CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219491Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	219491		
Applicant Name	Entasis Therapeutics Inc.		
Drug Product Name	Zoliflodacin for oral suspension		
Dosage Form.	For suspension		
Proposed Strength(s)	3 grams		
Route of Administration	Oral		
Maximum Daily Dose	3 grams		
Rx/OTC Dispensed	Rx		
Proposed Indication	Treatment of uncomplicated urogenital gonorrhea due to *Neisseria gonorrhoeae* in adult and pediatric patients 12 years and older, weighing at least 35 kg.		
Drug Product Description	Zoliflodacin is a new molecular entity (NME), a first-in-class, single-dose, oral spiropyrimidinetrione antibacterial. The drug product is formulated as immediate-release granules for oral suspension, packaged in a laminated aluminum foil sachet as a single dose (3 grams).		
Co-packaged product information	The drug product will be supplied in a convenience kit: a carton containing one sachet and a mixing container to prepare the suspension in water.		
Device information:	The mixing container is made of (b) (4) with a (b) (4) cap and has a 120 mL capacity with molded gradations for accurate measurement.		
Storage Temperature/ Conditions	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]		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Sivakoteswara Mandadapu	Katherine Windsor

	Drug Product	Saki Golafale	Dorota Matecka
	Labeling	Saki Golafale	David Claffey
	Manufacturing/ Microbiology	Yan Zhang	James Norman
	Biopharmaceutics	Hardikkumar Patel	Elsbeth Chikhale
	Other (specify):	N/A	N/A
	RBPM	Megan Nguyen	
	ATL	Dorota Matecka	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: 36 months when stored 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]

b. Additional Comments for Action: N/A

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The NDA, as amended, has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed drug substance (zoliflodacin) and drug product (zoliflodacin for oral suspension). That includes information included in the initial NDA submission and subsequent amendments, which adequately addressed all comments and information requests issued by drug substance, drug product, manufacturing process and biopharmaceutics reviewers during the NDA review. Several product quality related labeling comments and recommendations were identified and will be conveyed to the Applicant

(the labeling is currently under review by the NDA multidisciplinary team). The overall information provided in the NDA was found adequate and supportive of the proposed 36-month expiry dating for the drug product to be stored under controlled room temperature conditions. Furthermore, all manufacturing and testing facilities listed in the NDA have been found acceptable and the Overall Manufacturing Inspection Recommendation of "Approve" was entered into Panorama by the Office of Pharmaceutical Manufacturing Assessment on October 3, 2025. Therefore, this NDA is recommended for approval by the OPQ review team.

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

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**N/A**

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

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments: N/A

Comparability Protocols (PACMP): No
Comments: N/A

Additional Lifecycle Comments: N/A

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Title:	NDA IQA Template CHAPTER IV-LABELING
Document ID:	OPQ-ALL-TEM-0045
Effective Date:	18 Sep 2023 Revision: 00
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Template Revision: 03

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	219491
Assessment Cycle Number	1
Drug Product Name	Zoliflodacin for Oral Suspension, 3 g

Assessment Recommendation: Adequate Pending revisions

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information	Adequate after the recommended changes are made	1
Container Labels	Adequate after the recommended changes are made	1
Carton Labeling	Adequate after the recommended changes are made	1

Brief Description of Outstanding Issues:

The applicant must address several labeling deficiencies before approval, including: (1) revising Section 3 to specify "each unit-dose packet of white to off-white granules contains 3 g of zoliflodacin," (2) updating Section 11 to clarify that "NUZOLVENCE for oral suspension contains zoliflodacin, an oral spiropyrimidinetrione bacterial type II topoisomerase inhibitor," (3) revising Section 16 storage condition language to conform to USP <659> standard language for storage conditions, and (4) adding mandatory placeholders for lot number and expiration date on both container and carton labels per 21 CFR 201.10(i)(1) and 21 CFR 201.17, respectively. Additionally, package type terminology must be corrected from (b) (4) to "unit-dose" per USP <659> standards.

