CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216686Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	216686 (Resubmission)
Applicant Name	Spes Pharmaceuticals, Inc.
Drug Product Name	FOCINVEZ® (fosaprepitant injection)
Dosage Form.	Injection
Proposed Strength(s)	150 mg/50 mL (3 mg/mL)
Route of Administration	Intravenous
Maximum Daily Dose	150 mg
Rx/OTC Dispensed	Rx
Proposed Indication	Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high dose cisplatin in adults and pediatric patients 6 months of age and older.
Drug Product Description	FOCINVEZ® (fosaprepitant injection), 150 mg/50 mL (3 mg/mL) is a sterile, ready-to-use, clear and colorless solution formulation containing fosaprepitant dimeglumine, a prodrug of aprepitant, a substance P/neurokinin-1 (NK1) receptor antagonist, an antiemetic agent. It is intended for prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high dose cisplatin in adults and pediatric patients 6 months of age and older. The drug product is packaged as 50 mL of solution in a single-use vial each containing 150 mg of fosaprepitant equivalent to 245.3 mg of fosaprepitant dimeglumine salt as the active ingredient and the following inactive ingredients: Betadex sulfobutyl ether sodium (8 g), edetate disodium (5.4 mg), sodium hydroxide (for pH adjustment) in water for injection. Excipients used in the composition of the drug product are all compendial materials.

	The 50-mL container closure consists of [redacted] glass vial and the 20 mm [redacted] rubber stopper [redacted] sealed with a 20 mm aluminum seal with a red [redacted] flip-off cap. This drug product should be stored at refrigerated at 2°C to 8°C (36°F to 46°F).with an expiration dating period of 24 months. This drug product can be kept in original carton at room temperature 20°C to 25°C (68°F to 77°F) for up to 90 days. Sufficient stability data supporting the proposed shelf-life and storage condition have been submitted to the application. For additional information refer to the original IQA dated September 30, 2022.		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	This drug product is stored at refrigerated temperature conditions (2° to 8°C) with a proposed shelf life of 24 months. The drug product can be kept at room temperature for up to 90 days (3 months) after being removed from the refrigerator.		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Sharon Kelly, Ph.D.	Lawrence Perez, Ph.D.
	Drug Product/ Labeling	Zhengfang Ge, Ph.D.	Nina Ni, Ph.D.
	Manufacturing	Catherine Gilbert, Ph.D.	Yan Zheng, Ph.D.
	Biopharmaceutics	Leah Falade, Ph.D.	Tapash Ghosh, Ph.D.
	Microbiology	Catherine Gilbert, Ph.D.	Yan Zheng, Ph.D.

	Other (specify):	.N/A	N/A
	RBPM	Megan Nguyen, Pharm.D.	
	ATL	Hamid Shafiei, Ph.D..	
Consults	N/A		

`

2. Final Overall Recommendation - *Approval*

Spes Pharmaceuticals, Inc. originally submitted this 505(b)(2) New Drug Application for FOCINVEZ® (fosaprepitant injection), 150 mg/5 mL intended for prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high dose cisplatin in adults and pediatric patients 6 months of age and older on December 23, 2021.

This application was reviewed and received a complete response (CR) due to inadequate manufacturing facilities on October 19, 2022 (refer to original IQA dated September 30, 2022). This application was resubmitted on February 28, 2023. This resubmission included updates to manufacturing section of this NDA including the facilities. The manufacturing updates have been reviewed and the manufacturing facilities involved in this application have now been found to be adequate. Therefore, this application is now recommended for approval from the OPQ perspective with expiration dating period of 24 months.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:
This resubmission only included updates to manufacturing section of this NDA.

- The applicant of this 505(b)(2) new drug application has provided sufficient information that assures the identity, strength, purity, and quality of the drug substance, fosaprepitant and the drug product, FOCINVEZ® (fosaprepitant injection), 150 mg/50 mL (3 mg/mL).

