

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206056Orig1s000

PRODUCT QUALITY REVIEW(S)



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	4		



Template Revision: 03

NDA Executive Summary

1. Application/Product Information

NDA Number.	206056
Applicant Name	B. Braun Medical Inc.
Drug Product Name	Piperacillin and Tazobactam for Injection and Sodium Chloride Injection
Dosage Form.	Powder for reconstitution and diluent
Proposed Strength(s)	▪ 2.25 g (2 g piperacillin and 0.25 g tazobactam) and 50 mL of 0.45% Sodium Chloride Injection ▪ 3.375 g (3 g piperacillin and 0.375 g tazobactam) and 50 mL of 0.3% Sodium Chloride Injection ▪ 4.5 g (4 g piperacillin and 0.5 g tazobactam) and 100 mL of 0.45% Sodium Chloride Injection
Route of Administration	Intravenous
Maximum Daily Dose	18 g (16 g piperacillin and 2 g tazobactam)
Rx/OTC Dispensed	Rx
Proposed Indication	Piperacillin and Tazobactam for Injection and Sodium Chloride Injection, is a combination of piperacillin, a penicillin-class antibacterial, and tazobactam, a beta-lactamase inhibitor, indicated for the treatment of: • Intra-abdominal infections in adult and pediatric patients 2 months of age and older • Nosocomial pneumonia in adult and pediatric patients 2 months of age and older • Skin and skin structure infections in adults • Female pelvic infections in adults • Community-acquired pneumonia in adults
Drug Product Description	The finished drug product contains two components: a powder for injection containing piperacillin (as piperacillin sodium) and tazobactam (as tazobactam sodium), and the sodium chloride injection, which are co-packaged in separate chambers of a proprietary dual-chamber IV bag, known as a Duplex container. The drug product is manufactured by (b) (4)



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	(b) (4) to provide the finished co-packaged drug product, which contains a white to off-white powder in one chamber, and a clear, colorless solution in the other chamber of the Duplex container. The two chambers are separated by a peelable seal; after removal of this seal, the diluent is released into the drug powder chamber, allowing for preparation of a solution that can be administered intravenously. The powder for injection is procured as a sterile (b) (4) powder and contains two excipients, edetate disodium dihydrate (EDTA) as a (b) (4) and sodium citrate dihydrate as a (b) (4) in addition to two drug substances, piperacillin sodium and tazobactam sodium. The sodium chloride injection contains sodium chloride and water for injection. Three finished drug product strengths in three co-packaged drug-diluent combinations (as described above) are proposed for marketing.		
Co-packaged product information	See above		
Device information:	N/A (see above)		
Storage Temperature/ Conditions	20°C to 25°C (68°F to 77°F)		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Daniel Chan	Katherine Windsor
	<i>Drug Product</i>	Hudson Roth	Dorota Matecka
	<i>Labeling</i>	Hudson Roth	David Claffey
	<i>Manufacturing</i>	Ann-Marie Afrifa	Christine Falabella
	<i>Biopharmaceutics</i>	Haodan Yuan	Elsbeth Chikhale
	<i>Microbiology</i>	Shannon Heine	John Metcalfe
	<i>Other (specify):</i>	N/A	



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	RBPM	Dahlia Walters
	ATL	Dorota Matecka
Consults	N/A	

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

24 months 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 has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed drug substances and the drug product (Piperacillin and Tazobactam for Injection and Sodium Chloride Injection). The CMC information for piperacillin and tazobactam was provided via a reference to a Type II DMF (b) (4), which was found adequate (refer to the Drug Substance review, below). In addition, all issues, comments, and requests for additional information, identified during the review by the Microbiology, Drug Product, Manufacturing reviewers have been adequately addressed and resolved (for details refer to the Microbiology, Drug Product, Manufacturing reviews, below). Also, the labeling comments (as outlined in the Labeling review, below) have been adequately addressed by the Applicant. The stability information, including in-use stability data, provided in the initial NDA and subsequent amendments have been found acceptable to support the proposed by the Applicant drug product expiration dating of 24 months (to be stored at room temperature), and the proposed in-use storage statements in the labeling (*after reconstitution, use within 24 hours if stored at room temperature or within 7 days if stored under refrigeration*). In addition,



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the manufacturing and testing facilities have been found acceptable and an overall “Approve” recommendation for this NDA was entered into Panorama by the Office of Pharmaceutical Manufacturing Assessment (OPMA) on February 5, 2025. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ).

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: N/A

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Title:	NDA IQA Template CHAPTER IV-LABELING
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CHAPTER IV: LABELING

NDA Number	206056
Assessment Cycle Number	1
Drug Product Name	Piperacillin and Tazobactam for Injection and Sodium Chloride Injection

Assessment Recommendation: Adequate

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Adequate	SDN 21
Patient Information	N/A	
Instruction for Use (IFU)	N/A	
Container Labels	Adequate	SDN 18
Carton Labeling	N/A	

Brief Description of Outstanding Issues:

N/A

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
eCTD 0002, SDN 3	6/7/2024	Container Labels and Prescribing Information
eCTD 0017, SDN 18	1/22/2024	Container Labels
eCTD 0020, SDN 21	3/18/2025	Prescribing Information

1.0 PRESCRIBING INFORMATION¹

Assessment of Product Quality Related Aspects of the Prescribing Information:

Revisions to the PI discussed with OND and DMEPA were conveyed to the Applicant on March 13, 2025. The Applicant adequately responded to the revisions on March 18, 2025.

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)]		
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)]		

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

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

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

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Dosage 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	
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	Adequate	

Assessment: *Adequate*

The following revisions were sent to the Applicant: remove the USP descriptors and relocating the concentration of the sodium chloride for clarity and conciseness.

The Applicant agreed to relocate the sodium chloride concentration, but requested to keep the USP descriptors to clearly indicate the drug product complies with the USP monograph. The proposal to keep the USP descriptors is acceptable.

