CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217512Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

- **Application/Product Information**

NDA Number	217512
Applicant Name	Baxter Healthcare Corporation
Drug Product Name	Pantoprazole Sodium in 0.9% Sodium Chloride Injection
Dosage Form	Injection
Proposed Strength(s)	40 mg/100 mL (0.4 mg/mL) 40 mg/50 mL (0.8 mg/mL) 80 mg/100 mL (0.8 mg/mL) The strength of the drug product has been defined based on the active moiety pantoprazole. 40 mg of pantoprazole is equivalent to 45.1 mg of pantoprazole sodium.
NDA Classification	Type 5 – New Formulation or New Manufacturer
Route of Administration	Intravenous
Maximum Daily Dose	240 mg
Rx/OTC Dispensed	Rx
Proposed Indication	• Indicated for short-term treatment (7 to 10 days) of adult patients with gastroesophageal reflux disease (GERD) and a history of erosive esophagitis (EE). • Indicated for the treatment of pathological hypersecretory conditions including Zollinger-Ellison (ZE) Syndrome in adults,
Drug Product Description	Baxter Healthcare Corporation (Baxter) has submitted this 505(b)(2) new drug application for Pantoprazole Sodium in 0.9 % Sodium Chloride Injection, 40 mg/100 mL (0.4 mg/mL), 40 mg/50 mL (0.8 mg/mL), and 80 mg/100 mL (0.8 mg/mL) indicated for short-

	term treatment (7 to 10 days) of adult patients with gastroesophageal reflux disease (GERD) and a history of erosive esophagitis (EE) and for the treatment of pathological hypersecretory conditions including Zollinger-Ellison (ZE) Syndrome in adults. PROTONIX IV (pantoprazole sodium) for injection, 40 mg (NDA 020988) is used as the listed drug for this application. This drug product is a frozen, pre-mixed (ready to use), iso-osmotic, sterile, nonpyrogenic solution. intended for intravenous administration. The 40 mg/100 mL (0.4mg/mL) strength per 100mL quantitatively contains 40 mg of pantoprazole equivalent to 45.1 mg of pantoprazole sodium as the active ingredient, and 1 mg of edetate disodium, 155 mg of histidine, hydrochloric acid (for pH adjustment), 900 mg sodium chloride, sodium hydroxide (for pH adjustment (b) (4) as inactive ingredients. The 80 mg/100 mL (0.8 mg/mL) strength per 100mL quantitatively contains 80 mg of pantoprazole equivalent to 90.2 mg of pantoprazole sodium as the active ingredient, and 2 mg of edetate disodium, 155 mg of histidine, hydrochloric acid (for pH adjustment), 900 mg sodium chloride, sodium hydroxide (for pH adjustment (b) (4) as inactive ingredients. The qu of 40 mg/50 mL strength is similar to the 80 mg/100 mL strength in which each component is present in 50 mL half of the amount presented in 80 mg/100 mL. Pantoprazole Sodium in 0.9 % Sodium Chloride Injection is packaged and supplied in GALAXY plastic container (I.V. bag). This drug product should be stored frozen at -20°C (4°F) for up to 12 months of shelf-life protected from light. Thawed drug product can be stored refrigerated at 2°C – 8°C (36°F – 46°F) for up to 21 days protected from light. Also, thawed drug product can be stored at room temperature at 20°C – 25°C (66°F – 77°F) for up to 3 days.
Co-packaged product information	N/A
Device information	N/A

Storage Temperature/ Conditions	• Long-term (shelf-life) storage -20°C (4°F) for up to 12 months protected from light. • Thawed storage under refrigeration 2°C – 8°C (36°F – 46°F) for up to 21 days protected from light. • Room temperature storage 20°C – 25°C (66°F – 77°F) for u (b) (4)		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Friedrich Burnett, PhD	Lawrence Perez, PhD
	Drug Product/ Labeling	Caroline Strasinger, PhD	Hamid Shafiei, PhD
	Manufacturing	Dacie Bridge, PhD	Yan Zheng, PhD
	Biopharmaceutics	Assadollah Noory, PhD	Tapash Ghosh, PhD
	Microbiology	Catherine Gilbert, PhD	Yan Zheng, PhD
	Other (specify) Labeling	Caroline Strasinger, PhD	Julia Pinto, PhD
	RBPM	Megan Nguyen	
	ATL	Hamid Shafiei, PhD	
Consults	N/A		

