CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219141Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	219141		
Applicant Name	Novitium Pharma LLC		
Drug Product Name	INZIRQO (hydrochlorothiazide) powder for oral suspension		
Dosage Form.	Powder		
Proposed Strength(s)	10 mg/mL		
Route of Administration	Oral		
Maximum Daily Dose	100 mg		
Rx/OTC Dispensed	Choose an item.		
Proposed Indication	• The treatment of hypertension in adult and pediatric patients alone or in combination with other antihypertensive agents, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarction. • The treatment of edema associated with congestive heart failure, hepatic cirrhosis or renal disease.		
Drug Product Description	INZIRQO (hydrochlorothiazide) is supplied as an off-white to light-brown colored powder for oral suspension in one strength containing 800 mg of hydrochlorothiazide, USP in a HDPE bottle.		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	20°C to 25°C		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Stephanie Springer	Zhengfu Wang

	Drug Product/ Labeling	Charudharshini Srinivasan	Theodore Carver
	Manufacturing	Lixia Cai	Alexander Gontcharov
	Biopharmaceutics	Min Sung Suh	Haritha Mandula
	Microbiology	Xia Xu	Nandini Bhattacharya
	Other (specify):	N/A	
	RBPM	Grafton Adams	
	ATL	Theodore Carver	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

A shelf life of 24 months is granted for the drug product when stored at 20°C to 25°C.

b. Additional Comments for Action
None.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

1) Background

The Applicant, Novitium Pharma, has submitted NDA 219141 for Hydrochlorothiazide Powder for Oral Suspension, 10 mg/mL in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The basis for approval is comparative bioavailability studies conducted for the proposed drug product compared to a reference standard, (50 mg tablets,

ANDA 83177, Teva Pharmaceuticals). The drug product 800 mg powder for suspension in bottles to be reconstituted at a final concentration of 10 mg/mL. For the OPQ review, all disciplines were included (drug substance, drug product, manufacturing, biopharmaceutics, and microbiology).

2) Drug Substance

NDA 218038 references the drug substance diltiazem hydrochloride in DMF [redacted] (diltiazem hydrochloride). The DMF was found to be adequate to support this NDA. A Letter of Authorization dated April 21, 2023 was provided in the NDA.

3) Drug Product

The proposed drug product Hydrochlorothiazide Powder for Oral Suspension is considered a non-sterile solid dosage form. All the excipients (except for the flavoring agents) are compendial and conforms to USP/NF acceptance criteria and found to be acceptable. The specification, batch analysis data, and stability data were determined to be acceptable after the applicant responded to information requests related to testing, including reconstitution times, and agreed to reduce the time required for suspension based on the data provided in the application. As part of the risk assessment for [redacted] impurities, the Applicant provided results from three exhibit batches at 6 months accelerated and as well as 24 months long term condition to demonstrate that [redacted] levels were below the detection limit, which was less than [redacted]% of the daily acceptable intake limit. Therefore, no additional controls for [redacted] impurities were required. A 24-month shelf life is acceptable based on the accelerated and long-term stability data provided for three primary batches of the drug product. The in-use storage period for the liquid product after suspension is supported by the in-use stability studies provided.

4) Manufacturing

Process – The manufacturing process includes [redacted] The proposed [redacted] and [redacted] are established based on [redacted] and were determined to be acceptable to support product quality.

Facilities – All facilities were determined to be acceptable based on compliance status and inspection history.

5) Biopharmaceutics

The biopharmaceutics review primarily concerned the proposed dissolution method for the drug product After the Applicant accepted the agency

recommendations and revised the dissolution method, release and stability specifications, the review team recommends approval for this NDA.

6) Microbiology

The microbiology review concluded that the supporting studies and specification, after revisions to the post approval stability protocol, support the proposed in-use storage period of 30 days after suspension. The review team recommends approval for this NDA.

7) Quality labeling

The labeling was determined to be adequate from the quality perspective after the Applicant revised the labeling.

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

Recommendation by Subdiscipline:

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

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

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments: None.

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CHAPTER III: ENVIRONMENTAL

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

R REGIONAL INFORMATION

Environmental

The applicant is requesting a categorical exclusion from the requirements of an environmental impact analysis statement under 21 CFR § 25.31. Applicant stated that "*In accordance with 21 CFR 25.31(c), this NDA meets the criteria for a categorical exclusion because the approval of this 505(b)(2) NDA is not expected to increase the use of the active moiety, Hydrochlorothiazide*". Applicant provided justification that the proposed contains the same active moiety/ingredient (Hydrochlorothiazide) as the now discontinued Listed Drug (LD), Hydrodiuril® (NDA 011835 from Merck & Co's) and the designated Reference Standard (RS) from Teva Pharmaceuticals (ANDA 83177) in strengths of 25 mg, 50 mg (b) (4) tablets, except that (b) (4) is in a different dosage form (b) (4) Powder for Oral Suspension) given by the same route of administration.