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

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

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

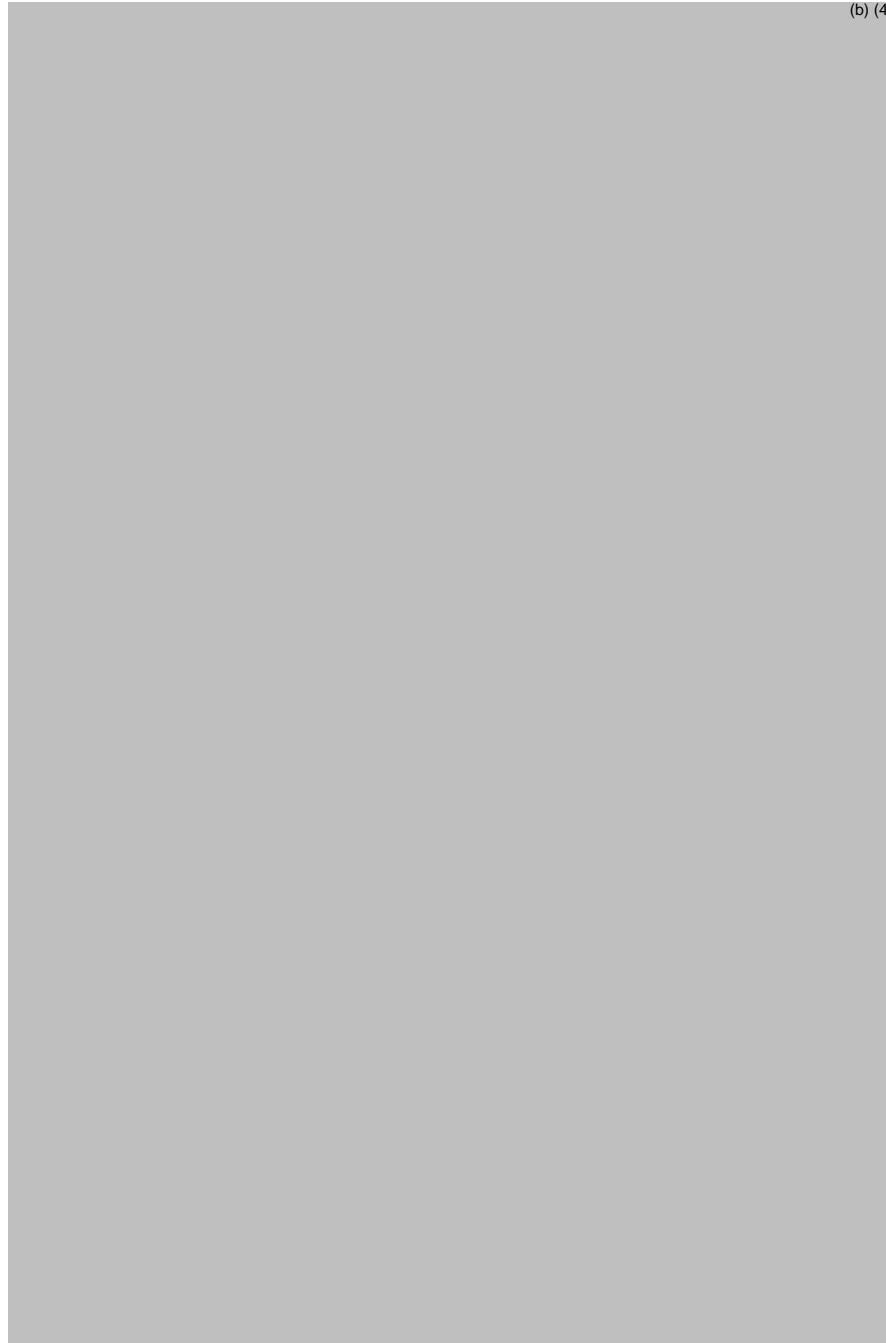
⁷ Guidance: *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013)

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

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)⁹

Originally proposed language:



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

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)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents and/or soft food ¹⁰ , storage conditions needed to maintain the stability of the reconstituted or diluted product).	Adequate	
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food).	Adequate	
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	Adequate	
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).	Adequate	
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</i>	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

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)
<i>applicable special handling and disposal procedures.^x</i> with x numerical citation to "OSHA Hazardous Drugs."		

Assessment: Inadequate

Inadequate in-use and compatibility stability data were provided in the NDA to support the preparation instructions provided in Section 2. An IR was sent to the Applicant requesting particulate matter testing be conducted; the Applicant committed to providing these data by March 24, 2025. The inclusion of the in-use storage period and the compatibility statements for co-administration with aminoglycosides depends on these data.

In addition, the Applicant adequately addressed the need to include temperature ranges for the storage conditions for the reconstituted drug product.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)¹³

Originally proposed language:



Revised language:



¹³ See § 201.57(c)(4); Labeling Review Tool (March 2022, page 29)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	
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 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>).	Adequate	

Assessment: *Adequate*

The following revisions were conveyed to the Applicant: include the required physical description of the drug product powder and diluent, and remove the unnecessary (b) (4) statement.

The Applicant adequately revised Section 3.

1.2.3 Section 11 (DESCRIPTION)¹⁴

Originally proposed language:



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



(b) (4)

Revised language:



(b) (4)

(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)].	Adequate	Recommended the Applicant remove the "USP" descriptors. Applicant requested to keep them to clearly indicate the product complies with the corresponding USP monograph.
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	Adequate	

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).

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)
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)].		
List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order. ¹⁶ Avoid brand names. [§ 201.57(c)(12)(i)(C)].	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)].	Adequate	
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)].	Adequate	
Pharmacological/Therapeutic class ¹⁷ [§ 201.57(c)(12)(i)(E)].	Adequate	

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

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.

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)
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).	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).	Adequate	As per the USP monograph for Piperacillin and Tazobactam for Injection, "If a test for <i>Organic Impurities</i> other than <i>Procedure 1</i> is used, then the labeling states with which <i>Organic Impurities</i> test the article complies." As <i>Procedure 3</i> is used, a statement is needed in Section 11.

Assessment: *Adequate*

The following revisions were conveyed to the Applicant: editorial revisions to improve the clarity, flow, and conciseness of the text, include the required salt equivalency statement, list inactive ingredients in alphabetical order, and include statement on analytical method used for related substances as required by the USP monograph.

The Applicant adequately revised Section 11.