2. Final Overall Recommendation - Approval

This application is recommended for approval with the expiration dating periods of 12 months when packaged in the proposed container closure and stored at the proposed long-term storage condition of -20°C (4°F).

The CMC-recommended PI labeling as well as container and carton labels revisions have been communicated to the applicant on January 2, 2024 and on December 15, 2023, respectively. The applicant has accepted all CMC-recommended revision and will submit the finalized PI labeling as well as container and carton labels to the application prior to the action date. Therefore, no additional labeling memorandum is needed for the approval of this application from the OPQ perspective.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

- The applicant of this 505(b)(2) new drug application has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance, pantoprazole sodium, and drug product, Pantoprazole Sodium in 0.9% Sodium Chloride Injection, 40 mg/100 mL, 40 mg/50 mL, and 80 mg/100mL.

- The Office of Pharmaceutical Manufacturing Assessment has made the overall recommendation of adequate for the facilities involved in this application.

- The CMC revisions on labels/labeling have been communicated to the applicant and the recommended CMC revisions have been accepted by the applicant.

- The applicant's request for categorical exclusion from preparation of environmental assessment has been found adequate and is granted.

Therefore, from the OPQ perspective this application is recommended for approval with an expiration dating period of 12 months.

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): Yes

5. Life-Cycle Considerations
Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments: None

Application Technical Lead Name and Date:

Hamid Shafiei, PhD
Senior Pharmaceutical Quality Assessor
Branch IV/DNDP II/ONDP/OPQ

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CHAPTER IV: LABELING

NDA Number	217512
Assessment Cycle Number	1
Drug Product Name	PANTOPRAZOLE SODIUM IN 0.9% SODIUM CHLORIDE INJECTION

Assessment Recommendation: Adequate

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Adequate	**Pending concurrence from Applicant (comments conveyed 02-JAN-2024)**
Patient Information	N/A	**N/A**
Instruction for Use (IFU)	N/A	**N/A**
Container Labels	Adequate	**Pending concurrence from Applicant (comments conveyed 15-DEC-2023)**
Carton Labeling	Adequate	**Pending concurrence from Applicant (comments conveyed 15-DEC-2023)**

Brief Description of Outstanding Issues:

The Labeling and Label of NDA 217512 **is ADEQUATE from the OPQ perspective, pending the Applicant's concurrence** with the Label (Container/Carton) comments conveyed on 15-DEC-2023 and the Labeling comments conveyed on 2-JAN-2024.

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
0001	17-AUG-2023	Carton and Container Labels
0001	17-AUG-2023	PI

1.0 PRESCRIBING INFORMATION[1]

Assessment of Product Quality Related Aspects of the 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]	Inadequate	**In the product title of the highlights, the (b) (4) should be removed. Everywhere else the full established name "PANTOPRAZOLE SODIUM IN 0.9% SODIUM CHLORIDE INJECTION" should be used. This was confirmed by OPPQ on 12/5/23.** Communicated to Applicant 2-JAN-24
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]	Inadequate	Need to include per mL amounts in parenthesis. Communicated to Applicant 2-JAN-24
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).[6]	Inadequate	Add pantoprazole after strength (mismatch is acceptable based on historical context) Communicated to Applicant 2-JAN-24
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]	Inadequate	Add single dose Communicated to Applicant 2-JAN-24

Assessment: *Inadequate*

All deficiencies were communicated to OND on 12-DEC-2023 and the Applicant on 2-JAN-2024. Once agreed to by the applicant, the labeling for Highlights is adequate.