- In this review cycle, the Office of Pharmaceutical Manufacturing Assessment has made the overall recommendation of adequate for the facilities involved in this application.
- The CMC labeling/label comments/concerns were satisfactorily addressed during the first review cycle
- The applicant's request for categorical exclusion from preparation of environmental assessment was found adequate in the first review cycle and is granted.

Therefore, from the OPQ perspective this application is recommended for approval with an expiration dating period of 24 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: None

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments: None

Hamid Shafiei

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Yan Zheng

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/s/

HAMID R SHAFIEI
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RECOMMENDATION

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

NDA 216686

Assessment 1

Drug Product Name	FOCINVEZ (fosaprepitant injection), 150 mg/50 mL (3 mg/mL)
Dosage Form	Injection
Strength	150 mg/50 mL (3 mg/mL)
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Spes Pharmaceuticals Inc. (SPES)
US agent, if applicable	NA

Submission(s) Assessed	Document Date	Discipline(s) Affected
Submission, eCTD SN 0000	12/23/2021	DS, DP, OPMA, labeling, and micro
Amendment, SN 0001	01/21/2022	Labeling
Amendment, SN 0002	02/01/2022	Labeling
Amendment, SN 0004	02/09/2022	DP, OPMA, micro
Amendment, SN 0005	03/16/2022	DP, OPMA, micro
Amendment, SN 0006	03/28/2022	Biopharmaceutics, OPMA, micro
Amendment, SN 0007	04/28/2022	DP, OPMA
Amendment, SN 0008	05/24/2022	DP
Amendment, SN 0009	07/18/2022	DP, OPMA
Amendment, SN 0010	07/28/2022	DP, OPMA, micro
Amendment, SN 0012	09/12/2022	Labeling

QUALITY ASSESSMENT DATA SHEET

For more details about the items in this template, please see the Quality Assessment Data Sheet chapter of the NDA IQA Guide

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Adequate	07/20/2022	Adequate to support NDA
	III			Not reviewed	N/A	Sufficient information provided in NDA
	III			Not Reviewed	N/A	Sufficient information provided in NDA

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

Document	Application Number	Description
IND	140555	IND to conduct clinical studies
NDA	22023, 21549, & 207865	Listed drugs

2. CONSULTS

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

NDA Executive Summary

1. Application/Product Information

NDA Number.	NDA 216686
Applicant Name	Spes Pharmaceuticals Inc. (SPES)
Drug Product Name	FOCINVEZ (fosaprepitant injection), 150 mg/50 mL (3 mg/mL)
Dosage Form.	Injection
Proposed Strength(s)	150 mg/50 mL (3 mg/mL)
Route of Administration	Intravenous
Maximum Daily Dose	150 mg
Rx/OTC Dispensed	Rx
Proposed Indication	For the treatment of adult and pediatric patients 6 months of age and older for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin; and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).
Drug Product Description	Fosaprepitant injection, 3 mg/mL is a sterile solution of fosaprepitant that is ready for administration without further dilution. Each single-use 50 mL vial contains 150 mg of fosaprepitant (equivalent to 245.3 mg of fosaprepitant dimeglumine salt) and the following excipient: betadex sulfobuty ether sodium (SBEβCD), USP, edetate disodium, USP, and water for injection (WFI), USP. Sodium hydroxide, NF (b) (4) (b) (4) may be used for pH adjustment The 50 mL (b) (4) glass vial and the 20 mm (b) (4) rubber stopper (b) (4) are the primary package components. Each container is sealed with a 20 mm aluminum seal with a red (b) (4) flip-off cap.

Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	The drug product is stored at the refrigeration temperature condition (2º to 8ºC) with a proposed shelf-life of 24 months. The drug product can be kept at room temperature for up to 90-days (3-months) after being removed from the refrigerator.		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Sharon Kelly	Lawrence Perez
	Drug Product/ Labeling	Zhengfang Ge	Nina Ni
	Manufacturing	Catherine Gilbert	Yan Zheng
	Biopharmaceutics	Leah Falade	Tapash Ghosh
	Microbiology	Catherine Gilbert	Yan Zheng
	Other (specify):	N/A	N/A
	RBPM	Melinda Bauerlien	
	ATL	Nina Ni	
Consults	N/A		

*: In the Amendment SN 0010, dated 07/28/2022, (b) (4) Refer to the DP addendum review for details.