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)

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

Originally proposed language:



Revised language:



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



Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
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	According to Section 1.14.1.1 of the NDA, the drug product will be supplied as 24 individual units packaged in a shipping case.
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s) [§ 201.57(c)(17)(iii)].	Adequate	
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>).	Adequate	

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)]	Adequate	
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: " <i>Not made with natural rubber latex. Avoid statements such as "latex-free."</i> ²¹	N/A	
Include information about child-resistant packaging ²² (if chosen by manufacturer).	N/A	

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

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

Assessment: Adequate

The following revisions were conveyed to the Applicant: include the required physical description for the drug product powder and diluent, (b) (4) and include a reference to Section 2, and include rationale for special storage instructions.

The Applicant adequately revised Section 16.

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.	Adequate	

Assessment: Adequate

The proposed language is adequate.

2.0 PATIENT LABELING

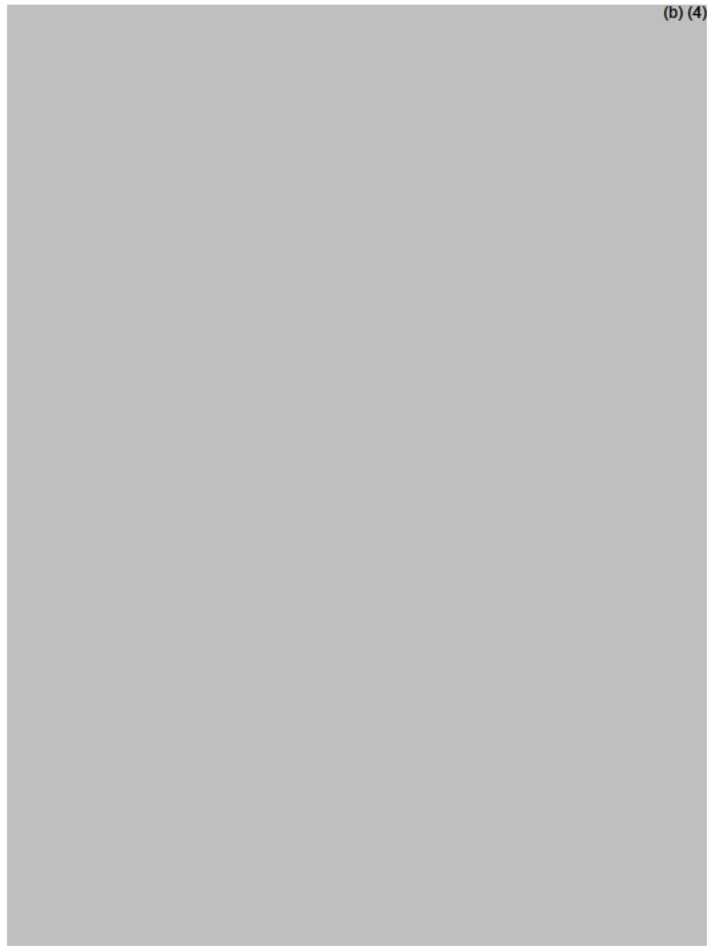
Assessment: N/A

No patient labeling is proposed for this drug product as it will be administered by a healthcare provided in the clinical setting.

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

3.0 CONTAINER AND CARTON LABELING²⁴

3.1 Representative Container Label²⁵



3.2 Carton Labeling

No carton labeling is proposed for this drug product as the it will be supplied as individual containers packaged in a shipping case.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	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 ²⁶ , (font size	Adequate	Recommended removing "USP" descriptor to the Applicant on January

²⁴ [Carton and Container Labeling Resources](#)

²⁵ 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.

²⁶ Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
and prominence) [§ 201.10(g)(2)].		8, 2025. Applicant requested to keep the USP descriptor in the main product title on the container label to clearly indicate the product complies with the corresponding USP monographs.
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)]. ²⁷	Adequate	
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Adequate	
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	
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)]. ²⁸	Adequate	
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Adequate	
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	
Lot number and expiration date [§ 201.18 & 201.17].	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	Adequate	Recommended to include (b) (4) on January 8, 2025. Applicant requested to not include these (b) (4) due to limited space on the container label.
For injectable drug products for parenteral administration,	Adequate	

²⁷ 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 \(May 2022\)](#)

²⁸ § 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”)	Assessor’s Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
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>).		
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)].	Adequate	
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)].	Adequate	
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	
Linear Bar code [§ 201.25(c)(2)]. ²⁹	Adequate	
Adequate directions for use: “Recommended Dosage: See Prescribing Information” [§ 201.5 & 201.55].	Adequate	
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	

²⁹ 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”)	Assessor’s Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
“Keep out of reach of children” statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)].	N/A	Rx only
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>).	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	Adequate	
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. ³⁰	N/A	
And others if space is available.	Adequate	

Assessment of Carton Labels and Container Labeling: Adequate

The following comments were conveyed to the Applicant on January 8, 2025, regarding the proposed container labels:

1. Recommend removing the “USP” descriptors for clarity and conciseness, e.g., revise “Piperacillin and Tazobactam for Injection USP and Sodium Chloride Injection USP” to “Piperacillin and Tazobactam for Injection and Sodium Chloride Injection”.

³⁰ USP General Notices 3.20 Indicating Conformance

2. Include the concentration of the sodium chloride injection on the label, e.g. “50 mL of 0.45% sodium chloride injection”.
3. Include a salt equivalency statement on the container label, e.g., “Each dry powder chamber provides 2 g of piperacillin (equivalent to 2.085 g of piperacillin sodium), 0.25 g tazobactam (equivalent to 0.269 g of tazobactam sodium)...”
4. Add sodium citrate dihydrate to the list of inactive ingredients, e.g., “Each dry powder chamber provides...0.5 mg of edetate disodium dihydrate, and 100 mg of sodium citrate dihydrate.”
5. Revise the statement “(b) (4)” to “Do not peel foil strip until ready for use in order to protect from light” to include the rationale for the special storage instruction, and for consistency across the labeling.
6. Revise the storage conditions for the reconstitution drug product solution from “...if stored at room temperature or within 7 days if stored under refrigeration...” to (b) (4)

The Applicant submitted revised container labels in SDN 18 based on the above recommendations and additional recommendations from DMEPA. The revised container labels are now adequate from the product quality perspective.