[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>

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	Thaw frozen container at room temperature 20°C to 25°C (68°F to 77°F) or under refrigeration 2°C to 8°C (36°F to 46°F). Product should not be thawed by immersion in water baths or by microwave irradiation. Do not force thaw.
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food).	Adequate	No further dilution necessary Administer intravenously over a period of approximately 15 minutes

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

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

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For parenteral products: include statement: *"Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*[11]	Adequate	Inspect thawed Pantoprazole Sodium in Sodium Chloride solution visually for particulate matter prior to and during administration. Thawed solution is expected to range from colorless to yellow over time.
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).	Inadequate	(b) (4) (b) (4) Communicated to Applicant 2-JAN-24
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.*[x]*"* with x numerical citation to "OSHA Hazardous Drugs."	N/A	

Assessment: *Inadequate*

All deficiencies were communicated to OND on 12-DEC-2023 and to the Applicant on 2-JAN-2024. Once agreed to by the Applicant, the labeling for Dosage and Administration is adequate.

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

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

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	Injection
Strength(s) in metric system	Adequate	40 mg/100 mL (0.4 mg/mL)
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). No equivalency statement.	Inadequate	"of pantoprazole" however (b) (4) should be removed Communicated to Applicant 2-JAN-24
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.	Inadequate	Add "thawed solutions are clear and range from colorless to yellow" Communicated to Applicant 2-JAN-24
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	Inadequate	Edited for clarity and simplification Communicated to Applicant 2-JAN-24

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)
imaging bulk package (see USP <659>).		

Assessment: *Inadequate*

All deficiencies were communicated to OND on 12-DEC-2023 and the Applicant on 2-JAN-2024. Once agreed to by the Applicant, the labeling for Dosage Forms and Strength is adequate.

1.2.3 Section 11 (DESCRIPTION)[14]

(b) (4)

[redacted]

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

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)[15] [§ 201.57(c)(12)(i)(A)].	Adequate	Pantoprazole Sodium in Sodium Chloride Injection
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Adequate	Injection; intravenous
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)" [§ 201.57(c)(12)(i)(C)].	Adequate	
List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order.[16] Avoid 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	Adequate	Edited for clarity Communicated to Applicant 2-JAN-24

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

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

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].		
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	PPI Inhibitor
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)].	Inadequate	Information matches Protonix IV but is unnecessary Communicated to Applicant 2-JAN-24
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").	Inadequate	Remove GALAXY Communicated to Applicant 2-JAN-24
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	N/A	

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

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

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

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

Assessment: *Inadequate*

All deficiencies were communicated to OND on 12-DEC-2023 and the Applicant on 2-JAN-2024. Once agreed to by the Applicant, the labeling for Description is adequate.

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

(*copy of proposed text*)

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	Injection
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.	Inadequate	Add of pantoprazole to strength presentation and revise table for clarity Communicated to Applicant 2-JAN-24
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Inadequate	Revise table for clarity Communicated to Applicant 2-JAN-24
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	

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

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package (see USP <659>).	Adequate	
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	Protect from light when frozen. Handle frozen product with care.
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).	Adequate	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*[21]	N/A	

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

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Include information about child-resistant packaging[22] (if chosen by manufacturer).	N/A	

Assessment: *Inadequate*

All deficiencies were communicated to OND on 12-DEC-2023 and the Applicant on 2-JAN-2024. Once agreed to by the Applicant, the labeling for How Supplied and Storage is adequate.