2. Final Overall Recommendation - Complete Response

3. Deficiencies

The drug product is manufactured and tested at two Pharmaceutics International Inc. (PII) facilities (FEI 3006503102 and FEI 1000513101, respectively). The cGMP inspection history review showed that both PII facilities have an OAI finding as of 10/2020 and a pOAI finding as of 09/2021. The pOAIs were

downgraded to VAI in 02/2022. A follow up cGMP inspection was begun for both sites in 05/2022. However, the inspections were paused due to facility shutdowns and could not be completed by the end of this review cycle. Thus, based on OPMA and ORA evaluations, a Withhold is recommended for both facilities. Satisfactory resolution of the facility deficiencies is required before this application may be approved.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

OPQ recommends COMPLETE RESPONSE of NDA 216686 for commercialization of fosaprepitant injection, 150 mg/50 mL (3 mg/mL). The applicant has not provided adequate information on the proposed drug product to ensure the identity, strength, purity, and quality of the proposed product. The overall manufacturing inspection recommendation is WITHHOLD for the facilities associated with this application: Pharmaceutics International, Inc. (FEI 3006503102 and FEI 1000513101, respective). The proposed labeling and labels have adequate information to meet the regulatory requirements.

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	**-**	**Inadequate**
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: N/A

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

Additional Lifecycle Comments: N/A

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(b) (4)

R REGIONAL INFORMATION

Environmental Assessment

The applicant, Spes Pharmaceuticals Inc., claims a categorical exclusion from the requirement of preparing and submitting Environmental Assessment (EA) as provided for fosaprepitant in 21 CFR 25.31(a).

The applicant explains that under 21 CFR 25.31(a), a categorical exclusion from the requirement to prepare an EA or an Environmental Impact Statement (EIS) is available for an agency action on NDA, ANDA, BLA, or a supplement to such applications, or actions on OTC monograph, if the action does not increase the use of the active moiety. The applicant states that per the FDA's current electronic listing of Approved Drug Products with Therapeutic Equivalence Evaluations (The Orange Book), there are currently 32 approved products marketed containing aprepitant as the active moiety, of which 12 are oral capsule and suspension products and 20 are parenteral products.

Once approved, use of the proposed drug product would likely displace use of one or multiple of the currently marketed products, and thus would not increase the use of the active moiety in the environment.

The applicant states that it will adhere to all Federal, State and Local environmental laws. In addition, as required by 21 CFR 25.21, the applicant states that no extraordinary circumstances exist which would preclude the categorical exclusion.

Assessment: Adequate

Methods Validation or Verification Package

Assessment: ***Adequate***

See review for Analytical Methods in section P.5.

Comparability Protocols

Assessment:

N/A

Post-Approval Commitments

Assessment:

N/A

Lifecycle Management Considerations

N/A

DRUG PRODUCT LIST OF DEFICIENCIES

None

Primary Drug Product Assessor Name and Date:

Zhengfang Ge, Ph. D.
Reviewer, BRANCH IV/DIVISION II
OFFICE OF NEW DRUG PRODUCT

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

Nina Ni, Ph. D.
SPQA, BRANCH IV/DIVISION II
OFFICE OF NEW DRUG PRODUCT

Zhengfang Ge

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Nina Ni

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Memorandum DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: **July 29, 2022**

From: **Zhengfang Ge, Ph.D.**
Reviewer, Branch IV/ Division II/ONDP

Through: **Nina Ni, Ph.D.**
SPQA, Branch IV/ Division II/ONDP

To: **Drug Product Quality Review #1 of NDA 216686**

Subject: **Revised Composition/Components in Amendment 0010 Dated 27-July-2022**

The applicant in this amendment (b) (4) in the Components/Composition Tables in the Sections 2.3.P.1 and 3.2.P.1 Description and Composition of the Drug Product to be consistent with the Batch Formula in the Section 3.2.P.3.2 (b) (4) in the manufacture process. The revised Components/Composition provided in the **Attachment** is adequate.