Assessment: *{Adequate}*
Applicant's claims for categorical exclusion per 21 CFR 25.31(c) and no extraordinary circumstances exist requiring an EA per 21 CFR 25.15(d) are acceptable.

Primary Environmental Assessor Name and Date: Charudharshini Srinivasan, Ph.D., 12/03/2024

Secondary Assessor Name and Date (and Secondary Summary, as needed): Theodore Carver, Ph. D., 01/08/2025.

Charudharshini Srinivasan

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Theodore Carver

Digitally signed by Theodore Carver
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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name(s)[1]	INZIRQO (hydrochlorothiazide), for oral suspension	Adequate	
Route(s) of administration	Oral	Adequate	
Summary of the dosage form(s) and strength(s) in metric system	For oral suspension: (b) (4) (b) (4) (3)	Adequate	The following changes are made in the Prescribing Information (PI) draft labeling: *To the Applicant: For oral suspension: 10 mg/mL (3)* *The Applicant has changed this to:* *For oral suspension, (b) (4) 10 mg/mL*
Assess if the tablet is scored. If product meets guidelines and criteria for a		N/A	

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

scored tablet, state "functionally scored".			
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.		N/A	
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).			

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Special instructions for product preparation (e.g., reconstitution and	INZIRQO is a powder for oral suspension. Gently shake the bottle to loosen the powder, add 66 mL of water and shake vigorously for minimum of 30 seconds. When	Adequate	*The Applicant has revised the reconstitution time in the package insert and the container labeling from* (b) (4) *to 30 seconds.*

resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	reconstituted as directed, (b) (4) (b) (4) of hydrochlorothiazide. • Advise patients to always shake the bottle well prior to each use.		
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	Advise patients to always shake the bottle well prior to each use.	Adequate	
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*		N/A	
If there is a USP monograph for the drug product and it contains a labeling		N/A	

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

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

APPEARS THIS WAY ON ORIGINAL

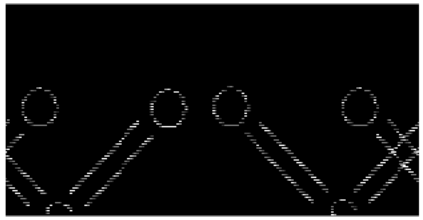
Item	Information Provided	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section			
Available dosage form(s)	INZIRQO (hydrochlorothiazide), for oral suspension	Adequate	
Strength(s) in metric system	When reconstituted as directed, INZIRQO is an off-white to light brown colored suspension with caramel, peppermint flavor containing (b) (4) mg of hydrochlorothiazide, USP (b) (4)	Adequate	The following changes are made in the Prescribing Information (PI) draft labeling: *To the Applicant: For oral suspension: 10 mg (b) (4) mL* *The Applicant has changed this to:* *For oral suspension, USP 10 mg/mL*
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).		N/A	

A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	When reconstituted as directed, INZIRQO is an off-white to light brown colored suspension with caramel, peppermint flavor containing (b) (4) mg of hydrochlorothiazide, USP (b) (4)	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 parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.		N/A	

Section 11 (DESCRIPTION)

Item	Information Provided	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section			
Proprietary and established name(s)	INZIRQO (hydrochlorothiazide), for oral suspension	Adequate	
Dosage form(s) and route(s) of administration	INZIRQO (hydrochlorothiazide) is supplied in one strength as an off-white to light-brown colored powder for oral suspension (b) (4) (b) (4). When reconstituted with 66 mL of water, the total volume of the suspension is 80 mL containing (b) (4) mg of hydrochlorothiazide, USP (b) (4) mL. In addition, INZIRQO ns the following inactive ingredients: sucrose, anhydrous citric acid, potassium sorbate, sucralose, cellulose, xanthan gum, talc, caramel flavor (maltodextrin, propylene glycol, sucrose, salt, caramel, molasses and artificial flavor), and peppermint flavor (acacia and natural flavor).	Adequate	The following changes are made in the Prescribing Information (PI) draft labeling: *<u>To the Applicant</u>: Recommend removing "suspension* (b) (4) (b) (4) *and revise it to "INZIRQO (hydrochlorothiazide) is supplied in one strength as an off-white to light-brown colored powder for oral suspension".* *<u>To the Applicant</u>: Recommend revising to "containing 10 mg/mL hydrochlorothiazide, USP"* *<u>To the Applicant</u>: Revise list of inactive ingredients to be in alphabetical order.* *The Applicant has made the above suggested revisions.*

