with exhibit batches. The following dissolution method and acceptance criterion are approved for the release of berotralstat from oral granules for future manufactured batches post-approval provided the new method is validated:

USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Acceptance criterion
II (Paddle)	50	0.1 N HCl/37°C ± 0.5°C	500	Q = $\frac{(b)}{(4)}$ % in 30 minutes

Above dissolution method and acceptance criterion comply with the FDA 2018 Guidance *Dissolution Testing and Acceptance Criteria for IR Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances* as the drug substance is considered highly soluble. The dissolution method was not able to show discriminating ability, however, this is acceptable as demonstration of discriminating ability is not required for dug products containing highly soluble drug substances. Overall, the proposed dissolution method is acceptable for QC purposes for the release and stability testing of berotralstat from berotralstat oral granules.

Bridging of Clinical Formulations: Adequate

The to-be-marketed and pivotal clinical Phase 3 formulations are same. Hence, no bridging is needed. All clinical and registration batches have similar drug dissolution profiles. The Applicant has bridged initial capsule formulation to oral granule formulation via a comparative bioavailability study (BCX7353-114). The assessment of BE study is under the purview of Office of Clinical Pharmacology (OCP). The dissolution profiles for both the capsule and oral granule formulations showed comparable profiles.

Biowaiver Request: Not applicable

The Applicant has not requested any biowaiver. Four strengths of the granules are proposed in the application. It is noted that the final strengths of the product are determined by the number of oral pellets (each pellet = $\frac{(b)}{(4)}$ mg) filled into packets. In addition, various strengths of granules were used in Pivotal Phase 3 study (Study BCX7353-304) according to the body weight of pediatric subjects aged 2 to < 12 with HAE as shown below:

≥ 40 kg: 150 mg (oral capsule)
32 to < 40 kg: 108 mg (oral granule)
24 to < 32 kg: 96 mg (oral granule)
12 to < 24 kg: 78 mg (oral granule)

132 mg was not directly used in the clinical studies; however, 150 mg granule was found to be bioequivalent to 150 mg capsule on both Day 1 and Day 7 in study BCX7353-114. Therefore, no biowaiver request is needed because 132 mg is bracketed between the highest strength and lower strengths tested in clinical studies.

List of Submissions reviewed:

Application 219776 - Sequence 0001/Multiple Categories/Subcategories
Application 219776 - Sequence 0012/IR response-07/04/2025

Highlight Key Outstanding Issues from Last Cycle: None. This is the first review cycle.

Concise Description of Outstanding Issues Remaining: None. Please refer to Appendix for the deficiencies conveyed to the Applicant in the current review cycle and resolved.

Conclusion: From Biopharmaceutics perspective, NDA 219776 for berotralstat oral granules $\frac{(b)}{(4)}$ mg, 96 mg, 108 mg, and 132 mg is recommended for APPROVAL. The currently proposed dissolution method (Apparatus II at 75 rpm in 500 mL of 0.1 N HCl) and acceptance criterion ($Q = \frac{(b)}{(4)}\%$ in 30 minutes) for berotralstat oral granules are approved on an interim basis for the ongoing stability program. The revised dissolution method (Apparatus II at 50 rpm in 500 mL of 0.1 N HCl) and acceptance criterion ($Q = \frac{(b)}{(4)}\%$ in 30 minutes) are approved for the release of berotralstat from oral granules for future manufactured batches.

BCS Designation**Reviewer's Assessment: Adequate**

The Applicant has not claimed or requested any BCS classification for their drug product in the current submission. In NDA 214094 for berotralstat capsules, 110 mg and 150 mg, the Applicant claimed that berotralstat dihydrochloride drug substance is a BCS class 1 compound based on the solubility and permeability data. Therefore, the Agency asked the Applicant to submit a complete report of BCS classification of the berotralstat compound. In response, the Applicant withdrew the request for BCS class 1 classification. Refer to [Biopharmaceutics review](#) for NDA 214094 for detail information. Based on the solubility data in aqueous solvent at different pH, berotralstat was considered as highly soluble compound.

The maximum amount of aqueous solvent required to dissolve 150 mg (highest strength) of berotralstat dihydrochloride was below 250 mL in pH 1.2-pH 6.8.

Drug Product

Berotralstat oral granules are manufactured to contain 6 mg of berotralstat as the free base (b) (4)

The proposed commercial foil packets are presented in unit doses of (b) (4) mg, 96 mg, 108 mg, and 132 mg strengths ((b) (4), 16, 18, and 22 granules, respectively).