1.2.5 Other Sections of Labeling

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

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

1.2.6 Manufacturing Information After Section 17 (for drug products)[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	**Baxter Healthcare Corporation** Deerfield, IL 60015 USA

Assessment: *Adequate*

[22] Guidance: *Child-Resistant Packaging Statements in Drug Product Labeling* (August 2019)
[23] § 201.1(h)(5) and 201.1(i); Labeling Review Tool (March 2022, page 74)

2.0 PATIENT LABELING

Not provided for this NDA

3.0 CONTAINER AND CARTON LABELING[24]

Refer to the submission for all carton and container labels

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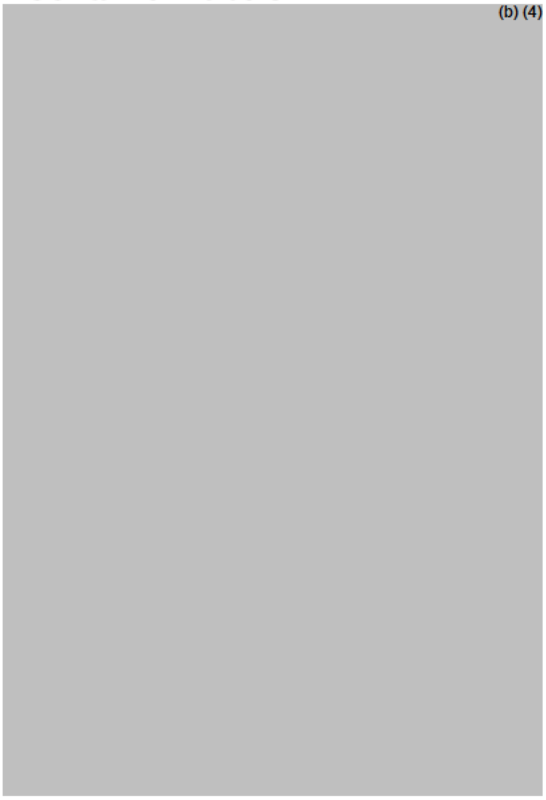
Example container label provided below for quick reference

3.1 Container Labels[25]



[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.

3.2 Carton Labeling

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[26], (font size and prominence) [§ 201.10(g)(2)].	Adequate	Yes	
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)].[27]	Adequate	Yes	
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Adequate	Yes	DEMPA has requested the removal of the wor (b) (4) OPQ has no objection.
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	Yes	
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)].[28]	Inadequate	No	See packaging type comment below
"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	Location on container present. Position is described on carton (V.S.C). "Baxter confirms that the V.S.C. label for commercial product will contain a 2-dimensional data matrix barcode, and data in human readable form. The human readable product identifiers consist of the NDC number (embedded in

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

[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")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
			the GTIN number), serial number, expiration date, and lot number as required by the Drug Supply Chain Security Act. The machine readable and human readable expiration date format will be YYMMDD and YYYY-MM-DD, respectively.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	Inadequate	Yes	Revise to read: "Store frozen at or below -20°C (-4°F). Thaw at room temperature 20°C to 25°C (68°F to 77°F) or under refrigeration 2°C to 8°C (36°F to 46°F)."
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>).	Inadequate	No	Replace "GALAXY" with "flexible" in container description (e.g.100 mL single-dose flexible container) Revise Carton to read: "6 x 50 mL single-dose flexible containers" or "12 x 100 mL single-dose flexible containers" (DMEPA has recommended the 6 x 50 mL presentation)
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)].	Inadequate	Yes	Remov (b) (4) from all inactive ingredients See additional comment below
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)].	Inadequate	Yes	Adjust quantitative amounts to parenthetical presentation, and add "and sodium hydroxide and/or hydrochloric acid to adjust pH" e.g.,

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)
			*Each 100 mL contains: 40 mg of pantoprazole (equivalent to 45.1 mg of pantoprazole sodium), edetate disodium (1 mg), histidine (155 mg), sodium chloride (900 mg), and sodium hydroxide and/or hydrochloric acid to adjust pH
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)].[29]	Adequate	Yes	DMEPA has requested a relocation of barcode. OPQ has no objection to this request.
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	Yes	
"Keep out of reach of children" statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)].	N/A	Choose an item.	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	Choose an item.	