If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"		N/A	
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Inactive ingredients: sucrose, anhydrous citric acid, potassium sorbate, sucralose, cellulose, xanthan gum, talc, caramel flavor (maltodextrin, propylene glycol, sucrose, salt, caramel, molasses and artificial flavor), and peppermint flavor (acacia and natural flavor).	Adequate	See above comment: Inactive ingredients are listed and pH indicated but they are not in alphabetical order. The following changes are made in the Prescribing Information (PI) draft labeling: *To the Applicant: Revise list of inactive ingredients to be in alphabetical order.* *The Applicant has made the above suggested revision.*
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.		N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol		N/A	
Sterility statement (if applicable)		N/A	

Pharmacological/Therapeutic class	Hydrochlorothiazide, USP is a diuretic and antihypertensive	Adequate	
Chemical name, structural formula, molecular weight	 It is the 3,4-dihydro derivative of chlorothiazide. It is chemically designated as 6-chloro-3,4-dihydro-2 H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. The molecular formula is $C_7H_8ClN_3O_4S_2$ and the molecular weight is 297.74.	Adequate	
If radioactive, statement of important nuclear characteristics.		N/A	
Other important chemical or physical properties (such as pKa or pH)		Adequate	

2. Section 11 (DESCRIPTION) Continued

Item	Information Provided	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)		N/A	

Remove statements that may be misleading or promotional (e.g., “synthesized and developed by Drug Company X,” “structurally unique molecular entity”)		N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).		N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

APPEARS THIS WAY ON ORIGINAL

Item	Information Provided	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING			
Available dosage form(s)	oral suspension	Adequate	
Strength(s) in metric system	(b) (4)	Adequate	The following changes are made in the Prescribing Information (PI) draft labeling: *To the Applicant: For oral suspension: 10 mg/mL (3)* *The Applicant has made the above suggested revision.*
Available units (e.g., bottles of 100 tablets)	INZIRQO (hydrochlorothiazide) is supplied as an off-white to light-brown colored powder for oral suspension in one strength containing 800 mg of hydrochlorothiazide, USP in a HDPE bottle.	Adequate	

Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	When reconstituted as directed, INZIRQO forms an off-white to light brown colored suspension with caramel, peppermint flavor. The total volume of the suspension is 80 mL containing (b) (4) mg of hydrochlorothiazide, USP (b) (4) (70954-522-10).	Adequate	The following changes are made in the Prescribing Information (PI) draft labeling: ***To the Applicant:*** *We recommend revising this statement to "The total volume of the suspension is 80 mL containing 10 mg of hydrochlorothiazide, USP per mL (70954-522-10)".* *The Applicant has made the above suggested revisions.*
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"		N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.		N/A	

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."	(b) (4) (b) (4) Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Do not freeze. Keep this and all medication out of the reach of children. (b) (4) (b) (4)	Adequate	

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

Item	Information Provided	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	(b) (4) (b) (4) Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].	Adequate	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic		N/A	

derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*			
Include information about child-resistant packaging		N/A	

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug review division if the product contains any of these inactive ingredients.

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

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17			
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Distributed by: ANI Pharmaceuticals, Inc., Baudette, MN 56623	Adequate	

2.0 PATIENT LABELING

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

Patient Information provided.

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

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels

The Novitium Pharma LLC container label: INZIRQO (hydrochlorothiazide), for oral suspension:
In response to the IR dated 11/08/2024, the Applicant revised the container label for the reconstitution time (Seq#0012, 11/12/2024). In addition, in Seq#0015 (12/20/2024) amendment, in response to Agency's Labeling Discussion Comments dated 12/13/2024, Novitium Pharma revised the Labeling Container Label and the Prescribing Information. The revised label is shown below.[2],[3], [4]

(b) (4)

[2] \\CDSESUB1\EVSPROD\nda219141\0012\m1\us\11411-draft-container-label.pdf
[3] \\CDSESUB1\EVSPROD\nda219141\0015\m1\us\12-coverlettersequence0015.pdf
[4] \\CDSESUB1\EVSPROD\nda219141\0015\m1\us\11411-draft-container-label.pdf

3.2 Carton Labeling

There is no carton labeling provided.