Berotralstat oral granule (b) (4) consist of the drug substance (berotralstat dihydrochloride), and the following excipients: pregelatinized starch, crospovidone, colloidal silicon dioxide, and magnesium stearate. The granule (b) (4) are coated (b) (4) for taste-masking purposes. The composition of the drug product is provided below.

Table 1: Composition of berotralstat oral granules

Component	Function	Quality Standard	Quantity	Quantity per Dose (mg)			
			(% w/w)	(b) (4) mg	96 mg	108 mg	132 mg
(b) (4)							
Berotralstat Dihydrochloride*	Active	In-house	(b) (4)	108.44	122.00	149.11	(b) (4)
Pregelatinized Starch ^{a,b}	(b) (4)	NF, Ph. Eur., JPE					
Crospovidone		NF, Ph. Eur., JP					
Colloidal Silicon Dioxide ^c		NF, Ph. Eur., JP					
Magnesium Stearate		NF, Ph. Eur., JP					
(b) (4)							
Coating							(b) (4)
(b) (4)							
Total, Coated Granule							(b) (4)
(b) (4)							

^b Global Substance Registration System (GSRS) name is Starch, pregelatinized.
^c GSRS name is silicon dioxide, colloidal.
(b) (4)

Dissolution Method and Acceptance Criterion

Reviewer’s Assessment: Adequate

The Biopharmaceutics review is focused on the evaluation of dissolution method and acceptance criterion for berotralstat oral granules.

Proposed dissolution method and acceptance criterion

The following dissolution methods and acceptance criteria were initially proposed:

Table 2: Dissolution method for the release of berotralstat from oral granules

USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Acceptance criterion
II (Paddle)	75	0.1 N HCl/37°C ± 0.5°C	500	Q = ^(b) (4)% in 30 minutes

Dissolution method development

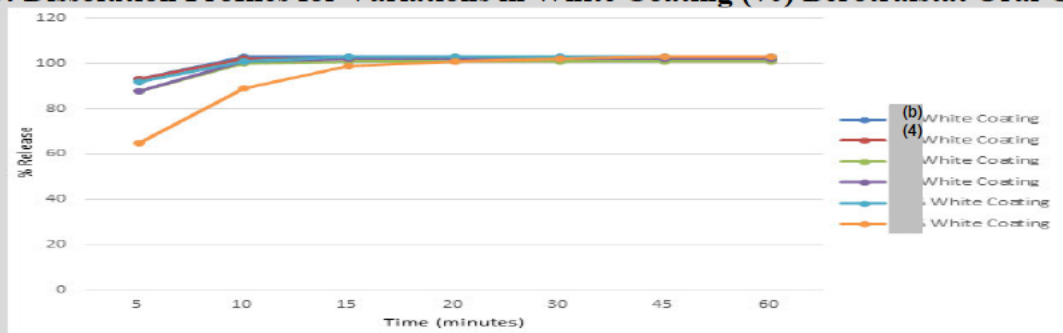
(b) (4)

Discriminating ability of the dissolution method

Berotrastat oral granules with varying percentages of coating were tested to determine if any notable difference was observed. Coating was selected due to its potential impact on dissolution performance. The granule formulation has a target of (b) (4)% for the coating. The results are presented in Figure 5

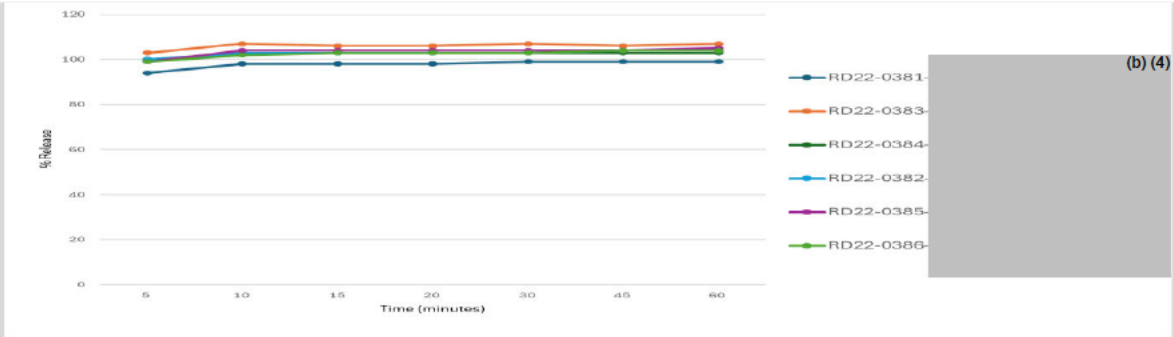
Berotrastat oral granules rapidly dissolved at approximately 15 minutes, therefore no significant difference was observed in the (b) (4)% through (b) (4)% profiles. Variations in coating levels up to (b) (4)% only impact the taste-masking ability of the coating and not the dissolution profiles. At coating levels above (b) (4)% (i.e. (b) (4)% weight gain), a slightly slower rate of dissolution was observed at earlier time points indicating that the method has the ability to differentiate changes in coating above the target weight gain. Although the (b) (4)% coating profile was slightly slower, the drug was still completely released by 30 minutes, meeting release specification.