[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")	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)
No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>).	N/A	Choose an item.	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	Choose an item.	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.[30]	N/A	Choose an item.	
And others if space is available.	Adequate	Yes	Refrigerated Storage: Use within 21 days Room Temperature Storage: Use within 48 hours

Assessment of Carton Labels and Container Labeling: *Inadequate*

In collaboration with DMEPA comments, the OPQ deficiencies identified above were communicated to the Applicant on 15-DEC-2023. Once agreed to by the Applicant, the label (carton and container) are adequate.

[30] USP General Notices 3.20 Indicating Conformance

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

OPQ Label (Carton and Container) comments were sent to the Applicant in the Communication dated 15-DEC-2023. OPQ Labeling comments were sent to the Applicant in the Communication dated 2-JAN-2024.

The Labeling and Label of NDA 217512 is ADEQUATE from the OPQ perspective, pending the Applicant's concurrence with the above two Label/Labeling communications.

Primary Labeling Assessor Name and Date:

Caroline Strasinger, PhD
CDER/OPQ/ONDP/DNDP2
01/08/2024

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

Julia Pinto PhD
CDER/OPQ/ONDP
01/08/2024

Caroline Strasinger

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Julia Pinto

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CHAPTER VI: BIOPHARMACEUTICS

Product Information	
NDA Number	217512
Assessment Cycle Number	1
Drug Product Name/ Strength	Pantoprazole Sodium in 0.9% Sodium Chloride Injection (40 mg/100 mL, 40 mg/50 mL, and 80 mg/100 mL)
Route of Administration	Intravenous
Applicant Name	Baxter Healthcare Corporation
Therapeutic Classification/ OND Division	
RLD/RS Number	020988
Proposed Indication	Short-term treatment (7 to 10 days) of gastroesophageal reflux disease (GERD) associated with a history of Erosive Esophagitis (EE) in adults.

Assessment Recommendation: **Adequate**

Assessment Summary: Pantoprazole Sodium in 0.9% Sodium Chloride Injection solution is a frozen, pre-mixed (ready to use), iso-osmotic, sterile, nonpyrogenic solution supplied in a flexible GALAXY plastic container (I.V. bag) intended for intravenous administration. The drug product is stored frozen for intravenous administration after thawing at room temperature or under refrigeration. The listed drug (LD) is Protonix IV, NDA 020988. Baxter's proposed drug product is qualitatively and quantitatively the same as the LD except for the dilution fluids. The Applicant provided comparative physiochemical properties for their proposed product and the listed drug (LD) including the pH and osmolality. The pHs of the final products are similar. Thought the osmolality of the reference product is little lower compared to the proposed product, both are within acceptable range. The difference in formulation of the proposed product and the LD is the histidine which is used as a (b) (4) and hydrochloric acid which is used as a pH adjustor; neither one of these agents can alter the bioavailability of Pantoprazole. The scientific bridge between the proposed product and the listed drug is established.

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
Original Submission	08/17/2023

Highlight Key Issues from Last Cycle and Their Resolution: This is a first cycle review.

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

B.1 BCS DESIGNATION

Assessment: The Applicant did not provide a BCS classification for their IV product.

Solubility: Solubility in various pH buffer solutions at about 25°C±2°C are shown below:

Sr. No.	pH	Result
1	pH 1.2 Solution (Hydrochloric acid buffer)	10 mg/100 mL
2	pH 3.0 Solution (Acid phthalate buffer)	10 mg/100 mL
3	pH 4.5 Solution (Acetate buffer)	10 mg/100 mL
4	pH 6.8 Solution (Phosphate buffer)	10 mg/100 mL
5	pH 7.2 Solution (Phosphate buffer)	10 mg/100 mL
6	pH 8.0 Solution (Phosphate buffer)	10 mg/100 mL

Permeability: No Permeability data was provided.

Dissolution: The product is a solution for IV administration; however, the following table shows dissolution of pantoprazole sodium in mixing tank.