APPEARS THIS WAY ON ORIGINAL

Item	Information Provided	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Container and Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[5], (font size and prominence)	INZIRQO™ (hydrochlorothiazide), for oral suspension, USP (b) (4)	Adequate	*The Applicant has changed this to:* *For oral suspension, USP 10 mg/mL*
Strength(s) in metric system	(b) (4)	Adequate	See above comment
Route(s) of administration	Oral	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.		N/A	
Net contents (e.g., tablet count, volume of liquid)	80 mL	Adequate	
"Rx only" displayed on the principal display	Yes	Adequate	
NDC	Yes	Adequate	
Lot number and expiration date	Yes	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Discard any unused suspension 30 days after reconstitution. Discard after: ___ / ___ / _____.	Adequate	

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

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a “Not for direct infusion” statement.		N/A	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.		N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol		N/A	
Linear Bar code	Yes	Adequate	

Item	Information Provided	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Container and Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Yes	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	No Patient Information guide	Adequate	(b) (4)
No text on Ferrule and Cap overseal, unless a cautionary statement is required.		N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.		N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.		N/A	

And others, if space is available.	Inactive ingredients list is not provided on the Container label. The Applicant has provided only container labeling. Carton labeling is not provided.	Adequate	

Assessment of Carton and Container Labeling: {Adequate}

Container Labeling is Adequate.

3. ITEMS FOR ADDITIONAL ASSESSMENT

N/A

Overall Assessment and Recommendation:

NDA 219141 Labeling review is Adequate.

Primary Labeling Assessor Name and Date: Charudharshini Srinivasan, Ph.D., 12/09/2024; 01/08/2025.

Secondary Assessor Name and Date (and Secondary Summary, as needed): Theodore Carver, Ph. D., 01/08/2025.

Charudharshini Srinivasan

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Theodore Carver

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CHAPTER VI: BIOPHARMACEUTICS

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

Product Information	
NDA Number	219141
Assessment Cycle Number	1
Drug Product Name/ Strength	(b) (4) Hydrochlorothiazide Powder for Oral Suspension, (b) (4)
Route of Administration	Oral
Applicant Name	Novitium Pharma, LLC
Therapeutic Classification/ OND Division	Division of Cardiology and Nephrology
LD/RS Number	RS: ANDA 083177, 505 (b)(2) LD: NDA 011793 (Discontinued)
Proposed Indication	Treatment of hypertension and edema

Assessment Recommendation: **Adequate**

Assessment Summary:

The Applicant, Novitium Pharma, LLC., submitted this 505(b)(2) NDA for approval of Hydrochlorothiazide Powder for Oral Suspension, (b) (4) relied upon the Reference Standard (RS, ANDA 083177), Hydrochlorothiazide Tablets. The proposed drug product is indicated for the treatment of hypertension and edema, and the recommended dose is a single or divided dose up to 100 mg, depending on indications and populations. Comparative bioavailability studies under fasted and fed conditions were conducted to establish a clinical bridge between the proposed product and RS. This Biopharmaceutics review is focused on the following aspects:

Quality control (QC) dissolution method and acceptance criterion: In the NDA, the Applicant originally proposed a dissolution method of USP Apparatus 2 (paddles) at 50 rpm in 900 mL of 0.1N HCl at 37°C with an acceptance criterion of Q=(b) (4)% in (b) (4) minutes for the QC of the proposed drug product at batch release and on stability testing. In the submitted dissolution method development report, the Applicant identified levels of the suspending agents (b) (4) cellulose and xanthan gum) as Critical Formulation Variables (CFVs) and evaluated the discriminating ability of the originally proposed dissolution method towards changes in the levels of the suspending agents. The results indicated that changes in formulation have no significant impact on dissolution of the proposed drug product.

Based on the solubility data over the physiological pH range, hydrochlorothiazide is a high solubility drug substance per BCS criteria. Thus, the Applicant was

requested to provide complete dissolution data using USP Apparatus 1 (Basket) at 100 rpm in 500 mL of 0.1N HCl and batch information tested in the study via Information Request (IR#1). In the IR response on 08/02/2024, the submitted dissolution data showed that the proposed drug product met the standard dissolution methodology (dissolution method and acceptance criterion) per the 2018 FDA Guidance for Industry titled "Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances". Based on the assessment of the dissolution data in both USP apparatus 1 (Basket) and 2 (Paddle), it was concluded that the originally proposed dissolution method using a USP Apparatus 2 (Paddle) is adequate given that the proposed dissolution method shows better discriminating ability and USP Apparatus 2 (Paddle) is more appropriate for the proposed drug product (powder for oral suspension).
The Applicant was requested to implement the proposed dissolution method and a data-driven acceptance criterion of Q=(b) (4)% in 20 minutes via IR#2. In the IR response on 09/18/2024, the Applicant accepted the recommendation and revised release and stability specification accordingly. Therefore, the following dissolution method and acceptance criterion are found acceptable for the QC testing of Hydrochlorothiazide Powder for Oral Suspension, (b) (4) at batch release and on stability/shelf-life:

Apparatus	USP Apparatus 2 (Paddle)
Medium	0.1N HCl
Volume	900 mL
Vessel Temperature	37 ± 0.5 °C
Paddle Speed	50 rpm
Acceptance Criterion	Q (b) (4)% in 20 minutes

Overall, from a Biopharmaceutics perspective, NDA 219141 for Hydrochlorothiazide Powder for Oral Suspension, (b) (4) is **adequate** and recommended for **approval**.