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
eCTD 0001, SDN 1	04/15/2025	Prescribing Information Instruction for Use Carton and Container Labeling

1.0 PRESCRIBING INFORMATION[1]

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

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

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

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

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

[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: *Adequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) ***Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"***

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)[9]

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state	N/A	

[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>
[9] 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)
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.		
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	Adequate after the recommended changes are made
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 type terms include pharmacy bulk package and imaging bulk package (see USP <659>).	N/A	

Assessment: *Inadequate*

The applicant should revise section 3 to include the following: each unit-dose packet of white to off-white granules contains 3 g of zoliflodacin.

Note: Adequate after the recommended changes are made

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) ***Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"***

1.2.3 Section 11 (DESCRIPTION)[10]

(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)[11] [§ 201.57(c)(12)(i)(A)].	Adequate	
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg	N/A	

[10] See § 201.57(c)(12); Labeling Review Tool (March 2022, page 56)
[11] 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).

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)
of drug-x hydrochloride)" [§ 201.57(c)(12)(i)(C)].		
List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order.[12] Avoid brand names. [§ 201.57(c)(12)(i)(C)].	Adequate	
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[13] [§ 201.57(c)(12)(i)(E)].	Adequate	
Chemical name[14], structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Adequate	

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

[13] 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.

[14] 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).

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)
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)].	N/A	
For oral prescription drug products, include gluten statement[15] (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").	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*

1. Applicant should revise description:

NUZOLVENCE for oral suspension contains zoliflodacin, an oral spiropyrimidinetrione bacterial type II topoisomerase inhibitor. The chemical name of zoliflodacin is (2R,4S,4aS)-11-Fluoro-1,2,4,4a-tetrahydro-2,4-dimethyl-8-[(4S)-4-methyl-2-oxo-3-oxazolidinyl]spiro[isoxazolo[4,5-g][1,4]oxazino[4,3-a]quinoline-5(6H),5′(2′H)-pyrimidine]-2′,4′,6′(1′H,3′H)-trione. Its molecular formula is $C_{22}H_{22}FN_5O_7$ and molecular mass is 487.4 g/mol. Its chemical structure is depicted below.

Each unit dose packet of NUZOLVENCE for oral suspension contains 3 g of zoliflodacin and the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, mannitol, microcrystalline cellulose, talc, and xanthan gum.

Note: Adequate after the recommended changes are made

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

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) ***Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"***

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

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) [§ 201.57(c)(17)].	Adequate	
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	Adequate	

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

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
applicable); Include NDC(s) [§ 201.57(c)(17)(iii)].		
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	
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	Adequate after the recommended changes are made
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*	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)
made with natural rubber latex. Avoid statements such as "latex-free."[17]		
Include information about child-resistant packaging[18] (if chosen by manufacturer).	N/A	

Assessment: *Inadequate*

1. Applicant should revise packaging configuration statement:
   - 1 unit-dose packet of white to off-white granules containing zoliflodacin
   - One 120 mL mixing container with lid
   - Instructions for Use.
2. Should conform to USP <659> standard language for storage condition:
3. Delete, (b) (4)

Note: Adequate after the recommended changes are made

Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"

1.2.6 Manufacturing Information After Section 17 (for drug products)[19]

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

Assessment: *Adequate*

[17] Guidance: *Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex* (December 2014)
[18] Guidance: *Child-Resistant Packaging Statements in Drug Product Labeling* (August 2019)
[19] § 201.1(h)(5) and 201.1(i); Labeling Review Tool (March 2022, page 74)

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) ***Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"***

2.0 PATIENT LABELING

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

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[20]	Adequate	
Special preparation instructions (if applicable).	Adequate	
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).	Adequate	
Alphabetical listing of inactive ingredients (if applicable).	Adequate	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer.	Adequate	

Assessment: *Adequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) ***Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"***

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

3.0 CONTAINER AND CARTON LABELING[21]

3.1 Container Labels[22]

(b) (4)

[redacted]

[21] Carton and Container Labeling Resources

3.2 Carton Labeling

(b) (4)

[redacted]

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[23], (font size and prominence) [§ 201.10(g)(2)].	Adequate	Yes	
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)].[24]	Adequate	Yes	
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Adequate	Yes	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance	N/A	Yes	