Mixing Time[a] (Minutes)	Visual Inspection Result	Pantoprazole Concentration (mg/100 mL)	% Difference[b]
10	Clear without particles	(b) (4)	
20	Clear without particles		
30	Clear without particles		
40	Clear without particles		
50	Clear without particles		
60	Clear without particles		
Dissolution Limits at (b) (4)% Batch Volume (b) (4) mL)		(b) (4) mg/L	

N/A = Not Applicable

[a] Elapsed time is from complete addition of Pantoprazole Sodium to mix tank until time of sample collection.

[b] % difference = percent difference from previous concentration.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: The product is a solution for IV administration; therefore, no dissolution data was provided.

B.3 FORMULATIONS

The Applicant provided qualitative comparison of Baxter proposed premix product (40 mg/100mL) to Protonix I.V. shown below.

Attribute	Protonix I.V (Listed Drug Product)	Baxter (Proposed Premix Product)
Product	Protonix IV	Pantoprazole Sodium in 0.9% Sodium Chloride Injection (40 mg/100 mL)
Concentration	0.4 mg/mL (upon reconstitution and further dilution)	Same
Dosage Form	Injectable	Same
Route of Administration	Intravenous infusion	Same
Presentation (How Supplied)	Lyophilized powder in a glass vial	Frozen premix solution in a Galaxy container
Reconstitution required	Yes	No
Reconstituted with	10 mL of 0.9% Sodium Chloride	N/A
Dilution required prior to administration	Yes	No
Diluent	Further diluted with: 100 mL of 5% Dextrose Injection, USP, 0.9% Sodium Chloride Injection, USP, or Lactated Ringer's Injection, USP	Not applicable as premixed with 0.9% Sodium Chloride
Volume	10 mL upon reconstitution or 100 mL upon reconstitution and further dilution	100 mL
Container Closure System	Single-dose Glass vial	Single-use Galaxy plastic container
pH (reconstituted solution)	pH range 9.0 to 10.5	N/A
pH (further diluted solution / Premix)	Not available in the listed drug product insert	9.0 to 10.5
Dosing Regimen and Indication	Gastroesophageal Reflux Disease Associated with a History of Erosive Esophagitis – 40 mg once daily And Pathological Hypersecretion Including Zollinger-Ellison Syndrome – 80 mg every 12 hours or 80 mg every 8 hours	Same

The difference in the formulation components between Baxter proposed premix product and LD as prepared for I.V. administration is shown below.

Parameter	Protonix (after reconstitution and Dilution)	Pantoprazole in 0.9% Sodium Chloride (Baxter proposed premix products)	Justification
(b) (4)	None	1.55 mg/mL (10 mM) Histidine	Histidine was used as a (b) (4) to (b) (4) (b) (4) It is an essential amino acid that is commonly used in parenteral nutrition product.
pH Adjusters	Sodium Hydroxide	Sodium Hydroxide and/ or Hydrochloric Acid	Hydrochloric Acid is included as a pH adjuster that is only used when needed and is a commonly used excipient in a large number of pharmaceutical products for this purpose.

B. 4 BRIDGING REQUEST

The Applicant provided comparative physicochemical characteristics of their proposed product and the listed drug (LD), shown below.

Qualitative comparison of Baxter proposed premix (40 mg/ 50 mL and 80 mg/ 100 mL) to Protonix IV