List of Submissions Being Assessed:

Document(s) Assessed	Date Received
Orig-1 NDA	**03/28/2023**
Response to IR#1[1]	**08/02/2024**
Response to IR#2[2]	**09/18/2024**

Highlight Key Issues from Last Cycle and Their Resolution: None. This is the first review cycle.

[1] \\CDSESUB1\EVSPROD\nda219141\0006\m1\us\12-ir-responsesequence0006.pdf
[2] \\CDSESUB1\EVSPROD\nda219141\0009\m1\us\12-ir-response-sequence0009.pdf

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

B.1 BCS DESIGNATION

Assessment: *Adequate*
Solubility: High

The solubility data of hydrochlorothiazide over the physiological pH range is provided in Table 1 below. Based on the solubility data, the recommended dose (up to 100 mg) is completely soluble in ≤ 250 mL of aqueous media over the physiological pH range, and thus hydrochlorothiazide is considered as a high solubility substance per the ICH M9 BCS criteria.

Table 1. Solubility of hydrochlorothiazide in various pH media at 37°C

pH Media	Solubility (mg/mL) 37°C
Water	8.53
0.1N HCl	7.12
pH 4.5	8.16
pH 6.8	6.53

Permeability: Not determined
The Applicant did not provide permeability data of hydrochlorothiazide in this submission but the pharmacokinetic (PK) data in the clinical studies appear that the permeability may not be the rate-limiting step for drug absorption because the median T_{max} values are 1.18~1.33 hrs under fasted condition.

Dissolution: See "B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA"

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: *Adequate*

- **Drug Product Background**

The proposed drug product is an immediate-release powder for oral suspension that contains (b) (4) of hydrochlorothiazide drug substance and the following excipients: (b) (4) cellulose (b) (4), xanthan gum (b) (4) (b) (4), talc (b) (4) sucrose (b) (4) sucralose (b) (4) potassium sorbate (b) (4), citric acid (b) (4), and flavor.

(b) (4)

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(b) (4)

[redacted]

Based on all the above results, the Applicant finalized the following dissolution method as shown in Table 2.

Table 2. Proposed dissolution method and acceptance criterion

Apparatus	USP Apparatus 2 (Paddle)
Medium	0.1N HCl
Volume	900 mL
Vessel Temperature	37 ± 0.5 °C
Paddle Speed	50 rpm
Acceptance Criterion	Q=(b) (4)% in(b) (4) minutes

Discriminating Power

The Applicant identified the following Critical Formulation Variables (CFVs) as shown to evaluate the discriminating ability of the proposed dissolution method in Table 3. During product development, the Applicant identified that the initial risk assessment of API particle size distribution (PSD) is medium but mitigated to low risk based on the solubility data and formulation development studies. The Applicant also identified that there are no Critical Process Parameters (CPPs) that can affect the dissolution of the proposed drug product.

Table 3. Critical Formulation Variables (CFVs) for discriminating ability of proposed dissolution method

Formulation variable	Initial evaluation
Sucrose	Not expected to have an impact
Sucralose	Not expected to have an impact
Potassium sorbate	Not expected to have an impact
Citric acid	Not expected to have an impact
Talc	Not expected to have an impact
(b) (4) cellulose	*May have an impact on dissolution*

(b) (4)

Xanthan gum	(b) (4)	(b) (4)

The following aberrant batches were utilized to support the discriminating ability of the proposed method (Table 4).

Table 4. Aberrant batches used in discriminating power study

Hydrochlorothiazide (b) (4)										
Batch #		RB-42-19	RB-42-20	RB-42-21	RB-42-22	RB-42-23	RB-42-24	RB-42-25	RB-42-26	RB-42-27
Item	Ingredients	(b) (4)								
1	Hydrochlorothiazide, USP									
2	Sucrose, NF									
3	Sucralose, NF									
4	Potassium Sorbate, NF									
5	Citric acid anhydrous, USP									
6	(b) (4) Caramel flavor (b) (4) Art									
7	(b) (4) cellulose, NF									
8	Xanthan gum, NF									
9	Peppermint flavor Nat (b) (4) (b) (4)									
10	Talc, USP									
11	Total									
14	(b) (4)									

The batch (Unit# RB-0042-023) represents the proposed final formulation. Levels of the formulation variables were investigated to evaluate the effects of the variables on dissolution. The comparative dissolution profiles of the aberrant batches indicated that there are no significant effects of the formulation variables on dissolution although a slower dissolution rate at early timepoints (5 and 10 minutes) was observed in the dissolution profiles of the aberrant batches prepared with different levels of the suspending agents (Figure 4). It was also observed that there is no trend or correlation between dissolution profiles of the batches.