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

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

[24] 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)
and MAPP [§ 201.10(d)(1) & 201.100(b)(4), USP <1121>].			
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)].[25]	Adequate	No	
"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	Yes	
Lot number and expiration date [§ 201.18 & 201.17].	Adequate	Yes	Adequate after the recommended changes are made
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	Adequate	Yes	
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>).	Adequate	Yes	Adequate after the recommended changes are made
Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5) or limited space per § 201.10(i)(2)].	N/A	Yes	

[25] § 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)
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	Yes	
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	Yes	
Linear Bar code [§ 201.25(c)(2)].[26]	Adequate	Yes	
Adequate directions for use: "Recommended Dosage: See Prescribing Information" [§ 201.5 & 201.55].	Adequate	Yes	
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	No	
"Keep out of reach of children" statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)].	Adequate	Yes	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Adequate	No	Adequate after the recommended changes are made
No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>).	N/A	Yes	

[26] 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)
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	Yes	
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.[27]	N/A	Yes	
And others if space is available.	N/A	Yes	

Assessment of Carton Labels and Container Labeling: *Inadequate*

- Must include placeholders for lot number (per 21 CFR 201.10(i)(1)) and expiration date (per 21 CFR 201.17) Should be "unit-dose" per USP <659>
- Must include statement about dispensing Medication Guide to each patient

Note: Adequate after the recommended changes are made

Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

1. We recommend the applicant revise Section 3 to For Oral Suspension: "each unit-dose packet of white to off-white granules contains 3 g of zoliflodacin"
2. We recommend the applicant revise Section 11 (Description) to include "NUZOLVENCE for oral suspension contains zoliflodacin, an oral spiropyrimidinetrione bacterial type II topoisomerase inhibitor." Additionally,

[27] USP General Notices 3.20 Indicating Conformance

the applicant should include “each unit dose packet of” and delete (b) (4) after NUZOLVENCE.
3. We recommend the applicant storage condition language conforms to USP <659> standard language for storage conditions
4. We recommend the applicant revise the configuration in Section 16.1
5. We recommend the applicant to remove the statement, (b) (4) from Section 16.2 (Storage and Handling).
6. We recommend carton and container labels must include mandatory placeholders for lot number (per 21 CFR 201.10(i)(1)) and expiration date (per 21 CFR 201.17)
7. We recommend the Correct terminology from (b) (4) to "unit-dose" per USP <659> standards

Primary Labeling Assessor Name and Date:

Saki Golafale, Ph.D., 10/06/2025

Secondary Assessor Name and Date (and Secondary Summary, as needed):
David Claffey, Ph.D. 10/06/2025

Saki Golafale

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David Claffey

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Date: 10/07/2025 08:48:49AM
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Comments: Adequate after recommended changes are made

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CHAPTER VI: BIOPHARMACEUTICS

Application type	505(b)(1)
NDA Number	219491
Assessment Cycle Number	1
Drug Product Name/ Strength	Nuzolvence (zoliflodacin) Kit, granules for suspension, 3 g
Route of Administration	Oral
Applicant Name	Entasis Therapeutics Inc
Therapeutic Classification/ OND Division	CDER/OND/OID/DAI
Proposed Indication	Uncomplicated gonorrhea

Assessment Recommendation: **Adequate**

Assessment Summary: Entasis Therapeutics is seeking approval for Zoliflodacin granules for oral suspension, 3 g under section 505(b)(1) for the treatment of uncomplicated gonorrhea due to Neisseria gonorrhoeae in adult and pediatric patients 12 years and older, weighing at least 35 kg. Zoliflodacin is a New Molecular Entity (NME) because it is a first-in-class antibiotic with an active moiety that has not been previously approved by the FDA, and it has been granted Qualified Infectious Disease Product (QIDP) designation.

Review Objective: The focus of the current Biopharmaceutics review is to assess the dissolution method and dissolution acceptance criterion for the proposed drug product quality control (QC). In addition, the need for a biowaiver and/or bridging will be evaluated.

Recommendation: Based on the totality of data/information provided, the following dissolution testing method and acceptance criterion are found acceptable for the QC of the proposed drug product at batch release and for stability testing.