Attribute	Protonix I.V	Baxter (Proposed Premix Products)	
Product	Protonix IV	Pantoprazole Sodium in 0.9% Sodium Chloride Injection (40 mg/ 50 mL)	Pantoprazole Sodium in 0.9% Sodium Chloride Injection (80 mg/ 100 mL)
Concentration	0.8 mg/mL (upon reconstitution and further dilution)	Same	Same
Dosage Form	Injectable	Same	Same
Route of Administration	Intravenous infusion	Same	Same
Presentation	Lyophilized powder in a glass vial	Frozen premix solution in a Galaxy container	Frozen premix solution in a Galaxy container
Reconstitution required	Yes	No	No
Reconstituted with	Each vial: 10 mL of 0.9% Sodium Chloride	N/A	N/A
Dilution required prior to administration	Yes	No	No
Diluent	Contents of the 2 vials further diluted with: 80 mL of 5% Dextrose Injection, USP, 0.9% Sodium Chloride Injection, USP, or Lactated Ringer's Injection, USP	Not applicable as premixed with 0.9% Sodium Chloride to 0.8 mg/mL	Not applicable as premixed with 0.9% Sodium Chloride to 0.8 mg/mL
Volume	10 mL upon reconstitution or 100 mL upon reconstitution and further dilution	50 mL	100 mL
Container Closure System	Single-dose Glass vial	Single-use Galaxy plastic container	Single-use Galaxy plastic container
pH (reconstituted solution)	pH range 9.0 to 10.5	N/A	N/A
pH (further diluted solution / Premix)	Not available in the listed drug product insert	9.0 – 10.5	9.0 – 10.5
Dosing Regimen and Indication	Gastroesophageal Reflux Disease Associated with a History of Erosive Esophagitis – 40 mg once daily And Pathological Hypersecretion Including Zollinger-Ellison Syndrome – 80 mg every 12 hours or 80 mg every 8 hours	Same	

pH of Baxter pantoprazole sodium in 0.9% sodium chloride injection and Protonix I.V. (3 batches for each strength), shown below.

Product		40 mg/ 100 mL			80 mg/ 100 mL			40 mg/ 50 mL		
Baxter	Lot #	2022040	2022041	2022042	2022087			2022043	2022044	2022045
	pH	9.7	9.8	9.8	9.7			9.7	9.8	9.9
		9.7	9.8	9.8	9.7			9.7	9.8	9.9
		9.6	9.7	9.8	9.6			9.7	9.8	9.9
Protonix I.V.	Lot #	486256	487400	488975	486256	487400	488975	486256	487400	488975
	pH	9.2	9.1	9.1	9.4	9.4	9.4	9.3	9.4	9.3
		9.2	9.2	9.2	9.4	9.4	9.4	9.4	9.4	9.3
		9.2	9.2	9.1	9.5	9.3	9.4	9.3	9.3	9.2

Osmolality of Baxter pantoprazole sodium in 0.9% sodium chloride injection and Protonix I.V. (3 batches from each strength), shown below.

Product		40 mg/ 100 mL			80 mg/ 100 mL			40 mg/ 50 mL		
Baxter	Lot #	2022040	2022041	2022042	2022087			2022043	2022044	2022045
	Osmolality	302	303	302	308			303	308	305
	(mOsm/Kg)	303	303	302	309			305	307	305
		304	303	302	309			305	308	305
Protonix I.V.	Lot #	486256	487400	488975	486256	487400	488975	486256	487400	488975
	Osmolality	281	282	282	284	286	284	288	292	286
	(mOsm/Kg)	280	281	281	284	286	283	286	289	287
		280	282	280	283	285	282	286	290	286

No BA/BE, efficacy, or safety studies were conducted for this NDA. The Applicant submitted its justification to bridge the proposed drug product to the LD (NDA 022023 Protonix IV for injection) and requested a waiver of in-vivo bioavailability studies pursuant to 21 CFR 320.24(b)(6). The applicant's scientific bridge between the LD and the proposed drug product is based on:

1. Qualitative and quantitative composition of the formulations for the proposed drug product and the LD

2. Comparative physicochemical data for at least three production lots of the proposed drug product and three lots of the LD

3. Justification that the use of histidine as a (b) (4) and sodium hydroxide and/or hydrochloric acid as pH adjusters in the proposed product, as opposed to use of only sodium hydroxide in the LD, would not affect product quality and in vivo drug disposition.

The difference in formulation of the proposed product and the LD is the histidine which is used as (b) (4) and hydrochloric acid which is used as a pH adjustor.