Based on the assessment of the above results, the Applicant was requested to provide complete dissolution profiles of the pivotal clinical batches (EB-788A, EB-789A and EB-790A) using the standard dissolution method of USP Apparatus I (Basket) at 100 rpm in 500 mL of 0.1N HCl per the 2018 Guidance for Industry via IR#1. As requested, the test samples were prepared in the same way as described in the proposed labeling instructions. The results appeared that rapid dissolution was observed at the first time point (5 minutes) as shown in Figure 5.

Table 5. Dissolution profiles of clinical batches

EB-788A

Unit No.	Hydrochlorothiazide Powder for Oral Suspension, (b) (4) (Novitium Pharma LLC, Batch: EB-788A) 0.1N HCl, 100 RPM Basket, 500 mL % of Hydrochlorothiazide Dissolved							
	5 min	10 min	15 min	20 min	30 min	45 min	60 min	70 min
V1	(b) (4)							
V2								
V3								
V4								
V5								
V6								
V7								
V8								
V9								
V10								
V11								
V12								
Avg	98	101	103	103	103	104	105	105
Min	82	86	90	94	97	102	103	103
Max	102	105	106	106	106	107	107	107
%RSD	6.0	5.0	4.1	3.0	2.5	1.5	1.3	1.1

EB-789A

Unit No.	Hydrochlorothiazide Powder for Oral Suspension, (b) (4) (Novitium Pharma LLC, Batch: EB-789A) 0.1N HCl, 100 RPM Basket, 500 mL % of Hydrochlorothiazide Dissolved							
	5 min	10 min	15 min	20 min	30 min	45 min	60 min	70 min
V1	(b) (4)							
V2								
V3								
V4								
V5								
V6								
V7								
V8								
V9								
V10								
V11								
V12								
Avg	98	100	100	100	100	100	101	101
Min	97	99	99	99	99	99	99	99
Max	101	101	102	101	102	102	102	103
%RSD	1.3	0.8	0.9	0.7	0.9	0.8	0.8	1.0

EB-790A

Unit No.	Hydrochlorothiazide Powder for Oral Suspension, (b) (4) (Novitium Pharma LLC, Batch: EB-790A) 0.1N HCl, 100 RPM Basket, 500 mL % of Hydrochlorothiazide Dissolved							
	5 min	10 min	15 min	20 min	30 min	45 min	60 min	70 min
V1	(b) (4)							
V2								
V3								
V4								
V5								
V6								
V7								
V8								
V9								
V10								
V11								
V12								
Avg	97	98	98	99	99	99	99	100
Min	94	96	96	96	97	97	97	97
Max	99	100	100	100	100	101	101	102
%RSD	1.7	1.3	1.0	1.0	1.0	1.1	1.0	1.4

Based on the above results, it was concluded that the proposed method conditions are adequate given that the proposed dissolution method shows better discriminating ability and USP Apparatus 2 (Paddle) is more appropriate for the proposed drug product (powder for oral suspension).
The Applicant was requested to implement the proposed dissolution method and a data-driven acceptance criterion via IR#2 as shown in Table 6. In response to the IR#2, the Applicant implemented the recommended dissolution method and acceptance criterion for the QC of the proposed drug product.

Table 6. Proposed and Revised (acceptable) dissolution method and acceptance criterion

	Proposed	Revised(acceptable)
Apparatus	USP Apparatus 2 (Paddle)	USP Apparatus 2 (Paddle)
Medium	0.1N HCl	0.1N HCl
Volume	900 mL	900 mL
Temperature	37 ± 0.5 °C	37 ± 0.5 °C
Paddle Speed	50 rpm	50 rpm
Acceptance Criterion	Q (b) (4) % in (b) (4) minutes	Q (b) (4) % in 20 minutes

Based on the totality of the provided information and data, the above revised dissolution method and acceptance criterion are deemed acceptable for the QC of the proposed Hydrochlorothiazide Powder for Oral Suspension.

- **Dissolution Variability**

Variabilities in the dissolution data meet the recommendations (%CV < 10% at all timepoints).

- **Dissolution Acceptance criteria**

See the dissolution method review addressed above.

B.3 CLINICAL RELEVANCE OF DISSOLUTION METHOD & ACCEPTANCE CRITERIA *(e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)*

Assessment: *N/A*

Hydrochlorothiazide is highly soluble in 0.1N HCl buffer which is considered physiologically relevant to gastric environments after oral administration.

B.5 MODIFIED RELEASE ORAL DRUG PRODUCTS – *In-Vitro Alcohol Dose Dumping*

Assessment: *N/A*

The proposed drug product is an immediate-release oral suspension.