Recommendation:

This NDA remains recommended for approval from the drug product quality perspective.

Attachment:

Table 1: Composition of Fosaprepitant Injection, 150 mg/50 mL (3 mg/mL)

Ingredient	Quality Standard	Amount per Vial (mg)	Concentration	Function
Fosaprepitant	In-House	150 mg*	3 mg/mL	Active Ingredient
Edetate Disodium	NF	5.4 mg	0.108 mg/mL	(b) (4)
Betadex Sulfobuty Ether Sodium	USP	8 gram	160 mg/mL	
Sodium Hydroxide	USP/NF	(b) (4)	§	pH Adjusting Agent
Water for Injection	USP		NA	(b) (4)
(b) (4)				

* Fosaprepitant used in the drug product formulation is a fosaprepitant dimeglumine salt form. 150 mg of fosaprepitant is equivalent to 245.3 mg of fosaprepitant dimeglumine.

§ Sodium hydroxide solution (1N) may be used for pH adjustment.

Zhengfang Ge

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Nina Ni

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

The Prescribing Information is deemed ADEQUATE with minor editorial changes in the prescribing information that were implemented in the final labeling in the SharePoint which will be conveyed to the applicant.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	FOCINVEZ	**Adequate**
Established name(s)	FOCINVEZ (fosaprepitant injection) for intravenous use	**Adequate** - injection in the parathesis to be a part of established name, consistent with the c/c label. The applicant is aware that including dosage form in the parenthesis implies that FOCINVEZ is available only in an injection
Route(s) of administration	Injection, for intravenous infusion	**Adequate**
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Injection: 150 mg/50 mL (3 mg/mL) of fosaprepitant, in a single-dose vial. (3)	**Adequate** - The applicant updated this section per Agency's recommendation
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	single-dose vial	**Adequate**

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	See proposed Section "2.3 Preparation of Focinvez" above, copied from the proposed PI	**Adequate** - The applicant deleted (b) (4) per DMEPA's recommendation. The compatibility of the drug product with 0.9% sodium chloride injection is supported by the compatibility data submitted in NDA

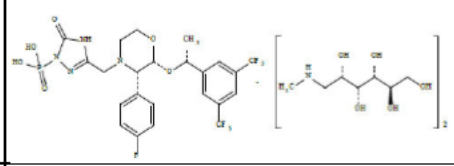
1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Injection	**Adequate**
Strength(s) in metric system	Injection: 150 mg/50 mL (3 mg/mL) of fosaprepitant	**Adequate**
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Provided in section 11	**Adequate**
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	a clear and colorless ready-to-use solution in a single-dose vial	**Adequate**
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	single-dose vial	**Adequate**

1.2.3 Section 11 (DESCRIPTION)

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	FOCINVEZ (fosaprepitant injection)	**Adequate**
Dosage form(s) and route(s) of administration	Each 50 mL vial of FOCINVEZ for administration as an intravenous infusion…	**Adequate**
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Each 50 mL vial of FOCINVEZ for administration as an intravenous infusion contains 150 mg of fosaprepitant (equivalent to 245.3 mg of fosaprepitant dimeglumine) …	**Adequate**
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	betadex sulfobutyl ether sodium (8 g), edetate disodium (5.4 mg), sodium hydroxide (b) (4) (for pH adjustment)	**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.	betadex sulfobutyl ether sodium (8 g), edetate disodium (5.4 mg), sodium hydroxide (b) (4) (for pH adjustment)	**Adequate**
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	sterile, ready-to-use, clear and colorless solution	**Adequate**
Pharmacological/ therapeutic class	an antiemetic agent	**Adequate**
Chemical name, structural formula, molecular weight	Name: 1-Deoxy-1-(methylamino)-Dglucitol[3-[[(2R,3S)-2-[(1R)-1-[3,5bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-2,5-dihydro-5-oxo-1H-1,2,4triazol-1-yl]phosphonate (2:1) (salt) Molecular formula: $C_{23}H_{22}F_7N_4O_6P \cdot 2(C_7H_{17}NO_5)$ Molecular weight 1004.83 (salt) 	**Adequate**
If radioactive, statement of important nuclear characteristics.	N/A	