Figure 5: Dissolution Profiles for Variations in White Coating (%) Berotrastat Oral Granules



In order to understand the discrimination potential of the dissolution method for processing parameters, granules from process development design of experiment (DOE) batches were tested for dissolution using the selected method. Results are summarized in Figure 6 below. No difference was observed in the profiles for the different samples tested.

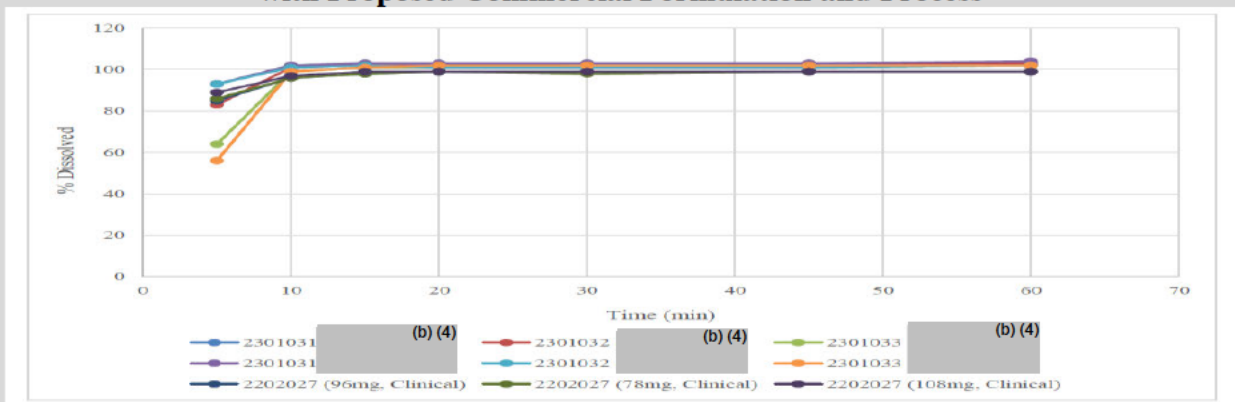
Figure 6: Dissolution Results for DOE Berotrastat Oral Granules (n=12)



Dissolution acceptance criterion

The proposed berotralstat dissolution acceptance criterion is $Q = \frac{(b)}{(4)}\%$ in 30 minutes. The dissolution profiles of berotralstat for pivotal clinical and registration batches are shown below.

Figure 7: Dissolution Profile of Berotralstat Oral Granules-Clinical and Registration batches with Proposed Commercial Formulation and Process



Based on the submitted in vitro dissolution profile data, the proposed dissolution acceptance criterion for berotralstat is $Q = \frac{(b)}{(4)}\%$ not acceptable. An IR (see in Appendix) was sent to implement the acceptance criterion of $Q = \frac{(b)}{(4)}\%$ in 30 minutes based primarily on the provided dissolution profile data of pivotal batch/registration batches. In the response, the Applicant accepted Agency recommended accepted criterion and committed to implement the new acceptance criterion for all future batches.