B.11 EXTENDED RELEASE DOSAGE FORMS –*Extended Release Claim*

Assessment: *N/A*

The proposed drug product is an immediate-release oral suspension.

B.12 BRIDGING OF FORMULATIONS

Assessment: *Adequate*

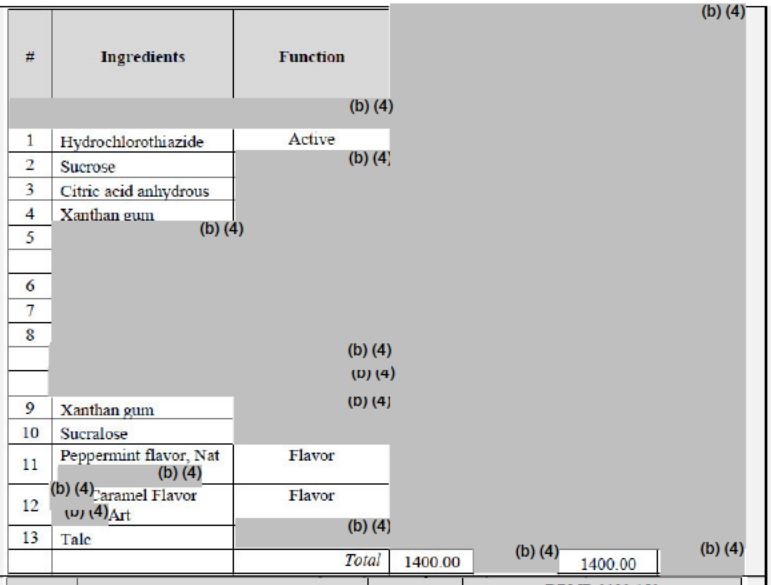
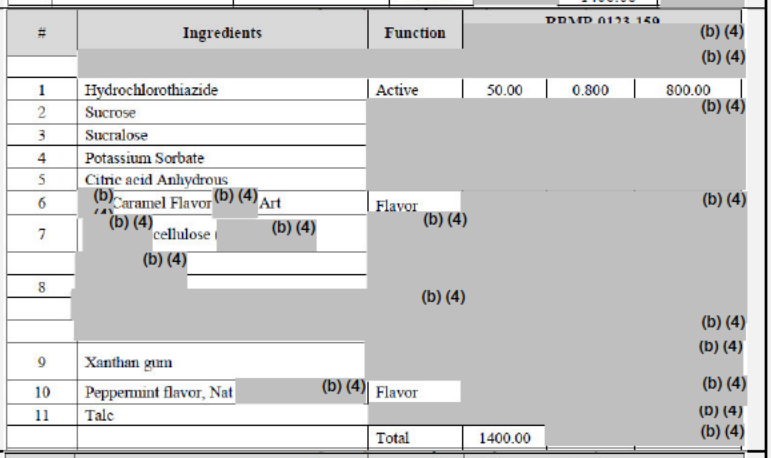
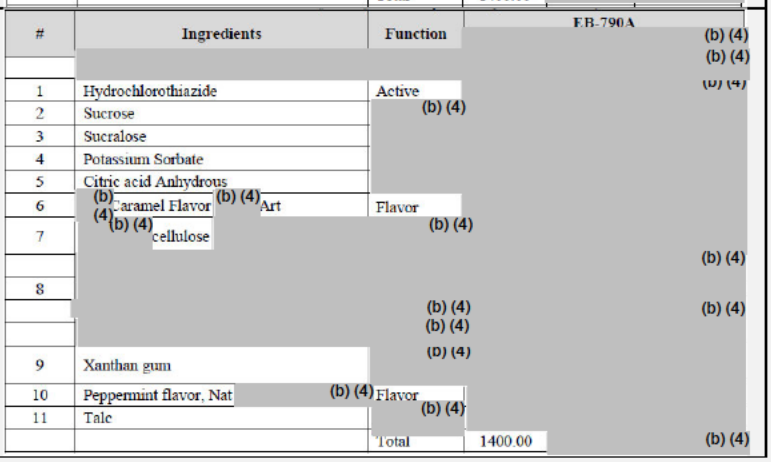
According to the Applicant, the following formulations were used for the comparative bioavailability studies in Table 7 and 8.

Table 7. Overview of clinical batches

Study No.	Formulation	Reference
HYDR-20-114 (Pilot)	Two prototype formulations with different levels of excipients	Hydrochlorothiazide Tablets (ANDA 083177)
HYDR-20-115 (Pilot)	Final formulation	Hydrochlorothiazide Tablets (ANDA 083177)
HYDR-21-047 (Pivotal)	Final formulation	Hydrochlorothiazide Tablets (ANDA 083177)

Table 8. Formulation comparison between clinical batches

Formulation	Composition

Prototype Formulations (EB-658 and RB-0123-059) used in HYDR-20-114 (Pilot)	
Final formulation (RBMP-0123-159) used in HYDR-20-115 (Pilot)	
Final formulation (EB-790A) used in HYDR-21-047 (Pivotal)	

The formulation composition has been unchanged through the pivotal clinical study (HYDR-21-047). Therefore, from a Biopharmaceutical perspective, no further bridging data/information are needed.