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

N/A

Primary Labeling Assessor Name and Date:

Hudson Roth, Ph.D., 03/26/2025

Secondary Assessor Name and Date:

David Claffey, Ph.D., 03/26/2025



Hudson
Roth

Digitally signed by Hudson Roth
Date: 3/27/2025 10:50:27AM
GUID: 6179adc200758f92383849fa56daa5d6



Dorota
Matecka

Digitally signed by Dorota Matecka
Date: 3/27/2025 11:45:59AM
GUID: 508173530000859092c69506374d0011
Comments: Signing on behalf of Dr. Claffey

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

CHAPTER VI: BIOPHARMACEUTICS

NDA Number	NDA-206056-ORIG-1 (505(b)(2))
Assessment Cycle Number	1
Drug Product Name/ Strength	Piperacillin and Tazobactam for Injection USP and Sodium Chloride Injection USP in a Duplex Container Piperacillin/Tazobactam, 2.0/0.25 g, 3.0/0.375 g, and 4.0/0.5 g
Dosage Form	Powder for Injection and diluent (Drug-Device Combination Product (Type 2 - Prefilled Drug Delivery Device/System))
Route of Administration	Intravenous Administration
Applicant Name	B. Braun Medical Inc. (B. Braun)
Therapeutic Classification/ OND Division	DAI
LD Number	LD: Zosyn (piperacillin and tazobactam) for Injection, 2.25 g, 3.375 g, and 4.5 g (in glass vials) (NDA# 050684, owned by Wyeth Pharmaceuticals (now Pfizer)), discontinued.
Proposed Indication	For the treatment of appendicitis (complicated by rupture or abscess) and peritonitis caused by beta-lactamase producing isolates of Escherichia coli or the following members of the Bacteroides fragilis group: B. fragilis, B. ovatus, B. thetaiotaomicron, or B. vulgatus.

Assessment Recommendation: Adequate

Background

B. Braun Medical Inc. (B. Braun) is seeking approval under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Piperacillin and Tazobactam for Injection USP and Sodium Chloride Injection USP in a Duplex Container, 2.25 g, 3.375 g, and 4.5 g. The proposed drug product is comprised of a (b) (4) drug powder and diluent in the Duplex (b) (4) Container. After mixing the powder with the diluent, the parenteral solution is intended solely for administration by intravenous infusion and indicated in adults and pediatric patients (2 months of age and older) for the treatment of appendicitis (complicated by rupture or abscess) and peritonitis caused by beta-lactamase producing isolates of Escherichia coli or the following members of the Bacteroides fragilis group: B. fragilis, B. ovatus, B. thetaiotaomicron, or B. vulgatus.

The listed drug (LD) to support approval of the proposed drug product is Zosyn (Piperacillin and Tazobactam) for Injection, 2.25 g, 3.375 g, and 4.5 g in glass vials (NDA 050684, approved in 1993, owned by Wyeth Pharmaceuticals (now Pfizer)). NDA 050684 has been discontinued (not for safety or effectiveness reason)¹.

The drug powder portion of the proposed drug product has the same ingredients, qualitatively and quantitatively, as the FDA approved LD, Zosyn for Injection. The only difference of the proposed drug product and Zosyn for Injection is that the proposed product is comprised of the (b) (4) drug powder and the diluent in the Duplex (b) (4) Container while the Zosyn for Injection is only the lyophilized drug powder in glass vial, which need to be constituted with a desired solution for injection (which is not co-packaged) before drug administration.

The Applicant did not conduct a BA/BE study between the proposed drug product and the LD, and instead submitted a request of a waiver of the in-vivo bioavailability or bioequivalence (BE) study in accordance with 21 CFR 320.22 (b)(1)(i)(ii)².

Because the proposed drug product is an injection solution upon constitution intended for administration by intravenous infusion, there is no dissolution test proposed as part of the drug product quality control. This is acceptable.

Assessment Summary

This Biopharmaceutics review focuses on the evaluation of the biowaiver request for the proposed drug product. Because the concentrations of all active and inactive ingredients upon dilution of the proposed drug product and the LD are not exactly the same, a biowaiver under 21 CFR 320.22 (b)(1)(i)(ii) is not feasible. However, the Applicant has submitted sufficient information to support the bridge between the proposed drug product and the LD based on 21 CFR 320.24 (b)(6), thereby justifying reliance of this NDA on the LD without conducting a BA/BE study.

Recommendation

From the Biopharmaceutics perspective, NDA 206056 for the proposed Piperacillin and Tazobactam for Injection USP and Sodium Chloride Injection

¹ Orange book:

https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?AppI_Type=N&AppI_No=050684#5698

² Request for waiver of in vivo bio studies: \\CDSESUB1\EVSPROD\nda206056\0002\m1\us\112-other-corr\biowaiver.pdf

USP in the Duplex Container, 2.25 g, 3.375 g, and 4.5 g, is adequate and recommended for **approval**.

Biopharmaceutics Review

Drug Product Composition

Composition of the Proposed Drug Product

The proposed drug product, Piperacillin and Tazobactam for Injection USP and Sodium Chloride Injection USP in the Duplex Container, 2.25 g, 3.375 g, and 4.5 g (2.0/0.25 g, 3.0/0.375 g, and 4.0/0.5 g) is an injectable antibacterial combination consisting of piperacillin sodium and tazobactam sodium (8:1 ratio as piperacillin acid to tazobactam acid) solely for intravenous administration.

The proposed drug product is packed in a Duplex (b) (4) container which contains two chambers. The two chambers are separated by a peelable seal. The sterile (b) (4) powder is filled into one chamber and the provided diluent, sodium chloride injection USP, is filled in the second chamber. Prior to administration, the peelable foil is removed and pressure is applied on the diluent chamber. This releases the diluent into the drug chamber and allows the drug product powder to be mixed and dissolved in the diluent in a closed and sterile system. Using the Duplex (b) (4) container, the final constituted drug product provides the end users a ready-to-administer fixed dose drug product in solution form.

The proposed drug product is formulated with sodium citrate dihydrate and edetate disodium dihydrate (EDTA). Table 1 listed the components and the functions of each component of the drug product powder and the component of the diluent. The active ingredients, piperacillin sodium and tazobactam sodium, and the excipients, sodium citrate dihydrate and EDTA, are a (b) (4) powder³.