Final dissolution method and acceptance criterion

USP Apparatus	Speed	Medium	Volume/ Temperature	Acceptance Criterion
II (Paddle)	60 rpm	pH 6.8 Phosphate buffer with 0.6% SLS	900 mL/ 37 ± 0.5 °C	Q= (b) (4)% in 30 minutes

The Applicant provided adequate justification for the proposed dissolution method parameters. Additionally, the proposed dissolution method shows sensitivity to changes in drug substance physical form ((b) (4)). Based on the dissolution data from the clinical batch and registration batches, the proposed dissolution acceptance criterion of Q= (b) (4)% in 30 minutes is acceptable.

Risk Assessment for dissolution:

CQA	Initial Risk	Comments	Updated Risk	Comments
Drug substance (b) (4) form	Medium	(b) (4)	Low	The proposed dissolution method shows sensitivity to changes in drug substance physical form (b) (4)

Bridging: The zoliflodacin granules for oral suspension used in the pivotal Phase 3 trial (STI Zoli001) were manufactured at Patheon, USA, (b) (4) , manufacturing was transferred to Dr. Reddy's, India during the Phase 3 trial. (b) (4) To bridge this drug product manufacturing site change from the clinical drug product (Patheon) to the to-be-marketed commercial drug product (Dr. Reddy's), the Applicant conducted in vivo bioequivalence (BE) studies which will be assessed by the Office of Clinical Pharmacology (OCP) to support the changes.

Biowaiver: A biowaiver request is neither requested nor needed.

Overall recommendation:
From a Biopharmaceutics perspective, NDA 219491 for Zoliflodacin granules for oral suspension, 3 g is recommended for APPROVAL.

List of Submissions Being Assessed:

Document(s) Assessed	Date Received
New NDA	**04/15/2025**
Biopharm IR response	**07/14/2025**
Biopharm IR#2 response	**09/08/2025**
Biopharm amendment	**09/26/2025**

Highlight Key Issues from Last Cycle and Their Resolution: Not applicable, this is the first review cycle.

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

B.1 BCS DESIGNATION

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

The Applicant claims that zoliflodacin (b) (4) is a Biopharmaceutics Classification System (BCS) Class II compound, characterized by limited aqueous solubility. (b) (4) The equilibrium solubility of (b) (4) zoliflodacin drug substance was evaluated across the physiological pH range of 1.2 to 6.8, with results presented in Table 1.

Table 1: Solubility of (b) (4) Zoliflodacin in Aqueous Buffers at 37 ºC

Media pH	Solubility (mg/mL)
1.2	0.26
2.0	0.23
4.5	0.22
6.8	0.34

The proposed commercial formulation consists of zoliflodacin granules for oral suspension with a strength of 3.0 grams per unit dose. Solubility testing demonstrates that this unit strength does not achieve complete dissolution in 250 mL or less of buffer solutions (without surfactant) across the tested pH range of 1.2 to 6.8.

The Applicant claims (Pg 8-9) high permeability for zoliflodacin based on the results of in vitro Caco-2 Studies, however, the permeability data are not evaluated in this Biopharmaceutics review.