Other important chemical or physical properties (such as pKa or pH)	Fosaprepitant dimeglumine is a white to off-white amorphous powder with a molecular weight of 1004.83. It is freely soluble in water.	**Adequate**

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	injection	**Adequate**
Strength(s) in metric system	FOCINVEZ (fosaprepitant injection) contains 150 mg/50 mL of fosaprepitant as a clear and colorless ready-to-use injection solution in a single-dose vial.	**Adequate** - "(3 mg/mL)" added after "150 mg/50 mL" in the updated labeling in sharePoint
Available units (e.g., bottles of 100 tablets)	1 vial per carton	**Adequate**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	clear and colorless ready-to-use injection	**Adequate**
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	single-dose vial	**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.)	N/A	
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store FOCINVEZ vials in the refrigerator at 2°C-8°C (36°F-46°F). FOCINVEZ vials, when kept in its original carton, can remain at room temperature for up to 90 days.	**Adequate**
Latex: If product does not contain latex and manufacturing	N/A	

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."		
Include information about child-resistant packaging	N/A	

1.2.5 Other Sections of Labeling

N/A

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured for: Spes Pharmaceuticals Inc., North Brunswick, NJ 08536, USA Manufactured by: Pharmaceutics International Inc., Hunt Valley, MD 21031, USA	**Adequate** - zip code for Spes Pharma changed from (b) (4) to "08902" in the updat sharePoint to be consistent to the zip code in c/c labels and PPI label

2.0 PATIENT LABELING

The following CMC information is provided in the Patient Information. The excipients changed to alphabetic order in updated PPI in SharePoint.

(b) (4)

3.0 CARTON AND CONTAINER LABELING

Bottle Label

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Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	FOCINVEZ (Fosaprepitant Injection)	**Adequate**
Dosage strength	150 mg/50 mL (3 mg/mL)	**Adequate**
Route of administration	FOR INTRAVENOUS USE ONLY	**Adequate**
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Carton: Each vial contains: Fosaprepitant, 150 mg (equivalent to 245.3 mg of fosaprepitant dimeglumine)	**Adequate**
Net contents (e.g. tablet count)	Bottle: 150 mg Single-Dose Vial Carton: Single-use vial. Each vial contains: Fosaprepitant, 150 mg (equivalent to 245.3 mg of fosaprepitant dimeglumine)	**Adequate**
"Rx only" displayed on the principal display	Provided	**Adequate**
NDC number	Provided	**Adequate**
Lot number and expiration date	Location allocated	**Adequate**
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Must be refrigerated at 2°C to 8°C (36°F to 46°F) FOCINVEZ vials, when kept in original carton, can remain at room temperature 20°C to 25°C (68°F to 77°F) for up to 90 days.	**Adequate**
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Single-dose vial	**Adequate**
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	Attention: This is a ready-to-use injection of fosaprepitant (3 mg/mL). Fosaprepitant is available in different concentrations.	**Adequate**
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Provided	**Adequate**

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Manufactured For: Spes Pharmaceuticals Inc., North Brunswick, NJ 08902, USA Made in USA	**Adequate**
Medication Guide (if applicable)	Recommended Dosage: See Prescribing Information	**Adequate**
No text on Ferrule and Cap overseal	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available	Inactive ingredients: betadex sulfobutyl ether sodium (8 g) edetate disodium (5.4 mg), sodium hydroxide (for pH adjustment) in water for injection.	**Adequate**

Assessment of Carton and Container Labeling: *Adequate*

ITEMS FOR ADDITIONAL ASSESSMENT

List of Deficiencies

Minor editorial changes listed in the above tables of each section of the PI review were updated in the final labeling in the SharePoint which will be conveyed to the applicant.