³ Description and composition of the drug product: <\\CDSESUB1\EVSPROD\nda206056\0002\m3\32-body-data\32p-drug-prod\piptazinjandnaclinjusp-injectable\32p1-desc-comp\description-and-composition.pdf>

Table 1. Description and Composition of the Proposed Drug Product

Component		Compendial Status	Function	2.25 g	3.375 g	4.5 g	Overfill	
				mg/unit	mg/unit	mg/unit		
Powder Chamber	Piperacillin and Tazobactam (Sterile (b) (4))	Piperacillin	In-house/ USP	Active Pharmaceutical Ingredient	2000	3000	4000	(b) (4)
		As Piperacillin Sodium			2085	3127	4170	
		Tazobactam	In-house/ USP	Active Pharmaceutical Ingredient (Beta-Lactamase Inhibitor)	250	375	500	
		As Tazobactam Sodium			269	402	538	
		Edetate Disodium Dihydrate (EDTA)	USP	Inactive Ingredient - (b) (4)	0.5	0.75	1	
		Sodium Citrate Dihydrate	USP	Inactive Ingredient - (b) (4)	100	150	200	
Diluent Chamber	Sodium Chloride		USP	Inactive Ingredient - (b) (4)	225	150	450	
	Water for Injection		USP	Inactive Ingredient - Diluent	50 mL (0.45% (w/v) Sodium Chloride Injection)	50 mL (0.3% (w/v) Sodium Chloride Injection)	100 mL (0.45% (w/v) Sodium Chloride Injection)	

Comparison of the proposed drug product and the LD, Zosyn for Injection

The Listed Drug (LD) is Zosyn (piperacillin and tazobactam) for Injection, 2.25 g, 3.375 g, and 4.5 g for Injection (NDA 050684) is owned by Pfizer and is currently discontinued (not for safety and effectiveness reason). The comparison of the proposed drug product and Zosyn for Injection is listed in Table 2⁴.

Zosyn is a sterile (b) (4) lyophilized powder filled in a glass vial. The proposed powder (packaged in one chamber of the proposed drug product) and the LD product, Zosyn®, have the same qualitative and quantitative composition. The only difference between them is that Zosyn allows for the use of various diluents ranging from Sterile Water for Injection to 0.9% Sodium Chloride (see Table 2), and the recommended volume per dose ranges from 50 mL to 150 mL⁵, whereas for the proposed drug product, the diluent is packed as part of the drug product, and the volume of the diluent cannot be changed. The diluents packed in the DUPLEX® container of the proposed drug product are:

⁴ Comparison of the proposed drug product and LD Zosyn:
<\\CDSESUB1\EVSPROD\nda206056\0012\m1\us\112-other-corr\comp-w-rlid.pdf>

⁵ Annotated comparison with the listed drug summary:
<\\CDSESUB1\EVSPROD\nda206056\0002\m1\us\114-labeling\114c-list-drug-label\annot-summ.pdf>

- 50 mL of 0.45% Sodium Chloride Injection USP for Piperacillin and Tazobactam for Injection USP 2.25 g
- 50 mL of 0.3% Sodium Chloride Injection USP for Piperacillin and Tazobactam for Injection USP 3.375 g
- 100 mL of 0.45% Sodium Chloride Injection USP Piperacillin and Tazobactam for Injection USP 4.5 g

Table 2. Comparison of the proposed drug product and the LD, Zosyn®:

	Proposed Drug	Reference Listed Drug
Application #	206056	050684
Product Name	Piperacillin and Tazobactam for Injection USP and Sodium Chloride Injection USP	Zosyn® (piperacillin and tazobactam) for Injection
Packaging System	DUPLEX® Container	Glass Vials
Indications	• Intra-abdominal infections in adult and pediatric patients 2 months of age and older • Nosocomial pneumonia in adult and pediatric patients 2 months of age and older • Skin and skin structure infections in adults • Female pelvic infections in adults • Community-acquired pneumonia in adults	• Intra-abdominal infections in adult and pediatric patients 2 months of age and older • Nosocomial pneumonia in adult and pediatric patients 2 months of age and older • Skin and skin structure infections in adults • Female pelvic infections in adults • Community-acquired pneumonia in adults
Active Ingredients	Piperacillin and Tazobactam	Piperacillin and Tazobactam
Inactive Ingredients	• Sodium Citrate Dihydrate* • Edetate Disodium Dihydrate (EDTA)* • Sodium Chloride • Water for Injection	• Sodium Citrate Dihydrate • Edetate Disodium Dihydrate (EDTA)
Diluents	• 2.25 g - 0.45% Sodium Chloride Injection USP • 3.375 g - 0.3% Sodium Chloride Injection USP • 4.5 g - 0.45% Sodium Chloride Injection USP	• 0.9% sodium chloride for injection • Sterile water for injection • Dextran 6% in saline • Dextrose 5% • Lactated Ringer's Solution
Dosage Form	Injectable (Powder + Diluent)	Injectable (Powder)

Table 2. Comparison of the proposed drug product and LD, Zosyn®, continued:

	Proposed Drug	Reference Listed Drug
Dosage Form (when administered)	Solution	Solution
Route of Administration	Injection (Intravenous)	Injection (Intravenous)
Strengths	• 2.25 g (eq. to 2 g piperacillin and 0.25 g tazobactam) • 3.375 g (eq. to 3 g piperacillin and 0.375 g tazobactam) • 4.5 g (eq. to 4 g piperacillin and 0.5 g tazobactam)	• 2.25 g (eq. to 2 g piperacillin and 0.25 g tazobactam) • 3.375 g (eq. to 3 g piperacillin and 0.375 g tazobactam) • 4.5 g (eq. to 4 g piperacillin and 0.5 g tazobactam)
Dosing Regimens	The dosing regimens are the same for the proposed product and the RLD except for the following introductory statement in the “Dosage and Administration” section of the labeling: “Piperacillin and Tazobactam for Injection and Sodium Chloride Injection in the DUPLEX® Container should be used only in patients who require the entire 2.25 g, 3.375 g, or 4.5 g dose and not any fraction thereof.”	
Labeling	The proposed labeling for the proposed product is identical to the labeling for the reference listed drug EXCEPT for the differences because B. Braun is seeking approval of a product supplied in the DUPLEX® Container with diluent, while the RLD is a lyophilized powder in a glass vial. The labeling also contains differences because of different manufacturers and/or distributors. Please refer to Module 1.14.3.1 for the annotated (side-by-side) labeling. Please refer to Module 1.14.3.3 for the current RLD labeling.	
Bioavailability / Bioequivalence	In accordance with 21 CFR § 320.22(b)(1)(i-ii), a waiver has been requested in Module 1.12.15 (Request for Waiver for <i>in-vivo</i> Studies).	