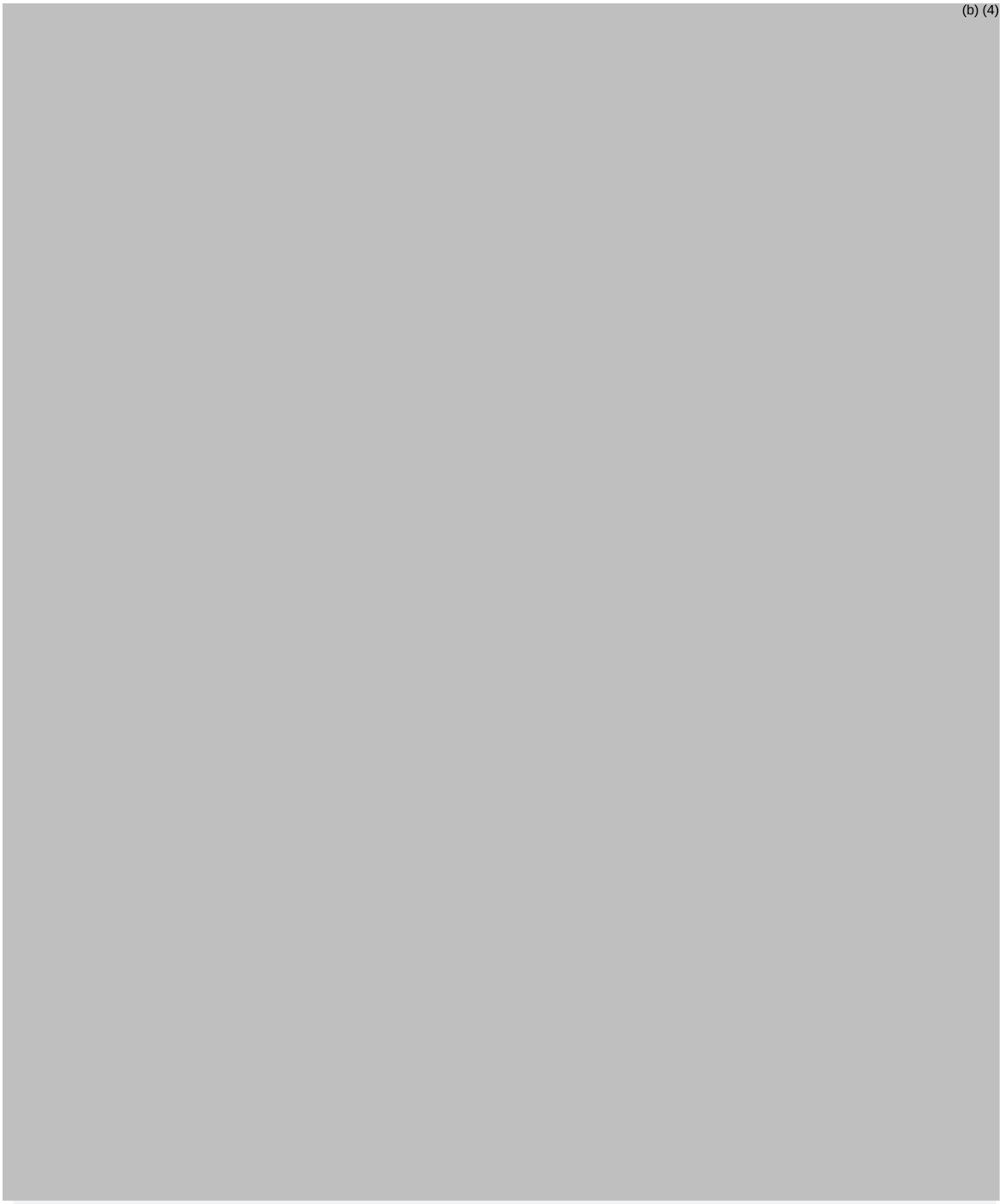
B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: Adequate

The Applicant originally (dissolution method development report, Pg 8) proposed the following QC dissolution method and acceptance criterion for the proposed drug product:

Apparatus	Speed	Medium	Volume/ Temperature	Acceptance Criterion
USP Apparatus II (Paddle)	(b) (4) rpm	pH 6.8 Phosphate buffer with (b) (4) % SLS	900 mL/ 37 ± 0.5 °C	Q=(b) (4)% in (b) (4) minutes

(b) (4)



Dosage form for the dissolution test sample: The proposed drug product zoliflodacin granules for oral suspension, 3 g is administered as an oral suspension after reconstitution with water. However, the Applicant is using granules directly from sachets for the dissolution test. In general, dissolution testing should be conducted on the administered dosage form (i.e., oral suspension). The Applicant provided dissolution data using the original dissolution method comparing granules and reconstituted suspension as dissolution samples. As shown in Table 12 of the dissolution method

development report, dissolution testing of batch ET22104 demonstrated comparable dissolution profiles between granules tested directly from sachets and reconstituted oral suspension samples at multiple time points (T=0, T=60 min, and T=120 min), with mean dissolution values within 1-2% at each sampling interval and acceptable %RSD values (0.9-4.0%).