Histidine is an endogenous essential amino acid that has several roles in normal body functions. It is (b) (4) in several drug products, and it is listed on the FDA Inactive Ingredient Database as a component of formulations administered intravenously. It is also routinely delivered intravenously as part of the amino acid component of parenteral nutrition in doses that far exceed the levels found in Pantoprazole Sodium in 0.9% Sodium chloride. As such, its presence in the formulation will not impact the safety of pantoprazole for the intended indications. Further, differences in pH adjustor hydrochloric acid (also commonly used in many pharmaceutical products) are not expected to impact the in vivo performance of pantoprazole. In summary, the proposed Pantoprazole Sodium in 0.9% Sodium Chloride frozen premix product should be bioequivalent to the LD, given the compositional similarity, physicochemical comparability, similarities in the clinical use for administration as an intravenous infusion, and recognizing the linear pharmacokinetics of pantoprazole as demonstrated in the clinical literature and by the prescribing information. Therefore, the proposed Pantoprazole Sodium in 0.9% Sodium Chloride frozen premix product should be bioequivalent to the LD and the applicant's scientific bridge between the LD and the proposed drug product is established from Biopharmaceutics perspective.

Assessment: Adequate

Post-Approval Commitments

Assessment: None

Links to Data:

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Primary Biopharmaceutics Assessor's Name and Date:
Assadollah Noory, Ph. D.

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

Tapash Ghosh, Ph. D.

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Assadollah Noory

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Tapash Ghosh

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CHAPTER VII: MICROBIOLOGY

For more details about the items in this template, please see Chapter VII (Microbiology) of the NDA IQA Guide (OPQ-ALL-WI-0006)

Product Information	
NDA Number	217512
Assessment Cycle Number	01
Drug Product Name/ Strength	Pantoprazole Sodium in 0.9% Sodium Chloride Injection [0.4 mg/mL (100 mL) and 0.8 mg/mL (50 mL, 100 mL)]
Route of Administration	IV injection
Applicant Name	Baxter Healthcare Corporation
Therapeutic Classification/ OND Division	Division of Gastroenterology
Manufacturing Site	Baxter Healthcare Corporation 25212 W Illinois Route 120, Round Lake, IL 60073 FEI: 1416980
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary (b) (4)

(b) (4)

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
Original (0001)	**08/17/2023**
IR Response (0005)	**12/07/2023**

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

Remarks: The applicant stated that this is a drug shortage product, however at the time of the filing review the product was no longer on shortage.

Concise Description of Outstanding Issues *(list bullet points with key information and update as needed)*: N/A

Supporting Documents:

- (b) (4)

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –** Pantoprazole Sodium in 0.9% Sodium Chloride Injection (40 mg/100 mL, 40 mg/50 mL, 80 mg/100 mL), is a sterile, pyrogen-free, clear colorless to yellow solution indicated for the treatment of GERD and pathological hypersecretion. It is administered via IV infusion.
- **Drug product composition –**

Ingredient	Content per mL		Function
	0.4 mg/mL	0.8 mg/mL	
Pantoprazole Sodium, USP	0.4 mg/mL	0.8 mg/mL	API
Sodium chloride, USP	9.0 mg/mL	9.0 mg/mL	(b) (4)
EDTA, USP	0.01 mg/mL	0.02 mg/mL	
Histidine, USP	1.55 mg/mL	1.55 mg/mL	
NaOH, NF	q.s.	q.s.	pH adjuster
HCl, NA	q.s.	q.s.	pH adjuster
(b) (4)			

- **Description of container closure system –**

Component	Packaging	Description (Gland material code)	Manufacturer
Bag	Primary	50 mL and 100 mL single-port PL2040 Plastic (GALAXY) bags	Baxter Healthcare Corporation
Port	Primary	(b) (4)	

The GALAXY bag is an IV bag with a single port.

Assessment: *Adequate*

The applicant has adequately described the drug product composition and the container closure system designed to maintain product sterility.

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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