As shown in Table 2, the proposed drug product and LD, Zosyn, after dilution, have the same indication, active and inactive ingredients, dosage form, route of administration and strengths. The detail of the composition comparison is listed in Table 3³.

Table 3: Composition of the proposed drug product and the LD, Zosyn® for Injection:

		<i>Proposed Product, Piperacillin and Tazobactam for Injection USP and Sodium Chloride Injection USP in the DUPLEX® Container</i>			<i>RLD, Zosyn® for Injection</i>			
		<i>2.25 g</i>	<i>3.375 g</i>	<i>4.5 g</i>	<i>2.25 g</i>	<i>3.375 g</i>	<i>4.5 g</i>	
<i>Labeled Dose Strength/Unit</i>		<i>mg/unit</i>	<i>mg/unit</i>	<i>mg/unit</i>	<i>mg/unit</i>	<i>mg/unit</i>	<i>mg/unit</i>	
Powder Chamber	Piperacillin and Tazobactam (Sterile Bulk)	Piperacillin	2000	3000	4000	2000	3000	4000
		Piperacillin Sodium	2085	3127	4170	2085	3127	4170
		Tazobactam	250	375	500	250	375	500
		Tazobactam Sodium	269	402	538	269	402	538
		Edetate Disodium Dihydrate (EDTA)	0.5	0.75	1	0.5	0.75	1
		Sodium Citrate Dihydrate	100	150	200	100	150	200
Diluent Chamber	Sodium Chloride	225	150	450	--	--	--	
	Water for Injection	50 mL	50 mL	100 mL	--	--	--	

Bridging

The proposed drug product is relying on FDA's finding of safety and efficacy of the LD, Zosyn® for Injection. The Applicant did not conduct a BA/BE study between the proposed drug product and the LD to justify this reliance, and instead submitted a request of a waiver of the in-vivo bioavailability or bioequivalence (BE) study².

The powder portion of the proposed drug product, Piperacillin and Tazobactam for Injection USP and Sodium Chloride Injection USP in the Duplex Container, has the same ingredients, qualitatively and quantitatively, compared to the FDA approved LD, Zosyn® for Injection. The only difference between the proposed drug product and Zosyn® for injection is the diluent and the packaging of the diluent used for the constitution of the drug product powder. For the proposed drug product, the diluent (pre-packed in the diluent chamber of the Duplex (b) (4) container) is "50 mL of 0.45% (w/v) Sodium Chloride Injection" for the 2.25 g strength; "50 mL of 0.3% (w/v) Sodium Chloride Injection" for the 3.375 g strength and "100 mL of 0.45% (w/v) Sodium Chloride Injection" for the 4.5 g strength (Table 1). (b) (4)

⁶ Pre-NDA meeting request: \\CDSESUB1\EVSPROD\nda206056\0002\m1\us\16-meetings\written-response.pdf

The diluents that can be used for the LD, Zosyn®, are Sterile Water for Injection, 0.9% Sodium Chloride, dextran 6% in saline, dextrose 5%, or Lactated Ringer's.

The constituted solution for both the proposed drug product and the LD, Zosyn® have a pH between 5.0 and 7.0. As indicated on the proposed drug product's draft labelling and the draft container labels, the osmolality of the reconstituted solution of the proposed drug product is approximately 318 mOsm/kg for the 2.25 g strength, approximately 348 mOsm/kg for the 3.375 g strength, and approximately 318 mOsm/kg for the 4.5 g strength⁷, however, the source of these osmolality values was not clear in the submission. An IR letter was sent to the Applicant on 11/15/2024 requesting the Applicant to provide a clarification on how these osmolality values were obtained. In the response (dated 11/19/0024) to the IR letter, the Applicant stated that the osmolality values were obtained experimentally⁸. The experimental procedure is described in the report (RPT-PH-1011246)⁹.

The Applicant manufactured four registration batches for each strength. The osmolality of the registration batches measured at batch release is listed in Table 4 below.

Table 4. Osmolality of the registration batches:

2.25 mg		3.375 mg		4.5 mg	
Batch	Osmolality (mOsm/kg)	Batch	Osmolality (mOsm/kg)	Batch	Osmolality (mOsm/kg)
23H00070	(b) (4)	23H00082	(b) (4)	23H00096	(b) (4)
23H00071	(b) (4)	23H00083	(b) (4)	23H00097	(b) (4)
23H00074	(b) (4)	23H00084	(b) (4)	23H00098	(b) (4)
23H00075	(b) (4)	23H00085	(b) (4)	23H00099	(b) (4)
Acceptance criterion:		(b) (4)			

The osmolality value of the registration batches of the proposed drug product (b) (4) (b) (4) The osmolality value of the infusion solution prepared from LD Zosyn is not available.

The concentrations of the ready-to-administer infusion solution of the proposed drug product are listed in Table 5.

⁷ Draft labelling text, p21: \\CDSESUB1\EVSPROD\nda206056\0008\m1\us\114-labeling\114a-draft-label\ld-803-1-y36-003-084-r2-drafttext.pdf

⁸ Biopharm info amendment (SDN12): \\CDSESUB1\EVSPROD\nda206056\0012\m1\us\111-info-amend\ir-response.pdf

⁹ Determination of NaCl concentration: \\CDSESUB1\EVSPROD\nda206056\0002\m3\32-body-data\32p-drug-prod\piptazinjandnaclinjusp-injectable\32p2-pharm-dev\pharmaceutical-development-57.pdf

Table 5. Concentrations of the IV infusion solution after reconstitution of the proposed drug product

Strength	2.25 g		3.375 g		4.5 g	
	(50 mL Diluent) *		(50 mL Diluent) *		(100 mL Diluent) *	
Ingredients	mg/unit	Conc. of IV solution (mg/mL)	mg/unit	Conc. of IV solution (mg/mL)	mg/unit	Conc. of IV solution (mg/mL)
Piperacillin	2000	(b) (4)	3000	(b) (4)	4000	(b) (4)
Tazobactam	250	(b) (4)	375	(b) (4)	500	(b) (4)
EDTA	0.5	(b) (4)	0.75	(b) (4)	1	(b) (4)
Sodium Citrate Dihydrate	100	(b) (4)	150	(b) (4)	200	(b) (4)
Diluent	50 mL 0.45% NaCl		50 mL 0.3% NaCl		100 mL 0.45% NaCl	
* Diluent volume pre-packed in Duplex container chamber for constitution						

The approved label for the LD product, Zosyn®, recommends the use of various solutions for the initial reconstitution and secondary dilution prior to infusion ranging from Sterile Water for Injection to 0.9% Sodium Chloride. The recommended volume per dose is 50 mL to 150 mL¹⁰. The concentrations of the intravenous infusion solutions after constitution with 50 mL and 150 mL diluent are listed in Table 5.