B. 13 BIOWAIVER REQUEST

Assessment: *N/A*

The Applicant proposes only one strength (b) (4).

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

Primary Assessor's Name and Date: Min Sung Suh, Ph.D. 11/19/2024

Secondary Assessor's Name and Date: Haritha Mandula, Ph.D. 11/25/2024

Min Sung Suh

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Haritha Mandula

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FDA U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VII: MICROBIOLOGY

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

Product Information	Treatment of Hypertension and Edema.
NDA Number	219141
Assessment Cycle Number	01
Drug Product Name/ Strength	(b) (4) (Hydrochlorothiazide) Powder for Oral Suspension, (b) (4)
Route of Administration	Oral
Applicant Name	Novitium Pharma LLC
Therapeutic Classification/ OND Division	OCHEN/DCN
Manufacturing Site	Novitium Pharma LLC. 70 Lake Drive East Windsor, NJ 08520 FEI # 3012541241 DUNS # 080301870
Method of Sterilization	Drug product is non sterile.

Assessment Recommendation: **Adequate**

Assessment Summary: This is a multi-dose non-sterile oral drug product. The manufacturing process is to be controlled for microbial quality and absence of specified microorganisms. Supporting data meet the quality microbiology review criteria.

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
Supporting document # 1 (Seq-0001)	03/28/2024
Supporting document # 2 (Seq-0002)	05/13/2024
Supporting document # 3 (Seq-0003)	05/15/2024
Supporting document # 7 (Seq-0007)	08/15/2024
Supporting document # 9 (Seq-0009)	09/18/2024
Supporting document # 12 (Seq-0012)	11/12/2024
Supporting document # 13 (Seq-0013)	11/12/2024

Highlight Key Issues from Last Cycle and Their Resolution: None.

Remarks: N/A

Concise Description of Outstanding Issues: None.

Supporting Documents: None.

S DRUG SUBSTANCE

The drug substance (Hydrochlorothiazide, USP), manufactured by [redacted], is supplied as non-sterile powder. There is no microbiological testing on the drug substance. Excipients [redacted] xanthan-gum, talc, [redacted] cellulose, and Sucralose) are tested for microbiological quality (section 3.2.P.4.1).

Assessment: Drug substance is non-sterile. No quality microbiological testing is proposed.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Description of drug product

Hydrochlorothiazide powder for oral suspension [redacted] is a non-sterile, multi-dose, preserved powder for oral suspension containing 800 mg of hydrochlorothiazide USP in a HDPE bottle. To reconstitute the product, 66 mL of water (not co-packaged with the finished drug) is added to the product bottle to provide [redacted] mg of hydrochlorothiazide [redacted] of suspension. The total volume of the suspension is 80 mL.

Drug product composition

S. No	Materials	Functions	[redacted]	
			mg/mL	% w/w
	[redacted]			
1	Hydrochlorothiazide, USP	Drug Substance		
2	Sucrose, NF	[redacted]		
3	Citric acid anhydrous [redacted]			
4	Potassium Sorbate, NF			
5	Sucralose, NF			
6	[redacted] Caramel Flavor [redacted] Art [redacted]	Flavoring Agent		
	• *Maltodextrin* [redacted]	-		
	• *Propylene Glycol* [redacted]	-		
	• *Sugar* [redacted]	-		
	• *Artificial Flavor* [redacted]	-		
	• *Salt* [redacted]	-		
	• *Caramel Color* [redacted]	-		
	• *Molasses* [redacted]	-		
7	[redacted] Cellulose	[redacted]		
8	[redacted]	[redacted]	--	--
9	[redacted]		--	--
	[redacted]			
10	Xanthan Gum, NF	[redacted]		
11	Peppermint Flavor, Nat [redacted]	Flavoring Agent		
	[redacted]	-		
	• *Natural Flavor* [redacted]	-		
12	Talc, USP	[redacted]		
	Total	[redacted]	**1400.000**	**100.00**

[redacted] mg/mL should be mg [redacted] mL.

Description of container closure system

Components	Description	Manufacturer
Bottle	(b) (4)	
Closure		

Assessment: ***{Adequate}***

The drug product composition and container-closure system are adequately described. The container-closure system is adequate for the drug product oral administration.

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

(b) (4)

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Theodore Carver

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