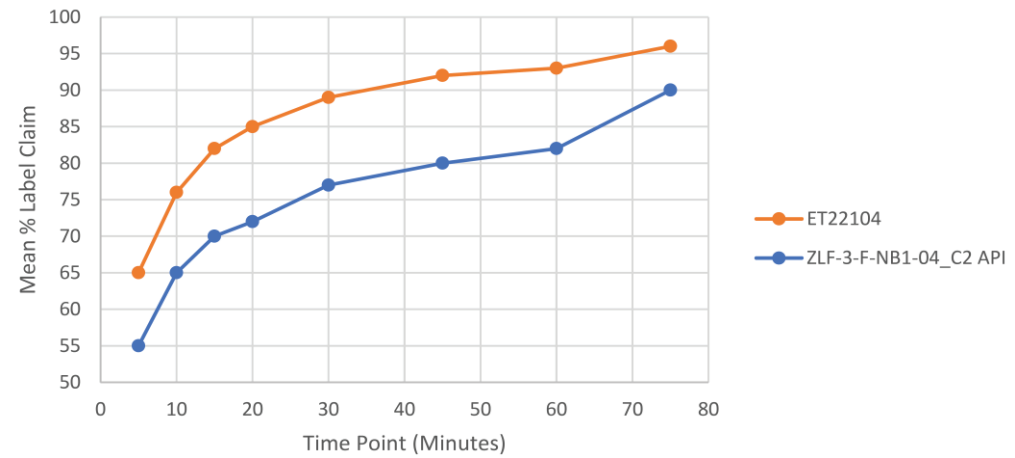
As per the drug product label, it requires a total of 120 mL of water for reconstitution of the granules (60 mL initial addition followed by 60 mL rinse), which may cause temperature fluctuations of the dissolution medium maintained at 37.0 ± 0.5°C after addition of the reconstituted suspension prepared at room temperature. In addition, the dissolution of the granules is theoretically more sensitive and discriminating than the dissolution on the oral suspension because for the oral suspension in water, the disintegration of the granules takes place prior to the dissolution test. This could limit the detection of key formulation attributes which consequently may impact the discriminating capabilities of the dissolution method. Therefore, the proposal to use the granules from sachet for the dissolution testing is found acceptable.

Discriminating ability: The Applicant has identified various Critical Bioavailability Attributes (CBAs): drug substance solid state (b) (4) form, granule size, composition change, and process parameters and evaluated the proposed dissolution method's sensitivity towards them.

1) **Drug substance (b) (4) form:** The proposed drug substance is in the (b) (4) form. During the drug substance process development, atypical (b) (4) form (Pg 23) variations were detected in the drug substance batches at trace levels. One batch of the drug product was manufactured using a drug substance batch with an atypical (b) (4) form that had failed to meet the drug substance specification for solid-state form.

(b) (4)

Figure 2: Dissolution profiles of drug product batches containing the proposed [redacted] drug substance (ET22104) and atypical [redacted] drug substance (ZLF-3-F-NB1-04_C2 API) in 900 mL pH 6.8 sodium phosphate buffer + 0.6% SLS, USP apparatus 2, 60 rpm (infinity spin after 60 minutes)



As shown in Figure 2, the dissolution profiles (IR response, Pg 14-15) obtained using the revised dissolution method are not similar and demonstrate the discriminating ability of the revised dissolution method towards changes in drug substance solid state form. The proposed dissolution acceptance criterion (Q= [redacted]% in 30 minutes) will reject the drug product batch containing atypical [redacted] drug substance (ZLF-3-F-NB1-04_C2 API) that failed the drug substance specification. However, it should be noted that dissolution testing cannot be used as a primary control method for drug substance solid state form in the drug product, since the exact content and extent of the solid-state variation in the variant batch is not precisely known. The dissolution method serves as a secondary discriminating tool that can detect significant changes in solid state form. The potential need for additional [redacted] controls for the drug substance solid state in the drug product will be assessed by the drug product reviewer as part of the overall control strategy evaluation.

2) Formulation change:

A) [redacted] levels: The proposed drug product contains [redacted] The Applicant manufactured a variant batch with [redacted] and tested it using the original dissolution method. The dissolution profile (Pg 26-27) of the drug product batch with [redacted] showed a slower dissolution profile compared to the target drug product, however, both batches will pass the proposed dissolution acceptance criterion of Q= [redacted]% at 30 minutes.