Reviewer’s comments

The Applicant proposed using Apparatus II at 75 rpm in 500 mL of 0.1 N HCl at 37°C for quality control purposes. Based on the submitted data, the Applicant was requested to change dissolution testing from 75 rpm to 50 rpm in 500 mL of 0.1 N HCl for quality control purposes. The Applicant was also requested to $\frac{(b)}{(4)}$ dissolution acceptance criterion to $Q = \frac{(b)}{(4)}\%$ in 30 minutes. In the IR response dated 07/04/2025, the Applicant accepted the recommended method change and committed to using the new method (50 rpm) for all future manufactured batches at release and on stability. As the stability program with exhibit batches is ongoing using the proposed dissolution method and acceptance criterion, the applicant requested that they should be permitted to use the changes in the method (75 rpm to 50 rpm) and acceptance criterion ($Q = \frac{(b)}{(4)}\%$ at 30 min to $Q = \frac{(b)}{(4)}\%$ at 30 min) in the future manufactured batches. They specifically requested that current process validation batches will continue using the existing 75 rpm method but proposed to update all relevant documentation after

new method validation is complete and will implement that as well as the Agency recommended acceptance criterion ($Q = \frac{(b)}{(d)}\%$ in 30 minutes) in all future batches. Upon review, the Applicant's response appears reasonable, and the Agency accepted the applicant's commitment to implement the new method and acceptance criterion upon proper validation and for all future batches.

The proposed method and acceptance criterion complies with the FDA 2018 Guidance *Dissolution Testing and Acceptance Criteria for IR Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances* as the drug substance is considered highly soluble. The dissolution method was not able to show discriminating ability against particle size, coating or process parameters. This is acceptable as demonstration of discriminating ability is not required for highly soluble drug substances. Overall, the proposed dissolution method is acceptable for QC purposes for the release and stability testing of berotralstat from berotralstat oral granules.

Bridging of Formulations

Reviewer's Assessment: Adequate

Initial Formulation Development:

The initial development focused on a capsule formulation. Oral granules formulation was later developed as an age-appropriate dosage form for patients 2 years and older. A comparative bioavailability study (BCX7353-114) was conducted to bridge the capsule and oral granules formulations.

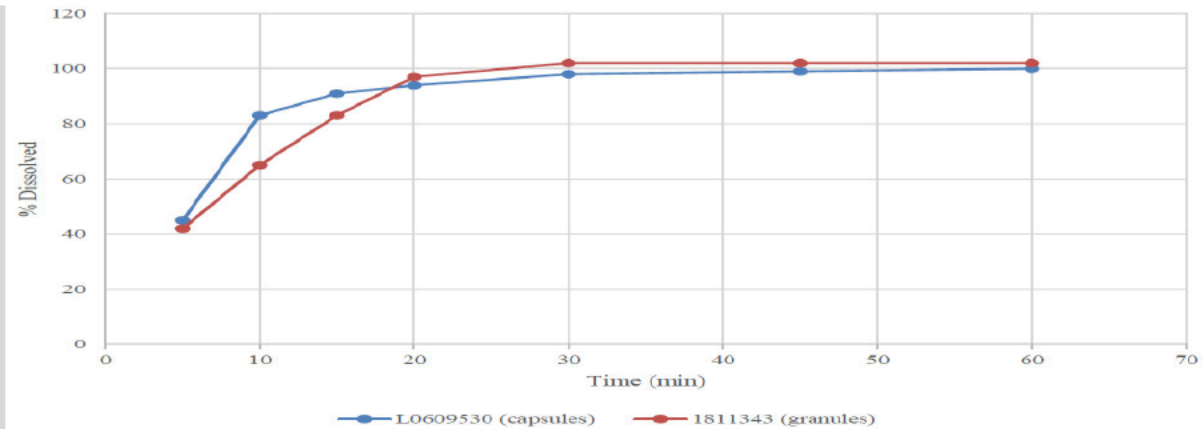
The BE study compared:

- Regimen D: 150 mg capsule formulation (reference)
- Regimen E: 150 mg oral granules formulation (test)
- Regimen F: 300 mg oral granules formulation (test)

The oral granules and capsule formulations were considered bioequivalent for prophylactic HAE treatment, where berotralstat is dosed chronically to steady state. The assessment of BE study is under the purview of OCP.

The Applicant provided dissolution profiles for both the capsule and oral granules formulations, allowing for comparison of their in vitro performance. As seen in the figure below, the dissolution profiles of the two samples showed comparable profiles (98% and 102% release in 30 minutes for L0609530 and 1811343, respectively).

Figure 8: Dissolution Profile Comparison of Berotralstat Oral Granules and Berotralstat Capsules Studied in BCX7353-114



Pivotal Phase 3 formulation and commercial formulation

Pivotal Phase 3 formulation and commercial formulations are same as shown in the table below. Hence no bridging is needed. All clinical and registration batches have similar dissolution profiles as seen in Figure 8 above.