Table 5. Concentrations of the intravenous infusion solution after constitution for the LD, Zosyn® for Injection

Strength	2.25 g		3.375 g		4.5 g	
	mg/unit	Conc. of IV solution*		mg/unit	Conc. of IV solution*	
		(mg/mL)			(mg/mL)	
Ingredients		50 mL Diluent	150 mL Diluent		50 mL Diluent	150 mL Diluent
Piperacillin	2000	(b) (4)	(b) (4)	3000	(b) (4)	(b) (4)
Tazobactam	250	(b) (4)	(b) (4)	375	(b) (4)	(b) (4)
EDTA	0.5	(b) (4)	(b) (4)	0.75	(b) (4)	(b) (4)
Sodium Citrate Dihydrate	100	(b) (4)	(b) (4)	150	(b) (4)	(b) (4)
Diluent	Allows for the use of various diluents ranging from Sterile Water for Injection to 0.9% Sodium Chloride					
*Recommended volume per dose of 50 mL to 150 mL as per LD drug product labelling6, section 2.5						

¹⁰LD prescribing insert: \\CDSESUB1\EVSPROD\nda206056\0008\m1\us\114-labeling\114c-list-drug-label\rld-prescribing-insert.pdf

The concentrations presented in Table 4 and Table 5 show that after dilution with the diluent in the proposed DUPLEX container or addition of the diluent per labeling instructions of the LD, Zosyn, infusion solutions with the same active ingredient concentrations can be produced (i.e. if 50 mL diluent is used for the 2.25 g or 100 mL diluent is used for the 4.5 mg strength, the infusion solution has a concentration of (b) (4) mg/mL Tazobactam and (b) (4) mg/mL Piperacillin or if 50 mL diluent is used for 3.375 g strength, the infusion solution has a concentration of (b) (4) mg/mL Tazobactam and (b) (4) mg/mL Piperacillin). However, the concentration of NaCl in the infusion solution is different between the proposed drug product and the LD, because the proposed drug product is diluted with 0.45% NaCl and the LD is diluted with water or 0.9% NaCl. Therefore, a biowaiver based on 21 CFR 320.22 (b)(1)(i)(ii) cannot be granted.

The NaCl concentration in the proposed drug product (0.45%) is within the range of the NaCl concentrations in the LD (0-0.9%). The differences in the NaCl concentrations do not affect the plasma concentrations of the two APIs, Piperacillin and Tazobactam. Therefore, the plasma concentrations of Piperacillin and Tazobactam after administration of the same dose of LD and the proposed drug product are expected to be the same. The Applicant has submitted sufficient information to support the bridge between the proposed drug product and the LD based on 21 CFR 320.24 (b)(6), thereby justifying reliance of this NDA on the LD without conducting a BA/BE study.

Overall Review Recommendation:

From a Biopharmaceutics perspective, NDA 206056 for Piperacillin and Tazobactam for Injection USP and Sodium Chloride Injection USP in the Duplex Container, 2.25 g, 3.375 g, and 4.5 g is adequate and recommended for **approval**.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
NDA 206056 (SDN03)	06/07/2024
NDA 206056 (SDN12)	11/20/2024

Highlight Key Issues from Last Cycle and Their Resolution:

- N/A, this is the first review cycle

Concise Description of Outstanding Issues:

- There are no outstanding issues from a Biopharmaceutics perspective.

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

BIOPHARMACEUTICS LIST OF INFORMATION REQUESTS

NA

Primary Biopharmaceutics Assessor's Name and Date: Haodan Yuan, Ph.D. 02/10/2024

Secondary Assessor Name and Date: Elsbeth Chikhale, Ph.D. 02/10/2024



Haodan
Yuan

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Elsbeth
Chikhale

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CHAPTER VII: MICROBIOLOGY

IQA ANDA Assessment Guide Reference

Product Information	
NDA Number	206056
Assessment Cycle Number	1
Drug Product Name / Strength	Piperacillin and Tazobactam for Injection USP and Sodium Chloride Injection USP/ 2.25 gram, 3.375 gram, and 4.5 gram
Route of Administration	Intravenous (IV)
Applicant Name	B. Braun Medical Inc.
Therapeutic Classification/ OND Division	Type 5- New Formulation or New Manufacturer/ CDER/OND/OID/DAI
Manufacturing Site	ACS DOBFAR S.p.A. Castellalto plant (ACSD9) Via Enzo Ferrari SNC Zona Industriale Villa Zaccheo 64020 Castellalto (TERAMO), Italy
Method of Sterilization	(b) (4)

Assessment Recommendation: Adequate

Assessment Summary:

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
Seq 0002 (1)	7 June 2024
Seq 0011 (12)	12 November 2024