Overall Assessment and Recommendation:

The NDA is now ready for approval in its present form per CFR 314.125(b)(6).

Primary Labeling Assessor Name and Date:

Zhengfang Ge, Ph. D.
Reviewer, BRANCH IV/DIVISION II
OFFICE OF NEW DRUG PRODUCT

Secondary Assessor Name and Date:

I concur with Dr. Zhengfang Ge's assessment of the currently proposed labeling/labels.

Nina Ni, Ph. D.
SPQA, BRANCH IV/DIVISION II
OFFICE OF NEW DRUG PRODUCT

Zhengfang Ge

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Nina Ni

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CHAPTER VI: BIOPHARMACEUTICS

NDA Number	NDA-216686-ORIG-1
Drug Product Name/ Strength	Fosaprepitant Injection/150 mg/50 mL (3 mg/mL in 50 mL vials)
Route of Administration	Intravenous
Applicant Name	Spes Pharmaceuticals Inc.
Therapeutic Classification/ OND Division	Anti-emetics/Division of Gastroenterology (DG)
LD Number	EMEND® (fosaprepitant dimeglumide) for injection, lyophilized powder for solution for injection/NDA 022023
Proposed Indication	In adults and pediatric patients 6 months of age and older for the prevention of: acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin. & - delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).
Primary Reviewer	Leah W. Falade, Ph.D.
Secondary Reviewer	Tapash Ghosh, Ph.D.
Recommendation	**ADEQUATE**

EXECUTIVE SUMMARY

The Applicant is seeking approval to market Fosaprepitant Injection, 150 mg/50 mL (3 mg/mL) (in 50 mL vials), a ready-to-use (RTU) sterile solution for injection following the 505(b)(2) regulatory pathways relying on the previously established safety and efficacy for the Listed Drug (LD) EMEND® (fosaprepitant dimeglumine) injection, powder, lyophilized, for solution, 150 mg/vial marketed by Merck & Co., Inc. (NDA 022023). The proposed product contains the same active ingredient, fosaprepitant dimeglumine, and is also intended for the same indications in the same patient population, uses the route of intravenous administration, and follows the same dosing regimen as the LD.

The proposed product is a ready-to-use aqueous solution formulation containing 3 mg/mL of fosaprepitant, 0.108 mg/mL of edetate disodium (b) (4), and 160 mg/mL of Betadex sulfobutyl ether sodium (b) (4) in water for injection. The LD is a lyophilized powder (150 mg/vial). As per the approved labeling, the LD is diluted with 0.9% NaCl solution in the vial to a concentration of 1 mg/mL before adding to the IV infusion bag. The proposed test product is ready-to-use with a concentration of 3 mg/mL and does not require dilution before adding to the IV infusion bag.

The development strategy of the proposed drug product, therefore, is focused on bridging the difference between the proposed drug product and the LD, EMEND® lyophilized powder for

solution for injection. The Sponsor further relies on the Agency's findings of safety and efficacy from the LD, EMEND® for injection and related drug approvals.

The Applicant submitted a formal request to bridge the proposed drug product and the LD based on 21 CFR 320.24(b)(6).

The Biopharmaceutics review focuses on the waiver request for Fosaprepitant Injection, 150 mg/50 mL. A scientific bridge between the LD and the proposed drug product has been established under 21 CFR 320.24(b)(6) due to the following reasons:

1. The proposed drug product and the LD are both administered by IV infusion.

2. The proposed undiluted drug product and the reconstituted LD are compositionally similar and have comparable physicochemical properties.