B) [redacted] levels: The proposed drug product contains [redacted]. The Applicant manufactured a variant batch with [redacted] and tested it using the original dissolution method. The dissolution profile (Pg 28) of the variant drug product batch is similar to the target drug product.

3) **Process parameters:** Two drug product batches with different (b) (4) were tested using the original dissolution method. The dissolution profile (Pg 29) of the variant drug product batch is similar to the target drug product, as both batches show very rapid release (>85% in 15 minutes).

Note: In response (07/14/2025) to the IR#1, the Applicant committed to providing additional dissolution data to show the discriminating ability of the revised dissolution method using variant batches manufactured with changes in drug product composition and process parameters. Subsequently, in the amendment dated 09/26/2025, the Applicant provided the requested data. However, the data do not demonstrate that the revised dissolution method has discriminating ability against the studied changes in drug product composition and manufacturing process parameters. Since the Applicant has adequately justified the proposed dissolution parameters, the revised dissolution method is considered acceptable.

Acceptance criterion: The Applicant has proposed a revised dissolution acceptance criterion of Q= (b) (4) % in 30 minutes for the proposed drug product. Based on the dissolution data (Pg 13) using the revised dissolution method for the clinical batch (G-19-019, used for BE studies) and registration batches (ET22104, ET22105, and ET22106), the proposed dissolution acceptance criterion of Q= (b) (4) % in 30 minutes is found adequate. In response to the IR#2, the Applicant has updated the submission to reflect the revised dissolution method and acceptance criterion.

Based on the totality of the dissolution method development data provided, the following dissolution method and acceptance criterion are found acceptable for the QC of the proposed drug product at batch release and throughout the stability program/shelf-life:

Final dissolution method and acceptance criterion

USP Apparatus	Speed	Medium	Volume/ Temperature	Acceptance Criterion
II (Paddle)	60 rpm	pH 6.8 Phosphate buffer with 0.6% SLS	900 mL/ 37 ± 0.5 °C	Q= (b) (4) % in 30 minutes

Dissolution method validation: The Applicant did not provide dissolution method validation data in the submission. Therefore, IR#2 was issued to request that the Applicant provides the dissolution method validation information according to USP <1092>. In response, the Applicant committed to provide the requested validation data. However, in the amendment dated 09/26/2025, the Applicant provided HPLC method robustness and validation data instead of dissolution method validation data. Since the drug product has received QIDP designation and is an NME and since the method validation is primarily a cGLP issue and considering the current time constraints, from a Biopharmaceutics review perspective the revised dissolution method is considered acceptable.

B.12 BRIDGING

Assessment: Adequate

The zoliflodacin granules for oral suspension used in the pivotal Phase 3 trial (STI Zoli001) were manufactured at Patheon, USA, (b) (4) , manufacturing was transferred to Dr. Reddy's, India during the Phase 3 trial. (b) (4) To bridge this drug substance manufacturing change between drug substance used in the clinical drug product batches (Patheon) to the to-be-marketed commercial drug product (Dr. Reddy's), the Applicant conducted in vivo BE studies that will be assessed by the Office of Clinical Pharmacology (OCP) to support the changes in both the drug substance manufacturing process and the drug product manufacturing site.

B. 13 BIOWAIVER REQUEST

Assessment: Not Applicable

A biowaiver request is neither requested nor needed. The Applicant has conducted in vivo BE studies between the drug product used in the clinical trials and the proposed commercial to-be-marketed drug product. In addition, the proposed drug product is available in a single strength.

R. REGIONAL INFORMATION

Comparability Protocols

Assessment: Not Applicable

Post-Approval Commitments

Assessment: Not Applicable

BIOPHARMACEUTICS LIST OF DEFICIENCIES

Not Applicable

Primary Biopharmaceutics Assessor's Name and Date: Hardikkumar H Patel, PhD, 10/02/2025

Secondary Assessor Name and Date: Elsbeth Chikhale, PhD, 10/02/2025

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Elsbeth Chikhale

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On behalf of the OPQ team