Highlight Key Issues from Last Cycle and Their Resolution: N/A

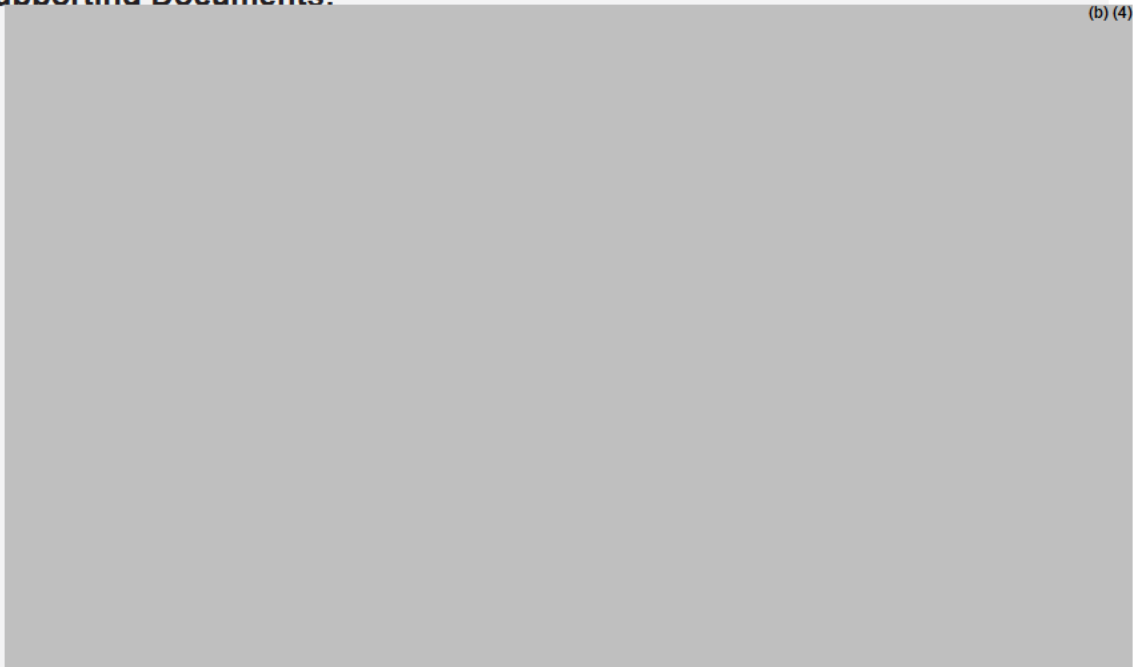
Remarks: The subject drug product is an injectable antibacterial combination consisting of Piperacillin Sodium and the β -Lactamase Inhibitor Tazobactam Sodium intended for intravenous administration for intra-abdominal infections in adult and pediatric patients 2 months of age and older. The finished drug

product consists of a sterile (b) (4) powder filled into one chamber and the diluent, sodium chloride injection USP, provided in the second chamber of the DUPLEX® (b) (4) container. The proposed product provides the end user with a ready-to-administer fixed dose of the combination drug after the unit is activated and the solution is constituted.

The submission is recommended for approval from the standpoint of product quality microbiology.

Concise Description of Outstanding Issues: N/A

Supporting Documents:



Select Number of Approved Comparability Protocols: 0

S DRUG SUBSTANCE

[REDACTED] (b) (4)

Letter of Authorization (LoA) for DMF # [REDACTED] (b) (4)

The applicant provided an LoA from [REDACTED] (b) (4) dated 8 February 2024, for DMF# [REDACTED] (b) (4) in regard to the Piperacillin and Tazobactam [REDACTED] (b) (4)

The manufacturing process for the sterile drug product was reviewed for sterility assurance and found inadequate, therefore the following deficiency was sent to the applicant on 22 October 2024.

DMF [REDACTED] (b) (4) has been reviewed for sterility assurance and found inadequate. The DMF holder will be notified.

Summary of DMF holder's response received 8 November 2024

(See Seq 0011, Section 1.11.1, pg. 2 of micro info amendment – 11/11/14)

The applicant states that the DMF [REDACTED] (b) (4) holder submitted a response to the FDA on October 24, 2024.

Assessment: Adequate

The manufacturing process for the sterile drug product was reviewed for sterility assurance and found adequate in Microbiology Review of DMF [REDACTED] (b) (4) ([REDACTED] (b) (4).docx), dated 21 January 2025.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

• **Description of drug product**

(See Section 3.2.P.1, description and composition of the drug product)

The finished drug product consists of sterile [REDACTED] (b) (4) Piperacillin and Tazobactam for Injection USP powder in one chamber and sterile Sodium Chloride Injection USP diluent solution in the other chamber so that the powder can be mixed and dissolved in the diluent in a closed and sterile System.

Three presentations are proposed:

- Piperacillin and Tazobactam for Injection USP 2.25 g in 0.45% Sodium Chloride Injection USP 50 mL
- Piperacillin and Tazobactam for Injection USP 3.375 g in 0.3% Sodium Chloride Injection USP 50 mL
- Piperacillin and Tazobactam for Injection USP 4.5 g in 0.45% Sodium Chloride Injection USP 100 mL

• **Drug product composition**

Powder Chamber (Piperacillin and Tazobactam (b) (4))

Component	mg/unit			Function
	2.25 g	3.375 g	4.5 g	
Piperacillin	2000	3000	4000	Active Pharmaceutical Ingredient
As Piperacillin Sodium	2085	3127	4170	
Tazobactam	250	375	500	Active Pharmaceutical Ingredient (Beta-Lactamase Inhibitor)
As Tazobactam Sodium	269	402	538	
Edetate Disodium Dihydrate (EDTA)	0.5	0.75	1	Inactive Ingredient - (b) (4)
Sodium Citrate Dihydrate	100	150	200	Inactive Ingredient - (b) (4)

Diluent Chamber

Component	mg/unit			Function
	2.25 g	3.375 g	4.5 g	
Sodium Chloride	225	150*	450	Inactive Ingredient - (b) (4)
Water for Injection	50	50	100	Inactive Ingredient - Diluent

* **Note:** (0.3% (w/v) Sodium Chloride Injection is used in this presentation while 0.45% (w/v) Sodium Chloride Injection is used for the other presentations.

• **Description of container closure system**

(See Section 3.2.P.7, *container closure system summary* and embedded documents)

The DUPLIFLEX® (b) (4) container is fabricated at B. Braun (b) (4) (b) (4)

Component	Description	Category of solution contact
(b) (4) container body	(b) (4)	(b) (4)
Peelable Foil Barrier for drug		(b) (4)

compartment	(b) (4)
Flanged Set Port	
Peelable foil for Set Port Cover	
Product Label	
Inks (b) (4)	
Ink (b) (4)	
Adhesive sticker	

The following figures were provided depicting the DUPLEX container:
50mL Container



Assessment: Adequate

The applicant provided an adequate description of the drug product composition and the container closure system.

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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/

DOROTA M MATECKA
03/27/2025 06:24:24 PM