3. Although the proposed product has a higher pH and osmolarity than the LD, nonclinical studies demonstrated that administration of the proposed fosaprepitant injection product results in comparable ADME and PK profiles when compared to administration of the LD.

The adequacy of the nonclinical data to support acceptance of the new excipient sulfobutyl ether – beta cyclodextrin at its proposed concentration and demonstrate that the differences between the proposed product and the LD will not impact the safety of fosaprepitant injection for the prevention of CINV was reviewed by the Pharm/Tox group as described in Section 5.

RECOMMENDATION:

From a Biopharmaceutics perspective, NDA-216686-ORIG-1 for Fosaprepitant Injection, 150 mg/50 mL is recommended for **approval**.

BIOPHARMACEUTICS ASSESSMENT

LIST of SUBMISSIONS BEING REVIEWED

eCTD # (SD #)	Received date	Document
0006 (SD 7)	03/28/2022	Filing Communication

BIOWAIVER REQUEST

The proposed drug product is not eligible for a biowaiver because inactive excipients are not Q1/Q2 to the LD. The comparative formulation data are presented in **Table *1***. The LD contains Polysorbate 80 (b) (4), while the proposed drug product contains sulfobutyl ether-beta-cyclodextrin. The purpose of the using Betadex sulfobutyl ether sodium (SBECD) in the proposed drug product is (b) (4)

Table 1. Comparison of Formulation Compositions between the Proposed Drug Product and the LD

EMEND® (fosaprepitant dimeglumine) Injection, lyophilized powder, for solution 150 mg/vial		**Fosaprepitant Injection, 150 mg/50 mL (3 mg/mL), an aqueous solution 150 mg/vial**		**Function in Formulation**
Ingredient	**Quantity/vial**	**Ingredient**	**Quantity/vial**	
Fosaprepitant (As fosaprepitant dimeglumine)	150 mg (Equivalent to 245.3 mg of fosaprepitant dimeglumine)	Fosaprepitant (As fosaprepitant dimeglumine)	150 mg (Equivalent to 245.3 mg of fosaprepitant dimeglumine)	Active ingredient
Edetate Disodium	5.4 mg	Edetate Disodium	5.4 mg	(b) (4)
Polysorbate 80	75 mg	*Sulfobutyl Ether-beta-cyclodextrin*	8.0 g	
Lactose Anhydrous	375 mg	Water for Injection	(b) (4)	
NaOH/HCl	(b) (4)	NaOH/ (b) (4)	(b) (4)	pH adjusting agent
(0.9% Sodium Chloride Injection)	*150 mL (For reconstitution and dilution)*	*(0.9% Sodium Chloride Injection)*	*No required but can be used as a diluent*	*IV diluent*

To support the scientific bridge, the Applicant submitted comparison of physicochemical properties of the LD and the proposed drug product as presented and further diluted to match the LD concentration (1 mg/mL). The diluted proposed product (1 mg/mL) has viscosity and osmolarity slightly higher than the diluted LD (1 mg/mL). Since the RTU test product will further be diluted in the IV infusion bag, This Reviewer finds the difference acceptable. The final determination will be made by the clinical division.

The pH of the RTU proposed drug product is higher than the reconstituted diluted LD. The Applicant provided FDA approved IV infusion drugs that have a higher pH than the range of 5 to 9. An in vitro blood mixing study was also conducted to show that the administration of the proposed drug product would not cause significant pH changes in the blood and adult patients, or pediatric patients aged 6 months and older. Based on the results, the pH of the drug after the proposed dosage does not change and the higher pH is acceptable.