Table 4: Comparison of Berotralstat Oral Granules Formulations

Phase of Development	R&D & Clinical ^a		Clinical		Registration	
	% w/w	mg/granule	% w/w	mg/granule	% w/w	mg/granule
Components						(b) (4)
Berotralstat Dihydrochloride ^b						
Pregelatinized Starch ^b						
Crospovidone,	(b) (4)					
Colloidal Silicon Dioxide,	(b) (4)					
Magnesium Stearate,	(b) (4)					
	(b) (4)					
Total						
Coating						(b) (4)
						(b) (4)

Biowaiver Request

Reviewer's Assessment: Not applicable

The Applicant has not requested any biowaiver. Four strengths of the drug product are proposed in the application. It is noted that the final strengths of the product are determined by the number of oral pellets (each pellet = $\frac{(b)}{(4)}$ mg) filled into packets. In addition, various strengths of granules were used in Pivotal Phase 3 study (Study BCX7353-304) according to the body weight of pediatric subjects aged 2 to < 12 with HAE as shown below:

≥ 40 kg: 150 mg (oral capsule)
32 to < 40 kg: 108 mg (oral granule)
24 to < 32 kg: 96 mg (oral granule)
12 to < 24 kg: 78 mg (oral granule)

132 mg was not directly used in the clinical studies; however, 150 mg granule was found to be bioequivalent to 150 mg capsule on both Day 1 and Day 7 in study BCX7353-114. Therefore, no biowaiver request is needed because 132 mg is bracketed between the highest strength and lower strengths tested in clinical studies.

Conclusions and recommendation

From Biopharmaceutics perspective, NDA 219776 for berotralstat oral granules $\frac{(b)}{(4)}$ mg, 96 mg, 108 mg, and 132 mg is recommended for APPROVAL.

Appendix

List of Deficiencies communicated to the Applicant during current review cycle

Information Request 1 (IR 1)-sent on 01 July 2025

1. You proposed to use USP Apparatus II at 75 rpm in 500 mL of 0.1 N HCl at 37° C for quality control (QC) purposes of your drug product. We noted that complete release ($\geq \frac{(b)}{(4)}\%$) of all the strengths of the proposed granules occurs at 50 rpm. Therefore, we recommend that you use USP Apparatus II at 50 rpm in 500 mL of 0.1 N HCl at 37° C for QC purposes. We request that you acknowledge your acceptance of the recommended method for all the strengths of your drug product at release and on stability and update the documents accordingly.
2. Submit the complete multi-point dissolution profile data [individual (n=12), mean, range, % CV at each time point, and mean profiles until complete release] of the registration batches undergoing stability testing using the revised dissolution conditions. Provide all data in *Microsoft Excel “.xls or .xlsx” format*.
3. Based on the submitted in vitro dissolution profile data, the proposed dissolution acceptance criterion $Q = \frac{(b)}{(4)}\%$ in 30 minutes for your drug product is permissive and not acceptable. Per Agency's current guideline for proper setting of the dissolution specification, we recommend that you implement the acceptance criterion of $Q = \frac{(b)}{(4)}\%$ in 30 minutes for berotrastat.

We request that you acknowledge your acceptance of the recommended acceptance criterion for all the strengths of your drug product at release and on stability and update the specifications table accordingly. In addition, please be advised that all proposed exhibit batches are expected to meet the revised dissolution specification in your stability program through your proposed expiry period. If dissolution failures are observed on stability these should be described. Discuss any corrective actions to avert such dissolution failures and provide a new batch to demonstrate correction of the issue, if needed.

Reviewer's comment

The response was received on July 08, 2025, and is available in the link below:

<\\CDSESUB1\EVSPROD\nda219776\0012\m1\us\m1-11-1-quality-information-amendment.pdf>

Primary Biopharmaceutics Reviewer: Kalpana Paudel, Ph.D.

Secondary Reviewer Name: Tapash Ghosh, Ph.D.



Kalpana
Paudel

Digitally signed by Kalpana Paudel
Date: 7/14/2025 12:51:42PM
GUID: 562e1e15002f200f35c6ccac959cdb34



Tapash
Ghosh

Digitally signed by Tapash Ghosh
Date: 7/14/2025 01:29:08PM
GUID: 508da7230002a2433ddcef616ca190df

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CRAIG M BERTHA
10/23/2025 11:05:23 AM