Table 2. Comparison of Physical and Chemical Characteristics

Tests		Emend For Injection (Reconstituted and diluted, 1 mg/mL)			Fosaprepitant Injection (RTU, 3 mg/mL)			Fosaprepitant Injection (Diluted, 1mg/mL)		
		Lot # T034387	Lot # N028441, Vial #1	Lot # N028441, Vial #2	Lot # 27201.001	Lot # 27201.002	Lot # 27201.003	Lot # 27201.001	Lot # 27201.002	Lot # 27201.003
Appearance (*)		Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
pH		8.3	8.2	8.2	10.5	10.6	10.6	10.4	10.5	10.5
		(b) (4)			(b) (4)			(b) (4)		
Osmolarity (mOsm/kg)		287	288	286	499	498	500	332	329	334
		(b) (4)			(b) (4)			(b) (4)		
Viscosity (cp)		0.99	0.96	0.95	1.83	1.85	1.85	1.13	1.13	1.12
		(b) (4)			(b) (4)			(b) (4)		
Assay (%LC)		87.2	84.7	87.6 (b) (4)†	101.9	102.6	101.5	89.4	89.6	89.2 (b) (4)†
		Average: 86.5 (b) (4)† %RSD:1.8			Average: 102.0 %RSD: 0.5			Average: 89.4 (b) (4)† %RSD: 0.2		
Related Substances(%)		(b) (4)								
	Individual Unknown Impurity	(b) (4)								
	Total**									

* Clear and colorless solution and free from visible particulate matter ** Impurities excluding (b) (4)
NA: Less than 0.1% † Value corrected (b) (4)

Table 3. Effect of Fosaprepitant Injection on the pH of Human Whole Blood in Vitro

Parameters	Adult Subjects	Pediatric Subjects (Age 6 months)*
Total Blood Volume	5 L	0.59 L
Dosage Volume of Fosaprepitant Injection	50 mL	12.67 mL
pH of Fresh Human Whole Blood (pooled)	7.15 ± 0.01	7.15 ± 0.01
pH of Fresh Human Whole Blood Mixed with Fosaprepitant Injection	7.16 ± 0.01 (50 mL into 5 L)	7.14 ± 0.01 (12.6 mL into 0.59 L)

* Average body weight ~ 7.6 kg and total blood volume ~ 0.59 L; dosage volume for Fosaprepitant Injection ~12.67 mL (7.6 kg * 5 mg/kg / 3 mg/mL = 12.67 mL)

Leah Falade

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Tapash Ghosh

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	216686
Assessment Cycle Number	01
Drug Product Name/ Strength	Fosaprepitant Injection, 3 mg/mL
Route of Administration	IV injection
Applicant Name	SPES Pharmaceuticals, Inc.
Therapeutic Classification/ OND Division	Division of Gastroenterology
Manufacturing Site	Pharmaceutics International, Inc 103 Beaver Court, Cokeysville, MD 21030 FEI: 3006503102
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:

The drug product is (b) (4)

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Original (1)	12/23/2021
Facility IR Response (5)	02/09/2022
Filing IR Response (6)	03/16/2022
Labeling IR Response (7)	03/28/2022
DRL Response (10)	07/19/2022

Highlight Key Issues from Last Cycle and Their Resolution: Issues regarding (b) (4) were identified in the Microbiology Filing Review for this NDA.

Remarks: This is an eCTD submission. DMA previously provided feedback on microbial specifications, in-use post-dilution studies, and the inclusion of discard after use statements in the product label in reviews i140555 20180930 MR01.docx dated 09/17/2018 and I140555-2021-MR01.docx dated 09/16/2021.

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 –** Fosaprepitant Injection, 3 mg/mL, is a sterile, pyrogen-free, clear, colorless solution indicated for the treatment of nausea and vomiting associated with chemotherapy. It is administered via IV injection.
- **Drug product composition –**

Ingredient	Content per mL	Function
Fosaprepitant (in house)	3 mg	API
Edetate disodium, NF	0.108 mg	(b) (4)
Betadex Sulfobutyl Ether Sodium, USP	160 mg	
NaOH, USP/NF	(b) (4)	pH adjusting agent
(b) (4)		(b) (4)
WFI, USP		
(b) (4)		

- **Description of container closure system –**

Component	Packaging	Description (Gland material code)	Manufacturer
Vial	Primary		(b) (4)
Stopper	Primary		
Seal	Secondary		

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

Adequate

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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